

**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
INNOVATION RESEARCH (SBIR) PROGRAM**

PROGRAM SOLICITATION PHS 2017-1

Closing Date: October 21, 2016, 5:00 PM Eastern Daylight 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 received by October 21, 2016, 5:00 PM Eastern Daylight Time.

Please read the entire solicitation carefully prior to submitting your proposal.

IMPORTANT: All proposals must be submitted using the electronic contract proposal submission (eCPS) website.

Paper proposals will not be accepted.

Please go to https://www.sbir.gov/sites/default/files/sbir_pd_with_1-8-14_amendments_2-24-14.pdf to read the SBIR/STTR Policy Directive issued by the Small Business Administration for further information.

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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 contains opportunities to submit a proposal under a variety of different Topics, which are summarized below. Some Topics allow for only a Phase I proposal to be submitted. Some Topics allow for only a Phase II proposal to be submitted, through the ‘Direct to Phase II’ process. Some Topics allow for ‘Fast Track’ proposals, which include both a Phase I proposal and a Phase II proposal. For more information on the three phase program and the Fast Track and Direct to Phase II processes, refer to Section 2.

| TOPIC NUMBER | PHASE I PROPOSAL ALLOWED? (Includes only a Phase I Proposal) | FAST TRACK PROPOSAL ALLOWED? (Includes a Phase I Proposal and a Phase II Proposal) | DIRECT TO PHASE II ALLOWED? (Includes only a Phase II Proposal) | TOPIC TITLE |
|--------------|---|---|--|---|
| NIH/NCI 355 | Yes | Yes | Yes | Cell and Animal-Based Models to Advance Cancer Health Disparity Research |
| NIH/NCI 356 | Yes | No | No | Tools and Technologies for Monitoring RNA |
| NIH/NCI 357 | Yes | Yes | Yes | Innovative Tools for Interrogating Tumor Microenvironment Dynamics |
| NIH/NCI 358 | Yes | No | No | Modulating the Microbiome to Improve Therapeutic Efficacy of Cancer Therapeutics |
| NIH/NCI 359 | Yes | No | No | Technologies for Differential Isolation of Exosomes and Oncosomes |
| NIH/NCI 360 | Yes | Yes | No | Manufacturing Innovation for the Production of Cell-Based Cancer Immunotherapies |
| NIH/NCI 361 | Yes | No | No | Highly Innovative Tools for Quantifying Redox Effector Dynamics in Cancer |
| NIH/NCI 362 | Yes | Yes | No | Informatics Tools to Measure Cancer Care Coordination |
| NIH/NCI 363 | Yes | Yes | No | Connecting Cancer Caregivers to Care Teams: Digital Platforms to Support Informal Cancer Caregiving |
| NIH/NCI 364 | Yes | Yes | No | Methods and Software for Integration of Cancer Metabolomic Data with Other –Omic and Imaging Data |
| NIH/NCI 365 | Yes | Yes | No | Imaging Informatics Tools and Resources for Clinical Cancer Research |
| NIH/NCI 366 | Yes | No | No | Clonogenic High-Throughput Assay for Screening Anti-Cancer Agents and Radiation Modulators |
| NIH/NCI 367 | Yes | Yes | No | Predictive Biomarkers to Improve Radiation Treatment |

| TOPIC NUMBER | PHASE I PROPOSAL ALLOWED? (Includes only a Phase I Proposal) | FAST TRACK PROPOSAL ALLOWED? (Includes a Phase I Proposal and a Phase II Proposal) | DIRECT TO PHASE II ALLOWED? (Includes only a Phase II Proposal) | TOPIC TITLE |
|---------------------|--|--|---|---|
| NIH/NCI 368 | Yes | Yes | No | Molecularly Targeted Radiation Therapy for Cancer Treatment |
| NIH/NCI 369 | Yes | Yes | No | Development of Pediatric Cancer Drug Delivery Devices |
| NIH/NCATS 015 | Yes | No | No | Development of a Drone to be used in Laboratory Automation Projects |
| NIH/NHLBI 098 | No | Yes | Yes | Testing and Validation of Technologies for Inclusion in the CART Demonstration Project for Collaborative Aging Research |
| NIH/NHLBI 099 | Yes | Yes | No | Inhalational 5A Apolipoprotein A-I Mimetic Peptide for the Treatment of Asthma (SBIR-TT) |
| NIH/NHLBI 100 | Yes | Yes | Yes | MRI Myocardial Needle Chemoablation Catheter |
| NIH/NHLBI 101 | Yes | Yes | Yes | Membranous Ventricular Septal Defect (pmVSD) Transcatheter Occluder System |
| NIH/NHLBI 102 | Yes | Yes | Yes | Transcatheter Occluder Device for Paravalvular Leaks |
| NIH/NIAID 040 | Yes | No | Yes | Effective Targeted Delivery of RNA-based Vaccines and Therapeutics |
| NIH/NIAID 041 | Yes | Yes | No | Simplified Sequencing for TB Drug Resistance Testing |
| NIH/NIAID 042 | Yes | No | Yes | Qualitative HIV RNA Home Test |
| NIH/NIAID 043 | Yes | No | Yes | Adjuvant Development |
| NIH/NIAID 044 | Yes | No | Yes | Vaccine Adjuvant Screening and Discovery |
| NIH/NIAID 045 | Yes | No | Yes | Database Resources Integration |
| NIH/NIAID 046 | Yes | Yes | Yes | Rapid Point-of-Care Diagnostics to Detect Serologic Status of Individuals for Select Viral Infections |
| NIH/NIAID 047 | Yes | Yes | Yes | Development of Microbiome-based Products for Infectious Diseases |
| NIH/NIAID 048 | Yes | Yes | Yes | Non-Invasive Rapid Diagnostics for Respiratory Diseases in Children |

| TOPIC NUMBER | PHASE I PROPOSAL ALLOWED? (Includes only a Phase I Proposal) | FAST TRACK PROPOSAL ALLOWED? (Includes a Phase I Proposal and a Phase II Proposal) | DIRECT TO PHASE II ALLOWED? (Includes only a Phase II Proposal) | TOPIC TITLE |
|---------------------|--|--|---|---|
| NIH/NIAID 049 | Yes | Yes | Yes | Phage-based Diagnostic Platforms for Rapid Detection of Bacterial Pathogens |
| NIH/NIDA 161 | Yes | No | No | Virtual Reality Tools to Enhance Evidence Based Treatment of Substance Use Disorders |
| NIH/NIDA 162 | Yes | Yes | Yes | Analytical Tools and Approaches for (Multidimensional) Scholarly Research Assessment and Decision Support in the Biomedical Enterprise. |
| CDC/ NCCDPHP 038 | Yes | No | No | Improve Contextual Awareness using Social Network Data |
| CDC/ NCEZID 014 | Yes | No | No | Multiplexed Digital Counting of Single Molecules for Advanced Molecular Diagnosis |

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.

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.

Phase I: Feasibility

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 II: Full R/R&D Effort

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 I contractors will be informed of the opportunity to apply for Phase II, if a Phase II proposal was 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.*

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 Fast Track Proposals (NIH Only)

If a Topic notes that Fast Track proposals will be accepted, a Phase I proposal and a Phase II proposal may be submitted simultaneously. As described in Section 8.2 "Fast Track Proposal Instructions," a Fast Track submission consists of one complete Phase I proposal and one complete Phase II proposal, separately paginated. The Phase I proposal and Phase II proposal will be separately evaluated as set forth in Section 6.0 "Method of Evaluation."

A Fast Track submission may result in award for Phase I with a contractual option for Phase II. The Government is not obligated to fund the Phase II portion unless and until the awarding HHS Component exercises that option. This mechanism allows for streamlined processes that have the potential to minimize the funding gap between Phase I and Phase II.

If the Phase II proposal of a Fast Track submission is not found suitable to include as an option, the Phase I proposal will still be considered for Phase I only award. In this instance, the SBC is treated as other Phase I awardees are in regards to submitting a Phase II proposal in accordance with Section 1.0, "Introduction."

Refer to the table in Section 1.0 "Introduction" and [Section 12.0](#) "Research Topics," for notation of Topics allowing Fast Track proposals.

2.4 Direct to Phase II Proposals (NIH Only)

If a Topic notes that Direct to Phase II proposals will be accepted, a small business concern that has already performed Phase I stage-type research through other funding sources (not SBIR/STTR Phase I funding) may submit a Phase II only proposal. Direct to Phase II awards 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 Phase II type R&D that tests the functional viability of the prototype according to scientific methods and potential for commercial development. Refer to the table in Section 1.0 "Introduction" and [Section 12.0](#) "Research Topics," for notation of Topics allowing Direct to Phase II proposals.

2.5 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 or 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-16-009](#)) and the NHLBI Small Market Award ([RFA-HL-17-012](#)). Contact Jennifer Shieh, Ph.D., at 301-496-2149 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 Fertigs, M.B.A., at 301-496-1779 or fertigs@ninds.nih.gov for additional information.

2.6 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:

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

National Center for Emerging Zoonotic and Infectious Diseases (NCEZID)

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) firm. A small business concern that is participating in the Small Business Administration's 8(a) Business Development Program for firms that are owned and controlled at least 51% by socially and economically disadvantaged individuals.

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. How does SBA determine affiliation? (Available at http://www.ecfr.gov/cgi-bin/text-idx?SID=b02d16dbfcddf646e5c0728d5e632a61&mc=true&node=se13.1.121_1103&rgn=div8). Further information about SBA's affiliation rules and a guide on affiliation is available at www.SBIR.gov and www.SBA.gov/size.

Animal. Any live, vertebrate animal used or intended for use in research, research training, experimentation, or biological testing or for related purposes.

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 (VCOs), 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.

eCPS. The Electronic Contract Submission (eCPS) website is a component of the Government's integrated, secure system for the electronic submission, capture, tracking, and review of contract proposals. The eCPS website will be the only way to submit proposals under this solicitation. See the Section on Proposal Submissions for further information.

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.

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.

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.

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.

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 (Historically Underutilized Business Zone) Small Business Concerns maintained by the Small Business Administration (13 CFR 126.103).

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. A joint venture is an association of individuals and/or concerns with interests in any degree or proportion consorting to engage in and carry out no more than three specific or limited-purpose business ventures for joint profit over a two year period, for which purpose they combine their efforts, property, money, skill, or knowledge, but not on a continuing or permanent basis for conducting business generally. See [13 CFR 121.103\(h\)](#) for further information.

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 a veteran. Service-disabled veteran means a veteran, as defined in 38 U.S.C. 101(2), with a disability that is service-connected, as defined in 38 U.S.C. 101(16).

Small Business Concern (SBC). 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 Concern. Consistent with 13 CFR 124.1002, means a small business concern under the size standard applicable to the acquisition, that: is at least 51 percent unconditionally and directly owned (as defined at 13 CFR 124.105) by one or more socially disadvantaged (as defined at 13 CFR 124.103) and economically disadvantaged (as defined at 13 CFR 124.104) individuals who are citizens of the United States; and, each individual claiming economic disadvantage has a net worth not exceeding \$750,000 after taking into account the applicable exclusions set forth at 13 CFR 124.104(c)(2); and, the management and daily business operations of which are controlled (as defined at 13 CFR 124.106) by individuals who meet the criteria in paragraphs (1)(i) and (ii) of this definition.

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 Small Business Concern. A small business concern that is at least 51% owned by one or more women, or in the case of any publicly owned business, at least 51% of the stock is owned by women, and women control the management and daily business operations.

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 18 years (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-010.html>.) 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. This policy is separate from considerations of protections and consent for children to participate in research.

HHS Regulations ([45 CFR part 46, Subpart D, Sec.401-409](#)) provide additional protections for children involved as subjects in research, based on this definition: "Children are persons who have not attained the legal age for consent to treatments or procedures involved in research, under the applicable law of the jurisdiction in which the research will be conducted." Generally, state laws define what constitutes a "child." Consequently, the age at which a child's own consent is required and sufficient to participate in research will vary according to state law. For example, some states consider a person age 18 to be an adult and therefore one who can provide consent without parental permission.

Clinical Research. NIH defines human clinical research as research with human subjects that is:

- (1) Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects.

Excluded from this definition are in vitro studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes:

- (a) mechanisms of human disease,
 - (b) therapeutic interventions,
 - (c) clinical 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 research study¹ in which one or more human subjects² are prospectively assigned³ to one or more interventions⁴ (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes⁵.

¹ See Common Rule definition of research at 45 CFR 46.102(d).

² See Common Rule definition of human subject at 45 CFR 46.102(f).

³ The term “prospectively assigned” refers to a pre-defined process (e.g., randomization) specified in an approved protocol that stipulates the assignment of research subjects (individually or in clusters) to one or more arms (e.g., intervention, placebo, or other control) of a clinical trial.

⁴ An intervention is defined as a manipulation of the subject or subject’s environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints. Examples include: drugs/small molecules/compounds; biologics; devices; procedures (e.g., surgical techniques); delivery systems (e.g., telemedicine, face-to-face interviews); strategies to change health-related behavior (e.g., diet, cognitive therapy, exercise, development of new habits); treatment strategies; prevention strategies; and, diagnostic strategies.

⁵ Health-related biomedical or behavioral outcome is defined as the pre-specified goal(s) or condition(s) that reflect the effect of one or more interventions on human subjects’ biomedical or behavioral status, or quality of life. Examples include: positive or negative changes to physiological or biological parameters (e.g., improvement of lung capacity, gene expression); positive or negative changes to psychological or neurodevelopmental parameters (e.g., mood management intervention for smokers; reading comprehension and/or information retention); positive or negative changes to disease processes; positive or negative changes to health-related behaviors; and positive or negative changes to quality of life.

For additional information see [NOT-OD-15-015](#).

- *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:

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.

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.

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.

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:

- 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

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. If using live vertebrate animals, HHS policy requires that offerors address the criteria in the Vertebrate Animal Section (VAS) of the Technical Proposal. Each of the criteria must be addressed in the VAS portion of the Technical Proposal. For additional information see [Office of Laboratory Animal Welfare – Vertebrate Animals Section](#) and use [Contract Proposal VAS Worksheet](#).

Research Involving Human Subjects

All research involving human subjects, to include use of identifiable 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 following six categories of research meet the basic definition of human subjects research but are considered to be exempt from the HHS human subject regulations:

- (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 April 2016 as amended. The guidelines can be found at: http://osp.od.nih.gov/sites/default/files/NIH_Guidelines.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.

Valid Analysis. This term means an unbiased assessment. Such an assessment will, on average, yield the correct estimate of the difference in outcomes between two groups of subjects. Valid analysis can and should be conducted for both small and large studies. A valid analysis does not need to have a high statistical power for detecting a stated effect. The principal requirements for ensuring a valid analysis of the question of interest are: allocation of study participants of both sexes/genders (males and females) and from different racial and/or ethnic groups to the intervention and control groups by an unbiased process such as randomization; unbiased evaluation of the outcome(s) of study participants; and use of unbiased statistical analyses and proper methods of inference to estimate and compare the intervention effects by sex/gender, race, and/or ethnicity.

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 applicant 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. Additionally, each 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.

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.

For both Phase I and II, the principal investigator must be primarily employed with the SBC. Primary employment means that more than one half (50%) of the employee's time is spent with the small business. Primary employment with the SBC 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 SBC 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 as follows:

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.

Phase II to Phase III Commercialization Benchmark

As required by the SBIR/STTR Reauthorization Act of 2011, HHS SBIR/STTR programs are also implementing the Phase II to Phase III Commercialization Rate benchmark for Phase I applicants. The Commercialization Rate Benchmark was published in a Federal Register notice on August 8, 2013 (78 FR 48537). This requirement applies to companies that have

received more than 15 Phase II awards from all agencies over the past 10 years, excluding the two most recently-completed Fiscal Years.

Companies that meet this criterion must show an average of at least \$100,000 in revenues and/or investments per Phase II award or at least 0.15 (15%) patents per Phase II award resulting from these awards.

Applicants to this solicitation that may have received more than 15 Phase II awards across all federal SBIR/STTR agencies over the past ten (10) years should, prior to application preparation, verify that their company's Commercialization Benchmark on the Company Registry at SBIR.gov meets or exceeds the benchmark rate listed above. Applicants that fail this benchmark will be notified by SBA annually and will not be eligible to receive new Phase I, Fast-track or Direct Phase II awards for a period of one year. Information on the Phase II to Phase III Commercialization Benchmark is available at SBIR.gov.

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. Ultimately, the decision to submit a proposal using multiple PIs versus a 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. At least one proposed PI must be primarily employed with the applicant, as discussed in Section 4.2 "Offeror Eligibility and Performance Requirements."

4.4 Joint Ventures and Limited Partnerships

Joint ventures and limited partnerships are eligible, provided that each entity to the joint venture qualifies as a small business in accordance with the Small Business Act. Refer to the definition of "Small Business Concern" and "Joint Venture" in Section 3.1 "General Definitions," for further information.

4.5 Majority Ownership in Part by Multiple Venture Capital, Hedge Fund, and Private Equity Firms

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, **but 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.

Answer the 3 questions and check the certification boxes.

The authorized business official must sign the certification.

The signed SBIR Application VCOC Certification must be submitted as part of the Pricing Proposal.

Applicant small business concerns who are NOT owned in majority part by multiple venture capital operating companies (VCOCs), hedge funds, or private equity funds, as described above, should NOT fill out a "SBIR Application VCOC Certification" and should NOT attach it to their application package.

4.6 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.

4.7 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.

4.8 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. Clearance may take several months to obtain and it is therefore not practical to propose any such activity for Phase I, which has a brief period of performance.

4.9 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)

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.

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.

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 the HHS human subjects regulations (see section 3.2 above).

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).

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 (known as the Federalwide Assurance or FWA), 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 (IRB) shall consider the relevant regulatory criteria for IRB approval under 45 CFR 46.111. 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](#).

Offerors may consult with OHRP for advice or guidance concerning either regulatory requirements or ethical issues pertaining to research involving human subjects.

4.10 Inclusion of Women, Minorities, and Children in Clinical Research

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.** More information on the inclusion of women and minorities may be found at http://grants.nih.gov/grants/funding/women_min/women_min.htm.

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 18 years (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-010.html>.) 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. More information about the inclusion of children in clinical research can be found at <https://grants.nih.gov/grants/funding/children/children.htm>.

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 (December 18, 2015)

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 awarding a contract to an offeror, 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, the Guide for the Care and Use of Laboratory Animals (National Academy Press, Washington, DC). In accordance with the PHS Policy, offerors must establish an Institutional Animal Care and Use Committee (IACUC), qualified through the experience and expertise of its members, to oversee the institution’s animal program, facilities, and procedures. Offerors must provide verification of IACUC approval prior to receiving 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 involving live vertebrate animals of the Assurance and verification of IACUC approval requirement. 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 OLAW website 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 [NIH Guidelines for Research Involving Recombinant 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 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 calendar 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 Information

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.

Type of Funding Agreement. Each Phase I proposal selected for award will be funded under negotiated contracts. Firm fixed price contracts are anticipated for Phase I projects. A firm-fixed-price contract establishes a payment amount that is not subject to adjustment on the basis of the contractor's actual costs in performing the contract.

Dollar Value. Phase I contract value varies among Topics. It is therefore important for proposing firms to review the Topic description in Section 12.0, which includes a Budget for each Phase of each Topic. **The applicant's Pricing Proposal (Appendix C) may not exceed the Budget for that Topic, including all direct costs, indirect costs, and profit** (consistent with normal profit margins provided to profit-making firms for R/R&D work).

4.15 Phase II Award Information (For Fast Track and Direct to Phase II Proposals)

Number of 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.

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-reimbursement type. A firm-fixed-price contract establishes a payment amount that is not subject to adjustment on the basis of the contractor's actual costs in performing the contract. A cost-reimbursement type contract provides for payment of allowable incurred costs, up to the ceiling amount established in the contract.

Dollar Value. Phase II contract value varies among Topics. It is therefore important for proposing firms to review the Topic description in Section 12.0, which includes a Budget for each Phase of each Topic. **The applicant's Pricing Proposal (Appendix C) may not exceed the Budget for that Topic, including all direct costs, indirect costs, and profit** (consistent with federal and HHS acquisition regulations and normal profit margins provided to profit-making firms for R/R&D work).

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.

Navigate to the SBA Company Registry.

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".

If you are a first time applicant, click the [New to the SBIR Program?](#) link on lower right of registry screen.

Fill out the required information on the "Basic Information" and "Eligibility Statement" screens.

Press "Complete Registration" on the lower right of the "Eligibility Statement" screen and follow all instructions.

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.

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 equivalent work (see definition in Section 3.1) in response to NIH/CDC solicitations and funding opportunity announcements for the SBIR program.

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. In addition, a firm that receives a Phase I SBIR contract may submit a Phase II grant application.

It is permissible, with proposal notification, to submit proposals containing essentially equivalent work for consideration under another federal program solicitation in addition to one NIH/CDC solicitation or funding opportunity announcements for the SBIR program.

IMPORTANT – 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 SBIR Support office at https://www.sbir.gov/state_services for further information.

Technical Assistance

NIH offers distinct [technical assistance programs](#) to NIH and CDC 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.

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. Offerors should indicate the need for advanced payments in Appendix C – Contract Pricing Proposal, Section III. If you are notified that your proposal is being considered for award, communicate with the point of contact named in that notification regarding procedures for requesting advanced payment. 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 identified by asterisks (*).

For Phase I proposals, also note each page number that contains proprietary information in the appropriate field in Appendix A. For Phase II proposal, please include the following language 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. The outline that follows is illustrative of the types of clauses required by the Federal Acquisition Regulations that will be included in contracts resulting from this solicitation. This is not a complete list of clauses to be included, nor does it contain specific wording of these clauses. An award document reflecting all contract requirements applicable to your proposal will be made available prior to award.

- a. **Inspection.** Work performed under the contract is subject to Government inspection and evaluation at all reasonable times.
- b. **Audit and Examination of Records.** The Contracting Officer and the Comptroller General, or a fully authorized representative of either, shall have the right to examine and audit all records and other evidence sufficient to reflect properly all costs claimed to have been incurred or anticipated to be incurred directly or indirectly in performance of this contract.
- c. **Default.** The Government may terminate the contract if the contractor fails to perform the work contracted.
- d. **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.
- e. **Disputes.** Any dispute concerning the contract which cannot be resolved by agreement shall be decided by the Contracting Officer with right of appeal.
- f. **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.
- g. **Salary Rate Limitation.** None of the funds appropriated in this title shall be used to pay the direct annual salary of an individual at a rate in excess of Executive Schedule, Level II of the Federal Executive Pay Scale. **Effective January 2016, Executive Schedule, Level II of the Federal Executive Pay Scale is \$185,100.**
- h. **Items Unallowable Unless Otherwise Provided.** Unless authorized in writing by the Contracting Officer, the costs of the following items or activities shall be unallowable as direct costs: purchase or lease of any interest in real property; special rearrangement or alteration of facilities; purchase or lease of any item of general purpose office furniture or equipment regardless of dollar value; travel to attend general scientific meetings; foreign travel; non-expendable personal property with an acquisition cost of \$1,000 or more.
- i. **Continued Ban on Funding Abortion and Continued Ban on Funding of Human Embryo Research.** The Contractor shall not use contract funds for (1) any abortion; (2) the creation of a human embryo or embryos for research purposes; or (3) 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, Federal funds shall not be used for the cloning of human beings.

- j. **Use of Funds for Conferences, Meetings and Food.** The Contractor shall not use contract funds (direct or indirect) to conduct meetings or conferences in performance of this contract without prior written Contracting Officer approval. In addition, the use of contract funds to purchase food for meals, light refreshments, or beverages is expressly prohibited.
- k. **Use of Funds for Promotional Items.** The Contractor shall not use contract funds to purchase promotional items. Promotional items include, but are not limited to: clothing and commemorative items such as pens, mugs/cups, folders/folios, lanyards, and conference bags that are sometimes provided to visitors, employees, grantees, or conference attendees. This includes items or tokens given to individuals as these are considered personal gifts for which contract funds may not be expended.
- l. **Electronic and Information Technology Accessibility.** Contracts including the development of Electronic and Information Technology (EIT) products and services shall require accessibility provisions in compliance with **Section 508** of the Rehabilitation Act of 1973 (29 U.S.C.794d), as amended by the Workforce Investment Act of 1998. Information about Section 508 provisions is available at <http://www.section508.gov/>.
- m. **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).
- n. **Equal Opportunity.** The contractor will not discriminate against any employee or applicant for employment because of race, color, religion, sex, or national origin.
- o. **Equal Opportunity for Veterans.** The contractor will not discriminate against any employee or applicant for employment because he or she is a disabled veteran.
- p. **Equal Opportunity for Workers with Disabilities.** The contractor will not discriminate against any employee or applicant for employment because he or she is physically or mentally handicapped.
- q. **Anti-Kickback Procedures.** The contractor is prohibited from offering or accepting any money, gifts, things of value, etc. for the purpose of improperly obtaining or rewarding favorable treatment in connection with a federal contract or subcontract and shall have procedures in place to prevent and detect violations.
- r. **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.
- s. **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.
- t. **Patent Infringement.** The contractor shall report each notice or claim of patent infringement based on the performance of the contract.
- u. **Employment Eligibility Verification.** The contractor shall be enrolled as a Federal Contractor in E-Verify and verify all employees assigned to the contract as well as all new employees hired by the contractor.
- v. **Needle Exchange.** 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.
- w. **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.

- x. **Dissemination of False or Deliberately Misleading Information.** The Contractor shall not use contract funds to disseminate information that is deliberately false or misleading.
- y. **Anti-Lobbying.** Pursuant to the current appropriations act, except for normal and recognized executive legislative relationships, the contractor shall not use any contract funds for (i) publicity or propaganda purposes; (ii) the preparation, distribution, or use of any kit, pamphlet, booklet, publication, radio, television or video presentation designed to support or defeat legislation pending before the Congress or any State legislature, except in presentation to the Congress or any State legislature itself; or (iii) payment of salary or expenses of the Contractor, or any agent acting for the Contractor, related to any activity designed to influence legislation or appropriations pending before the Congress or any State legislature.
- z. **Gun Control.** The contractor shall not use contract funds in whole or in part to advocate or promote gun control.
- aa. **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 Human Subjects Contract Requirements

Contracts involving Human Subjects Research shall include the following requirements:

- a. The Contractor agrees that the rights and welfare of human subjects involved in research under this contract shall be protected in accordance with 45 CFR part 46 and with the Contractor's current Federal-wide Assurance (FWA) on file with the Office for Human Research Protections (OHRP), Department of Health and Human Services. The Contractor further agrees to provide certification at least annually that the Institutional Review Board has reviewed and approved the procedures, which involve human subjects in accordance with 45 CFR part 46 and the Assurance of Compliance.
- b. The Contractor shall bear full responsibility for the performance of all work and services involving the use of human subjects under this contract and shall ensure that that work is conducted in a proper manner and as safely as is feasible. The parties hereto agree that the Contractor retains the right to control and direct the performance of all work under this contract. Nothing in this contract shall create an agency or employee relationship between the Government and the Contractor, or any subcontractor, agent or employee of the Contractor, or any other person, organization, institution, or group of any kind whatsoever. The Contractor agrees that it has entered into this contract and will discharge its obligations, duties, and undertakings and the work pursuant thereto, whether requiring professional judgment or otherwise, as an independent Contractor without creating liability on the part of the Government for the acts of the Contractor or its employees.
- c. Contractors involving other agencies or institutions in activities considered to be engaged in research involving human subjects must ensure that such other agencies or institutions obtain their own FWA if they are routinely engaged in research involving human subjects or ensure that such agencies or institutions are covered by the Contractors' FWA via designation as agents of the institution or via individual investigator agreements (see OHRP Website at: <http://www.hhs.gov/ohrp/policy/guidanceonalternativetofwa.pdf>).
- d. If at any time during the performance of this contract the Contractor is not in compliance with any of the requirements and or standards stated in paragraphs (a) and (b) above, the Contracting Officer may immediately suspend, in whole or in part, work and further payments under this contract until the Contractor corrects the noncompliance. The Contracting Officer may communicate the notice of suspension by telephone with confirmation in writing. If the Contractor fails to complete corrective action within the period of time designated in the Contracting Officer's written notice of suspension, the Contracting Officer may, after consultation with OHRP, terminate this contract in whole or in part.

- e. NIH policy requires education on the protection of human subject participants for all investigators receiving NIH contract awards for research involving human subjects. For a complete description of the NIH Policy announcement on required education in the protection of human subject participants, the Contractor should access the [NIH Guide for Grants and Contracts](http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html) Announcement dated June 5, 2000 at the following website: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html> .

5.3 Vertebrate Animals Contract Requirements

Contracts involving vertebrate animals shall include the following requirements:

- a. Before undertaking performance of any contract involving animal-related activities where the species is regulated by the United States Department of Agriculture (USDA), the Contractor shall register with the Secretary of Agriculture of the United States in accordance with 7 U.S.C. 2136 and 9 CFR 2.25 through 2.28. The Contractor shall furnish evidence of the registration to the Contracting Officer.
- b. The Contractor shall acquire vertebrate animals used in research from a dealer licensed by the Secretary of Agriculture under 7 U.S.C. 2133 and 9 CFR 2.1 2.11, or from a source that is exempt from licensing under those sections.
- c. The Contractor agrees that the care, use, and intended use of any live vertebrate animals in the performance of this contract shall conform with the Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals (PHS Policy), the current Animal Welfare Assurance (Assurance), the Guide for the Care and Use of Laboratory Animals (National Academy Press, Washington, DC) and the pertinent laws and regulations of the United States Department of Agriculture (see 7 U.S.C. 2131 et seq. and 9 CFR subchapter A, Parts 1-4). In case of conflict between standards, the more stringent standard shall govern.
- d. If at any time during performance of this contract, the Contracting Officer determines, in consultation with the Office of Laboratory Animal Welfare (OLAW), National Institutes of Health (NIH), that the Contractor is not in compliance with any of the requirements and standards stated in paragraphs (a) through (c) above, the Contracting Officer may immediately suspend, in whole or in part, work and further payments under this contract until the Contractor corrects the noncompliance. Notice of the suspension may be communicated by telephone and confirmed in writing. If the Contractor fails to complete corrective action within the period of time designated in the Contracting Officer's written notice of suspension, the Contracting Officer may, in consultation with OLAW, NIH, terminate this contract in whole or in part, and the Contractor's name may be removed from the list of those contractors with Animal Welfare Assurances.

Note : The Contractor may request registration of its facility and a current listing of licensed dealers from the Regional Office of the Animal and Plant Health Inspection Service (APHIS), USDA, for the region in which its research facility is located. The location of the appropriate APHIS Regional Office, as well as information concerning this program may be obtained by contacting the Animal Care Staff, USDA/APHIS, 4700 River Road, Riverdale, Maryland 20737 (Email: ace@aphis.usda.gov ; Web site: (<http://www.aphis.usda.gov/wps/portal/aphis/ourfocus/animalwelfare>) .

- e. 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). The PHS Policy can be accessed at: <http://grants1.nih.gov/grants/olaw/references/phspol.htm> . 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, which is incorporated by reference.

5.4 NIH Policy on Enhancing Reproducibility Through Rigor and Transparency

Contractors shall adhere to the NIH policy of enhancing reproducibility through rigor and transparency by addressing each of the four areas of the policy in performance of the Statement of Work and in publications, as applicable: 1) Scientific Premise; 2) Scientific Rigor; 3) Consideration of Relevant Biological Variables, including Sex; and 4) Authentication of Key Biological and/or Chemical Resources. This policy applies to all NIH funded research and development, from basic through advanced clinical studies. See [NIH Guide Notice, NOT-OD-15-103 , "Enhancing Reproducibility through Rigor and Transparency"](#) and [NOT-OD-15-102 , "Consideration of Sex as a Biological Variable in NIH-funded Research"](#) for more

information. In addition, publications are expected to follow the guidance at <http://www.nih.gov/research-training/rigor-reproducibility/principles-guidelines-reporting-preclinical-research>, whether preclinical or otherwise, as appropriate. More information is available at <http://grants.nih.gov/reproducibility/index.htm>, including FAQs and a General Policy Overview.

5.5 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.

5.6 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.

5.7 Patents and Invention Reporting

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 to allow the awardee to pursue a patent.

The reporting of inventions is accomplished by submitting information through the [Edison Invention Reporting System](#) for those awarding components participating in “Interagency Edison”, or iEdison. The NIH has developed the iEdison electronic invention reporting system to assist contractors in complying with invention reporting requirements. NIH requires contractors to use iEdison, which 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.

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

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.

Inquiries or information about invention reporting or requirements imposed by 37 CFR 401 may also be directed 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) 451-4235
Fax: (301) 480-0272
E-mail: hammerslaa@mail.nih.gov

6 METHOD OF EVALUATION

All proposals will be evaluated and judged on a competitive basis. Using the technical evaluation criteria specified below, a panel of experts knowledgeable in the disciplines or fields under review will evaluate proposals to determine the most promising technical and scientific approaches. For NIH, this peer review panel of experts will be composed of nongovernment personnel. For CDC, this panel will be composed of internal governmental scientific and technical experts.

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 reviewed by a panel of experts selected for their competence in relevant scientific and technical fields. Each 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 items, which reviewers will factor into the determination of a proposal's scientific and technical merit:

- Resource Sharing https://grants.nih.gov/grants/peer/guidelines_general/Resource_sharing_plans.pdf
 - Data Sharing Plan http://grants.nih.gov/grants/policy/data_sharing
 - Model Organism Sharing Plan http://grants.nih.gov/grants/policy/model_organism/
 - Genome Data Sharing <http://gds.nih.gov/>
- 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
- Biohazards/Select Agents/Recombinant DNA <http://grants.nih.gov/grants/guide/notice-files/not95-209.html>
- Dual Use Research of Concern: <http://phe.gov/s3/dualuse/Documents/oversight-durc.pdf>

The review panel provides a rating for each proposal and makes specific recommendations related to the scope, direction and/or conduct of the proposed research. For those proposals found technically acceptable, the review panel 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. For NIH only, the program staff of the awarding component will conduct a second level of review. Recommendations of reviewers 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 technically 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. While technical factors are of paramount consideration, 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.

The Phase I proposal and the Phase II proposal in a Fast Track submission will be evaluated and scored individually. However, if a Phase I proposal is evaluated and found to be Technically Unacceptable, the corresponding Phase II portion of the Fast Track proposal will not be evaluated.

6.2 Phase I Technical Evaluation Criteria

Phase I proposals will be evaluated based on the criteria outlined below – subfactors are considered to be of equal importance:

| FACTORS FOR PHASE I PROPOSALS | WEIGHT |
|--|--------|
| 1. The soundness and technical merit of the proposed approach. <ul style="list-style-type: none"> a. Identification of clear, measureable goals (<i>i.e.</i>, milestones) that have a reasonable chance of meeting the topic objective in Phase I. b. Demonstration of a Strong Scientific Premise for the Technical Proposal. (<i>I.e.</i>, Sufficiency of proposed strategy to ensure a robust and unbiased approach, as appropriate for the work proposed. Adequacy of proposed plan to address relevant biological variables, including sex, for studies in vertebrate animals and/or human subjects.) | 25% |
| 2. The potential of the proposed research for technological innovation. | 25% |
| 3. The potential of the proposed research for commercial application, including: <ul style="list-style-type: none"> a. Whether the outcome of the proposed research activity will likely lead to a marketable product or process; and, b. The offeror’s discussion of the potential barriers to entry in the competitive market landscape as well as method to overcome. | 20% |
| 4. The qualifications of the proposed Project Directors/Principal Investigators, supporting staff and consultants. | 20% |
| 5. The adequacy and suitability of the proposed facilities, equipment, and research environment. | 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 Phase II Technical Evaluation Criteria

Phase II proposals will be evaluated based on the criteria outlined below. This includes Direct to Phase II proposals, Phase II proposals included in Fast Track submissions, and Phase II proposals subsequently submitted by contractors who are awarded a Phase I contract under this solicitation.

| FACTORS FOR PHASE II PROPOSALS | WEIGHT |
|--------------------------------|--------|
|--------------------------------|--------|

| FACTORS FOR PHASE II PROPOSALS | WEIGHT |
|--|--------|
| 1. The soundness and technical merit of the proposed approach <ul style="list-style-type: none"> a. Identification of clear, measureable goals (<i>i.e.</i>, milestones) that have a reasonable chance of meeting the topic objective in Phase II b. Demonstration of a Strong Scientific Premise for the Technical Proposal. (<i>I.e.</i>, Sufficiency of proposed strategy to ensure a robust and unbiased approach, as appropriate for the work proposed. Adequacy of proposed plan to address relevant biological variables, including sex, for studies in vertebrate animals and/or human subjects.) c. For Direct to Phase II only: Demonstrated feasibility of the methodology or technology equivalent to meeting Phase I-level objectives, providing a solid foundation for the proposed Phase II activity. | 25% |
| 2. The potential of the proposed research for technological innovation. | 25% |
| 3. The potential of the proposed research for commercialization, as documented in the offeror's Commercialization Plan and evidenced by: <ul style="list-style-type: none"> 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/or c. Any other indicators of commercial potential for the proposed research. | 25% |
| 4. The qualifications of the proposed PDs/PIs, supporting staff and consultants. 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. | 15% |
| 5. The adequacy and suitability of the facilities and research environment. | 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.

6.4 Award Decisions

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

1. Ratings resulting from the scientific/technical evaluation process;

Areas of high program relevance;

Program balance (*i.e.*, balance among areas of research);

Availability of funds, and.

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.

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 1, 2016**. 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 Pre-Proposal Conference

HHS will hold a pre-proposal conference, via webinar, on August 24, 2016 at 2:00 PM Eastern Daylight Time. This informational webinar will discuss this solicitation, and in particular will discuss the new electronic contract proposal submission (eCPS) website. For this solicitation, proposals will only be accepted via the eCPS website.

Offerors may register for the webinar at: <https://attendee.gotowebinar.com/register/6309703982537321475> . Following registration, a confirmation e-mail will be sent containing information about joining the webinar.

Presentation material from this webinar shall be posted on FedBizOpps and the NIH [SBIR/STTR webpage](#) following its completion.

7.3 Limitation on the Length of the Technical Proposal (Item 1)

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.). Page margins must be at least one inch on all sides. 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.

7.4 Submission, Modifications, Revision, and Withdrawal of Proposals

- (a) Offerors are responsible for submitting proposals, including any revisions or modifications, to the electronic Contract Proposal Submission (eCPS) website at <https://ecps.nih.gov/sbirsttr> by the date and time specified on the first page of this solicitation.

Offerors must use this electronic transmission method. No other method of proposal submission is permitted.

- (b) Instructions on how to submit a proposal into eCPS are available at <https://ecps.nih.gov/sbirsttr/home/howto>. Offerors may also reference Frequently Asked Questions regarding online submissions at <https://ecps.nih.gov/sbirsttr/home/faq>.
1. Be advised that registration is required to submit a proposal into eCPS and registration may take several business days to process.
 2. The proposal must be uploaded in 2 parts: Technical and Business.

The Technical Proposal shall consist of Item 1, as described in Sections 8.3 and 8.4. The Technical Proposal must consist of a single PDF file.

The Business Proposal shall consist of Items 2, 3, and 4, as applicable, as described in Section 8.3 and 8.4. The Business Proposal must consist of a single PDF file. Offerors may also choose to submit an optional Excel Workbook spreadsheet providing a cost breakdown, in addition to the single PDF file.

3. Proposal Naming Conventions:

- a. The 'Proposal Name' entered into eCPS for your proposal submission shall include, in order: (1) the Phase the proposal is for; (2) the name of the Offeror; (3) the NIH or CDC Awarding Component and the Topic being proposed under.

Examples are provided below:

- Phase I_XYZ Company_ NCEZID_Topic_014
- Phase II_XYZ Company_NIAID_Topic_049

If submitting a Fast Track Proposal, include "FAST TRACK" after the Phase, as shown below:

- Phase I FAST TRACK_XYZ Company_NIAID_Topic_049
- Phase II FAST TRACK_XYZ Company_NIAID-Topic_049

- b. Files uploaded for your proposal submission shall include, in order: (1) the name of the Offeror; (2) the NIH or CDC Awarding Component and the Topic being proposed under; and, (3) the type of proposal (i.e., Technical, Business, or Excel Workbook). Use the format set forth in the examples below when naming your files, prior to uploading them into eCPS:

- *Example for a proposal under National Institutes of Health / National Institute of Allergy and Infectious Diseases Topic 033:*

Technical Proposal: XYZ Company_NIAID_TOPIC_033_Technical.pdf
Business Proposal: XYZ Company_NIAID_TOPIC_033_Business.pdf
Excel Workbook (Optional): XYZ Company_NIAID_TOPIC_033_Business.xlsx

- *Example for a proposal under Centers for Disease Control / National Center for Immunization and Respiratory Diseases Topic 031:*

Technical Proposal: XYZ Company_NCIRD_TOPIC_031_Technical.pdf
Business Proposal: XYZ Company_NCIRD_TOPIC_031_Business.pdf
Excel Workbook (Optional): XYZ Company_NCIRD_TOPIC_031_Business.xlsx

4. To submit a Fast Track Proposal (NIH Only):

- Upload the Phase 1 Technical Proposal and Phase 1 Business Proposal and Submit.
- After you submit the Phase 1 proposal, then click the "Submit new/alternate Proposal" button for Phase 2 submission.
- Upload the Phase 2 Technical Proposal and Phase 2 Business Proposal and Submit.

(c) Any proposal, modification, or revision, that is received after the exact time specified for receipt of proposals is "late" and will not be considered for award.

(d) If an emergency or unanticipated event interrupts normal Government processes so that proposals cannot be received at the eCPS website 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. A copy of withdrawn proposals will be retained in the contract file.

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, Fast Track, and Direct to Phase II 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 Fast Track Proposal Instructions (NIH Only)

To identify the submission as a Fast Track proposal, check the box marked “Yes,” next to the words “Fast Track Proposal” shown on the Phase I Proposal Cover Sheet (Appendix A).

For a Fast Track submission, both a complete Phase I proposal and a separate, complete Phase II proposal must be submitted. The Phase I proposal shall follow the instructions set forth in Section 8.3 “Phase I Proposal Instructions.” The Phase II proposal shall follow the instructions set forth in Section 8.4. “Phase II Proposal Instructions.”

The Phase I proposal and the Phase II proposal in a Fast Track submission will be evaluated and scored individually. However, if a Phase I proposal is evaluated and found to be Technically Unacceptable, the corresponding Phase II Fast Track proposal will not be evaluated.

8.3 Phase I Proposal Instructions

A complete Phase I proposal consists of four elements:

TECHNICAL PROPOSAL

Item 1: Technical Element

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

BUSINESS PROPOSAL

Item 2: Pricing Proposal (Appendix C)

Item 3: SBIR Application VCOC Certification, if applicable

(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)

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 any Federal Agency, you must reveal this on the Cover Sheet and provide the information required.

8.4 Phase II Proposal Instructions

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

TECHNICAL PROPOSAL

Item 1: Technical Element

- a. Technical Proposal Cover Sheet (Appendix D)
- b. Table of Contents
- c. Abstract of the Research Plan, (Appendix B)
- d. Content of the Technical Element
- e. Draft Statement of Work (Appendix E)
- f. Summary of Related Activities (Appendix F)
- g. Proposal Summary and Data Record (Appendix G)

BUSINESS PROPOSAL

Item 2: Pricing Proposal (Appendix C)

Item 3: SBIR Application VCOC Certification, if applicable

(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 proposals for this solicitation will only be accepted for Topics that allow for Fast Track proposals or Direct to Phase II proposals.

SBCs who receive a Phase I-only award will receive Phase II proposal instructions in a separate solicitation from the HHS Awarding Component for the Topic.

8.5 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 Phase II proposals (including Direct to Phase II Proposals and the Phase II Proposal of a Fast Track submission), 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 (NIH 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.

8.6 Table of Contents (Item 1)

Include a Table of Contents. Number all pages of your proposal consecutively. 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.

8.7 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.

| |
|---|
| <p>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</p> |
|---|

‘PROPOSAL FUNDAMENTALS’. ADDRESS THESE ITEMS IN A SEPARATE SECTION OF YOUR TECHNICAL PROPOSAL AND LABEL AS REQUIRED.

8.8 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 (NIH Only).** 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) Research Plan for Phase II proposals (including Direct to Phase II Proposals and the Phase II Proposal of a Fast Track submission)

1) 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.

- 2) **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 Sections 4.9, 4.10, 8.9 and/or 8.11 of this solicitation for further guidance.
- 3) **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.
 - 4) **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.)
 - 5) **Other considerations** - Provide a brief narrative of any unique arrangements, safety procedures in place, animal welfare issues, human subjects protections, inclusion of women, minorities, and children, etc. Note: If the research plan includes the use of human subjects or vertebrate animals, refer to Sections 4.9, 4.10, 8.9 and/or 8.11 of this solicitation for further guidance.
 - 6) **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.
 - 7) If budget allocation is planned, the distribution of resources to specific components of the project or the individual PDs/PIs should be delineated in the Leadership Plan. In the event of an award, the requested allocations may be reflected in Contract Award.
 - 8) **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 ([15 U.S.C. 631](#), et seq., as amended), 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](#).
- 9) **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.
- 10) **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.

8.9 Enhancing Reproducibility through Rigor and Transparency

The offeror shall demonstrate compliance with the NIH Policy on enhancing Reproducibility through Rigor and Transparency as described in NIH Guide Notice NOT- OD-15-103 . Specifically, the offeror shall describe in its technical proposal the information described below:

- a. Describe the scientific premise for the Technical Proposal. The scientific premise is the research that is used to form the basis for the proposed research. Offerors should describe the general strengths and weaknesses of the prior research being cited by the offeror as crucial to support the proposal. It is expected that this consideration of general strengths and weaknesses could include attention to the rigor of the previous experimental designs, as well as the incorporation of relevant biological variables and authentication of key resources.
- b. Describe the experimental design and methods proposed and how they will achieve robust and unbiased results.

- c. Explain how relevant biological variables, including sex, are factored into research designs and analyses for studies in vertebrate animals and humans. For example, strong justification from the scientific literature, preliminary data, or other relevant considerations, must be provided for proposals proposing to study only one sex. If your proposal involves human subjects, the sections on the Inclusion of Women and Minorities and Inclusion of Children can be used to expand your discussion and justify the proposed proportions of individuals (such as males and females) in the sample. Refer to [NOT-OD-15-102](#) for further consideration of NIH expectations about sex as a biological variable.
- d. If applicable to the proposed science, briefly describe methods to ensure the identity and validity of key biological and/or chemical resources used in the proposal. Key biological and/or chemical resources may or may not be generated with NIH funds and: 1) may differ from laboratory to laboratory or over time; 2) may have qualities and/or qualifications that could influence the research data; and 3) are integral to the proposed research. These include, but are not limited to, cell lines, specialty chemicals, antibodies, and other biologics.

Standard laboratory reagents that are not expected to vary do not need to be included in the plan. Examples are buffers and other common biologicals or chemicals. If the Technical Proposal does not propose the use of key biological and/or chemical resources, a plan for authentication is not required, and the offeror should so state in its proposal.

8.10 Human Subjects Research and Protection from Risk

Instructions and Required Information

If your project involves human subjects research as defined in Section 3.2 of this solicitation, or involves the use of human data or biological specimens, you must submit this information 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

If your project does not meet the definition of human subjects research, but involves the use of human data and/or biological specimens, you must provide a justification for your claim that no human subjects are involved. For example: Human cell lines will be purchased commercially from ‘Vendor X’ and will be provided without identifiers.

If **all** of your proposed human subjects research meets the criteria for one or more of the six human subjects exemption categories, identify which exemptions you are claiming and justify why your proposed research meets the criteria for the exemptions you have claimed. This justification should explain how the proposed research meets the exemption criteria and should not merely repeat the criteria or definitions themselves.

Offerors must address the following human subjects protections issues if this contract will be for research involving non-exempt 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.
 - Where appropriate, describe plans for handling incidental findings that may be uncovered as a result of the research, such as incidental findings from research imaging, results of screening tests, or misattributed paternity.

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.

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.

Data and Safety Monitoring Plan

- If the proposed research includes a clinical trial (as defined in Section 3.2. of this solicitation), create a heading entitled "Data and Safety Monitoring Plan."
- For clinical trials, NIH requires a data and safety monitoring plan (DSMP) that is commensurate with the risks of the trial and its size and complexity. In this section, you must provide a description of the DSMP that you are proposing to establish for each clinical trial proposed, including:
 - The overall framework for safety monitoring and what information will be monitored.
 - The frequency of monitoring, including any plans for interim analysis and stopping rules (if applicable).
 - The process by which Adverse Events (AEs), including Serious Adverse Events (SAEs) such as deaths or hospitalizations, and life threatening events and Unanticipated Problems (UPs), will be managed and reported as required to the Institutional Review Board (IRB), the person or group responsible for monitoring, the funding IC, the NIH Office of Biotechnology Activities (OBA; <http://osp.od.nih.gov/office-biotechnology-activities/biosafety/nih-guidelines>), and the Food and Drug Administration (FDA; <http://www.fda.gov/>).
 - The individual(s) or group that will be responsible for trial monitoring and advising the appointing entity. Because the monitoring plan will depend on potential risks, complexity, and the nature of the trial, a number of options for monitoring are possible. These include, but are not limited to, monitoring by a:
 - Principal Investigator (PI): While the PI must ensure that the trial is conducted according to the protocol, in some cases (e.g., low risk trials, not blinded), it may be acceptable for the PI to also be responsible for carrying out the DSMP.
 - Independent safety monitor/Designated medical monitor: a physician or other expert who is independent of the study.
 - Independent Monitoring Committee or Safety Monitoring Committee: A small group of independent investigators and biostatisticians.
 - Data and Safety Monitoring Board (DSMB): a formal independent board of experts including investigators and biostatisticians. NIH generally requires the establishment of DSMBs for multi-site clinical trials involving interventions that entail potential risk to the participants, and for Phase III clinical trials. If a DSMB is used, please describe the general composition of the Board without naming specific individuals.
- 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 <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html>

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. NIH is developing a policy to require all NIH supported trials to be registered and final data reported in ClinicalTrials.gov; the final policy about this will be published in the NIH Guide for Grants and Contracts.
- 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) (<https://www.gpo.gov/fdsys/pkg/PLAW-110publ85/html/PLAW-110publ85.htm>). 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.

8.11 Inclusion of Women, Minorities, and Children in Clinical Research

Instructions for Addressing the Inclusion of Women and Minorities

NIH-conducted and –supported clinical research must comply with the NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research (http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm), in accord with Public Health Service Act sec. 492B, 42 U.S.C. sec 289a-2.

The NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding IC Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. This policy applies to research subjects of all ages.

The inclusion of women and members of minority groups and their subpopulations must be addressed in developing a research design appropriate to the scientific objectives of the study. The research plans described in the technical proposal should describe the composition of the proposed study population in terms of sex/gender, race, and ethnicity, and provide a rationale for selection of subjects. It is important to justify the proposed sample on the basis of sex/gender, race, and ethnicity in the context of the scientific goals of the proposed study(s) with discussion of the demographics of the population under

study and/or who is at risk for the disease/condition. Such a plan should contain a description of the proposed outreach programs for recruiting women and minorities as participants. See http://grants.nih.gov/grants/funding/women_min/women_min.htm.

In addition, as detailed below, when conducting an NIH-defined Phase III clinical trial, there are additional requirements and considerations related to valid analysis to explore differences on the basis of sex/gender, race, and ethnicity.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research, Amended October 2001," published in the NIH Guide for Grants and Contracts on October 9, 2001 at the following web site:

http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm

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

Information Required for ALL Clinical Research Proposals

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

Reviewers will assess each proposal as being acceptable or unacceptable with regard to the scientifically justified inclusion (or exclusion) based on sex/gender, race, and ethnicity in NIH-defined clinical research. This section is required for all studies meeting the NIH definition for clinical research, not just clinical trials. This section does NOT take the place of considering relevant biological variables (such as sex) in the research strategy. It is important to provide a detailed plan of who will be included (and/or excluded) and how the distributions of individuals on the basis of sex/gender, race, and ethnicity are justified in the context of the scientific goals of the proposal. Simply stating that certain individuals will not be excluded or that individuals of either sex/gender or any race/ethnicity are eligible is not sufficient. Details about why the individuals are the appropriate individuals to accomplish the scientific goals of the study should be provided.

In this section, address, at a minimum, the following four points:

1. Describe the planned distribution of subjects by sex/gender, race, and ethnicity for each proposed study and complete the format in the PHS Inclusion Enrollment Report.
2. Describe the subject selection criteria and rationale for selection of sex/gender, racial, and ethnic group members in terms of the scientific objectives and proposed study design. The description may include, but is not limited to, information on the population characteristics of the disease or condition under study.
3. Provide a compelling rationale for proposed sample specifically addressing exclusion of any sex/gender, racial, or ethnic group that comprises the population under study.
4. Describe proposed outreach programs for recruiting sex/gender, racial, and ethnic group members as subjects. This is particularly important if difficulty recruiting certain groups is anticipated.

Additional Considerations for justifying inclusion: There may be reasons why the proposed sample is limited by sex/gender, race, and/or ethnicity. This should be addressed as part of the four points detailed above.

Inclusion of certain individuals would be inappropriate with respect to their health;

The research question addressed is only relevant to certain groups or there is a gap in the research area;

Evidence from prior research strongly demonstrates no difference on the basis of sex/gender, race, and/or ethnicity;

Sufficient data already exist with regard to the outcome of comparable studies in the excluded group(s) and duplication is not needed in this study;

A certain group or groups is excluded or severely limited because the purpose of the research constrains the offeror's selection of study subjects (e.g., uniquely valuable stored specimens or existing datasets are limited by sex/gender, race, and/or ethnicity; very small numbers of subjects are involved; or overriding factors dictate selection of subjects, such as matching of transplant recipients, or availability of rare surgical specimens); and/or

Representation of specimens or existing datasets cannot be accurately determined (e.g., pooled blood samples, stored specimens, or data-sets with incomplete sex/gender documentation are used), and this does not compromise the scientific objectives of the research.

In general, the cost of recruiting certain groups and/or geographic location alone are not acceptable reasons for exclusion of particular groups. This should be considered when developing outreach plans. Establishing collaborations or other arrangements to recruit may be necessary.

Additional guidance for research utilizing existing datasets or resources:

Inclusion must be addressed when conducting NIH-defined clinical research, even if the samples or data have already been collected as part of a different study. Details about the sex/gender, race, and ethnicity composition of the existing dataset/resource should be provided and justified as appropriate to the scientific goals of the proposed study.

For the purposes of inclusion policy, an existing dataset may be constructed of different types of data including but not limited to survey data, demographic information, health information, genomic information, etc. Also included would be data to be derived from existing samples of cells, tissues, or other types of materials that may have been previously collected for a different purpose or research question but will now be used to answer a new research question. In general, these will be studies meeting the NIH definition for clinical research with a prospective plan to analyze existing data and/or derive data from an existing resource and where no ongoing or future contact with participants is anticipated. More information about what is considered an existing dataset or resource for inclusion policy is available [here](#).

Additional guidance on completing the PHS Inclusion Enrollment Report(s) when working with existing datasets or specimens is available below.

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

In addition to the above requirements, for solicitations for **NIH defined Phase III clinical trials** (see this website for definition: http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm), the section on Inclusion of Women and Minorities also **MUST** address plans for how sex/gender, race, and ethnicity will be taken into consideration in the design and valid analysis of the trial. Valid analysis means an unbiased assessment which will, on average, yield the correct estimate of the difference in outcomes between two groups of subjects. Valid analysis can and should be conducted for both small and large studies. A valid analysis does not need to have a high statistical power for detecting a stated effect.

The reviewers will assess each proposal as being acceptable or unacceptable with regard to the scientifically justified inclusion plans, including these additional requirements for NIH-defined Phase III clinical trials.

- Offerors should address the following issues for ensuring valid analyses:
 - Inclusive eligibility criteria – in general, the cost of recruiting certain groups and/or geographic location alone are not acceptable reasons for exclusion of particular groups;
 - Allocation of study participants of both sexes/genders (males and females) and from different racial and/or ethnic groups to the intervention and control groups by an unbiased process such as randomization;
 - Unbiased evaluation of the outcome(s) of study participants; and

- Use of unbiased statistical analyses and proper methods of inference to estimate and compare the intervention effects by sex/gender, race, and/or ethnicity, particularly if prior evidence strongly suggests that differences exist.
- Offerors also should address whether they plan to test or not test for differences in effect among sex/gender, racial, and/or ethnic groups and why that is or is not appropriate. This 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. Additional factors may include planned primary and secondary outcomes and whether there are previous studies that support or negate the likelihood of differences between groups.
- The plans must include selection and discussion of one of the following analysis plans:
 - Plans to conduct 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 one or more 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.

8.12 Instructions for Completing the PHS Inclusion Enrollment Report(s) for Sex/Gender, Race, and Ethnicity

8.12.1.1 When Completing each PHS Inclusion Enrollment Report(s) provide the following information:

Study Title: Provide a unique study title that will facilitate identification of each PHS Inclusion Enrollment Report table.

Is the study delayed onset?: Select whether the study is delayed onset. Additional guidance on whether a study meets the criteria to be considered delayed onset may also be found [here](#). If a study is considered delayed onset, it generally means that it has not been developed and cannot be described in terms of human subjects' protections and inclusion. This does NOT apply to a study that can be described but will not start immediately. If the study is delayed onset, select YES. If the study is not delayed onset, select NO.

Enrollment Type: Select whether the table reflects planned enrollment of subjects to be recruited into the study or cumulative (e.g., actual) enrollment for participants already recruited into the study. For additional information and FAQs about working with studies spanning funding periods, click [here](#).

Use of Existing Datasets or Resources?: Select whether this study involves use of an existing dataset or resource. This generally means that investigators are utilizing data from a previous study or data bank. Do NOT answer Yes for individuals previously recruited specifically for this study. Any proposal using existing datasets or specimens that meet the NIH definition for clinical research should include the PHS 398 Inclusion Enrollment Report(s), even if the entire sample is unknown/not reported. Please be sure to select Yes to the question on the form about working with an existing dataset. If the proposed study involves use of an existing dataset as well as the prospective enrollment of new participants, provide separate tables. For additional guidance on working with existing datasets see: http://grants.nih.gov/grants/funding/women_min/women_min.htm

US and Non-US Sites: Select whether the study involves subjects at US sites or non-US sites (i.e., domestic or foreign subjects). If proposed studies involve participants at non-US sites, investigators are encouraged to design culturally sensitive and appropriate data collection instruments that allow research participants to self-identify their racial and/or ethnic affiliation. However when reporting these data to NIH, these items should be designed in a way that they can be aggregated by the investigator into the OMB-required defined below. Also, the investigator can report on any racial or ethnic subpopulations or culturally relevant descriptors by listing this information in the Inclusion of Women and Minorities narrative section and/or in the comments section of the PHS Inclusion Enrollment Report(s). This may be particularly useful when distinctive subpopulations are relevant to the scientific hypotheses being studied. Also, as previously instructed,

subjects at US and non-US sites must be provided on separate PHS Inclusion Enrollment Report forms, even if part of the same study.

Clinical Trial: Select whether the study meets the NIH definition for a clinical trial.

NIH-Defined Phase III Clinical Trial: Select whether the study is considered an NIH-Defined Phase III Clinical Trial. Note that you will not be able to select “Yes” unless the Clinical Trial field (above) is also “Yes.”

Completing the sex/gender, race, and ethnicity fields: Provide the information as the number of subjects (not percentages). If the sample is likely to include individuals who identify with more than one race, they should be accounted for in the “More than one race” category. If including individuals identifying as more than one race is not expected, enter zeroes in that category. Any proposed racial or ethnic subpopulations may be described in the inclusion plans as well as listed in the comment field of the PHS Inclusion Enrollment Report.

More on Completing PHS Inclusion Enrollment Report(s)

Proposal involves more than one study: If the proposal includes more than one study, provide separate PHS Inclusion Enrollment Report for each unless otherwise directed by the Request for Proposals (RFP). At a minimum, studies involving subjects at non-US sites (even if part of the same study) must be reported separately from studies involving subjects at US sites.

Multi-site studies: If the proposal includes a study recruiting subjects at more than one site/location, investigators may create one PHS Inclusion Enrollment Report or separate multiple PHS Inclusion Enrollment Reports to enable reporting by site or for all sites together, depending on the scientific goals of the study and whether monitoring of inclusion enrollment would benefit from being combined or separated. Please review the Request for Proposals (RFP) to determine if there are any specific requirements about how to complete the PHS Inclusion Enrollment Report(s).

NOTE: Duplicative Inclusion Reports: It is important that the PHS Inclusion Enrollment Report table(s) for a given study only be associated with one proposal and be provided only once in a given proposal. If submitting individual proposal(s) as part of a network or set of linked proposals, please provide the PHS Inclusion Enrollment Report table(s) with the individual site proposals unless otherwise directed by the RFP.

Additional Guidance Information: For additional guidance information and FAQs related to inclusion policy and inclusion data forms, please see: http://grants.nih.gov/grants/funding/women_min/women_min.htm. **NOTE 1 :** *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, which may be found at :*

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

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

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

Instructions to Offerors regarding the Inclusion of Children in Research Involving Human Subjects

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

For purposes of this policy, a child is defined as an individual under the age of 18 years. The definition of child described above will pertain to this solicitation (notwithstanding the FDA definition of a child as an individual from infancy to 16 years of age, and varying definitions employed by some states). Generally, State laws define what constitutes a "child," and such definitions dictate whether or not a person can legally consent to participate in a research study. However, State laws vary, and many do not address when a child can consent to participate in research. Federal Regulations (45 CFR 46, subpart D, Sec.401-409) address DHHS protections for children who participate in research, and rely on State definitions of "child" for consent purposes. Consequently, the children included in this policy (persons under the age of 18) may differ in the age at which their own consent is required and sufficient to participate in research under State law.

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 other policy notices and resources at the following URL address:

<https://grants.nih.gov/grants/funding/children/children.htm>

Offerors also may obtain copies from the contact person listed in the RFP.

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

Instructions for this item of the Research Plan **including addressing the following points:**

Describe the age(s) or age range of all individuals to be included in the proposed study.

Specifically discuss whether children under the age of 18 (as a whole or a subset of individuals under 18) will be included or excluded.

The description of the plan should include a rationale for selecting a specific age range of children.

The plan also must include a description of the expertise of the investigative team for working with children at the ages included, of the appropriateness of the available facilities to accommodate the children, and the inclusion of a sufficient number of children to contribute to a meaningful analysis relative to the purpose of the study.

When children are involved in research, the Additional Protections for Children Involved as Subjects in Research ([45 CFR part 46 Subpart D](#)) apply and must be addressed under the Protections Against Risk subheading (4.1.2.b).

Justifications for Exclusion of Children

For the purposes of this policy, individuals under 18 are defined as a child; however, exclusion of any specific age or age range group should be justified in this section. It is expected that children will be included in all NIH-defined clinical research unless one or more of the following exclusionary circumstances apply:

- The research topic to be studied is not relevant to children.
- Laws or regulations bar the inclusion of children in the research.
- The knowledge being sought in the research is already available for children or will be obtained from another ongoing study, and an additional study will be needlessly redundant. Documentation of other studies justifying the exclusions should be provided. NIH program staff can be contacted for guidance on this issue if the information is not readily available.
- A separate, age-specific study in children is warranted and preferable. Examples include:
 - The condition is relatively rare in children, as compared to adults (in that extraordinary effort would be needed to include children, although in rare diseases or disorders where the applicant has made a particular effort to assemble an adult population, the same effort would be expected to assemble a similar child population with the rare condition); or
 - 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 or different age-related metabolic processes). While this situation may represent a justification for excluding children in some instances, consideration should be given to taking these differences into account in the study design and expanding the hypotheses tested, or the interventions planned, to allow inclusion of children rather than excluding them.
- Insufficient data are available in adults to judge potential risk in children (in which case one of the research objectives could be to obtain sufficient adult data to make this judgment). Although children usually should not be the initial group to be involved in research studies, in some instances, the nature and seriousness of the illness may warrant their participation earlier based on careful risk and benefit analysis.
- Study designs are aimed at collecting additional data on pre-enrolled adult study subjects (e.g., longitudinal follow-up studies that did not include data on children).
- Other special cases can be justified by the investigator and assessed by the review group and the Institute/Center Director to determine if acceptable.

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

8.13 Research Involving Human Fetal Tissue

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. An additional NIH Guide Notice reiterates these requirements: <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-143.html>

In addition, the NIH is committed to ensuring that research involving human fetal tissue is conducted responsibly and meets the highest ethical standards as reiterated in this NIH Guide Notice: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-033.html>. NIH-funded research involving human fetal tissue must be conducted in compliance with all applicable federal, state, and local laws and regulations (for more details see above). Current federal laws and regulations require informed consent for research involving the transplantation of human fetal tissue and for research with human fetal material associated with information that can identify a living individual. Most states require informed consent for

the use of fetal tissue in research. Accordingly, NIH expects informed consent to have been obtained from the donor for any NIH-funded research using human fetal tissue.

When obtaining primary human fetal tissue for research purposes, NIH expects grantees and contractors to maintain appropriate documentation, such as an attestation from the health care provider or a third party supplier, that informed consent was obtained at the time of tissue collection.

By signing the face page of the proposal, the offeror (authorized institutional official) certifies that researchers using human fetal tissue are in compliance with the regulations and NIH policies. The statutes specifically prohibit 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.

8.14 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 criteria must be addressed in a separate section of the Technical Proposal titled "Vertebrate Animals Section" (VAS):

Description of Procedures. Provide a concise description of the proposed procedures to be used that involve vertebrate animals in the work outlined in the Request for Proposal (RFP) Statement of Work. Identify the species, strains, ages, sex and total number of animals by species to be used in the proposed work. If dogs or cats are proposed, provide the source of the animals.

Justifications. Provide justification that the species are appropriate for the proposed research. Explain why the research goals cannot be accomplished using an alternative model (e.g., computational, human, invertebrate, in vitro).

Minimization of Pain and Distress. Describe the interventions including analgesia, anesthesia, sedation, palliative care and humane endpoints to minimize discomfort, distress, pain and injury.

Euthanasia. State whether the method of euthanasia is consistent with the recommendations of the American Veterinary Medical Association (AVMA) Guidelines for the Euthanasia of Animals. If not, describe the method and provide a scientific justification.

A concise (no more than 1-2 pages), complete description addressing these criteria 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 VAS, see http://grants.nih.gov/grants/olaw/vertebrate_animal_section.htm. For additional guidance see the *Worksheet for Review of the Vertebrate Animal Section under Contract Proposals*, <http://grants.nih.gov/grants/olaw/VAScontracts.pdf>.

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, see:

<http://grants.nih.gov/grants/olaw/Guide-for-the-Care-and-Use-of-Laboratory-Animals.pdf>. Methods of euthanasia used will be consistent with the recommendations of the American Veterinary Medical Association (AVMA) Guidelines for the Euthanasia of Animals, unless a deviation is justified for scientific reasons in writing by the investigator, see: <https://www.avma.org/KB/Policies/Documents/euthanasia.pdf>. 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, e-mail: olaw@mail.nih.gov.

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.

8.15 Dual Use Research of Concern

The offeror shall demonstrate compliance with the United States Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern (<http://www.phe.gov/s3/dualuse/Documents/durc-policy.pdf>) or “DURC” policy. If the offeror proposes using an agent or toxin subject to the DURC policy, the offeror shall provide in its technical proposal each of the following items:

- a. Identification of the agents or toxins subject to the DURC policy:
 - o Avian influenza virus (highly pathogenic)
 - o *Bacillus anthracis*
 - o Botulinum neurotoxin
 - o *Burkholderia pseudomallei*
 - o Ebola virus
 - o Foot-and-mouth disease virus
 - o *Francisella tularensis*
 - o Marburg virus
 - o Reconstructed 1918 influenza virus
 - o Rinderpest virus
 - o Toxin-producing strains of *Clostridium botulinum*
 - o Variola major virus
 - o Variola minor virus
 - o *Yersinia pestis*
- b. A description of the categories of experiments in which the identified agents or toxins produces or aims to produce or can be reasonably anticipated to produce one or more of the effects identified in Section 6 of the DURC policy.
- c. For projects involving any of the agents listed in the DURC policy and that involve or are anticipated to involve any of the categories of experiments listed in the DURC policy, an indication of whether or not the project meets the definition of “dual use research of concern” in Section 4C of the policy.
- d. For projects meeting the definition of “dual use research of concern,” a draft risk mitigation plan.
- e. Certification that the offeror is or will be in compliance with all aspects of the DURC policy prior to use of pertinent agents or toxins.

If the offeror does not propose using an agent or toxin subject to the DURC policy, the offeror shall make a statement to this effect in its technical proposal.

The Government shall not award a contract to an offeror who fails to certify compliance or whose draft risk mitigation plan is unsatisfactory to the Government. If selected for award, an approved risk mitigation plan shall be incorporated into the contract.

8.16 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 Phase 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. Describe reason for travel, location of travel, number of travelers, and number of nights of lodging in the Description fields in Appendix C.
- 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** – For SBIR offerors who propose a 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.
- **Prior, Current, or Pending Support of Similar Proposals or Awards.**

If a proposal submitted in response to this solicitation is for **essentially equivalent work** (as defined in this solicitation) as another proposal that was funded, is now being funded, or is pending with a Federal agency, you must make the appropriate certification on the Proposal Cover Sheet, as well as provide the following information in Appendix C:

- 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."

- If **essentially equivalent work** to what is contained in your proposal submitted in response to this solicitation is being funded by any other source outside of your company besides the Federal Government, identify and briefly describe the funding source and amount of support in Appendix C.

8.17 Reminders

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 proposed price adheres to the budget set forth under each Topic.

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 4.22.

Check that the header on each page of the technical proposal contains 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, due to OMB clearances.

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) | 35-59 | Scientific and Technical Merit Review: March-May 2017 Anticipated Award Date: August-September 2017 |
| National Institutes of Health (NIH) National Center for Advancing Translational Sciences (NCATS) | 1-2 | Scientific and Technical Merit Review: March-June 2017 Anticipated Award Date: August-September 2017 |
| National Institutes of Health (NIH) National Heart, Lung, and Blood Institute (NHLBI) | 8 | Scientific and Technical Merit Review: February-April 2017 Anticipated Award Date: July-September 2017 |
| National Institutes of Health (NIH) National Institute of Allergy and Infectious Diseases (NIAID) | 9-16 | Scientific and Technical Merit Review: March 2017 Anticipated Award Date: August 2017 |
| National Institutes of Health (NIH) National Institute on Drug Abuse (NIDA) | 4-6 | Scientific and Technical Merit Review: March 2017 Anticipated Award Date: August 2017 |
| Centers for Disease Control and Prevention (CDC) National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP) | 2 | Scientific and Technical Merit Review: May-June 2017 Anticipated Award Date: August 2017 |
| Centers for Disease Control and Prevention (CDC) National Center for Emerging Zoonotic and Infectious Diseases (NCEZID) | 1 | Scientific and Technical Merit Review: May-June 2017 Anticipated Award Date: August 2017 |

10 CONTRACTING OFFICER POINTS OF CONTACT FOR QUESTIONS RELATED TO SPECIFIC TOPICS

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)

Tiffany Chadwick

Procurement Analyst

Office of Acquisitions

Phone: 240-276-7293

E-mail: ncioasbir@mail.nih.gov

NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES (NCATS)

Jeffrey R. Schmidt

Contracting Officer

NINDS R&D Contracts Management Branch

Neurosciences Offices of Acquisition

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NATIONAL HEART, LUNG, AND BLOOD INSTITUTE (NHLBI)

John Taylor

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NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES (NIAID)

Charles H. Jackson, Jr.

Contracting Officer

Office of Acquisitions, DEA

National Institute of Allergy and Infectious Diseases

National Institutes of Health, DHHS

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Email: Charles.Jackson@nih.gov

NATIONAL INSTITUTE ON DRUG ABUSE (NIDA)

Andrew Hotaling

Contracting Officer

NIDA R&D Contracts Management Branch
Neurosciences Offices of Acquisition
Phone: (301) 443-6677
Fax: (301) 443-7595
E-mail: hotalingar@mail.nih.gov

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.
SBIR Program Manager
Office of Technology and Innovation
Office of the Associate Director for Science
Phone: 404-639-4641
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E-mail: SBIR@cdc.gov

Darlene Forrest, M.A. (Contractor)
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NATIONAL CENTER FOR CHRONIC DISEASE AND HEALTH PROMOTION (NCCDPHP)

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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

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-16-008.html>

In FY2011, the NCI expanded the Phase IIB Bridge Award program to allow previous SBIR Phase II contract awardees to compete for SBIR Phase IIB Bridge Awards. Provided it is available in the future, the Phase IIB Bridge Award program will be open to contractors that are successfully awarded a Phase II contract (or have an exercised Phase II option under a Fast-Track contract). NIH SBIR Phase II contractors who satisfy the above requirements may be able to apply for a Phase IIB Bridge Award under a future Phase IIB Bridge Award grant 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 proposals in the following areas:

355 Cell and Animal-Based Models to Advance Cancer Health Disparity Research

Fast-Track proposals will be accepted.

Direct-to-Phase II be will accepted.

Number of anticipated awards: 2-3

Budget (total costs, per award):

Phase I: \$300,000 for up to 9 months;

Phase II: \$2,000,000 for up to 2 years

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Summary

Cancer health disparities (CHDs) are defined as differences in the incidence, prevalence, morbidity, and mortality that contribute to an unequal burden of cancer and represent a major public health concern globally. In the United States, several racial/ethnic populations demonstrate increased incidence, mortality and/or more aggressive disease for numerous cancer types. The causes of these CHDs are multifactorial, including differences in access to health care, diet and lifestyle, cultural barriers, environmental exposures, and ancestry-related factors. A growing body of evidence suggests that biological factors may contribute to CHDs. The NCI specifically encourages and funds investigations of biological factors to better understand mechanisms that contribute to CHDs. One limitation in conducting basic, translational, and clinical research investigating the underlying biological causes of CHDs is a substantial lack of relevant in vitro and in vivo-based models. The development and validation of appropriate cell and animal-based models to study underrepresented population groups would greatly advance this field of research.

Project Goals

The primary goal of this topic is to develop new, commercially available models relevant to diverse racial/ethnic populations including American Indians, Alaska Natives, Asians, African Americans, Pacific Islanders, and Hispanic/Latinos. Solicited models include patient-derived cell lines, patient-derived xenograft (PDX) mouse models, and 3D human tissue model culture systems established from racially/ethnically diverse patient populations.

These models may be used to enhance research capabilities of basic scientists and/or provide novel tools to pharmaceutical companies for preclinical oncology studies. Establishing these novel models may influence CHD research in multiple ways including 1) benefiting investigators in this largely underexplored area of research, 2) improving the quality and acceptance of CHD research data, and 3) improving validation and commercialization of cancer therapeutics relevant to diverse patient populations. Lastly, achieving these goals will contribute to the long-term, overarching goal of reducing CHDs.

Cancer cell lines: The use of immortalized cell lines in cancer research has been standard practice for decades. Notably, the scientific integrity of cancer cell lines is critical for maintaining high standards in research. Any cell lines established via this solicitation must be fully confirmed through a rigorous and validated authentication and be contamination-free. Notably, offerors proposing to generate conditionally reprogrammed cells (CRCs) or cell lines matched to PDX animal models will be preferred. CRCs have marked benefits over traditional immortalized cell lines as they are generated using special in vitro conditions that permit cells to pharmacologically bypass replicative senescence without any detectable cell crisis.

PDX Mouse Models: PDX models are commonly used in many clinically relevant research applications including characterization of tumor heterogeneity, in vivo therapeutic target validation studies, therapeutic mechanism of action studies, and therapeutic sensitivity and resistance studies. Furthermore, PDX models are suggested to be a useful tool to mimic human clinical trials using animals.

3D human tissue model culture systems: While immortalized cell lines have been standard practice in cancer research for decades, adequate modeling of the heterogeneity of human cancer is an unmet need. Newly emerging 3D cell culture technologies enable the propagation of normal and malignant epithelial cells, as well as more

accurately mimicking the in vivo tumor microenvironment (e.g. organoid, spheroid, and organ-on-a-chip models). These 3D model systems need to be previously developed (preferably *with validation studies*) and either derived from diverse racial/ethnic populations or applicable to the study of CHDs in general.

Phase I Activities and Deliverables

Offerors must clearly demonstrate access to human samples from racial/ethnic minority populations, with appropriate informed consent in place.

Establish an experimental model derived from a racial/ethnic minority population and/or relevant to CHD research. This may include one of the following:

- Human derived cancer cell line
- PDX animal model
- 3D human tissue model culture system

Cancer cell line deliverables: Establish a stable cell line from human tumor cells and passage the cells in culture to determine viability and experimental relevance.

- Detailed documentation must be provided including patient clinical characteristics, passage history, mycoplasma testing results, Identifiler/STR profile of early and late passage showing concordance, and appropriate growth/preparation conditions.
- Develop a standardized, working protocol for establishment of additional cell culture models.
- Demonstrate utility in pre-clinical assays and technical validity for the proposed cell line
 - Perform comprehensive and robust studies to confirm model system is phenotypically stable.
 - Use a standard chemotherapeutic agent to confirm model system is appropriate to perform drug response assays (e.g. measure cell proliferation, cell death, migration, and/or invasion).
- Applications proposing CRCs or cell lines matched to PDX animal models are preferred due to the increased innovation and potential research applications of the models.

PDX animal model deliverables: Establish a serially transplantable, phenotypically stable, human cancer xenograft model in immunocompromised mice.

- Transplant fresh surgical tissue or biopsy (either subcutaneous or orthotopic) into recipient immunodeficient mice (Passage generation 1).
- Subsequent serial transplantations must be conducted following establishment of initial xenograft outgrowths, typically >10mm in diameter. A minimum of three generations (to passage generation 4) of transplantation is required to establish a stable line.
- Confirm genetic and phenotypic concordance of the tumors in passage generation 4 versus passage generation 1 and patient material (when available).
- Confirm percent human versus mouse DNA in each passage and confirm histopathology of each passage phenotypically matches the patient diagnoses.
- Cryopreserve and bank tumor fragments. Confirm re-growth success rate from a minimum of 5 cryopreserved tumor fragments.
- Develop a standardized, working protocol for establishment of additional models.
- Perform comprehensive molecular characterization of patient samples and earliest PDXs, including whole exome sequencing and mutational status analysis using a CLIA-approved panel.
- Demonstrate utility in pre-clinical assays and technical validity for the proposed model system
 - Perform comprehensive and robust studies to confirm model system is phenotypically stable.
 - Use a standard chemotherapeutic agent to confirm model system is appropriate to perform drug response assays (e.g. measure tumor growth, angiogenesis, cell proliferation, cell death, migration, and/or invasion).

3D human tissue model culture system: Establish a 3D culture that mimics the tumor microenvironment. Note that all proposed model systems must be using established technologies with previously demonstrated reproducibility in pre-clinical or chemo-sensitivity assays.

- The model system must address the following requirements:
 - Human tumor cells must be derived from a diverse racial/ethnic population
 - Heterogeneous population of cell types must be represented
 - Structural components that mimic the in vivo tumor microenvironment should be incorporated
- Demonstrate utility in pre-clinical assays and technical validity for the proposed model system
 - Perform comprehensive and robust studies to confirm model system is phenotypically stable.
 - Use a standard chemotherapeutic agent to confirm model system is appropriate to perform drug response assays (e.g. measure tumor growth, angiogenesis, cell proliferation, cell death, migration, and/or invasion).

All human tissues and cells used to generate the abovementioned models must be well characterized including validation of the genetic ancestry of patients (if applicable) using a panel of ancestry informative makers (AIMs). The AIM panel(s) selected should be relevant to the patient populations being investigated and capable of specifying admixture proportions.

Preferences will be placed on proposals that generate models for indications that have clearly demonstrated cancer health disparities and a paucity of models available to study.

Phase II Activities and Deliverables

Cancer cell lines: It is expected that a panel of cell lines be established from different patient sources. The exact number of cell lines will depend on technique used for establishing the lines (i.e. CRCs or cell lines matched to PDX-models) and the tumor type proposed.

PDX animal models: It is expected that multiple PDX models be established from unique patient sources using established protocols. The exact number of models will depend on the tumor type proposed and any known technical/biological limitations.

3D human tissue model culture system: Further demonstrate pre-clinical utility of the generated 3D model system, with a particular emphasis on the relevancy to CHD research. Furthermore, additional 3D models must be developed derived from diverse racial/ethnic populations and prepared for commercialization.

356 Tools and Technologies for Monitoring RNA

Fast-Track proposals will **not** be accepted.

Direct-to-Phase II will **not** be accepted.

Number of anticipated awards: 3-5

Budget (total costs, per award):

Phase I: \$250,000 for 9 months;

Phase II: \$1,500,000 for 2 years

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Summary

Chemical modifications play a crucial role in the regulation of biological processes. Protein function is often modulated by tagging with phosphates, sugars, or lipids, while epigenomic marks on DNA or histones can regulate gene expression up or down. One area that lags behind is the mechanistic understanding of the role of RNA chemical modifications, sometimes referred to as the 'epitranscriptome'.

The RNA Modification Database lists more than 60 RNA modifications that occur in eukaryotic cells. Transfer and ribosomal RNA have been shown to be heavily modified, and some of these same modifications also occur in messenger RNA and non-coding RNAs. However, the vast majority of these modifications have not been well-studied in messenger and non-coding RNAs. Even though much about RNA modifications remains to be elucidated, there is emerging evidence that RNA modifications are functionally significant and play important roles in biological processes and diseases in vertebrates.

Several RNA chemical modifications or the enzymes that catalyze the addition of modifications (writers), the removal of modifications (erasers), or translate the effects of modifications (readers) have been associated with a variety of cancers. For example, certain mutations in the N6-methyladenosine (m6A) demethylase (or ‘eraser’) FTO are associated with melanoma and breast cancer risk. Additionally, mutations in the pseudouridine ‘writer’ DKC1 cause dyskeratosis congenita, a disease associated with premature aging and increased tumor susceptibility. Furthermore, specific DKC1 mutations have been identified in human pituitary adenomas.

These early findings linking the disruption of RNA modifications to cancer initiation and progression highlight the potential importance of the field of epitranscriptomics to understanding cancer biology. However, a lack of experimental tools for monitoring RNA modifications has slowed the potential progress. The purpose of this topic is to incentivize small businesses to generate tools and technologies for monitoring covalently modified eukaryotic RNA.

Project Goals

The major obstacles hampering efforts to better understand RNA modifications are fundamentally technical in nature. Presently, we lack appropriate tools and technologies for investigating the epitranscriptome broadly and at single nucleotide resolution. Additionally, there is evidence that the availability of tools will drive research in this field. For example, an antibody-based assay for monitoring the m6A modification was developed in 2012, and by 2014 there had been a four-fold increase in the number of m6A publications.

Despite the growing interest in and importance of RNA modifications, the available tools that scientists have to monitor modified RNAs are limited. The purpose of this contract topic is to incentivize small businesses to generate tools, technologies, and products for monitoring covalently modified eukaryotic RNA, including messenger RNA and regulatory RNA. In the long term, these tools and products will allow the investigation of how altered RNA modifications contribute to the initiation and progression of cancer and potentially identify a new class of cancer biomarkers.

Potential tools, technologies, or products would include, but are not limited to:

- Well-validated antibodies, affinity reagents, or affinity-based assay kits for detection, quantitation, or immunoprecipitation of modified RNAs, or enzymes that write, erase, or bind to these modifications.
- Systems or kits that enable high-throughput mapping of specific RNA modifications to residues in individual RNA species using genome-wide sequencing approaches (i.e., approaches analogous to the bisulfite sequencing assays used for detecting methylcytosine or hydroxymethylcytosine in DNA).
- Approaches that enable researchers to sequence RNA without a cDNA intermediate or that otherwise preserve or amplify the RNA modification information. This could include the development or adaptation of nanoscale sequencing devices or other equipment for direct identification and quantitation of sequence-specific RNA modifications.
- Approaches that exploit the ability of certain RNA modifications to disrupt reverse transcription.
- Assay systems or reagents that facilitate the discovery, detection or quantitation of modified RNAs.
- Products or systems that enable simultaneous detection of many types of RNA modifications at high sensitivity.
- Assay systems or reagents that enable researchers to monitor the effect of an RNA modification on the structure or function of an individual RNA.
- Products that would enable the in vitro or in vivo imaging of modified RNA molecules.

- The development of analytical software tools to facilitate the identification of modified, circular, or edited RNA from high-throughput sequencing datasets. This could include algorithms that improve our ability to identify which base on a given RNA is modified.

Phase I Activities and Deliverables

The goal of Phase I is to develop proof-of-concept or prototype tools, technologies, or products for monitoring specific RNA modification(s). Activities and deliverables include:

- Identify and justify development of a tool or technology for monitoring a specific RNA modification or set of RNA modifications.
- Describe the current state of the art technologies, if any, for monitoring the specific RNA Modification(s) and outline the advantages that their approach will provide.
- Develop and characterize the tool or technology for monitoring the specific RNA Modification(s).
- Specify and justify quantitative milestones that can be used to evaluate the success of the tool or technology being developed.
- Develop an assay or system for testing and benchmarking the specificity and sensitivity of the tool or technology and comparing the tool or technology to existing approaches if applicable.
- Provide a proof-of-concept SOP for the tool or technology.

Phase II Activities and Deliverables

The goal of Phase II is an optimized commercial resource, product, reagent, kit, or device for monitoring specific RNA modification(s).

Decisions for continued product development into Phase II will be based on:

- Demonstration of the reliability and robustness of the tool, technology, or product. Offerors shall provide a technical evaluation and quality assurance plan with specific detail on shelf life, best practices for use, equipment required for use.
- Demonstration that the tool, technology, or product can be scaled up at a price point that is compatible with market success and widespread adoption by the basic research community.
- Demonstration of preliminary proof-of-concept data demonstrating the monitoring of the specific RNA Modification(s) in cell or animal cancer models with the potential to benchmark data across a variety of cancer models.

Deliverables and activities include:

- Scale up the synthesis and/or manufacture of necessary agents, chemicals, devices, or products.
- Design and implement quality assurance controls and assays to validate production.
- Validate scaled up tool, technology, or product. Specifically, demonstrate the utility, reliability, sensitivity, and specificity of the tool, technology, or product across relevant in vitro and/or in vivo cancer models (e.g., 2D and 3D tissue culture systems, in vivo animal models of cancer).
- Refine SOPs to allow for user friendly implementation of the tool, technology, or product by the target market.

357 Innovative Tools for Interrogating Tumor Microenvironment Dynamics

Fast-Track proposals will be accepted.

Direct-to-Phase II will 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

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Summary

Tumor microenvironment (TME) is composed of abnormal vasculature, stromal components, immune cells, all embedded in an extracellular matrix (ECM). TME plays a critical role in tumor initiation, malignant progression, metastasis and response and resistance to therapy. Characterized by hypoxia, elevated enzymatic activities, high interstitial fluid pressure and dense stroma structure, TME creates a hostile environment for drug delivery and other forms of cancer treatments. Research efforts and discoveries focusing on TME remediation are critical for improving cancer treatment efficacy. New drugs, molecular targets and agents that can manipulate TME are being discovered from known and novel molecular pathways, high-throughput genomics and proteomics and some of these agents are already in clinical trials. For example antiangiogenic agents, originally designed to starve tumors, were shown to transiently normalize tumor vasculature and improve therapeutic outcome in patients with newly diagnosed and recurrent GBM and several anti-angiogenic agents have been approved for multiple cancer types. Similarly, over the past few years, a few checkpoint inhibitors modulating the immune components of the TME have been approved for multiple cancer types and many more are currently undergoing clinical trials. Recently it was discovered that antifibrosis drugs are capable of normalizing the TME and improve the delivery and efficacy of nano- and molecular medicine. However, there are still very few new agents targeting TME that are reaching the stage of FDA approval. The slow pace in TME-oriented therapeutic discovery can be attributed to lack of techniques capable of rapid and effective in vivo evaluation of TME-manipulating dynamics for the purpose of selecting hit compounds and demonstrating efficacy.

In addition to being good therapeutic targets, TME could also act as biomarkers to:

- diagnose tumors at early stage
- assess tumor prognosis
- predict appropriate therapy to use
- evaluate response to therapy and modulate therapy accordingly

For example, the immune components of the tumor are modulated during tumor initiation and also in response to different therapies, and thus could be used as markers to diagnose tumors early and to determine therapeutic response and modulate therapy accordingly.

Assessment of TME is mostly based on histopathological analysis of tumor biopsies. However, these methods are invasive and non-dynamic (i.e. they lack the ability to evaluate progressive changes in the same tumor over time); thus, the ability to use TME as biomarkers for tumor diagnosis, prognosis and therapy response are rather limited. Imaging methods provide non-invasive and dynamic way to assess TME, even in lesions that are difficult to biopsy, and help determine heterogeneity and obtain serial measurements of the same tissue over time. So, imaging methods could be used to diagnose tumors early and to determine if a tumor is responding to therapies.

Recent advances in sensing and imaging techniques are enabling assessment of TME with improved accuracy due to higher monitoring speed, sensitivity and resolution. For example, magnetic resonance imaging techniques, with both excellent image resolution and depth penetration, are widely used to detect abnormal TME structures and conditions: blood oxygenation level dependent (BOLD)-MRI for hypoxic conditions, Chemical Exchange Saturation Transfer (CEST)-MRI for reduced pH, MR angiography for vascular structure and diffusion MRI for structural integrity. Positron Emission Tomography (PET) of radio-nuclei-labeled TME-associated molecular targets has been used in pre-clinical and clinical settings. There are also new developments related to designing bio-responsive sensors to monitor change in pH, oxygen levels, or enzymatic activities in TME directly through nanoparticle-based imaging modalities or indirectly through bio-fluid analyses. Biopsy-implantable chemical sensors allow to collect signals over long period of time (months) to monitor long term changes in TME. All these in vivo methods are valuable tools to dynamically examine the targeting efficiency, associated molecular events and provide insight into normalization of TME and its effect on anticancer drug delivery. 'Bio-activatable' delivery vehicles allow for controlled drug delivery, which is activated only with the change of a particular TME parameter. However, most of these studies still remain pre-clinical and the imaging modalities have mostly been limited to pre-clinical studies.

Identifying and monitoring TME-associated biomarkers in patient populations and effective strategies to manipulate the TME in vivo can enable early tumor detection and prognosis, provide therapy prediction and response information and also enhance effectiveness of anticancer therapies and improve treatment outcomes. To accelerate research and translational efforts focused on sensing, imaging, and manipulation of TME in real time, and TME-inspired drug delivery, the National Cancer Institute (NCI) requests proposals for the development of clinically viable in vivo probing/monitoring techniques of TME-manipulating strategies.

Project Goals

Tumor diagnosis at early stage, before it has grown too big or spread, is critical to improving survival of patients with the tumor. Similarly, being able to predict if a tumor responds to certain therapy is very essential to determining what treatment option would be the best for patients. This will increase overall survival and also prevent use of ineffective treatment options. Once the patient starts treatment, it is essential to monitor the response of tumor to the therapy to determine if it's working or if modulation in therapy is required.

As precision medicine is becoming an increasingly important area in cancer treatment, the ability to determine changes in TME in general and as related to individual patient, in particular is critical. The development of this knowledge can provide insight into effectiveness of treatment using existing drugs and enabling development of new drugs. TME studies can also further knowledge on local cellular environments and categorizing TME associated cells into small sub-groups defined by their molecular makeup.

Various components of TME can serve as a good biomarker for tumor diagnosis, prognosis, treatment prediction and therapeutic response. For example, the extent of immune cell infiltration and activation in solid tumors could be used to determine if immunotherapy is working in patients. The current methods to assess immune activation in response to immunotherapy involve biopsy procedures that are invasive and cannot be done on the same tumor over time. Thus it is important to develop methods that are non-invasive and that would enable longitudinal tracking of treatment response.

The **goal** of this solicitation is to develop non-invasive, in vivo platforms that can: image, assess or interrogate TME dynamics over time for tumor diagnosis and/or treatment prediction/response.

To apply for this topic, the proposed technology should be focused on interrogating one or more of the following TME parameters:

- Tissue oxygenation Level and/or pH
- Vasculature and/or stromal architecture
- Tissue integrity
- Enzymatic activities
- Indication of immunotherapy response
- Response in specific cell type(s) or subtype(s) at the molecular level

The goal of this contract topic is not to solicit any particular technology; so this topic is agnostic to the imaging modality used. New imaging modalities could be developed or agents targeting TME could be developed using any imaging modality currently available including X-ray, MRI, PET, SPECT, CT and ultrasound. The goal of the topic is to develop imaging tools for TME in the clinic; so the tools developed have to be clinically feasible and relevant.

Proposals with incremental improvement from the current state of art or having no immediate translational potential will not be considered responsive to this solicitation. Examples of non-responsiveness may include, but are not limited to: imaging methods that can work only in pre-clinical imaging modalities (i.e. ultrahigh-field MRI or unconventional PET radionuclei labeling), imaging agents, chemical constructs or linkers that are inherently toxic or immunogenic (i.e. Quantum Dots, Avidin) and probes that targets molecular targets that do not have human equivalent.

Phase I Activities and Deliverables

Phase I activities should generate scientific data to confirm clinical potential of the proposed agent. Expected activities and deliverables may include:

- Identification and validation of marker(s) for TME
 - Preparation of imaging agents based on the validated markers
 - Characterize the variation, reproducibility, and accuracy of the tool
 - Demonstrate that the agent produces high signal-to-noise ratio
 - Demonstrate specific binding/targeting of the agent/probe to the molecular target (TME target)
- Prepare, select and demonstrate TME-targeting probes/sensors based on target specificity and minimal toxicity in vitro
- Optimize detection scheme to demonstrate in vitro signal specificity and correlate signals to molecular target concentrations measured using conventional assays
- Determine optimal dose and detection window through proof-of-concept small animal studies with evidence of systemic stability and minimal toxicity
- Establish calibration curves correlating in vivo signal changes to concentration of molecular targets measured via conventional biological assays.
- Demonstrate robust signal changes in response to in vivo perturbation
- Benchmark experiments against currently state-of-the-art methodologies.
- Present Phase I results and development to NCI staff

For successful completion of benchmarking experiments, demonstrate a minimum of 5x improvement against compatible methodologies.

Phase II Activities and Expected Deliverables

Phase II activities should support commercialization of the proposed agent for clinical use. Expected activities and deliverables may include:

- Demonstrate fast in vivo clearance, rapid tumor accumulation, sufficient in vivo stability, good bioavailability, and low immunogenicity/toxicity of imaging agent or sensors
- Demonstrate high reproducibility and accuracy of the imaging agent in multiple relevant animal models
- Demonstrate superiority over currently available imaging tools
- Perform toxicological studies
- Demonstrate clinical utility
 - For diagnosis markers, demonstrate that the agent can detect tumors at early stages and demonstrate superiority to current diagnosis methods
 - For predictive/decision markers, validate the predictive capability of the marker by performing prospective pre-clinical animal trials: stratify the animals into treatment groups and demonstrate that the imaging agent accurately predicts appropriate therapy to use
 - For therapy response markers, demonstrate that the imaging tool can accurately visualize changes in response to therapy and validate characteristics of response and non-response
- Collect sufficient animal and safety data in preparation for an IDE application
- Submit IDE application to obtain necessary regulatory approval for clinical validation.

358 Modulating the Microbiome to Improve Therapeutic Efficacy of Cancer Therapeutics

Fast-Track proposals will **not** be accepted.

Direct-to-Phase II will **not** be accepted.

Number of anticipated awards: 2-4

Budget (total costs, per award):

Phase I: \$300,000 for 9 months;

Phase II: \$2,000,000 for 2 years

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Summary

Metagenomic studies in humans and animal models have established that there are alterations of the GI microbiota community during development of neoplastic and pre-neoplastic disease, and in tumor-bearing vs. healthy individuals. Understanding the impact of human host/microbiota interactions on the initiation, progression and treatment of cancer, and the molecular mechanisms that govern the outcomes of these interactions, will provide new therapeutic strategies and new targets for the treatment of many human tumors.

One promising approach emerging from recent research is alteration of microbiome function designed to enhance the efficacy of cancer therapies. Recent work demonstrated that individual variability in patient drug response to chemo (and other) therapies can be attributed to actions of the gastrointestinal (GI) microbiota, either through direct metabolic activity on the agent itself, or by effects on host barrier function and immunomodulation that affect drug efficacy. For example, microbial β -glucuronidase activity results in re-activation of toxic metabolites that affect the dose-limiting range of CPT-11, a prodrug form of the topoisomerase inhibitor Irinotecan that is widely used to treat a variety of solid tumors. Antibiotic co-therapy and specific inhibition of bacterial β -glucuronidase activity reduced chemotherapy-induced GI toxicity in several animal models. Other studies have shown that depletion of ROS-regulating *Lactobacillus* species by antibiotics, results in reduced tumoricidal activity of platinum based drugs. Similarly, the antitumor effects of radiotherapy and several cytotoxic chemotherapeutic drugs such as cyclophosphamide (CTX), oxaliplatin, and CpG-ODN, are achieved in part by an immune-mediated bystander effect that requires the recruitment and activation of an intense inflammatory infiltrate to regress tumors.

In addition, the anti-tumor response to immune checkpoint inhibitors of CTLA-1 and PD-L1 were found to be mediated through interactions with *B. fragilis* or *Bifidobacterium* respectively, in tumor xenograft models. When these bacteria were depleted, response to immunotherapy was significantly diminished. As we learn more about how the microbiome affects disease progression and response to treatments, the opportunity to exploit the microbiome for therapeutic benefit is an exciting new approach that should be explored.

Project Goals

The purpose of this SBIR contract solicitation is to develop innovative technologies and methods designed to modulate the GI microbiota in order to enhance the therapeutic efficacy of existing or novel cancer therapies, or ameliorate side effects of these therapies. The goal is to develop effective adjuvant strategies that specifically target critical microbial activities or populations that affect drug efficacy and/or tolerability. Ultimately, this activity will accelerate the development of novel strategies based on the rational targeting and manipulation of human GI microbiome functions for the treatment of human tumors.

To successfully meet this goal, applicants will need to demonstrate that their approach accomplishes the specific perturbation or modulation of microbial function that is desired, and that these approaches have demonstrable benefits in addressing a significant unmet medical need relevant to cancer (e.g. reduction of off-target toxicity). Phase I studies should focus on developing and refining the approach that will be used to modulate GI microbiota or functions performed by the microbiota (such as metabolic or immunomodulatory activity). Applicants should establish appropriate criteria to benchmark or evaluate the success of their approach, and these should be related to the expected level of perturbation or modulation that is required to have therapeutic benefits. Phase II studies should focus on demonstrating that the approaches developed in Phase I studies are effective in an appropriate *in vivo* model system. Lead candidates should be developed and tested for efficacy in appropriate animal models, and Phase II studies should also measure agent delivery (e.g., probiotics, engineered phage, lipids, nano-particles) and pharmacokinetic targeting (e.g., reduction/increase of specific microbial enzyme activity, signaling ligand, or host interaction) in addition to measured endpoints of tumor regression and/or ablation *in vivo*.

Applicants are required to identify and justify a cancer type and unmet medical need that can be addressed by their approach. They should also provide a scientifically justified rationale for exploring particular approach(es) for perturbing or modulating the microbiome, and justify the choice of model system to evaluate their approach(es).

It is anticipated that applicants will test perturbations of the GI microbiome such as, antibiotic treatments, bacteriophage therapies, probiotic supplements, dietary metabolites, drug metabolizing enzymes, modulators of bacterial metabolism, and immunomodulators. However, applicants are free to employ any approach.

The focus of this contract topic is not to search for new mechanisms or effects by which the microbiome affects cancer therapy or progression, but rather to explore microbiome directed intervention strategies that have a rational basis. The contract topic is not intended to develop screening approaches, though applicants may propose to refine or optimize lead compounds or other agents designed to modulate or perturb GI microbiota.

Phase I Activities and Deliverables

- Define and characterize a host/microbe interaction that affects therapeutic efficacy, demonstrated through appropriate in vitro and in vivo experiments.
- Develop targeted microbiota regulated/directed intervention strategies designed to improve, either alone or in combination, patient outcomes for new or current therapeutic agents. *Approaches may involve, but are not limited to:*
 - Narrow spectrum antibiotics
 - Bacteriophage therapies
 - Probiotics/Prebiotics
 - Dietary metabolites
 - Expression or delivery of novel drug metabolizing enzymes
 - Targeted Inhibitors of bacterial gene expression (miRNAs, small molecules)
 - Immunomodulators/vaccines
- Test and refine therapeutic approaches in order to identify lead candidates or agent (e.g. bacteriophage, bacterial strain, enzyme, dietary metabolite, vaccine, etc.) to develop further in Phase II studies
- The lead candidate or agent should be able to successfully accomplish the desired perturbation or modulation of the microbiome to a level that can reasonably be expected to have an impact on the efficacy of the therapeutic interventions and demonstrate proof of concept for the efficacy of their approach. Offeror should demonstrate proof of concept in an appropriate in vivo model
- Offeror should determine and justify the assays and endpoints that will be used to evaluate the success of their approach (e.g., biomarkers, enzymatic activity, presence or absence of specific microbial populations). If needed, offeror should develop alternative tools/methods to evaluate candidate effects on microbiome function.
- Submit a statement to NCI that specifies the metrics and criteria used to evaluate the success of the approach being developed, and justification for these metrics and criteria from a commercial and scientific perspective.

Phase II Activities and Deliverables

Phase II activities should support commercialization of the proposed agent for clinical use. Expected activities and deliverables may include:

- Demonstrate the efficacy of lead candidate(s) or agent(s) from Phase I studies in an appropriately characterized in vivo model
- Identify and measure appropriate pharmacokinetic, pharmacodynamics, and therapeutic endpoints
- Evaluate toxicity and efficacy of therapeutic candidate(s) or agent(s)
- Evaluate immune response to therapeutic approach where appropriate
- Determine the toxicology and safety profile of the lead candidate(s) or agent(s) using appropriate animal models and assays relevant to the specific therapeutic approach being pursued
- Optimize or scale up lead candidate(s) or agent(s) (e.g. bacteriophage, bacterial strain, enzyme, dietary metabolite, vaccine, etc.) from Phase I studies. Activities may include, but are not restricted to:
 - Medicinal chemistry to optimize small molecules for in vivo studies
 - Scale up production of lead therapeutic candidate(s) or agent(s)
 - Optimize delivery method for therapeutic candidate(s) or agent(s)

- Develop a plan for obtaining regulatory approval to conduct human studies. Offerors should provide plans and a detailed time table for obtaining this regulatory approval

359 Technologies for Differential Isolation of Exosomes and Oncosomes

Fast-Track proposals will **not** be accepted

Direct to phase II will **not** be accepted

Number of anticipated awards: 2-3

Budget (total cost per award):

Phase I: \$300,000 for 9 months

Phase II: 1,500,000 for 2 years

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Summary

Both normal and cancer cells shed exosomes and other microvesicles into body fluids. Exosomes collected from the blood and other body fluids of patients diagnosed with various cancers were shown to contain tumor suppressors, phosphoproteins, proteases, growth factors, bioactive lipids, mutant oncoproteins, oncogenic transcripts, microRNA, RNA and genomic DNA (gDNA) fragments. Exosomal trafficking and reciprocal exchange of molecular information among different organs and cell types was reported to contribute to cell-to-cell communication, horizontal cellular transformation, cellular reprogramming, functional alterations, regulation of immune response, and metastasis. Exosomes collected from cancer patients were reported to perform cell-independent miRNA biogenesis, and promote tumorigenesis by mediating an efficient and rapid silencing of miRNAs to reprogram the transcriptome of cells that they physically interact with. In functional studies, exosomes derived from serum collected from cancer patients were reported to activate normal epithelial cells to form tumors, while exosomes from healthy individuals appear to have anti-tumor characteristics. Since exosomes are continuously released by all tissue and carry molecular signatures and effectors of health and disease, they reflect the dynamic changes taking place in tissue microenvironments throughout the different stages of cancer progression. Of clinical significance is the possibility that exosomes in blood and other body fluids may offer a non-invasive or minimally invasive way to assess cancer initiation, progression, risk, survival and treatment outcomes of cancer.

Exosomes are found in several biofluids including amniotic fluid, breast milk, bronchoalveolar fluid, cerebrospinal fluid, malignant ascites, plasma, saliva and urine, and studies reported differential molecular profiles of extracellular vesicles (EVs) in cancer patients' sera/plasma from breast, prostate, lung, liver, gastric, esophageal, glioblastoma, Kaposi's sarcoma-associated herpesvirus-associated malignancies, and urine from prostate. In addition, it has been reported that the concentration of exosomes is higher in the blood of cancer patients. Unlike cell-free circulating nucleic acids (cfCNA), the exosomal cargo is protected by a phospholipid bilayer membrane. Therefore, the tissue specific biomolecules contained in the exosomes are stable in the body fluids compared to the cfCNAs. This stability and the possibility to collect serial samples of biofluids non-invasively or minimally invasively, over a period of time, offers an unprecedented opportunity to obtain reproducible time-varying tissue specific genotype and phenotype information in body fluids that resemble dynamic changes taking place during cancer initiation, tumor development and metastasis in tissues. Molecular profiles of exosomes in archived samples collected in retrospective and prospective studies may further offer valuable information needed to accelerate cancer research and options for clinical care.

The major bottle neck for using exosomes in cancer research or clinical care is in obtaining enriched preparations of oncosomes from body fluids, where "oncosomes" are defined in this solicitation as exosomes that contain oncogenic cargo and/or unique signatures of the tumor cells from which they emanate. Existing technologies are based on centrifugation, precipitation/centrifugation or affinity purification, which are labor intensive and time consuming. Currently, we do not have effective technologies that can differentially isolate tissue-specific exosomes and tumor-derived oncosomes from the general population of exosomes in archived body fluids.

The purpose of this contract proposal is 1) to support the development of technologies for differential isolation of tissue-specific exosomes and tumor-derived oncosomes from any body fluid(s), and 2) to obtain enriched, distinct

preparations useful for downstream comparative molecular profiling or therapeutic use. Applicants must propose to develop an efficient and cost effective platform for complete isolation and separation of exosomes/oncosomes, which are morphologically and functionally intact.

Project Goals

The goal of this contract proposal is to accelerate the use of exosomes from body fluids for cancer research and clinical care. It is also intended for developing technology for differential isolation of tissue-specific exosomes and oncosomes in serial collections of archived body fluids to enable assessment of cancer initiation, progression, risk, aggressiveness, prognosis and/or treatment outcomes. Since exosomes are continuously released from normal, pre-cancerous, tumor, and metastatic tissues, the time-varying genotype and phenotype of exosomes in body fluids may provide a mechanistic understanding of carcinogenesis, tumor initiation, promotion, development, and progression in tissues, and the knowledge gained may lead to better cancer prevention/care/control. Patient-derived exosomes may also serve as targeted drug/antibody delivery systems and immunomodulation agents to yield new precision medicine strategies.

Applicants are required to obtain distinct preparations of exosomes and oncosomes, which originated in a specific tissue/tumor, from routinely collected fresh/archived body fluids. They should demonstrate quality, quantity and reproducibility of isolation and separation using physicochemical and functional studies. The technology platform should be useful for profiling multiple body fluids from multiple cancer types. The technology should establish automated workflows to reduce human intervention and obtain exosome preparations suitable for research and therapeutic purposes.

To apply for this topic, offerors should:

Have a prototype platform with demonstrated capability for isolating exosomes from complex solutions. Preference will be given for proposals with demonstrated capability for further isolating oncosomes from the general exosome population.

Demonstrate sufficient expertise and necessary resources for robustly characterizing captured exosomes, and verifying persistence of their biological integrity.

Phase I Activities and Deliverables

- Develop a technology for differential isolation of exosomes and oncosomes, which originated in a specific tissue, from body fluid(s) collected from cancer patients (e.g., breast, prostate, colon, lung or brain). The technology must be sufficient for adoption in clinical workflows and therefore demonstrate capability for processing at least 10 mL of clinical fluid specimen in <1 hour.
- Demonstrate that the technology can obtain distinct preparations of exosomes and oncosomes from the routinely collected fresh/archived body fluids, and yields sufficient quantity for downstream analysis. Specifically, demonstrate sufficient yield of nucleic acids for NGS and proteins for LC-MS/MS
- Establish automated workflows sufficient to allow for minimal training for new users.
- Demonstrate that the reproducibility is >90% and yield is >70%
- Demonstrate collection of >75% intact and undamaged exosomes/oncosomes is using physicochemical methods (Transmission electron microscopy, AFM, dynamic light scattering, immunostaining/immunofluorescence).
- Benchmark the developed technology against at least 2 current techniques (e.g. centrifugation, density gradient, immunocapture, size-based filtration, etc.) and demonstrate comparable purity and yield from clinically appropriate sample sizes for the specific bodily fluid.
- Deliver to NCI the SOPs for exosome/oncosome isolation, and the data from physicochemical characterization that demonstrates the quality of the isolated exosomes/oncosomes

Phase II Activities and Deliverables

Adapt the technology to multiple body fluids (i.e., stored or freeze thawed) with varying complexity.

Demonstrate that the isolated exosomes/oncosomes are morphologically intact by physicochemical methods (Transmission electron microscopy, AFM, dynamic light scattering, immunostaining/immunofluorescence), and functionally active in in vitro systems (transmission of information from exosomes to cells in culture and/or co-culture).

Develop a pre-commercial prototype kit/tool/device for the differential isolation of exosomes/oncosomes.

360 Manufacturing Innovation for the Production of Cell-Based Cancer Immunotherapies

Fast-Track proposals will be accepted.

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

Number of anticipated awards: 2 – 4

Budget (total costs, per award):

Phase I: up to \$300,000 for up to 9 months

Phase II: up to \$2,000,000 for up to 2 years

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Summary

Cancer immunotherapy is a therapeutic approach that directs a patient's own immune system to eradicate their tumor cells. Past and current NCI investments in adoptive T cells, CAR-T cells, NK cells, and other cell-based cancer immunotherapies have resulted in the translation of many lab-specific approaches into early clinical trials. Importantly, reproducible and robust production methods are critical to ensure that advances in basic research result in successful translation of cell-based therapies. Clinical development of such therapies requires multi-center, randomized clinical trials that must be supported with high quality, consistent and reproducible cell-based products. Patient-specific autologous or allogeneic lots must be adequately characterized to ensure that similar products are given to all patients. For non-patient specific cell-based therapies, large-scale and reproducible manufacturing technologies are needed to produce high-quality products with uniform identity and potency. Current limitations in cell manufacturing can increase both the cost and time required to bring a therapy to market and can result in missed opportunities to evaluate promising new cell-based therapies. Product failures can be attributed to poor product design and characterization, as well as inadequate scale-up and manufacturing processes; therefore, further investments are needed to develop state-of-the art manufacturing technologies and processes to advance cell-based cancer immunotherapies at the commercial-scale. Effective use of science and engineering principles during the early development phase of a cell-based therapy can improve both the efficiency and reliability of the manufacturing process and the quality of the final product. Moreover, it is anticipated that standardized approaches to manufacturing, process analytics, release testing, and product characterization will result in more rapid, cost-effective product development and a higher level of regulatory success. Achieving the desired level of standardization for current and future cell-based cancer immunotherapy products will require both pragmatic research to establish consistent manufacturing processes, as well as the development of new innovations and technologies.

Project Goals

The overall goal of this contract topic is to facilitate the development of innovative methods and technologies capable of improving and modernizing product manufacturing processes for cell-based cancer immunotherapies. This includes the use of autologous, allogeneic, or pluripotent cells. To achieve this goal, offerors submitting proposals under this solicitation are strongly encouraged to establish collaborative relationships with clinical product development companies focused on the development of specific cell-based products. In all cases, it is expected that offerors will demonstrate the utility of their innovation(s) in the context of at least one cell-based product, which is representative of a particular class of cell-based cancer immunotherapies.

Examples of manufacturing innovations/advancements might include, but are not limited to:

- Automated closed systems for cell separation, genetic modification, differentiation, and/or expansion;
- Low-cost, high-efficiency methods for genetic modification to support cell engineering;
- Standardized assays and/or surrogates to evaluate cell attributes that ensure lot-to-lot consistency in terms of phenotype, functionality, quality and potency;
- Real-time non-destructive test methods with sensors and/or imaging technologies for assessing critical quality attributes (e.g., contamination);
- Process analytics capable of feedback control in response to real-time changes in critical attributes of the cell product.

Under this topic, it is expected that Phase I proposals will focus on novel inventions related to innovations or improvements in cell manufacturing processes, including in-line or on-line (i.e., continuous) process analytics to support product consistency and safety, as well as GMP production of a class of cell therapies. Phase II proposals should focus on demonstrating the scalability and validation of the novel production platform or process improvements developed in Phase I. Engineering and process solutions must be capable of regulatory compliance with FDA Guidelines. The long-term goal of this initiative is to provide the tools necessary for efficient, high-quality manufacturing of novel products in the emerging field of cell-based cancer immunotherapies.

Phase I Activities and Deliverables

- Develop a device/technology/process to support commercially-relevant manufacturing advancements or improvements for the production of a specific class of cell-based cancer immunotherapies (e.g., CAR-T cells, adoptive T-cells, NK cells)
- Establish defined specifications, assays and/or metrics to interpret scientific data supporting the feasibility of the device/technology/process, with respect to reproducible product manufacturing, process analytics, and/or process controls
- Demonstrate the suitability of the device/technology/process to improve relevant manufacturing metrics (e.g., product uniformity, quality, efficiency, cost-effectiveness) for at least one cell-based product, which is representative of a particular class of cell-based cancer immunotherapies
- Provide proof of collaboration or partnership with an entity that is developing a representative cell-based therapeutic agent OR otherwise demonstrate access to a representative cell-based therapeutic agent through other means (e.g., internal drug development program), that can be used for validation of the device/technology/process
- Demonstrate pilot-scale beta-testing of the production process to demonstrate reproducible performance within appropriate specifications for identity, purity, potency, and/or other relevant metric for the chosen cell-based immunotherapy product

Phase II Activities and Deliverables

- Generate scientific data demonstrating the proposed scalability (e.g. scale-up, scale-out, point-of-use) of the production platform, process analytics and/or process controls
- Develop an at-scale prototype of the device/technology/process with detailed specifications for hardware/software that supports the production platform or process analytics/process controls improvements
- Validate the production innovation and/or process improvements, including standards for calibrating any novel process analytics or process controls that monitor production

361 Highly Innovative Tools for Quantifying Redox Effector Dynamics in Cancer

Fast-Track proposals will **not** be accepted.

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

Number of anticipated awards: 2-4

Budget (total costs, per award):

Phase I: up to \$225,000 for up to 9 months

Phase II: up to \$1,500,000 for up to 2 years

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Summary

The generation and dynamic interplay of redox effector molecules (e.g., oxygen, free radicals, peroxides, nitrogen oxides, and hydrogen sulfide) are fundamental features underlying the genomic, structural, metabolic and functional alterations observed in cancers. Alterations in redox balance impact all phases of disease including carcinogenesis, disease progression, response to treatment and prevention. For example, the DNA damaging effects of free radicals can mutagenize key oncogenic sites. Redox imbalances occur by abnormalities commonly associated with cancers including mutations in p53, myc and ras pathways. Redox effectors operate to modify protein function at the post-translational level, which plays a significant mechanistic role in the phenotypic plasticity cancer cells demonstrate in the face of oxidative and reductive (hypoxia) stresses. Redox tone is a key regulator of the self-renewal properties of stem-like cancer cells, which has been shown to contribute to tumor resistance to current therapies.

Progress in the cancer biology and pre-clinical space has been limited by the lack of tools that can accurately measure redox parameters in animal models with sufficient spatio-temporal resolution and minimal perturbation of the system. NCI seeks input from the small business community to develop and optimize a new generation of quantitative and specific technologies that will enable and accelerate basic research aimed at understanding basic redox effector mechanisms and the roles they play in the cellular adaptations and complex biology of tumors.

Supporting the development of these technologies will allow researchers to validate and benchmark data obtained across different 3D cell culture platforms and pre-clinical animal model systems with the goal of accurately mimicking tumor environments experienced by patients with cancer. Moreover, an enhanced ability to screen, manipulate, or analyze redox dynamics is an invaluable index in the evaluation of cancer cell-tumor responses to therapeutic interventions in the critical pre-clinical testing phase. These redox data have potential to significantly improve our understanding of tumor biology and ability to better predict treatment responses and long-term efficacy when translated into patients.

Project Goals

There is an unmet need in basic cancer research for probes or technologies that can better measure, characterize, profile, or resolve the spatiotemporal dynamics of redox effectors at the subcellular to cellular levels. Genomic profiles, for instance, cannot capture post-translational redox regulation that occurs with changes in the tumor microenvironment. Redox probes have been traditionally reliant on organic dyes that experience spectral shifts with redox. The current state of the art is genetically encoded redox indicators that couple redox responsive enzyme motifs with indicator proteins. These genetically engineered redox probes have improved response kinetics, but may have limited optical qualities. Given the critical role played by redox effectors, developing a range of new tools will help us better understand how redox effectors regulate cell phenotypes in functional tumor populations.

The goal of this FOA is to develop quantitative tools to measure redox dynamics in biological systems. Ideally, probes or biosensor tools should be minimally invasive as to not significantly perturb the system. The technical approach should: (1) allow for in vivo measurements of redox effector spatiotemporal dynamics; and-or (2) be useable in high throughput systems, for example to allow the screening of cellular response to experimental perturbations, such as exposure to cytotoxic agents. The long term goal is that the technologies developed through this contract can help validate whether data gathered in model experimental systems faithfully represents the redox dynamics of human tumors.

Technologies that have the potential for in vivo use, especially those with potential clinical applications in the long term will be of particular interest, but methods that will be restricted to pre-clinical research applications are also of interest.

To successfully meet this goal, offerors shall develop a technology for the minimally to non-invasive measurement of one or more redox effectors, including but not limited to oxygen, free radicals, reactive oxygen species, peroxides, nitrogen oxides, and hydrogen sulfide. Phase I studies should focus on developing the technology and

demonstrating proof of concept in an in vitro system. Phase II studies further refine the technology and demonstrate the use of the technology to measure redox effectors. Offerors shall justify their choice of approach with respect to the scientific utility and commercial potential, and specify quantitative milestones that can be used to evaluate the success of the technology being developed.

It is anticipated that offerors shall develop a probe or similar agent that facilitates the measurement of redox effectors by one or more imaging modalities; however, offerors are not restricted to any particular technical approach and label or probe free approaches that can meet the requirements of this contract are welcome.

Offerors are not restricted to any particular technical approach and can propose resource and tool development that incorporates high-risk/high-impact technologies. Examples can include, but are not limited to:

- Redox probes that provide significant advances in sensitivity, selectivity, ratiometric capability, or resolution in reporting the spatial concentration gradients and temporal dynamics of redox effectors at the subcellular, cellular and/or tissue compartment levels.
- Genetically encoded redox biosensors that are expressed in a cell or tissue selective manner in small animal models of cancer for interrogation by non-invasive to minimally invasive imaging modalities.
- Biology-inspired redox sensors (e.g., based on bacterial chemosensors) that through synthetic biology techniques are genetically encoded for expression in a cell or tissue selective manner.
- Nanotechnology scaffolds multiplexed with sensors that permit functional parallel profile analyses of a combination of redox effectors (i.e., oxygen, nitric oxide, hydrogen peroxide, superoxide) and/or related species (e.g., proton, glutathione, ascorbate) across both time and space at the subcellular, cellular and/or tissue compartment levels.
- Instrumentation that enables label-free quantitative measurements of redox-related spatiotemporal dynamics in cancer cells and/or tumors (e.g., Raman spectroscopy-based microscopy, super resolution microscopy).

Technologies that have the potential for in vivo use, especially those with potential clinical applications in the long term will be of particular interest. However, Offerors with technologies that will advance pre-clinical or basic cancer research applications are also of high interest.

Phase I Activities and Deliverables

- Identify and justify development of a sensing tool or probe for specific redox effector species from both a cancer biology and commercial perspective.
- Offerors shall describe the current state of the art technologies for sensing and measuring the redox effector being addressed by their proposal, and outline the advantages that their approach will offer.
- Develop and characterize a redox probe, biosensor or detection platform. Offerors shall specify quantitative milestones that can be used to evaluate the success of the technology being developed, and justify these milestones from the viewpoint of both scientific utility and commercial value.
- Develop an assay or system that demonstrates proof-of-concept testing and benchmarking of specificity and sensitivity parameters of the agent or system for a range of redox effector species (e.g., oxygen, free radicals, hydrogen peroxide, nitric oxide, hydrogen sulfide, NAD/NADH, GSH/GSSG).
- For each redox effector or parameter, a technical description of methodology for each assessment shall be provided that includes how each measurement is calibrated. If measurements are collected serially, the rationale for the order of measurements shall be specified.
- Demonstrate feasibility to sense, interrogate, detect or resolve the spatiotemporal dynamics of redox effector species in live cells or animal model, ideally with a minimally invasive perturbation of the system.
- Provide NCI with proof-of-concept assay SOP.

Phase II Activities and Deliverables

The goal of the Phase II product is an optimized commercial resource, reagent, kit or device that can allow researchers to measure the relevant redox effector molecules in their laboratory. Decisions for continued project development into Phase II will be based on probes, biosensors, assays or systems that:

- Can demonstrate reliability and robustness. Offerors shall provide a technical evaluation and quality assurance plan with specific detail on shelf life, best practices for use, equipment required for use.
- Can be scaled up at a price point that is compatible with market success and widespread adoption by the basic research community.
- Have potential to benchmark data obtained across different cancer model systems.

Deliverables for the Phase II projects are:

- Scaled up synthesis or manufacture of agents, chemicals, device, or products necessary.
- Design and implement quality assurance controls and assays to validate production.
- Validate scaled up device, chemical or product. Offeror shall demonstrate the utility, reliability and sensitivity of their device, chemical or product across in vitro and/or in vivo models relevant to cancer research.
- Refine SOPs to allow for user friendly implementation of technology by the target market for the agents, chemicals, device, or products.

362 Informatics Tools to Measure Cancer Care Coordination

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: up to \$225,000 for up to 9 months

Phase II: up to \$1,500,000 for up to 2 years

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Summary

The rapid adoption of Electronic Health Records (EHRs), increased patient engagement, rapid adoption of mobile technology, and shift to value-based care have contributed to an increased use of health information technology (IT) to improve quality and outcomes of patient care.

There is a need for more coordination in cancer care due to the growing complexity of cancer treatment and the increase in cancer survivors that need better coordination within and across clinical teams and care settings. Poorly coordinated care leads to avoidable hospital readmissions, preventable medical errors, harm to patients and higher costs. Care coordination strategies share seven essential [tasks](#): assess patient, develop care plan, identify participants and specify roles, communicate with patients and other participants, execute care plan, monitor and adjust care, and evaluate outcomes. Health IT plays an important role in care coordination in diverse organizations like Kaiser Permanente and the VA.

The measurement process for care coordination is changing from the laborious process of manual chart reviews to EHR-based measurement. New EHR-based care coordination measures are being developed. The National Quality Forum recently endorsed [five EHR-based care coordination measures](#), none in cancer care. At least 12 cancer-specific care coordination measures are available in the [National Quality Measures Clearinghouse](#).

There is a need for informatics tools that automate measurement for existing care coordination measures and have the flexibility to add new measures as they are developed.

The interaction of people, technology, tasks, organization and environment creates a structure – a work system – that shapes workflows, which shape outcomes. Health IT-focused businesses understand (from experience) IT adoption changes workflows and work systems. This understanding coupled with the ability to innovatively use diverse data systems and methods is needed to create scalable informatics tools to measure care coordination to meet the marketplace needs.

Project Goals

The goal is to create scalable health IT-based informatics tools that measure care coordination in order to assess and improve quality of care and patient outcomes, assist the ongoing healthcare delivery system transformation and improve research efficiency. The tools will help managers and clinical teams realistically assess the effectiveness of existing care coordination and patient engagement processes and help identify areas for improvement, which will help their efforts to transform delivery systems to meet the triple aim objectives of improving patient experience, improving population health and reducing costs. The researchers will gain access to tools that measure the variability in cancer care coordination and patient engagement in diverse settings, which will help identify the characteristics of clinical teams, processes and health systems associated with delivery of high-quality care and to test interventions based on these characteristics.

Activities not responsive to announcement:

Tools that don't measure care coordination; tools that don't incorporate safeguards to protect privacy and confidentiality of information; design approaches that don't account for scalability, interoperability or user-centered design; approaches that don't plan for using tools in diverse sites and IT systems; validation of new measures.

Phase I Activities and Deliverables:

- Project team: Establish a project team, including proven expertise in: software development, user-centered design, care coordination measurement, team communication and clinical workflows, clinical oncology, and the design, deployment and use of health IT in a healthcare delivery organization. Knowledge and design of systems architecture, health IT interoperability, data security and HIPAA and other laws and regulations to protect privacy and confidentiality of patient information will be required.
- Develop a prototype platform to generate at least 5 cancer-relevant care coordination measures from EHRs and other relevant, IT platforms at one cancer care delivery site and to display them in the right format to the right user at the right time.
- Develop a prototype platform to assess clinical team composition; workflows and team interactions with health IT; flow of relevant data across diverse delivery sites; extent of patient engagement; type of health IT implementation, and organizational structure and policies relevant to the informatics tool development and implementation at one cancer care delivery site.
- Provide a report specifying approach to extend the platform by integrating additional
- care coordination measures and to scale the platform to multiple cancer care delivery sites with diverse IT systems.
- Provide a report detailing plans for implementation of technical assistance and delivery of software, platform, and measures developed, including a review of technical specifications for systems interoperability, within existing EHR and other health IT systems.
- Provide a report on the results of the first round of usability testing and the approach to modify the platform based on this user feedback. .
- Present phase I findings and demonstrate the functional prototype system to an NCI evaluation panel via webinar.

Phase II Activities and Deliverables:

- Enhance, beta test, and finalize system, data standards and protocols for a platform that measures and displays at least 12 existing cancer-related care coordination measures that are integrated within existing clinical workflows in at least three cancer care delivery sites that use at least two different IT systems.
- Enhance, beta test, and finalize system, data standards and protocols for a platform that assesses clinical team composition; workflows and team interactions; flow of relevant data across diverse delivery sites; extent of patient engagement; type of health IT implementation and organizational structure and policies relevant to informatics tool development in at least three cancer care delivery sites and at least two different IT systems.
- Provide a report that synthesizes feedback from all relevant categories of end-users (such as physicians, nurses, care managers and administrators) and summarizes the modifications made to the platform after each round of usability testing.

- Provide a report specifying lessons learned and recommended next steps to extend the platform by adding a broad set of care coordination measures and to scale the use of the platform to multiple cancer care delivery sites and IT systems.
- Provide a report detailing plans for implementation of technical assistance and delivery of software, platform, and measures developed, including a review of technical specifications for systems interoperability, within existing EHR and other health IT systems.
- Develop systems documentation and user guides to facilitate commercialization, including citation and details of how systems align with current regulations and best practices in user-centered design, interoperability and protection of privacy and confidentiality of information.
- Present phase II findings and demonstrate the system via a webinar at a time convenient to the offeror and NCI program staff.
- 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.

363 Connecting Cancer Caregivers to Care Teams: Digital Platforms to Support Informal Cancer Caregiving

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: \$225,000 for 9 months;

Phase II: \$1,500,000 for 2 years

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Summary

Informal cancer caregivers are individuals (usually family members or friends) who manage patient care which is typically uncompensated and delivered at home, involves significant amounts of time and energy, and requires the performance of tasks that may be physically, emotionally, socially, or financially demanding. These tasks include monitoring for treatment side effects, helping manage symptom burden, treatment decision-making, administering medication, and performing technical medical tasks (e.g., managing infusion ports, changing dressings). Despite these demands, caregivers are often underprepared to perform the many tasks required of them. Simultaneously, cancer treatment is more frequently provided in outpatient and community-based centers, which increases the day-to-day demands on informal caregivers.

Technology offers the potential of mitigating these demands and alleviating distress and burden for caregivers by offering decision-making tools, strategies for managing and communicating symptoms with providers, assistance with technical medical tasks, and care coordination. Furthermore, a majority of caregivers endorse the idea that technology may aid in preventing burnout and may reduce financial burden on both families and the healthcare system. Despite this, there is a lack of evidence-driven technologies to ease cancer caregiving burden available on the market.

The purpose of the proposed concept is to develop evidence-based technologies to alleviate cancer caregiving burden, assist family/informal caregivers to manage the needs of their care recipients, juggle their own healthcare needs, and enhance caregivers' connections with their care recipients' healthcare team. The SBIR mechanism is ideally suited to support this activity because it pairs investigators with software developers to create evidence-based technologies that can be scaled and disseminated with wide reach.

Purpose & Goals

The overall goal of this project is to develop software, database systems and mobile application tools to support cancer caregivers and connect them with their patients' care teams. These systems will enhance care quality and effectiveness and will allow care delivered beyond clinic walls into the home setting, ultimately aiming to improve patient outcomes. Systems should be designed to be flexible and customizable, to be modified based on feedback from patients, caregivers, or providers, and to evolve as patient and caregiver needs evolve. Development should utilize an iterative, user-centered design approach informed by actual cancer patients, caregivers, and healthcare providers.

A recent environmental scan of technological resources available to informal cancer caregivers was performed to determine current available software systems and capabilities. The following caregiving support categories were identified based on previous reviews in the topic area: consultation and clinical care delivery, medical skills training, therapy/counseling, financial resources, and peer-to-peer support. Of the ten software systems identified, none provided support in all areas (most provided support in only 1-2 areas). Many of the cancer-focused apps identified targeted patients only; only three targeted caregivers. None of the systems identified directly connected cancer caregivers back to the patients' healthcare provider team or associated electronic health record (EHR) and patient portals.

The following are specific modules that the caregiving platform should consider:

- (1) Direct communication with the patients' healthcare provider teams;
- (2) Care plan dissemination/updates pushed directly from healthcare provider teams to caregivers;
- (3) Tracking/monitoring of patients' care delivery, patient reported outcomes, side effects, etc. using structured data entry forms, standard measures (e.g., PROMIS®) or ecological momentary assessment;
- (4) Guidance for assisting with daily medical tasks;
- (5) Assistance with patient's activities of daily living;
- (6) Opportunities for peer-to-peer connection; including informal caregivers (e.g., family members) as well as informal caregiving communities for social support;
- (7) Guidance for caregiver self-care (including physical and emotional well-being);
- (8) Local information/service referrals when available and appropriate

The platform should allow end-users (i.e., patients and caregivers) the ability to opt in or opt out of studies.

Scope of activities to be supported:

- A review of currently available technological platforms for cancer caregivers to identify gaps, existing capabilities and resources.
- Interviews/focus groups with cancer caregivers, patients, healthcare providers, and caregiving researchers to further identify areas of unmet caregiving needs.
- The development of a software system with mobile application to connect cancer patients and their caregivers with healthcare provider teams to extend clinical interactions and provide further information resources and service referral. Key task domains should include organization-level (hospital or clinic), provider-level, caregiver-level, and patient-level dashboards that allow for assessment of adherence to treatment and post-treatment clinical practice guidelines, capability to identify high-risk patients, ability to identify care gaps and enable clinical data query functions.
- The development of secure bi-directional communication system to allow healthcare providers and authorized caregivers to push messages, including adjustments to the care plan, directly through the system.
- The development and testing of a prototype of a platform and caregiver-facing applications to be tested with cancer caregivers, patients and caregiving researchers.
- Further enhancement and refinement of the software system and mobile application.

Activities not responsive to announcement:

Tools that don't target cancer caregivers; tools that don't incorporate safeguards to protect privacy and confidentiality of information; design approaches that don't account for scalability, interoperability or user-centered design.

Phase I Activities and Deliverables:

- Establish a project team with expertise in the areas of software development, patient-centered design, health communication, oncology, oncology nursing, palliative care, family medicine behavioral science, health services, and computer programming. Note that team members may have dual expertise (eg. e.g., oncology nurse with palliative care expertise; behavioral scientist with communications background).
- Perform an environmental scan of available and relevant software systems designed to support cancer patients and caregivers to identify major gaps
- Conduct a small number of key informant interviews with cancer patients and caregivers to further refine and prioritize areas of unmet needs
- Provide a report including detailed description and/or technical documentation of the proposed system capabilities and specifications, including:
 - structure for the proposed caregiving support modules and user-interfaces (caregiver, patient, Database healthcare provider) and metadata requirements
 - Architecture that includes the following components:
 - A provider/ clinic health system dashboard to be able to communicate with the caregiver and download and upload information and integrate that information with electronic health records where possible and appropriate
 - A caregiver application and dashboard to be able to communicate with provider and download and upload information
 - A function within the application that allows the caregiver to communicate with other caregivers within the network of caregivers on the application "community"
- A dashboard/database that would communicate to caregivers, patients, and providers about community resources
 - Data and security standards for collection, transport, and storage of data inputs that ensure patient and caregiver privacy following standard NIH policies.
 - Data visualization, feedback and reporting systems for clinical monitoring and research applications
 - Data adaptation for mobile application(s)
- Develop a functional prototype of the software system that includes:
 - Front-end mobile application(s) to facilitate care plan dissemination, tracking and monitoring or care, communications and caregiver support.
 - Healthcare provider systems to facilitate care plan prescription, remote patient care monitoring, communications and resource provisions (e.g. content management for tailored caregiver support).
 - Required server systems architecture to facilitate interaction with necessary provider Health IT systems or patient facing portals and personal health records.
- Present Phase I findings and demonstrate functional prototype to an NCI evaluation Panel

Phase II Activities and Deliverables

- Establish a project team for Phase II activities and outcomes. This team should include personnel with training and research experience in chronic disease patient 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, 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.
- Evaluate, enhance as necessary and provide documentation that the technology and communications systems maintain compliance with HIPAA, data security, privacy, and consent management protocols as required for the proposed project.
- Develop a prototype into a pilot system for usability testing.
- Enhance systems interoperability for deployment in diverse software environments and provider networks. Provide a report detailing communication systems architecture and capability for data reporting to patients,

caregivers, healthcare providers, researchers, electronic health records, and health surveillance systems as appropriate for the proposed project.

- Conduct beta-testing of the software system and corresponding portals and mobile applications
- Conduct usability testing of caregiver/patient/care team/researcher facing mobile applications and care team/researcher facing user interface features including system management, analyses, and reporting applications.
- Test the integration of the technology into the target clinical, 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 trouble-shooting.
- 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.
- Develop appropriate human subjects protection / IRB submission packages and documentation of approval for your research plan.
- Develop 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.
- Create a publication plan outlining potential research and other publications resulting from the research
- Provide study progress reports quarterly, documenting recruitment and enrollment, retention, data quality assurance and control measures, 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.

364 Methods and Software for Integration of Cancer Metabolomic Data with Other –Omic and Imaging Data

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: \$225,000 for 9 months;

Phase II: \$1,500,000 for 2 years

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Summary

Metabolomics is the study of small molecules participating in cellular metabolism. Advances in metabolic profiling technologies have made it possible to simultaneously assay hundreds of metabolites, providing insight into an organism's metabolic status. Several studies suggest that metabolomics may identify novel biomarkers for a diverse range of disease, including cancer. Furthermore, metabolites may play important regulatory roles in disease pathways and even serve as effectors of disease processes.

The metabolome is particularly responsive to both environmental and biological regulatory mechanisms, such as epigenetic and post-translational modification and transcription. Additionally, metabolites are the closest link to the phenotype and therefore offer a unique opportunity for phenotype characterization. However, metabolomics alone is unlikely sufficient to achieve this. Therefore, developing bioinformatic methods for integration of metabolite data with other -omic (proteomics, transcriptomics, genomics, epigenomics) and/or cancer imaging data would allow for

significant advances in deciphering the biological relationships resulting in an observed phenotype. Importantly, this will also help leverage existing human data to combine metabolite and other –omics and/or cancer imaging data to detect subtler and more complex associations among variables, thereby promoting greater efficiency and return on investment. In turn, it will enhance opportunities to identify novel cancer biomarkers of risk, aggressiveness, therapeutic effectiveness, and prognosis, develop and/or enhance predictive models of cancer, and evaluate the tumor microenvironment. Ultimately, developing these bioinformatics methods will support precision medicine-focused clinical research.

Project Goals

The goal of this project is to develop new and innovative bioinformatic methods to integrate metabolite data with and other –omics and/or cancer imaging data and ultimately design scalable software tool(s) that apply these methods to automate the integration of the data. In Phase I, offerors should provide evidence that bioinformatic methods integrating identified metabolite data with other –omics and/or imaging data have been effectively developed, can be implemented across data inputs from at least one analytical technology used in metabolomics and at least one analytical technology used in genomics, proteomics, epigenomics, transcriptomics, or cancer imaging; and demonstrate readiness to proceed to Phase II. Additionally, phase I should be used to demonstrate the framework for scalable software tool(s) that apply the bioinformatic methods to automate the integration of metabolite and other –omics and/or cancer imaging data. In Phase II, offerors should expand the bioinformatic methods to include unidentified metabolite peaks, in addition to identified metabolite data, and demonstrate metabolite data integration other –omics and/or cancer imaging data.

To apply for this topic, offerors will need to demonstrate usability of scalable software through the following: 1) beta-test and finalize automated file transfer, data importation protocols, metabolite and genomic data integration applications and reporting tools developed in Phase I; 2) demonstrate that the software system adheres to established community data formats (e.g. standards of the Genomic Data Commons) and uses open application programming interfaces (APIs); 3) develop, beta-test, finalize and demonstrate the graphical user interface (GUI); and 4) demonstrate the software system’s ability to integrate data from planned Phase II technology compatibility matrix data sources using automated algorithms and bioinformatic methods.

Phase I Activities and Deliverables

- Establish a project team including proven expertise in metabolomics analytical technologies, genomics, proteomics, epigenomics, transcriptomics and/or cancer imaging analytical technologies (as appropriate), cancer biology, epidemiology, biostatistics/bioinformatics, statistical genetics (if genomic data is being integrated), computer technology, and software implementation (including requirements analyst, software engineer, user interface design, quality assurance, and technical documentation).
- Develop bioinformatic methods for identified metabolite data integration with other –omics and/or cancer imaging data for at least one analytical technology used in metabolomics (preferably liquid-chromatography-mass spectrometry (LC-MS), gas chromatography-mass spectrometry (GC-MS), and/or NMR) and at least one analytical technology used in in genomics, proteomics, epigenomics, transcriptomics, or cancer imaging. Datasets with cancer outcomes must be used.
- Develop data formats that support the import and export of individual datasets and “combined” datasets, store structured data from different sources of metabolite and other –omics and/or cancer imaging data, and are readily used for data integration and QC protocols.
 - Finalize data formats and structure, data collection, transport and importation methods for targeted Phase I data inputs.
- Provide wireframes and user workflows for the proposed graphical user interface (GUI) and software functions that:
 - Support the import and export of individual datasets and “combined” datasets;
 - Implement, script or automate all features and functions of the data integration tool(s); and
 - Conduct QC of “combined” datasets.
- Provide a report including a detailed description and/or technical documentation of the proposed:
 - Specific approach to metabolite and other –omic and/or cancer imaging data integration;

- Specific approach to QC;
- Data standards for transfer and importation of individual metabolite other –omic and/or cancer imaging data and storage of individual and “combined” metabolite and other –omic and/or cancer imaging data;
- Data visualization, feedback, and reporting systems for individual and “combined” metabolite and other –omic and/or cancer imaging data;
- Technology compatibility matrix for Phase I and Phase II metabolomics and other –omic and/or cancer imaging data sources, including identified metabolites (Phase I) / unidentified metabolite peaks (Phase II).
- Software tool(s);
- Transparent, documented, and non-proprietary bioinformatic methods; and
- Description of additional software and/or hardware required for use of the tool.
- Finalized data formats and structure, data collection, transport, and importation methods for targeted data inputs; and
- Includes funds in budget to present Phase I findings and demonstrate the wireframes and user workflows for the GUI and software functions to an NCI evaluation panel.
- Develop functional prototype software that integrates data from planned Phase I technology compatibility matrix data sources using automated algorithms and methods.
- Include funds in the Phase I budget to present project deliverable and the prototype software tools to an NCI panel for evaluation.

Phase II Activities and Deliverables

- Expand the bioinformatic methods to include unidentified metabolite peaks, in addition to identified metabolite data, and demonstrate metabolite data integration with other –omics and/or cancer imaging data, using at least one analytical technologies used in metabolomics (preferably liquid-chromatography-mass spectrometry (LC-MS), gas chromatography-mass spectrometry (GC-MS), and/or NMR) and at least one analytical technology used in in genomics, proteomics, epigenomics, transcriptomics, or cancer imaging. Datasets with cancer outcomes must be used.
- Demonstrate usability of scalable software through the following:
 - Beta-test and finalize automated file transfer, data importation protocols, metabolite and genomic data integration applications and reporting tools developed in Phase I.
 - Demonstrate that the software system adheres to established community data formats (e.g. standards of the Genomic Data Commons) and uses open APIs;
 - Develop, beta-test, finalize and demonstrate the GUI.
 - Demonstrate the software systems ability to integrate data from planned Phase II technology compatibility matrix data sources using automated algorithms and bioinformatic methods.
- Conducts usability testing of the GUI elements of the metabolomics and other –omic and/or cancer imaging data integration tool(s).
- Develop systems documentation where applicable to support the software and bioinformatic methods.
- 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.

365 Imaging Informatics Tools and Resources for Clinical Cancer Research

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: \$225,000 for 9 months;

Phase II: \$1,500,000 for 2 years

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Summary

The goal of this contract topic is to support the *sustainment and evolution* of advanced cancer imaging informatics tools and resources and their broad adoption for clinical research applications through innovative translation and commercialization. The primary focus of this contract topic is on cancer imaging informatics tools and resources that have garnered significant adoption in the cancer imaging research communities. Imaging informatics *tools* include computer software tools and platforms to deploy and organize the processing, analysis, and interpretation of medical images to extract and help interpret clinical information, for supporting diagnosis, informing treatment, and providing therapy monitoring and evaluation (using, for example, quantitative imaging tools). Imaging informatics *resources* include image and patient data repositories and platforms that provide data, workflow, and a workspace for online research collaboration, evaluation as well as dissemination of informatics tools and resources, and support for population-based research.

The SBIR contract award will support enhancement and ongoing support of advanced cancer imaging informatics tools and resources to address Big Data opportunities and challenges and target critical unmet needs for validated clinical decision support tools and resources towards meeting precision medicine goals in cancer clinical research.

Project Goals

The primary goal of the proposed SBIR contracts is to develop and implement solutions for sustained support for the advanced development, evolution, and broad adoption of cancer imaging informatics tools and resources. Successful solutions should address the following challenges: 1) Imaging informatics tools and resources developed in the academic research environment are typically not fully developed in terms of usability and documentation, or their interoperability with other tools and data types. 2) Due in part to the continuous development nature of the funded research projects, few imaging informatics tools and resources are comprehensively evaluated for specific clinical applications and translated to suitable commercial products for broader adoption. 3) The overall lack of solutions for sustaining support and evolution for these tools and resources has limited the development teams' ability to evolve these tools and resources to continually meet user needs.

The overall scope of proposed funding approach includes the entire spectrum of cancer imaging, extending from microscopic, pathological imaging to in vivo clinical imaging for all phases of cancer clinical research. Offerors will be expected to formulate and execute well designed project plans with clearly defined milestones that will eventually lead to commercially viable solutions for 1) sustained development and evolution of cancer imaging informatics tools and resources and 2) their broad adoption in clinical cancer research.

Awardees will deliver enhanced services such as training, documentation, and help desk support that improve the overall usability, user adoption, and evaluation of the tools and resources for commercial translation. They are expected to develop and implement necessary technical solutions and business processes for hosting the selected cancer imaging informatics tools and resources and providing other necessary user support services for engaging user communities to promote broad adoption. They will enhance the tools and resources to meet evolving user needs. Early phase R&D such as the development of novel imaging acquisition schemes, new image analyses algorithms or software is not responsive to the solicitation.

Phase I Activities and Deliverables

The Phase I proposal is expected to identify roadblocks and provide innovative yet feasible solutions necessary for commercial translation of the targeted cancer imaging informatics tools and resources. The offerors are required to demonstrate prior experience with the cancer imaging informatics tools and resources addressed in the proposal. Example of such proposals include improvements to the informatics tools and resources necessary for meeting key usability and interoperability metrics to enable phase II implementation on commercially viable platforms. Phase I work is expected to develop use indications for the underlying cancer imaging informatics tools and resources, performance requirements necessary for supporting clinical research and applications goals, as well as critical hardware and software system specifications of informatics platforms for Phase II deployment of the underlying informatics tools and resources.

Key deliverables will be:

- Design specifications for enhancing image informatics tools and resources to support required usability, data and tools interoperability, patient data protection, as well as other features required for supporting phase II commercialization,
- Clear documentation of the tools and resources, and
- An early phase product prototype and detailed project plan for phase II implementation, as well as a demonstration of the prototype to NCI (using funds set aside for this purpose).

An example might include a phase I proposal to improve existing open imaging informatics tools and resources for use in drug trials or co-clinical trials that support the requirements of traceability and reproducibility for FDA filing.

Phase II Activities and Deliverables

- Phase II projects will be expected to implement requirements identified in Phase I, and launch a commercially-viable prototype cancer imaging informatics product targeted to the usage defined in Phase I. The system design process should encourage user-user and user-developer interactions for evaluation and further evolution of the informatics tools and resources and associated documentation.
- The offerors are expected to develop and implement a business process that will promote broad adoption of the tools and resources by actively engaging the user communities; seek support and undertake efforts to achieve recognition, certification, and adoption by clinical trials groups and professional societies; and eventually engage with regulatory agencies such as the FDA for adoption in drug trials and co-clinical trials. The business process should also address plans for long term sustainability, such as sustained hosting of tools, data, training, and associated resources, as appropriate.
- The proposed product implementation should also address the unique requirements for clinical application of imaging informatics tools and resources, including legal, financial, and marketing complexities associated with the development and release of the targeted commercial product(s).

Key deliverables for phase II projects will be enhanced image informatics tools and resources that are evaluated by key user groups and are appropriately validated for use in a clinical cancer research setting.

366 Clonogenic High-Throughput Assay for Screening Anti-Cancer Agents and Radiation Modulators

Fast-Track proposals will **not** be accepted.

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

Number of anticipated awards: 3-5

Budget (total costs, per award):

Phase I: up to \$300,000 for up to 9 months

Phase II: up to \$2,000,000 for up to 2 years

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Summary

The ultimate goal of any cancer treatment modality is to specifically eradicate cancer cells by inducing cell death by mechanisms that include metabolic death, cell apoptosis, and/or reproductive death (clonogenic death). Clonogenic death is defined as the indefinite loss of the proliferative ability of a cancer cell and is best assessed by colony-forming assays. Colorimetric and metabolic assays for determining cell viability and apoptosis measure short-term endpoints, but are subject to artifacts since they do not measure the clonogenic potential of cancer cells. Clonogenic assays are longer-term and are more labor-intensive, but are less susceptible to these artifacts.

Over the past several decades in vitro high-throughput screening (HTS) systems have evolved and are routinely used to screen agents for cytotoxicity. However, current HTS methodologies do not directly measure clonogenic potential

and are thus not able to accurately predict the efficacy of an agent either in subsequent preclinical animal model testing or in clinical trials. Further, it is well known that cancer recurrence is a common problem after treatment. This results from the re-population and redistribution of surviving tumor cell clonogens. Direct measurement of a tumor's clonogenic potential provides an integrated output of all cell death mechanisms and measures any capacity of residual cells to regrow; the definition of treatment failure. HTS systems to screen agents based on their ability to inhibit clonogenic potential of cells have been developed mostly in the academic setting. Advances in automated microscopy and robotics are facilitating these efforts. Further development, integration of robotics and softwares and commercialization of HTS clonogenic assay for screening anti-cancer agents and radiation modulators could greatly enhance the predictive power of HTS results and be applied to chemotherapeutic, radiologic or combined modality treatment testing.

Chemotherapy is used for both solid and hematologic malignancies. In addition, more than half of US cancer patients undergo radiotherapy alone or in combination with drugs; percentage of which is expected to only increase. Screening that allows for more accurate testing of chemotherapeutic and combinatorial treatments will better focus development to more promising agents and accelerate development of drug and drug-radiotherapy combinations. With expanded global access to radiotherapy and increased utilization rate, pharma and academics will be further incentivized to discover agents with anti-cancer and radiation sensitizing properties. Assays that are adaptable to the incorporation of molecular targeting, imaging, and evaluation of genetically defined cell panels for drug screening and discovery will be required with ongoing precision medicine initiatives. Companies can utilize clonogenic HTS assays to screen for new agents and to test newly identified agents in combination for radiation. Results from this type of screen should improve success in subsequent in-vivo model testing and will accelerate translation.

Program Goals

The purpose of this contract topic is to: (i) promote stronger academic industry partnerships in radiobiology to develop clonogenic survival-based HTS systems (ii) to exploit recent advances in the technical maturity of HTS technologies and combine them with advances in clonogenic assays, (iii) encourage small businesses to specifically develop HTS systems for screening potential anti-cancer agents based on a clonogenic endpoint, and (iv) integrate relevant technologies. Colony-forming assay survival experiments currently involve the use of several drug and/or drug + radiation doses as well as several plated cell numbers for each cell line and hence the assays are labor and material intensive. Further, developing a HTS system with a clonogenic endpoint will enhance screening/cross validating chemotherapeutic agents as well as radiation effect modulators and combinatorial treatments, while reducing labor and costs.

To apply for this topic, offerors need may design integration of robotic instrumentation, micro-fluidics, thermal and gas control, colony counting microscopic imaging and image analysis. An integrated system may also require the development of "bridging" components and graphic user interfaces. Offerors are required to develop standard operating procedures matched to validated cell lines for use with the integrated system. Offerors must include an integration of microfluidics/culture system with radiation exposure under conditions allowing precise dosimetry, which is critical. Offerors are also required to integrate and adopt software to capture and calculate survival. This solicitation is not intended for development of systems with non-clonogenic endpoints.

Phase I Activities and Expected Deliverables

- Delivery of a prototype system with validated SOPs that are translatable to other laboratories.
- Defined cell line panels that have been shown to be appropriate for use with the system and the clonogenic endpoint. Validation of representative "hits" using conventional clonogenic assay.
- Licensing of individual components for use in the system as needed.

Phase II Activities and Expected Deliverables

- Demonstration of system validation with manually assessed comparator(s) using drugs, radiation and combinations of known activity (e.g. Cis-platinum, radiation and combined treatment)
- Demonstration of software integration for analysis and output of clonogenic survival data in an easily interpretable format.

367 Predictive Biomarkers to Improve 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

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE 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. Significant advances in delivery and distribution of dose for radiotherapy have been made over the years. Currently, treatment decisions in radiotherapy/radiochemotherapy are primarily defined by disease stage, tumor location, treatment volume, and patient co-morbidities, together with general guidelines concerning normal tissue tolerance for surrounding organs. However, treatment planning does not take into account individual patient's, or a cohort of patients' sensitivities or radiation sensitivity of tumors. This is an important limitation in personalized care, as there are known variations in individual patient normal tissue sensitivities to radiation, but treatments are based on population normal tissue as well as sensitivities of tumors to radiation. 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. Acute side effects (e.g. skin reactions, mucositis, etc.) are often dose limiting, but may be reversible in contrast to the late effects such as fibrosis in the lung, telangiectasia, and atrophy, which are irreversible and progressive. A biomarker-based test that can predict the risk of developing severe radiotherapy-related complications or predict the sensitivity/response of a tumor may allow customization of treatment or delivery of suitable alternative treatment. However, discovery, development, and validation of predictive biomarkers of individual and tumor radiation hypersensitivity are challenging. The challenges include low incidence of normal tissue complications in the clinic, the need for long-term studies for predicting late effects and the combination of chemotherapy with radiation as standard of care for most tumors. Differences in radiation sensitivity of tumors may allow modification of dose to the tumor to minimize normal tissue damage, or maximize tumor cell killing, or may also allow the use of radiation effect modulators to achieve better therapeutic outcome. However, spatial and temporal heterogeneity in tumor characteristics is an important paradigm in the development of tumor radiation sensitivity predictive tests.

Project Goals

The goal of this contract topic is to develop a simple cost effective test that can be used by clinicians to personalize radiation/chemoradiotherapy treatment regimens. This contract solicitation seeks to identify, develop, and validate a simple, cost-effective test to rapidly assess inter-individual differences in radiation sensitivity of an individual patient's tumor to radiation therapy and/or predict early and late complications among cancer patients prior to starting radiation therapy. The test developed in response to this solicitation may evaluate normal tissue to predict radiation-therapy related toxicities in specific patient populations, or be developed to predict heightened responsiveness to radiation-therapy.

Treatment decisions for personalized approach to radiotherapy should take into account the likelihood of a severe adverse event due to damage of normal tissue as well as a predicted sensitivity of the patient's individual tumor. A predictive biomarker of individual radiation sensitivity can measure any biological changes in response to absorbed ionizing radiation, which is able to predict imminent normal tissue injury prior to radiotherapy and help determine radiotherapy suitability. Similarly, a predictive biomarker of tumor radiation sensitivity allows, in advance of treatment, an indication of sensitivity or resistance to radiation treatment by a specific tumor type and subtype.

Radiation biomarkers are an emerging and rapidly developing area of research, with potential applications in predicting individual radiosensitivity, predicting severity of normal tissue injury among patients, assessing and monitoring of tumor response to radiation therapy as well as in estimating dose to accidentally radiation-exposed individuals. The purpose of this contract topic is to develop a radiation biomarker test that may allow personalization of radiation therapy with curative intent.

A variety of radiation biomarkers have already been explored or are currently under development at different technology readiness levels (TRLs) at different government agencies and programs. This contract topic intends to leverage on these advances. These assays include but are not limited to (i) fibroblast clonogenic assay, (ii) measurement of DNA damage foci, (iii) damaged base metabolites, (iv) various types of chromosome aberrations studied in different phases of cell cycles, serum biomarkers, gene expression changes, (v) protein and microRNA expression changes, (vi) and genetic tests.

To be of practical value in the clinic, where radiation exposures are well-defined in terms of dose, distribution and timing, and thus quite different from radiation accidents, a predictive radiation biomarker should be (i) able to predict heterogeneity of radiation responses among a specific group of patients or tumors in clinic, (ii) specific to radiation, (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 minimally-invasive sampling, (vi) amenable to automation to improve quality control and assurance, (vii) have a quick turn-around time between sampling and results (though speed is not as critical as in the countermeasures scenarios), (viii) and be cost effective. All applications must include a biological hypothesis and rationale for the selected patient population and indication (e.g. developing biomarkers to indicate mucositis in a patient population with a biological signature that may predispose them to mucositis).

This contract topic aims to encourage the development and validation of predictive radiation biomarkers for clinical applications as described above. Both the FDA and the Centers for Medicare and Medicaid Services (CMS) through 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 platform migration as may often be needed, and clinical validation with a locked-down assay before regulatory submission and commercialization. Early pre-IDE interaction with FDA is therefore critical. NCI’s Program Directors may be invited by the awardees to participate in the pre-IDE discussions with FDA. 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

Phase I contract proposals must describe (i) a quantitative estimate of the patient population that will benefit from the availability of such predictive radiation biomarkers for the applicable cancer type/organ site, (ii) a plan for generating evidence that the proposed biomarker or biomarkers are relevant in the prediction of radiation hypersensitivity among patients with cancer and logical approach in the developmental pathway to clinic from discovery, (iii) a description of assay characteristics including sensitivity and specificity and the effects of known confounders, if any, (iv) level of technological maturity, describing critical technology elements allowing technology readiness assessment by the reviewers, (v) and a description of the proposed regulatory pathway for approval and pre-IDE consultation with FDA.

Activities and deliverables include the following:

- Discovery and early development
 - Demonstrate biomarker prevalence and utility
 - Develop a working qualitative test correlating the presence or absence of the biomarker(s) with potential outcome or a quantitative assay to assess radiation sensitivity
 - Demonstrate feasibility
- Preclinical development and technical validity

- Provide assay characteristics, including but not limited to performance, reproducibility, specificity, and sensitivity data using frozen (or other) samples from past clinical trials, or retrospective clinical studies providing adequate power calculations
- Illustrate the performance of the biomarker(s) with receiver operating characteristic (ROC) data
- Demonstrate suitability of the test for use in the clinic, including kinetics of biomarker, if transient.
- Determine the effect of confounders, such as any induction or concurrent chemotherapy regimens.
- Provide defined metrics for measurements of success
- Deliver the SOP of the working test or assay to NCI.
- Benchmark the technology against quantitative milestones proposed by offers to measure success
- Provide description of proposed regulatory pathway for approval and pre-IDE consultation with FDA

Phase II Activities and Deliverables

Phase II contract proposals must describe (i) the setting and intended use of the predictive biomarker(s) in retrospective or prospective studies using human tissue samples (frozen or fresh), (ii) a logical approach to regulatory approval, (iii) a description of assay platform and platform migration, if necessary, (iv) a demonstration of clinical utility and clinical validation, (v) a proposed schedule for meeting with FDA regulators regarding approval.

Activities and deliverables include the following:

- Provide a schedule of proposed meetings with FDA regarding approval
- Early-trial development
 - Retrospective tests using archived, frozen samples from past clinical trials, or prospective trials using fresh human samples.
- Full development
 - Demonstrate clinical utility
 - Demonstrate clinical validity in a large prospective randomized clinical trial

368 Molecularly Targeted Radiation 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

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Summary

Targeted radionuclide therapy (TRT) enables personalized cancer treatment by combining the therapeutic effect of radiation therapy with the targeting capability of molecular therapies. In TRT, a cytotoxic dose of a radioactive isotope is attached to monoclonal antibodies, receptor ligands, or synthetic molecules that target malignant tumor cells selectively. The ability of these molecules to bind specifically to a tumor-associated structure ensures that the tumor gets a lethal dose of radiation, while normal tissue gets only a minimal dose. This minimizes toxicity to normal tissues and can increase therapeutic efficacy (therapeutic index) leading to a reduction of overall treatment costs.

Currently available TRT compounds such as Zevalin and Bexxar have been developed and approved in the United States for use in the treatment of non Hodgkins Lymphoma (NHL). Although these drugs have shown a response rate of approximately 80%, they have failed to show a survival advantage in patients. Large multicenter trials to

study long-term survival are currently underway. Because these drugs have had modest commercial success to date, private investment in molecularly-targeted radiation pharmaceuticals remains at low levels. As this class of treatments shows tremendous clinical potential, there is a need to encourage the development of next-generation technologies (see below) for cancers other than NHL, including solid tumors, where the clinical need is most acute.

Project Goals

This contract solicitation seeks to stimulate research, development, and commercialization of innovative TRT techniques that could potentially shorten treatment cycles and reduce toxicity to normal tissues. Proposals addressing the following technology areas are encouraged: new treatment strategies; design, synthesis and evaluation of innovative ligands and radiotracers for TRT; novel radioisotope generators and radioisotope production techniques; dosimetry techniques; new treatment planning strategies facilitating combination of TRT with conventional therapies; and new conjugation chemistries that can link the radioisotopes to targeting agents other than antibodies (e.g. existing small molecule chemotherapeutic drugs) are also encouraged.

The short-term goal of the project is to perform feasibility studies for development and use of possible radiotherapeutics for the treatment of cancer. The long-term goal of the project is to enable a small business to bring a fully developed TRT compound or TRT-supporting technology to the clinic and eventually to the market.

Phase I Activities and Deliverables

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

- Proof-of-concept of the conjugation or attachment of the radioisotope to the antibody or other targeting moiety.
- Radiation dosimetry studies in an appropriate small animal model
- Proof-of-concept small animal studies demonstrating an improved therapeutic efficacy and improved therapeutic index, assessment of toxicity to normal tissues, and pharmacokinetic/pharmacodynamic studies utilizing an appropriate animal model.

Phase II Activities and 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:
- Demonstration of the TRT manufacturing and scale-up scheme
- IND-enabling studies, preferably in consultation with FDA, carried out in a suitable pre-clinical environment.
- 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.

369 Development of Pediatric Cancer Drug Delivery Devices

Fast-Track proposals will be accepted.

Direct-to-Phase II will **not** be accepted.

Number of anticipated awards: 2-4

Budget (total costs, per award):

Phase I: \$300,000 for 9 months;

Phase II: \$2,000,000 for 2 years

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Summary

Drug delivery systems are continually advancing and greatly assist the capabilities of cancer therapies and cancer survival. Yet, the pediatric population has not benefited, to the same extent as adult populations, from these advances in cancer therapy delivery device design and technology. A tailored dosage system for delivering cancer therapeutics to pediatrics is required. In addition to biological response differences, pediatrics vary anatomical with age and therefore require cancer therapy delivery devices and ports to be tailored for compatibility with anatomical dimensions of the patient. This topic is focused on drug delivery devices as opposed to drug delivery materials and vehicles. For example, in the case of central nervous system tumors—implantable drug delivery ports, pumps and ommaya reservoirs required for drug delivery to the cerebrospinal fluid often pose many issues for pediatric patients. Issues of device displacement, catheter migration and catheter fracture have all been reported and are primarily due to anatomical miss-compliance. Additionally, complications such as infection and insufficient wound healing are common because of devices with large profiles designed for use in adults. Furthermore, developmental and behavioral characteristics of young children should also be considered when designing a tailored device for pediatric patients – this includes changes in anatomy size for long-term implantable devices and mobility needs of children at different stages of development.

There is a need for versatile, efficient cancer therapy delivery devices that meet the needs of pediatric populations. This solicitation aims to aid the development of appropriate cancer therapy delivery devices that reflect pediatric patient specific designs and dosage parameters for pediatrics.

Project Goals

The purpose of this announcement is to assist the development of cancer drug delivery systems compatible to the needs of pediatric patients. This topic includes pediatric focused therapeutic targets within acceptable dosages suitable for pediatric patients and/or drug delivery systems designed to suit the needs of pediatric anatomical dimensions. Successful applicants will develop technologies to aid the administration of cancer therapies to pediatric patients, taking into account pediatric specific issues which include but are not limited to: dosage limitations, size restraints, comfort level and mobility. Adaption of currently available delivery devices for the pediatric population is also encouraged. One example is in the treatment of pediatric retinoblastoma where there have been some recent advances in the development of an episcleral device for delivering localized therapy to the retina and choroid, which has been tested in rabbits and is now proposed for testing in pediatric patients. This solicitation is not limited to cancer type or site, yet, justification of the need for pediatric-specific design parameters is encouraged. The offeror is required to outline and indicate the clinical question and unmet clinical need that the pediatric drug delivery device will address. This solicitation is not intended for drug formulation or nano-delivery systems; instead it is focused on delivery mechanisms and devices. In Phase I, offerors should demonstrate the proof of concept for the device proposed. Phase II projects will validate the device in the clinical setting.

Expected Activities and Deliverables

Phase I Activities and Expected Deliverables

- Select cancer type(s), site(s) and cancer drugs for the development of delivery device with adequate justification
- Design and develop a prototype of a drug delivery device that is
 - Suitable for the anatomical restrictions of pediatric patients.
 - Suitable for the dosage limitations of pediatric patients.
- Demonstrate preliminary proof-of-concept of the device in a suitable animal model.
- Develop the required specifications necessary to make the device clinic ready.
- Demonstrate understanding of the requirements to file a regulatory application for the device

Phase II Activities and Expected Deliverables

- Build a device according to the specifications developed in Phase I.
- Optimize the device design and performance for a clinical setting, and
- Show the feasibility of this novel approach/technique that will fit in with current clinical workflow.
- Demonstrate the safety and efficacy of the device in relevant animal models as required by FDA.
- Develop and execute an appropriate regulatory strategy. If warranted, provide sufficient data to submit a regulatory application to obtain approval for clinical application.
- For offerors that have completed advanced pre-clinical work, NCI will support pilot human trials.

NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES (NCATS)

The mission of the National Center for Advancing Translational Sciences is to catalyze the generation of innovative methods and technologies that will enhance the development, testing, and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions. For additional information, please visit our home page at <http://www.ncats.nih.gov>.

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.

015 Development of a Drone to be used in Laboratory Automation Projects

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 THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Summary:

The objective of this contract is to develop an autonomous drone capable of taking a laboratory consumable (such as a well-plate) from one station to another.

Currently, there are many options for robots in the space of laboratory automation, especially in the area of High Throughput Screening (HTS). Over the years, many pieces of laboratory instrumentation have been designed to allow for the loading of microplates by robotic arms such that they can be used in a continuous fashion as part of an automated system. Although, initially a point of failure, over time the use of industrial quality robotic arms has led to a very high degree of reliability in ensuring a microplate can be delivered from one instrument to another. This has enabled high throughput and more complex experiments to be run on these systems.

These robotic arms bring tremendous benefit to a HTS environment; however, they are not without limitation. Some of the limitations of these robotic systems are the cost, the safety requirements, the work envelope and the expertise required to operate/repair them. Much as robotic arms have gotten steadily more reliable over time within the realm of HTS laboratories, the tremendous interest in commercially available drones has driven the creation of more capable flying vehicles. Some of the functionality has expanded to more accurate flight control even within an indoor environment and the ability to add additional components to the vehicle. The thought behind this contract proposal is that by using low cost commercially available drones and open source software the realm of fully automated laboratory operations could become more accessible to facilities not currently equipped or funded to do so.

NCATS currently has a small internal effort in creating a drone capable of performing these functions. NCATS has developed a high level system design in addition to a functional gripping mechanism and automatic charging station. Although NCATS has interest in this research area, we are not in a position to take this to the level required for a fully functional autonomous drone to be used in a laboratory environment.

Project Goals:

The purpose of this contract proposal is to create an indoor autonomous drone capable of moving commonly used industry standard SLAS footprint Microplates from one location to another. The locations will be commonly used

pieces of instrumentation in a laboratory setting with examples being plate readers, low volume liquid dispensers, multichannel pipette systems and others. Typically, in HTS systems, robotic arms have been used as a microplate transportation system; the goal of this contract is to replace these robotic arms with a drone.

Conceptually, this would involve a general series of events to happen in an automated and programmatic fashion as follows:

- The drone takes off from a base station
- The drone flies to the pick-up location to pick up a microplate
- The drone actuates a gripping mechanism of some sort to pick the microplate up
- The drone flies along a predetermined (or adaptive) flight path to the drop-off location
- The drone drops the microplate off at the drop-off location
- The drone returns to the base station
- This process should be able to repeat without interruption 24 hours per day

For this process to be possible several key components will be required as described in the Phase 1 Activities and Expected Deliverables section.

Phase I Activities and Expected Deliverables:

- A drone with a minimum of the following capabilities:
 - Self-contained motor/drive system
 - Built in stabilization/control system
 - Wireless communication system
 - Sensing capabilities to perform onboard in-room navigation
 - Lift and payload capability to support a gripper assembly and the weight of a microplate with a lid
 - Expansion capability to add additional on-drone computing capabilities as required to enable in-room navigation and control of the gripper assembly
 - The capability to recharge at a base station when not in flight such that manual swapping of batteries is not required and the drone can be used in a continuous fashion
- A Gripping Mechanism
 - The gripper must be capable of handling SLAS footprint microplates potentially with a lid
 - The microplate will adhere to current ANSI/SLAS Microplate Standards
 - ANSI/SLAS 1-2004 (R2012) Microplates – Footprint Dimensions (formerly ANSI/SBS 1-2004)
 - ANSI/SLAS 2-2004 (R2012) Microplates – Height Dimensions (formerly ANSI/SBS 2-2004)
 - ANSI/SLAS 3-2004 (R2012) Microplates – Bottom Outside Flange Dimensions (formerly ANSI/SBS 3-2004)
 - ANSI/SLAS 4-2004 (R2012) Microplates – Well Positions (formerly ANSI/SBS 4-2004)
 - The gripper should be able to extend or be in a default extended position away from the drone such that the plate can reach beyond the extent of the drone rotors
 - This is to ensure that existing plate nests that have already been designed to work with robotic arms that have the capability to extend to a location can continue to be used for a variety of peripheral devices without having to redesign these devices to accommodate a different loading mechanism, such as the payload being held and delivered directly underneath the bottom of the drone

- Ideally, this would be some sort of telescopic-boom mechanism; such that the center of gravity of the drone could remain at the center of the drone while in flight and not extend until it is time to pick-up or drop-off a plate
 - The gripper design can be flexible, such as electrical with motors or pneumatic with self-contained rechargeable pneumatic cylinders that could also be recharged at the base station or some other methodology; how the gripper works is not as important as the ability to do so
- A Control System with a minimum of the following capabilities:
 - Capable of controlling/monitoring the drone with regards to position/flight status
 - Capable of defining multiple flight paths and monitoring the drone as it performs the pick-up/drop-off process
- A base station
 - The base station is the resting place for the drone where it can recharge batteries and pneumatic components if part of the proposed design
- Provide NCATS with all data resulting from Phase I Activities and Deliverables.

Phase II Activities and Expected Deliverables:

- Build a prototype drone that meets the Phase I specifications.
 - Provide a test plan to evaluate every feature of the drone
 - Provide NCATS with all data from each executed test to properly evaluate each test condition
 - Develop a robust manufacturing plan for the drone, using off the shelf OEM and Open Source components where possible to minimize expense.
- Provide NCATS with all data resulting from Phase II Activities and Deliverables.

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE (NHLBI)

The NHLBI plans, conducts and supports research, clinical trials and demonstration and education projects related to the causes, prevention, diagnosis, and treatment of heart, 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-16-009](#); Small Market Award: [RFA-HL-17-012](#)). 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 \$3 million in total costs and project periods up to three years may be requested. Development efforts may include preclinical R&D 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 301-496-2149 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.

098 Testing and Validation of Technologies for Inclusion in the CART Demonstration Project for Collaborative Aging Research

Phase I only proposals will **not** be accepted.
Fast-Track proposals will be accepted.
Direct-to-Phase II proposals will be accepted.

Number of anticipated awards: 3

Budget (total costs):

Phase I: up to \$150,000 for up to 6 months

Phase II: up to \$1,000,000 for up to 24 months

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Summary

New strategies are needed to develop an evidence-based healthcare system for the aging population, including those with chronic disabilities. Technologies that combine data from multiple sources, create meaningful presentations and visualizations and integrate information into a patient's electronically accessible health record are needed. These technologies also need to be combined with systems that can interact with the health care team and respond with timely interventions. To date, evidence is lacking demonstrating that home-based healthcare technologies improve or stabilize health so that the aging population can remain at home longer and avoid unnecessary hospitalizations or admissions to a nursing home. This SBIR contract aims to develop research evidence to support the use of technologies in the home that address heart, lung, blood, or sleep diseases using the Collaborative Aging (in Place) Research Using Technology (CART) research infrastructure and provide evidence for scaling up after the demonstration project.

The purpose of the trans-NIH, inter-agency [Collaborative Aging \(in Place\) Research Using Technology \(CART\) grant funding opportunity \(RFA-AG-16-021\)](#) is to develop the infrastructure to improve the capacity of the research community to rapidly and effectively conduct research utilizing technology to facilitate aging in place, with a special emphasis on people from underrepresented groups. The underrepresented groups include those living in rural areas, section 202 housing, PACE Program and others. The CART grant funding opportunity focuses on the following: 1) Algorithmic and other data aspects of in-home technologies; 2) Validation of devices and sensed data; 3) Protecting privacy and security for in-home technologies; 4) Making sensed data actionable for home healthcare; and 5) Methods for successful engagement by patients, physicians, caregivers, and payers. This initiative grew out of a visioning workshop held by the National Heart Lung and Blood Institute, National Science Foundation, and the Computing Community Consortium on the technology needed to enable successful aging in place (<http://www.cra.org/ccc/visioning/visioning-activities/aging-in-place>). The workshop discussion centered on four main topics: designing for the population, sensing innovations required to enhance health, using technology to identify and support transitions in health and utilizing new non-health technologies to support health in smart homes. Workshop panelists highlighted the challenges of talking across disciplines and the need to develop standard metrics that allow better collaborations among diverse disciplines. More information is available in the [White Paper](#). This announcement solicits proposals relevant to heart, lung, blood or sleep disorders. Technologies for cardiovascular diseases are of interest, for example, because cardiovascular diseases account for over 17% of total health care dollars spent nationwide. This work is needed before the potential benefits of these devices can be fully leveraged in a health care system.

Project Goals

This contract solicitation will support the testing and validation of existing technologies within the context of the CART Demonstration Project being developed under a separate grant award ([RFA-AG-16-021](#)). The trans-agency CART Demonstration Project seeks to develop and test the feasibility of a research infrastructure supporting in-home care utilizing innovative technology targeted to reduce hospitalizations, emergency room visits or admissions to a nursing home for older populations. After iterative testing of in-home cardiovascular, respiratory, hematological, or sleep technologies, the results will be compiled and study outcomes assessed with the potential for adoption in future phases of the CART Programs.

Phase I Activities and Expected Deliverables

All proposals submitted under this topic must provide evidence that significant development milestones (detailed below) for a specific remote/mobile/wireless or other technology or system have already been achieved to demonstrate readiness for Phase II SBIR contract. In addition, the proposed technologies must be compatible with

the CART platform requirements. These milestones will be evaluated in addition to standard review criteria for all submissions. The following milestones are expected to be completed during Phase I prior to the start of a Phase II award, or should be demonstrated prior to submission of a Direct to Phase II proposal.

- Provide evidence that a working prototype, including all major functional components of the technology, is ready for formal validation in a Phase II SBIR project with minimal further development other than that required to perform the validation or outcomes research.
- Provide the process for installing and monitoring the technology installed for CART homes (approximately 5-10 homes and possibly more).
- 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.

Phase II Activities and Expected Deliverables

- Evaluate specific IT customization requirements specified by the CART grant funding opportunity ([RFA-AG-16-021](#)) 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. This will be done according to the CART specifications. The CART specifications will be developed within a year of the CART grant award and will require collaboration with the small business partner awarded a contract.
- Test the integration of the technology into the target clinical setting, health system or service, or other relevant software environment in preparation for validation. This may occur as an iterative process.
- Provide a report documenting the results of system testing, validation, 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.

Provide a report including the following at a minimum:

- Appropriate human subjects protection / IRB submission packages and documentation of approval for your research plan;
- 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 in collaboration with the CART collaborators 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 for the technology used in the CART home.

This small-scale, path-building work requires significant economies of effort and the basic organizational operations and execution responsibilities for the entire project will need to be shared between the CART and small business collaborators. The small business contractor will contribute and participate in the CART committees and provide feedback to the committees based on the technologies proposed. In addition, the small business contractor will fully comply or negotiate the CART requirements for testing and validation of the technologies proposed.

099 Inhalational 5A Apolipoprotein A-I Mimetic Peptide for the Treatment of Asthma (SBIR-TT)

Fast-Track proposals will be accepted.

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

Number of anticipated awards: 2

Budget (total costs):

Phase I: up to \$225,000 for up to 12 months

Phase II: up to \$1,500,000 for up to 24 months

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Summary

New treatments are needed for severe asthmatics who do not respond to standard therapy with inhaled steroids, especially those with a “type 2 low” phenotype, such as individuals with neutrophil-predominant inflammation. This solicitation is for the development and early commercialization of an inhalational formulation of the 5A apolipoprotein A-I (apoA-I) mimetic peptide that can be administered to asthmatic subjects in Phase I clinical trials and subsequently developed into a new treatment for severe asthma.

ApoA-I is the major protein component of high-density lipoproteins, which mediates reverse cholesterol transport out of cells by interacting with the ATP-binding cassette subfamily member 1 (ABCA1). ApoA-I also has anti-inflammatory, anti-oxidant, and immunomodulatory properties. NHLBI investigators have shown that systemic administration of the 5A apoA-I mimetic peptide, which is a bi-helical peptide that recapitulates the α -helical structure of apoA-I and mediates reverse cholesterol transport out of cells by interacting with ABCA1, attenuates the induction of airway inflammation, mucous cell metaplasia, and airway hyperresponsiveness in house dust mite (HDM)-challenged mice. In addition, they have shown that apoA-I has a protective effect in allergic asthma. *ApoA1*-knockout mice, which were sensitized and challenged with ovalbumin (OVA), have increased neutrophilic airway inflammation that was primarily mediated by increased G-CSF expression, with associated increases in type 1 (IFN- γ , TNF- α) and Th17 (IL-17A) cytokines. The increased neutrophilic airway inflammation in the OVA-challenged *ApoA1*-knockout mice was inhibited by intranasal administration of the 5A apoA-I mimetic peptide. Lastly, serum apoA-I levels are positively correlated with FEV₁ in atopic asthmatic subjects, which suggests that circulating apoA-I may improve airflow obstruction. These murine and human translational studies serve as the conceptual basis for developing the 5A apoA-I mimetic peptide into a novel inhalational treatment for severe asthma.

Project Goals

The overall goal of this project is to prepare, in both manufacturing processes and preclinical evaluation, an inhalational 5A apoA-I mimetic peptide that will be the subject of a future Investigational New Drug (IND) application to the US Food and Drug Administration (FDA) focused on the treatment of type 2 low phenotype asthma patients, such as those with neutrophil-predominant inflammation. Successful submission and allowance to proceed of the IND will enable the company to collaborate on the conduct of a clinical trial with intramural clinicians at the NIH Clinical Center, at the company’s discretion. During review, preference will be given to companies or teams with a demonstrated prior ability to successfully bring either a peptide therapeutic or an inhalational therapeutic to, at a minimum, Phase I clinical studies in the US.

Additional Project Information

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 (DIR) 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 provision of 5A apoA-I mimetic peptide for SBIR Phase I comparability studies, experimental designs and 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 NHLBI Licensing and Patenting Manager: Cristina Thalhammer-Reyero; thalhamc@nih.gov; (301) 435-4507. 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

Sethi AA, Stonik JA, Thomas F, Demosky SJ, Amar M, Neufeld E, Brewer HB, Davidson WS, D'Souza W, Sviridov D, Remaley AT. Asymmetry in the lipid affinity of bihelical amphipathic peptides. A structural determinant for the specificity of ABCA1-dependent cholesterol efflux by peptides. *J Biol Chem* 2008;283:32273-32282. <http://www.jbc.org/content/283/47/32273.long>

Amar MJ, D'Souza W, Turner S, Demosky S, Sviridov D, Stonik J, Luchoomun J, Voogt J, Hellerstein M, Remaley AT. 5A apolipoprotein mimetic peptide promotes cholesterol efflux and reduces atherosclerosis in mice. *J Pharmacol Exp Ther* 2010;334:634-641. <http://jpet.aspetjournals.org/content/334/2/634.long>

Tabet F, Remaley AT, Segaliny AI, Millet J, Yan L, Nakhla S, Barter PJ, Rye KA, Lambert G. The 5A apolipoprotein A-I mimetic peptide displays anti-inflammatory and anti-oxidant properties in vivo and in vitro. *Arterioscler Thromb Vasc Biol* 2010;30:246-252. <http://atvb.ahajournals.org/content/30/2/246.long>

Yao X, Dai C, Fredriksson K, Dagur PK, McCoy JP, Qu X, Yu ZX, Keeran KJ, Zywicke GJ, Amar MJ, Remaley AT, Levine SJ. 5A, an apolipoprotein A-I mimetic peptide, attenuates the induction of house dust mite-induced asthma. *J Immunol* 2011;186:576-583. <http://www.jimmunol.org/content/186/1/576.long>

Dai C, Yao X, Keeran KJ, Zywicke GJ, Qu X, Yu ZX, Dagur PK, McCoy JP, Remaley AT, Levine SJ. Apolipoprotein A-I attenuates ovalbumin-induced neutrophilic airway inflammation via a granulocyte colony-stimulating factor-dependent mechanism. *Am J Respir Cell Mol Biol* 2012;47:186-195. http://www.atsjournals.org/doi/abs/10.1165/rcmb.2011-0322OC?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed#.Vusaa-nVtNE

Barochia AV, Kaler M, Cuento RA, Gordon EM, Weir NA, Sampson M, Fontana JR, MacDonald S, Moss J,

Manganiello V, Remaley AT, Levine SJ. Serum apolipoprotein A-I and large high-density lipoprotein particles are positively correlated with FEV₁ in atopic asthma. *Am J Respir Crit Care Med* 2015;191:990-1000. http://www.atsjournals.org/doi/abs/10.1164/rccm.201411-1990OC?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed#.VusakunVtNE

Issued Patents, expiring 10/14/2025: NIH Reference Number E-114-2004/0 (<https://www.ott.nih.gov/technology/e-114-2004>)

- US 7,572,771, issued August 11, 2009;
- US 8,071,746, issued December 6, 2011;
- US 8,148,323, issued April 3, 2012;
- EP 05815961.7, issued May 26, 2010;
- JP 2007-536912, issued September 21, 2012

Phase I Activities and Expected Deliverables

A Phase I award should be used to demonstrate that a comparable 5A apoA-I mimetic peptide can be synthesized and attenuate allergen-induced airway inflammation when administered by a pulmonary route in a pre-clinical asthma model.

The specific deliverables would be:

- Synthesis of a non-GMP grade 5A apoA-I mimetic peptide for comparability studies with the 5A peptide that was previously utilized by NHLBI investigators. NHLBI investigators can provide reference test material for comparability studies.
- Dose ranging animal studies will be performed to reproduce experiments showing that the 5A apoA-I mimetic peptide significantly suppresses house dust mite (HDM)-induced airway inflammation. Three doses of the 5A apoA-I mimetic peptide or control peptide, 0.1, 1, and 10 mg/kg, in 10 µl of saline, will be administered by pulmonary delivery, 5 days per week for 4 weeks and compared to an untreated group that receives pulmonary delivery of the vehicle alone (e.g., saline). Inhibition of airway inflammation in HDM-challenged mice by pulmonary delivery of the 5A apoA-I mimetic peptide will be assessed by quantifying the number of eosinophils in bronchoalveolar lavage fluid. A greater than 25% reduction will be considered significant. NHLBI investigators had previously sensitized and challenged A/J mice by intranasal instillation of 25 µg of HDM in 10 µl of saline, 5 days per week, for 4 weeks and concurrently administered either the 5A apoA-I mimetic peptide (1 mg/kg/day) or a control peptide (that represented the scrambled sequence of an apolipoprotein E mimetic peptide). The 5A apoA-I mimetic peptide should be delivered via a pulmonary route in the morning and the HDM should be administered in the afternoon. NHLBI investigators performed three independent experiments with 10 mice per group (*J Immunology*, 2011, 186: 576).

Phase II Activities and Expected Deliverables

A Phase II award should be used to develop an inhaled formulation of the 5A apoA-I mimetic peptide for future use in human clinical trials. In addition, the deliverables will include stability testing of the inhaled formulation of the 5A apoA-I mimetic peptide and early pre-clinical animal studies. These deliverables will initiate safety testing and regulatory development of an inhaled formulation of the 5A apoA-I mimetic peptide.

The specific deliverables would be:

- Generation and synthesis of an inhaled GMP formulation of both the 5A apoA-I mimetic peptide and control peptide.
- Development and validation of GLP-bioanalytical test methods for the inhaled formulation of the GMP-grade 5A apoA-I mimetic peptide.
- GLP stability testing of the inhaled formulation of the GMP-grade 5A apoA-I mimetic peptide. The awardee should have expertise in peptide chemistry and analysis and devise a plan that adequately assesses

stability of the α -helical structure of the 5A apoA-I mimetic peptide, demonstrates that no chemical changes have occurred (e.g., hydrolysis, deamidation, oxidation, etc.), as well as performs cGMP release and serum stability assays.

- GLP toxicity studies to establish the NOAL (no observed adverse effect level) and MTD (maximum tolerated dose) of the inhaled 5A apoA-I mimetic peptide in the rat using GMP-grade 5A apoA-I mimetic peptide and appropriate controls (e.g., vehicle, control peptide).
- Acute GLP respiratory and systemic PK/TK studies in rats (males and females) using the GMP-grade 5A apoA-I mimetic peptide and appropriate controls (e.g., vehicle, control peptide).
- Daily repeat GLP dosing respiratory and systemic PK/TK studies in rats (male and female) using the GMP-grade 5A apoA-I mimetic peptide for a minimum of 14 days and appropriate controls (e.g., vehicle, control peptide).
- Generation of a development plan to support a successful IND application to the FDA for an inhaled formulation of the 5A apoA-I mimetic peptide. The development plan will address: (i) CMC manufacturing of the inhaled formulation of the 5A apoA-I mimetic peptide, (ii) pre-clinical studies, and (iii) Phase I clinical trials. The development plan will be discussed at a pre-IND meeting with the FDA and modified as necessary.

Offerors are encouraged to consider the NHLBI [Phase IIB Bridge](http://1.usa.gov/1q9yTyP) (<http://1.usa.gov/1q9yTyP>) and [Phase IIB Small Market Award](http://1.usa.gov/1v0Wxn1) (<http://1.usa.gov/1v0Wxn1>) programs to support additional development beyond Phase II.

100 MRI Myocardial Needle Chemoablation Catheter

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 \$300,000 for up to 18 months

Phase II: up to \$2,000,000 for up to 24 months

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Summary

Myocardial catheter ablation is commonly performed for the treatment of rhythm disorders, using radiofrequency energy, typically guided using X-ray and/or electromagnetic positioning. Available non-surgical technologies do not allow clear depiction of myocardium being ablated. MRI-guided needle catheter chemo-ablation, for example using focal injection of caustic agents such as acetic acid doped with MRI contrast agents, may allow targeted disruption of small segments of myocardium in the treatment of rhythm disorders such as ventricular tachycardia and in the treatment of structural heart disease such as hypertrophic cardiomyopathy. Preclinical feasibility of at least two different MRI injection needle catheter systems has been demonstrated and published for the application of direct endomyocardial cell injection, including by our labs. No commercial options are available.

An MRI myocardial needle injection catheter system may enable a new family of non-surgical cardiovascular treatments for rhythm and structural heart disease.

Project Goals

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

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.

Proposals must include a detailed description of the regulatory strategy, including plans for a pre-submission meeting with the US Food and Drug Administration (FDA) in Phase I. Offerors must include key personnel on the project with appropriate and relevant regulatory experience.

Offerors are advised to plan 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 support the development and testing of a myocardial injection needle prototype. The contracting DIR lab is willing to provide feedback about design at all stages of development. The contracting DIR lab will test the final deliverable device for success in vivo in swine.

Specific Phase I deliverables include:

- 9Fr or smaller.
- Suitable for use via femoral artery retrograde across aortic valve and via jugular and femoral venous access to the right sided cardiac chambers.
- A needle that can be delivered to multiple endomyocardial targets, achieve stable positioning, and that can penetrate the myocardium without causing significant harm while delivering injectate. Solutions should allow a user-selected injection depth and may be spring-loaded or offer alternative penetration capabilities.
- Sufficient radius of curvature to access all parts of left ventricle endocardial surface including left ventricle outflow tract, and all parts of right ventricle including septum and outflow tract. Suitable solutions incorporate deflectable catheters with extensible needle elements; alternative embodiments may use multiple coaxial curved catheters that can be torqued, or other approaches.
- Visibility during MRI: (1) “Active” design incorporating MRI receiver coils for mandatory shaft and tip and needle visibility during MRI; (2) Receiver coils should be conspicuous under MRI using “profiling” or “tracking” techniques as described in publications from the contracting NHLBI DIR laboratory (See Saikus CE and Lederman RJ, JACC Cardiovascular Imaging, 2009, <http://www.pubmed.gov/19909937>); (3) The “active” receiver coils must operate for testing on a Siemens *Aera* 1.5T MRI scanner installed at contracting NHLBI DIR laboratory.
- There should be a distinct imaging signature to confirm needle deployment. One suitable option is a separate receiver channel for the needle.
- Simultaneous ability to record intracardiac electrograms from the needle site, either bipolar or unipolar, including safe electrode transmission lines.
- Free from clinically-important heating (2°C at 1W/kg SAR) during continuous MRI at 1.5T.
- Proposals for alternative visualization and heat-mitigation strategies, such as “active” or “inductively-coupled” receiver coils, are encouraged, but must operate for testing on a Siemens *Aera* 1.5T MRI scanner installed at the contracting NHLBI DIR laboratory.
- A comprehensive report of test results, including in vivo test results if not performed at NHLBI.
- Sufficient devices to test the final device in vivo at the contracting NHLBI DIR laboratory.
- A detailed report of pre-submission interactions with the FDA Center for Devices and Radiological Health (CDRH) identifying requirements for Investigational Device Exemption (IDE) development under Phase II, including meeting minutes, if available.

Consideration for transition to Phase II funding will include regulatory progress toward US market access. Consideration may include the status of the contractor’s interactions with the FDA. NHLBI encourages contractors to consider requesting designation to the FDA’s Expedited Access for PMA Devices (EAP) program (<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM393978.pdf>) during the Phase I award period.

Phase II Activities and Expected Deliverables

A Phase II award would allow mechanical and safety testing and regulatory development for the device to be used in human investigation, whether under Investigational Device Exemption (IDE) or under 510(k) marketing clearance.

Activities in Phase II should align with the required testing and development milestones agreed upon with the FDA in Phase I. The contracting DIR lab offers to perform an IDE clinical trial at no cost to the awardee. IDE license or 510(k) clearance, along with twenty clinical investigational prototypes, would constitute the deliverable.

The offeror should provide clear project milestones that trigger review and payment, along with detailed research and development plans, risk analysis, and contingency plans.

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 such as animal explants.
- iteration for unexpected design or device failure.
- pre-submission meetings with FDA.
- chronic or acute GLP animal studies as required.
- 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.

Specific Phase II deliverables include:

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

101 Membranous Ventricular Septal Defect (pmVSD) Transcatheter Occluder System

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 \$400,000 for up to 21 months

Phase II: up to \$3,000,000 for up to 36 months

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Summary

Ventricular septal defect is the most common congenital heart defect. Membranous-type ventricular septal defect (pmVSD) accounts for over two thirds of ventricular septal defects, and approximately half require repair. Surgical repair is morbid, and may require two staged surgical procedures. No suitable device is marketed for transcatheter repair of pmVSD. Commercial development of catheter-based devices to treat structural heart disease in children is limited by the relatively small market size and the relatively large upfront costs.

The purpose of this solicitation is to support early-stage pre-clinical and clinical development of a transcatheter device system to treat pmVSD without surgery.

Project Goals

The goal of the project is to develop a device for percutaneous closure of membranous VSD in infants and children, with an acceptable low rate of complete heart block compared with surgical closure. 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.

Proposals must include a detailed description of the regulatory strategy, including plans for a pre-submission meeting with the US Food and Drug Administration (FDA) in Phase I. Offerors must include key personnel on the project with appropriate and relevant regulatory experience.

Offerors are advised to plan 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 support the development and testing of a pmVSD occluder prototype suitable for children and newborn infants. The NHLBI Division of Intramural Research laboratory offers to test a 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:

- A design specifically to achieve occlusion of membranous-type ventricular septal defects in children and newborn infants.
- The implant should accommodate a range of defects average diameters sized 2mm to 18mm, using multiple device sizes if necessary.
- The implant should be designed specifically to minimize or avoid conduction system injury that would risk immediate or late complete heart block.
- The implant should have mechanisms or a range of morphologies to avoid entrapment or distortion of the aortic valve or to avoid late injury to the aortic valve root or leaflets.
- The implant should be available with transmural or interventricular “neck” length and width dimension.
- The implant should conform to ventricular cavities without causing geometric distortion or obstruction of ventricular outflow tracts.
- The delivery system catheter outer diameter must be 9Fr or smaller and should be suitable for fully transcatheter repair without requiring surgical cardiac exposure.
- The implant and delivery system should avoid entrapment or early/late injury to tricuspid valve with attention to aneurysmal septal segments.
- The proposed solution should have a mechanism to assure proper orientation if that is important to the functionality of specific design.
- Designs amenable to both antegrade and retrograde delivery are desirable.
- The delivery system should secure against unplanned release.
- Proposals should include specific plans for operator recovery of the device if it embolizes after release.
- Implants must be MRI compatible so that cardiac function and flow can be measured unimpeded after implantation using MRI, and MRI conspicuity is desirable.
- The delivery system and implant must be conspicuous under the proposed image-guidance modality whether ultrasound or X-ray, and must be conspicuous under X-ray after release.
- The delivery system should be designed to mitigate hemodynamic embarrassment caused by interruption of tricuspid valve function during implant procedures.
- The device should accomplish acute or subacute occlusion without early or late thromboembolism, and proposals should specifically address these considerations.
- The system should be accompanied by a proposed robust methodology or device to select the appropriate device size.
- Build of a phantom for bench testing of the device design(s), retrieval tool, and size selection tool/methodology.

- The offeror must independently demonstrate satisfactory device performance in VSD, preferably pmVSD, *in vivo*.
- A comprehensive report of test results, including in vivo test results if not performed at NHLBI.
- A detailed report of pre-submission interactions with the FDA Center for Devices and Radiological Health (CDRH), indicating a sufficiently mature device and identifying requirements for Investigational Device Exemption (IDE) development under Phase II, including meeting minutes, if available.

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

Consideration for transition to Phase II funding will include regulatory progress toward US market access. Consideration may include the status of the contractor's interactions with the FDA. NHLBI encourages contractors to consider requesting designation to the FDA's Expedited Access for PMA Devices (EAP) program (<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM393978>) during the Phase I award period.

Phase II Activities and Expected Deliverables

In addition to meeting all requirements specified for Phase I, the Phase II award would allow mechanical and safety testing and regulatory development for the device to be used in human investigation. The NHLBI Division of Intramural Research laboratory offers but does not require to perform an IDE clinical trial at no cost to the awardee. Activities in Phase II should align with the required testing and development milestones agreed upon with the FDA in Phase I.

Complete IDE 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. For all purposes, a humanitarian device exemption (HDE) or an expedited Premarket Approval (PMA) would be considered responsive in place of IDE.

The offeror should provide clear project milestones that trigger review and payment, along with detailed research and development plans, risk analysis, and contingency plans. 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 validation and test plan, biocompatibility and sterility assessment and plan, design review, design freeze, design transfer to manufacturing.
- manufacturing plan.
- iterative ex vivo testing such as animal explants.
- iteration for unexpected design or device failure.
- pre-submission meetings with FDA.
- 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.

Offerors are encouraged to consider the NHLBI [Phase IIB Small Market Award](http://1.usa.gov/1v0Wxn1) (<http://1.usa.gov/1v0Wxn1>) program to support additional development beyond Phase II. The NHLBI Phase IIB Small Market Award provides up to an additional \$3M over 3 years, with an expectation that applicants secure independent third-party investor funds.

102 Transcatheter Occluder Device for Paravalvular Leaks

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 \$400,000 for up to 21 months;

Phase II: up to \$3,000,000 for up to 36 months

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Summary

Over fifty thousand prosthetic heart valves are implanted in the United States annually. A discrete fraction develop significant regurgitation around the implant site, related to technical dehiscence or poor seating related to calcification, friability, or infection. The problem affects both mitral and aortic valves, whether implanted surgically or via a transcatheter route. The problem persists especially after surgically implanted valves despite technical refinement of transcatheter devices. Paravalvular regurgitation manifests as congestive heart failure from volume overload, or hemolytic anemia from mechanical cell injury. Surgical revision confers high morbidity and mortality. A variety of nitinol cardiac occluder devices have been employed off-label, but most are poorly suited for the application and none achieve simple and reliable occlusion.

The purpose of this solicitation is to support early-stage pre-clinical and clinical development of a purpose-built transcatheter occluder device for paravalvular leaks, to address this important unmet need.

Project Goals

The goal of the project is to develop a device for percutaneous closure of paravalvular leak. First a prototype would be developed and tested in vitro. Ultimately a clinical-grade device would undergo regulatory development for clinical testing in the USA.

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.

Proposals must include a detailed description of the regulatory strategy, including a plan for a pre-submission meeting with the US Food and Drug Administration (FDA) in Phase I prior to the start of major engineering work or bench research. Offerors must include key personnel on the project with appropriate regulatory experience. Team members should have demonstrated experience with cardiovascular device product development, including permanent implants.

Offerors are advised to plan travel to NHLBI in Bethesda, Maryland, and are expected to plan for 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 support the development and testing of a catheter system for implantation of a paravalvular leak occluder. The offeror is expected independently to perform animal testing as needed to meet Phase I requirements.

Device requirements include:

- Up to 8Fr delivery system.
- Suitable to occlude regurgitation around surgically implanted aortic and mitral valve prostheses. Applicability to transcatheter valves is welcome.
- Ability to traverse complex geometry characteristic of paravalvular leaks.
- Ability to conform to complex and poorly visualized and highly variable regurgitant orifices.
- Demonstrating early hemostasis.
- Designs are encouraged that conform through bladder inflation or through expansion of superelastic materials or other novel approaches.
- Must be retrievable and removable before final implantation.
- Designs should avoid interference with function of the target prosthetic mechanical heart valves.
- Ability to reposition before final implantation is desirable.
- Low risk of embolization after implantation.
- Delivery designs are encouraged that retain delivery catheter position at the target (such as with a buddy guidewire) until conclusion of the procedure.
- Devices should be conspicuous during positioning and after final implantation, with attention to challenges imposed by metallic surgical valves.
- The devices should not impose an undue risk of thromboembolism and stroke after implantation.
- Implants should be MRI compatible so that cardiac function and flow can be measured unimpeded after implantation using MRI. MRI conspicuity is desirable.
- The delivery system and implant must be conspicuous under the proposed image-guidance modality whether ultrasound or X-ray, and must be conspicuous under X-ray after release.
- The system should be accompanied by a proposed robust methodology or device to select the appropriate device size.

Expected deliverables include:

- A detailed report of pre-submission interactions with the FDA Center for Devices and Radiological Health (CDRH), indicating a sufficiently mature device and identifying requirements for Investigational Device Exemption (IDE) development under Phase II, including meeting minutes, if available.
- A final prototype with phantom testing.

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

Consideration for transition to Phase II funding will include progress toward regulatory progress toward US market access. Consideration may include the status of the contractor's interactions with the FDA. NHLBI encourages contractors to consider requesting designation to the FDA's Expedited Access for PMA Devices (EAP) program (<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM393978>) during the Phase I award period.

Phase II Activities and Expected Deliverables

In addition to meeting all requirements specified for Phase I, the Phase II award would allow mechanical and safety testing and regulatory development for the device to be used in human investigation. The NHLBI Division of Intramural Research laboratory offers but does not require to perform an IDE clinical trial at no cost to the awardee. Activities in Phase II should align with the required testing and development milestones agreed upon with the FDA in Phase I.

Complete IDE 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. For all purposes, a humanitarian device exemption (HDE) or an expedited Premarket Approval (PMA) would be considered responsive in place of IDE.

The offeror should provide clear project milestones that trigger review and payment, along with detailed research and development plans, risk analysis, and contingency plans. Representative project milestones include, not necessarily sequentially:

- a device build and, if required, a 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 validation and test plan, biocompatibility and sterility assessment and plan, design review, design freeze, design transfer to manufacturing.
- manufacturing plan.
- iterative ex vivo testing such as animal explants.
- iteration for unexpected design or device failure.
- pre-submission meetings with FDA.
- modeling and fatigue study for chronic implant if required.
- chronic or acute GLP animal studies as required.
- 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.

Offerors are encouraged to consider the NHLBI [Phase IIB Bridge](http://1.usa.gov/1q9yTyP) (<http://1.usa.gov/1q9yTyP>) and [Phase IIB Small Market Award](http://1.usa.gov/1v0Wxn1) (<http://1.usa.gov/1v0Wxn1>) programs to support additional development beyond Phase II. The NHLBI Phase IIB programs provide up to an additional \$3M over 3 years, with an expectation that applicants secure independent third-party investor funds.

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>.

040 Effective Targeted Delivery of RNA-based Vaccines and Therapeutics

Direct to Phase II will be accepted

Fast Track will **not** be accepted

Number of anticipated awards: 1-2

Budget (total costs):

Phase I: \$300,000 for up to one year

Phase II: \$2,000,000 for up to 3 years

Background:

RNA-based vaccines and therapeutics have emerged as great promise for HIV prevention and treatment, respectively. However, many obstacles still need to be overcome, in particular RNA instability, manufacturing problems, and clinically relevant delivery mechanisms of RNA into target cells.

RNA vaccine approaches have some advantages in relation to other vaccine technologies; they can be delivered directly into the cytoplasm and do not require nuclear localization to generate expression. Improvements of methods for mRNA synthesis and stabilization and development of improved self-amplifying RNAs have recently yielded promising results. RNA approaches also stimulate the host's innate defense system, in part through activation of the TLR pathways that recognize single and double stranded RNAs.

Furthermore, RNA-based therapeutics have shown the potential to silence HIV effectively upon direct transfection *in vitro*, but delivery into cells *in vivo* is still unsatisfactory. Vector-based (lentivirus, adeno-associated virus) delivery to quiescent cells has proven inefficient, and the vectors themselves pose a risk to the host. To enhance stability and to confer vehicle-free delivery, RNA-based drugs have been chemically modified to improve their properties. Progress was also made in chemical-based delivery strategies, e.g., liposomes, molecular-sized chemical conjugates, and supramolecular nanocarriers. An additional advantage is that RNA can be produced *in vitro* in a cell-free manner, avoiding safety and manufacturing issues associated with cell culture. Despite these advances, nucleic acids *per se* are relatively large, negatively charged polymers, and significant clinical challenges from the standpoint of delivery to cells still persist.

Project Goals:

The primary goal of this contract solicitation is to encourage small businesses to develop improved platform technologies for the delivery of RNA into specific cells and tissues to improve the efficacy of HIV vaccines or therapeutics. Examples of HIV RNA vaccines include, but are not limited to mRNA and self-amplifying RNAs. Examples of RNA therapeutics include small interfering RNA (siRNA), microRNA (miRNA), microRNA antagonists, aptamers, messenger RNA (mRNA), splice-switching oligonucleotides, antisense oligonucleotides, and plasmid or other circular DNAs encoding messenger RNAs and transcription regulatory sequences. To enhance the efficacy of traditional HIV vaccines and therapeutics, combinations of cytokines, adjuvants, broadly neutralizing monoclonal antibodies, immune checkpoint inhibitors, etc. can also be co-delivered in mRNA form.

The short-term goal of this project is to perform feasibility studies for the development and use of delivery mechanisms for RNA-based HIV vaccines and therapies. The long-term goal of this project is to enable a small business to bring fully developed delivery systems for RNA-based HIV vaccines and therapies to the clinic and eventually to the market.

Phase I activities may include:

- Design and test in vitro small scale delivery strategies for RNA-based HIV vaccines or therapeutics, including exosomes, nanoparticles, liposomes, viral vectors, condensates, carriers, or delivery devices.
- Assess potency and stability of RNA-based HIV vaccines or therapeutics.
- Improve RNA stability through chemical modifications.
- Perform proof-of-concept HIV animal model studies for assessment of organ toxicity, HIV immune responses, innate immune responses (e.g., Toll-like receptor activation), and pharmacokinetic/pharmacodynamic studies, if applicable.
- For RNA-based therapeutics:
 - Evaluate off-target effects in cell lines and primary PBMC.
 - Develop strategies for eliminating off-target effects, including software tools for re-designing RNAs.

Phase II activities may include:

- Scale-up manufacturing of RNA-based vaccines or therapeutics
- IND-enabling studies, preferably in consultation with the FDA
- For RNA-based vaccines:
 - Test improved delivery mechanism for efficacy and mechanism of action in animal models of HIV.
- For RNA-based therapeutics:
 - Demonstrate that the RNA delivery approach is effective and non-toxic in animal models for HIV.
- When appropriate, demonstration of superiority of developed technology compared to other delivery mechanisms.

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.

041 Simplified Sequencing for TB Drug Resistance Testing

Direct to Phase II will be accepted

Fast Track will be accepted

Number of anticipated awards: 1-2

Budget (total costs):

Phase I: up to \$600,000 per year for up to two years;

Phase II: up to \$3,000,000 for up to 3 years

Background:

People living with HIV/AIDS have increased mortality when infected with MDR and XDR TB, worsened by delays starting an appropriate treatment regimen due to poor access to drug sensitivity testing (DST). While the WHO recommends routine DST at each new presentation of TB, only 12% of newly infected individuals globally had access to a resistance test in 2014. Poor laboratory infrastructure and high cost have been cited as primary factors blocking access to TB resistance testing. Current WHO-approved testing approaches, such as GeneXpert and line probe assays at present detect only a limited set of resistance mutations relevant for up to two TB drugs. Additionally, current molecular tests have been shown to have lower sensitivity in populations with a high HIV burden, due to the lower bacillary load among HIV/TB co-infected patients and higher prevalence of smear negative disease.

Sequencing-based diagnostics hold great promise for the establishment of low-cost, simplified TB drug resistance testing, capable of determining resistance to a broad range of drugs and in diverse TB strains. Crucially, the data generated from sequencing-based diagnostics can concurrently be used for individualizing therapy as well as allow surveillance of the prevalence and emergence of resistance, and accurately determining TB transmission patterns in a population.

In order to improve the quality of patient care through accurate testing, while concurrently enabling global surveillance of resistance patterns, a simplified sequencing device integrated with an accurate sequencing analysis software platform, is needed.

Project goal:

The goal of this project is to develop a low-cost, easy-to-use platform for TB drug resistance testing and surveillance for settings with high HIV prevalence and limited information technology and laboratory resources. The resulting platform must rapidly and accurately generate sequence data from smear negative sputum to enable the prediction of resistance to all first and second line anti-TB drugs while performing highly accurate analysis of the sequence data to produce clinically actionable resistance reports.

Phase I activities:

- Develop a technique allowing simultaneous sequencing from a single sputum sample (patient sample or spiked) of at least 40 key genes and genetic regions associated with resistance to at least the following tuberculosis drugs: isoniazid, rifampin, ethambutol, pyrazinamide, kanamycin, amikacin, capreomycin, streptomycin, moxifloxacin, ofloxacin, para-amino salicylic acid, cycloserine ethionamide/protonamide, terizidone.
- Refine technique to generate accurate sequencing data on first and second line drugs from single smear negative culture positive sputum sample.

Phase II activities:

- Develop a self-contained device for settings with limited laboratory resources incorporating the following :
 - Simple operation requiring few steps, and minimal operator training
 - No need for external electricity (battery power can be proposed)
 - Short per-sample running time with high sample throughput
 - Sufficient accuracy to allow clinically relevant results
 - Operate with no significant biosafety concerns,
 - Software to interpret data to provide immediate clear results for susceptibility to TB drugs listed above with no need for clinician interpretation, aligning with global efforts to standardize reporting language,
 - Ability to upload sequencing data to central data repository

042 Qualitative HIV RNA Home Test

Direct to Phase II proposals will be accepted

Fast-Track proposals will **not** be accepted

Number of anticipated awards: 1-2

Budget (total costs):

Phase I: up to \$300,000 for up to 1 year

Phase II: up to \$3,000,000 for up to 3 years

Background:

Approximately 37 million people are living with HIV, with 15 million accessing antiretroviral therapy (ART). Recently revised WHO guidelines recommend that all people diagnosed with HIV be offered ART at any CD4 count, which will result in many more people on ART. Current ART regimens are very potent and reduce HIV viral load in blood to undetectable levels in most patients, which in turn significantly reduces mortality and morbidity and reduces transmission of HIV. However, viral rebound can occur through non-adherence or resistance. In either case, it is critical to identify viral rebound as early as possible in order to avoid drug resistance and clinical progression. The ability to easily monitor HIV plasma RNA in blood at home would help identify viral rebound early and allow intervention. Ideally, HIV RNA testing at home should be as easy as glucose monitoring for diabetics. If priced appropriately, this technology may be useful for home monitoring in resource limited settings where patients live far from the clinical care site. Such a technology could also be used for home monitoring of individuals enrolled in clinical trials involving a treatment interruption who need to have their viral load monitored

very frequently, in-home monitoring for individuals using pre-exposure prophylaxis (PrEP), where HIV infection must be detected very early to avoid resistance to the drugs in the PrEP regimen, and in-home monitoring for high risk individuals to allow early detection and early treatment, which may lead to smaller HIV reservoirs and reduced transmission.

Project goal:

The goal of this solicitation is to develop a method for HIV RNA home testing. The method need not be quantitative, but should detect HIV RNA with a sensitivity of at least 98% and specificity of at least 98% if the viral load is 1000 HIV RNA copies per ml of blood or higher. The proposed method must include a procedure for obtaining finger stick blood such that the blood can be easily manipulated and transferred to the test medium. Proposals can include the use of a small handheld unit to be used with individual test strips or cartridges, but device free, disposable units are preferred. Test units may require refrigeration, but stability at room temperature is preferable. All necessary materials should be supplied with the test and no additional materials should be required. The amount of handling required by the operator should be suitable for home testing by untrained individuals.

Phase I activities may include:

- Development of simple methods for: a) obtaining finger stick blood and easily transferring blood or plasma to the test medium, b) detecting HIV plasma RNA, but not cell associated HIV DNA and RNA, with a cutoff of 1000 RNA copies per ml of blood, c) providing an easily readable output. (see additional specifications above)
- Combining the methods into an inexpensive, easy to use, integrated assay platform (up to \$100 for handheld unit, up to \$10 per test unit/cartridge)
- Initial testing on laboratory isolates, including several HIV subtypes

Phase II activities may include:

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

043 Adjuvant Development

Fast-Track proposals will **not** be accepted.

Direct-to-phase II proposals will be accepted

Number of anticipated awards: 1-3

Budget (total costs):

Phase I: \$225,000 for up to 1 year

Phase II: \$1,500,000 for up to 3 years

Background:

Adjuvants stimulate innate and/or adaptive immune responses. For the purpose of this SBIR, adjuvants are defined according to the U.S. Food and Drug Administration (FDA) as “agents added to, or used in conjunction with, vaccine antigens to augment or potentiate (and possibly target) the specific immune response to the antigen.” Currently, only three adjuvants have been licensed as components of vaccines in the United States - aluminum hydroxide/aluminum phosphate (alum), 4'-monophosphoryl lipid A (MPL), adsorbed to alum as an adjuvant for an HPV vaccine, and the oil-in-water emulsion MF59 as part of the Flud influenza vaccine for people age 65 years and older. Additional efforts are needed to more fully develop the potential capabilities of promising adjuvants, particularly for special populations such as the young, elderly and immune-compromised. In addition, adjuvants may facilitate the development of immunotherapeutics for immune-mediated diseases, such as allergen immunotherapy.

Project Goal:

The goal of this project is to accelerate pre-clinical development and optimization of a single lead adjuvant candidate or a select combination-adjuvant for prevention of human disease caused by non-HIV infectious pathogens. For this solicitation, a combination-adjuvant is defined as a complex exhibiting synergy between individual adjuvants, such as: overall enhancement of the immune response; potential for adjuvant-dose sparing to reduce reactogenicity while preserving immunogenicity; or broadening of effector responses, such as through target-epitope spreading or enhanced antibody avidity. The adjuvant products supported by this program must be studied and further developed toward human licensure with currently licensed or new investigational vaccines, and may not be developed as stand-alone agents.

Phase I Activities

Depending on the developmental stage at which an adjuvant is entered into the

Program, the offeror may choose to perform one or more of the following:

- Optimization of one candidate compound for enhanced safety and efficacy. Studies may include:
 - Structural alterations of the adjuvant or modifications to formulation; or
 - Optimization of heterologous prime-boost-regimens.
- Development of novel combinations of previously described individual adjuvants, including the further characterization of an adjuvant combination previously shown to enhance immune responses synergistically.
- Establishment of an immunological profile of activity and immunotoxicity that can be used to evaluate the capability of the adjuvant to advance to human testing.
- Preliminary studies in a suitable animal model to evaluate the protective efficacy of a lead adjuvant:vaccine or adjuvant/immunotherapeutic combination.
- Analysis of vaccine efficacy through the use of a combination adjuvant and studies to evaluate the safety profile of the combination adjuvant:vaccine or adjuvant/immunotherapeutic formulation.

Phase II Activities

Extended pre-clinical studies that may include IND-enabling studies such as:

- Additional animal testing of the lead adjuvant:vaccine or adjuvant/immunotherapeutic combination to evaluate immunogenicity, protective efficacy and immune mechanisms of protection.
- Pilot lot or cGMP manufacturing of adjuvant or adjuvant:vaccine or adjuvant/immunotherapeutic compound.
- Advanced formulation and stability studies.
- Toxicology testing.
- Establishment of quality assurance and quality control protocols.
- Pharmacokinetics/absorption, distribution, metabolism and excretion studies.

This SBIR will not support:

- The further development of an adjuvant that has been previously licensed for use with any vaccine.
- The design and conduct of clinical trials (see <http://www.niaid.nih.gov/researchfunding/glossary/pages/c.aspx#clintrial> for the NIH definition of a clinical trial).
- The discovery and initial characterization of adjuvant candidates.
- The development of adjuvants or vaccines to prevent or treat cancer.
- Development of Platforms, such as vehicles, or Delivery Systems that have no immunostimulatory activity themselves.

- The development and/or optimization of a pathogen-specific vaccine component.

044 Vaccine Adjuvant Screening and Discovery

Fast-Track proposals will **not** be accepted.

Direct-to-phase II proposals will be accepted

Number of anticipated awards: 1-3

Budget (total costs):

Phase I: \$225,000 for up to 1 year

Phase II: \$1,500,000 with appropriate justification by the applicant for up to 3 years

Background:

Vaccine adjuvants stimulate innate and/or adaptive immune responses. For the purpose of this SBIR, adjuvants are defined according to the U.S. Food and Drug Administration (FDA) as “agents added to, or used in conjunction with, vaccine antigens to augment or potentiate (and possibly target) the specific immune response to the antigen.” Currently, only three adjuvants have been licensed as components of vaccines in the United States - aluminum hydroxide/aluminum phosphate (alum), 4'-monophosphoryl lipid A (MPL), adsorbed to alum as an adjuvant for an HPV vaccine, and the oil-in-water emulsion MF59 as part of the Flud influenza vaccine for people age 65 years and older. The gaps that need to be addressed by new adjuvants include improvements to existing, insufficiently efficacious vaccines (*e.g.*, the acellular pertussis vaccine), and development of vaccines: for emerging threats (*e.g.*, Ebola outbreaks); for special populations that poorly respond to existing vaccines (*i.e.*, elderly, newborns/infants, immunosuppressed patients); or to treat/prevent immune-mediated diseases (*e.g.*, allergen immunotherapy, autoimmunity, transplant rejection). Recent advances in innate immunity have provided a significant number of new putative targets for vaccine adjuvants. Simultaneously, progress is slowly being made in the identification of *in vitro* correlates of adjuvanticity which allows the design of *in vitro* screening assays to discover novel adjuvant candidates in a systematic manner-

Project Goal:

The objective of this program is to support the screening for new adjuvant candidates, their characterization and early-stage optimization.

Phase I Activities include, but are not limited to:

- Optimize and scale-up screening assays to identify new potential adjuvant candidates
- Create targeted libraries of putative ligands of innate immune receptors
- Pilot screening assays to validate HTS approaches for identifying adjuvant candidates
- Develop *in silico* screening approaches to pre-select adjuvant candidates

Phase II Activities include, but are not limited to:

- High-throughput screening of compound libraries and confirmation of adjuvant activity of leads compounds
- Confirmatory *in vitro* screening of hits identified by HTS or *in silico* prediction algorithms
- Optimization of lead candidates identified through screening campaigns through medicinal chemistry and/or formulation
- Screening of adjuvant candidates for their usefulness in special populations, such as the use of cells from cord blood or infants and/or elderly/frail humans or animal models representing human special populations

045 Database Resources Integration

Fast-Track proposals will **not** be accepted

Direct-to-phase II proposals will 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 NIAID Division of Allergy, Immunology, and Transplantation (DAIT) has funded the following bioinformatics resources to meet the needs of immunology research community for data sharing, knowledge dissemination, standard development and integrative analyses:

- ImmPort (<https://immport.niaid.nih.gov/>): a unique resource primarily for public data sharing of immunological studies funded by DAIT
- ImmuneSpace (<https://www.immunospace.org/>): a data management and analysis platform where datasets from the Human Immunology Project Consortium (HIPC) program can be easily explored and analyzed using state-of-the-art computational tools
- ITN TrialShare (<https://www.itntrialshare.org/>): a web portal of the Immune Tolerance Network (ITN) that shares information about ITN's clinical studies and specimen, as well as data and analysis code underlying the consortium's publications
- IEDB (<http://www.iedb.org/>): a bioinformatics resource that offers easy searching of experimental data characterizing antibody and T cell epitopes, including epitopes involved in infectious disease, allergy, autoimmunity, and transplant, studied in humans, non-human primates, and other animal species. It also hosts tools for epitope analyses
- ImmGen (<https://www.immgen.org/>): a public resource that provides a complete microarray analysis of gene expression and regulation in the immune system of the mouse

While the data, knowledge and tools provided by these resources have been serving the research community well, there is a growing need for a search and retrieval system (e.g., NCBI Entrez, Google-like interface) that enables integrated access to these resources. The development of such system, supplemented with a set of data integration standards and tools, will position the research community to better utilize existing databases for immunology research.

Project Goal

The goal of this project is to support the development of a data retrieval and discovery system for integrated access to DAIT funded bioinformatics resource for data query, knowledge dissemination and integrative analyses.

Phase I Activities

Phase I activities should focus on providing evidence that bioinformatics methods have been developed effectively and can be applied to the data, information, knowledge and tools across the identified DAIT database resources. The offeror may choose to perform the following:

1. Prototyping an integrated retrieval system that has a user interface to enable searching of the identified databases. The system should support text searching using simple Boolean queries, downloading of data in various formats and linking of data, information and tools between these databases based on inferred relationships.
2. Implementation of data and metadata standards to facilitate the transformation and integration of data from the identified databases into analyzable datasets for immune modeling and biomarker prediction.
3. Implementation of bioinformatics pipelines to enable interoperation of data and tools of these databases.

Phase II Activities

Extend Phase I to include the following:

1. Production implementation of the bioinformatics systems prototyped during Phase I.

2. Add functionalities and capacities of these systems based on research community's needs.
3. Integration of more public databases relevant to immunology research.
4. Adoption of new integrative tools to support discovery and validation of biomarkers across multiple types of molecular data, clinical phenotypes, animal and cell line models.

This SBIR will not support:

The design and implementation of a data warehouse.

046 Rapid Point-of-Care Diagnostics to Detect Serologic Status of Individuals for Select Viral Infections

Fast-Track proposals will be accepted.

Direct-to-Phase II proposals will 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:

Congenital infection with cytomegalovirus (CMV) is one of the leading non-genetic causes of birth defects, affecting approximately one in every 150 children born in the U.S., and is a leading cause worldwide of sensorineural hearing loss in babies with or without other symptoms of congenital infection. Neonates infected with herpes simplex virus (HSV) manifest with one of three disease classifications (disseminated disease; central nervous system disease; or skin, eye, and mouth disease) with varying degrees of morbidity and mortality, depending on standards of medical practice across the world. The development of vaccines for CMV and HSV pose significant challenges for vaccine manufacturers. One of these challenges is how to efficiently identify and enroll eligible study subjects in large Phase III efficacy trials. Phase III studies would need to enroll thousands of seronegative subjects, and because the seroprevalence rates for CMV and HSV are high in the target population for vaccination (women of childbearing potential), this will require the screening of tens to hundreds of thousands of potential volunteers. The availability of rapid, accurate and cost-effective POC serodiagnostics would de-risk the development of CMV and HSV vaccines by vastly improving the logistics of enrollment for these large Phase III studies. Specifically, a rapid POC test that could be utilized during initial study screening visits would permit the efficient identification and enrollment of potential vaccinees. In addition, should a vaccine be licensed for seronegative women only, the POC test would permit the efficient implementation of a vaccination strategy in resource-limited countries. For small businesses interested in this topic, reagents such as recombinant CMV and HSV antigens are readily available from the research community to support the development of such a rapid POC serodiagnostic.

Project Goal:

The goal of this project is to develop rapid POC diagnostic tests that can determine whether a person has pre-existing antibody to HSV or CMV as an indicator of prior virus infection. The final product should be self-contained, require only a small blood sample (e.g., from a finger stick), provide an immediate (less than 30 minute) readout, and demonstrate the necessary sensitivity and specificity to allow screening of clinical trial subjects/patients for prior virus infection.

Phase I activities can include but are not limited to:

- Development of the prototype POC diagnostic product for detection of HSV or CMV antibodies.
- Determination of the sensitivity, specificity and other performance characteristics (e.g. time to result, limit of detection, test stability) of the product.

Phase II activities can include but are not limited to:

- Further development of the prototype POC diagnostic product for detection of HSV or CMV antibodies.
- Further determination of the sensitivity, specificity and other performance characteristics (e.g. time to result, limit of detection, test stability) of the product.
- Final validation testing and scale-up manufacturing of test kits.

This SBIR will not support:

- Nucleic acid-based diagnostics.
- Serodiagnostics that require extensive equipment or time (> 30 minutes) to conduct the assays.
- The design and conduct of clinical trials (see <http://www.niaid.nih.gov/researchfunding/glossary/pages/c.aspx#clintrial> for the NIH definition of a clinical trial). For clinical trial support, please refer to the [NIAID SBIR Phase II Clinical Trial Implementation Cooperative Agreement program announcement](#) or the NIAID Investigator-Initiated Clinical Trial Resources [webpage](#).

047 Development of Microbiome-based Products for Infectious Diseases

Fast-Track proposals will be accepted.

Direct to Phase II proposals will 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 majority of microbiome research to date has been largely descriptive and has focused on the characterization of the microbiome composition. However, there has been a recent shift in the microbiome field to focus on the functional capacity of the microbes present. This shift in microbiome research has led to the development of potential microbiome-based products for use as therapeutic interventions, thus presenting a need for innovation in the characterization and preclinical development of this novel product class. Currently, several microbiome-based products consisting of live bacteria are being developed as therapeutic interventions for vaginal and enteric infectious diseases. These products can be very complex, oftentimes originating from human stool or other diverse microbial communities. As such, there are many challenges associated with the preclinical development of these complex microbiome-based products. New and innovative ways to conduct IND-enabling studies (e.g. characterization assays to support lot release) are now needed to further advance these products for future human clinical trials.

Project Goal:

The goal of this project is to enable small businesses that have an existing microbiome-based product (consisting of live microorganisms, such as bacteria) intended for the treatment or prevention of infectious diseases to further their product development by focusing on preclinical studies. In particular, small businesses are encouraged to focus on IND-enabling studies to support the characterization, manufacture and release using product-specific assays. Focus should be on characterizing the product in terms of identity, genetic stability, purity, potency, transference of genetic material, and mechanism(s) of action. New methods to set appropriate specifications are also needed. In addition, novel methods to manufacture complex microbial ecosystems and raw materials are encouraged. Finally, novel formulations such as spray drying, lyophilization, and packaging of microbiome-based products for long-term stability are encouraged. The following FDA document, entitled “[Early Clinical Trials with Live Biotherapeutic Products: Chemistry, Manufacturing, and Control Information](#)”, should serve as guidance to small businesses seeking to submit proposals on this topic.

Phase I activities can include but are not limited to:

- Development of novel analytical methods to fully characterize individual and combinations of components (e.g. live microorganisms, such as bacteria) of microbiome-based products.
- Development or conduct of assays to support lot release testing, such as identity or potency testing.
- Development or conduct of assays to demonstrate product stability.
- Development of methods and analytical technologies to support chemistry, manufacturing and control information, such as formulation, encapsulation, and lyophilization.

Phase II activities can include but are not limited to:

- Development of methods and analytical technologies to support chemistry, manufacturing and control information, such as formulation encapsulation and lyophilization.
- Scale-up formulation activities that may help support future clinical trials.
- Conduct of appropriate safety (e.g. toxicology) studies of formulations intended for clinical evaluation in the appropriate systems.
- Conduct of long-term stability studies to ensure product shelf life.
- Validation of assays to support lot release testing.

This SBIR will not support:

The design and conduct of clinical trials (see <http://www.niaid.nih.gov/researchfunding/glossary/pages/c.aspx#clintrial> for the NIH definition of a clinical trial). For clinical trial support, please refer to the [NIAID SBIR Phase II Clinical Trial Implementation Cooperative Agreement program announcement](#) or the NIAID Investigator-Initiated Clinical Trial Resources [webpage](#).

Studies focused on discovering new microbiome-based products.

A new indication for an existing microbiome-based product (e.g. probiotics).

048 Non-Invasive Rapid Diagnostics for Respiratory Diseases in Children

Fast-Track proposals will be accepted.

Direct to Phase II proposals will be accepted.

Number of anticipated awards: 2-3

Budget (total costs):

Phase I: \$225,000 for up to one year

Phase II: \$1,500,000 for up to 3 years

Background:

Lower respiratory tract infections and pneumonias cause a significant burden of disease and mortality, particularly in children under the age of five. There is a need for simple tools to diagnose lung infections in children. Current clinical diagnostic methods for respiratory diseases typically take days-to-weeks, and may require multiple samples obtained by invasive methods. Sputum or bronchoalveolar lavage are the most common clinical specimens obtained for current diagnostic tests; however, most children and many adults are unable to produce sputum. Sputum induction and lavage sampling are highly invasive processes, causing discomfort to the patient and often resulting in unreliable sampling of potential pathogens. As a result, information from current diagnostics and specimens could be complicated by the presence of colonizing bacteria that are non-pathogenic and may not adequately define the underlying disease state. Non-invasive rapid diagnostic approaches are needed to enable a more timely and meaningful diagnosis and allow the patient to receive appropriate treatment before disease becomes severe. Potential benefits of non-invasive rapid diagnostics for lower respiratory tract infections include, but are not limited to:

- Improved patient compliance and willingness to seek early medical treatment
- Reduced risk of exacerbating disease due to diagnostic procedures
- Ability to monitor the patient's infectious status over time, and to monitor success of treatment

Project Goal:

The goal of this project is to develop rapid, sensitive diagnostics for lower respiratory tract infections (of bacterial, viral, and/or fungal origin) that would be suitable for children and utilize non-invasive specimen collection methods. Examples of non-invasive specimen types may include, but are not limited to analytes in exhaled breath, saliva, oral swabs, and bodily secretions (urine, tears, and sweat). The proposed diagnostic device (and associated components) should be simple to use, compatible with point-of-care use by healthcare personnel, employ reagents that can be stored under ambient conditions, and be compatible with U.S. regulatory guidelines for testing and validation. Utilization of appropriately consented, de-identified human-derived material in preclinical studies in support of compliance with regulatory requirements is permitted and encouraged. Additional human-derived sample collection is allowed under this solicitation.

Phase I activities can include but are not limited to:

- Development of an approach for the identification and examination of analytes associated with lower respiratory tract infections caused by a specific pathogen(s).
- Development of a prototype device to demonstrate its feasibility for pathogen detection.
- Determination of the sensitivity, specificity and other performance characteristics (e.g. time to result, limit of detection, test stability) of the product.

Phase II activities can include but are not limited to:

- Evaluation of the ability of diagnostic device to distinguish different types of respiratory infections (e.g. of bacterial, viral, and/or fungal origin).
- Assessment of the utility of the device to distinguish between bacterial colonization and active infection.
- In preclinical disease models, evaluation of changes in analyte pattern after antibiotic administration.
- Conduct of additional validation studies with de-identified human specimens to identify factors that may influence or confound the diagnostic result.
- Product development strategy for regulatory approval and demonstration of clinical utility.

This SBIR will not support:

- The design and conduct of clinical trials (see <http://www.niaid.nih.gov/researchfunding/glossary/pages/c.aspx#clintrial> for the NIH definition of a clinical trial). For clinical trial support, please refer to the [NIAID SBIR Phase II Clinical Trial Implementation Cooperative Agreement program announcement](#) or the NIAID Investigator-Initiated Clinical Trial Resources [webpage](#).
- Validation testing that would be reported back to the patient or the treating physician.
- The development of technologies that rely solely on nucleic acid amplification followed by a hybridization detection step for detection of a pathogen-specific antigen or a host-response antibody.
- The development of diagnostics requiring culture-bottle and/or streak plate incubations.
- Proposals that do not have the ultimate goal of detection and identification of pathogens in human clinical samples.
- The development of environmental or workplace pathogen/toxin detection technologies.
- The development of diagnostics for HIV.

049 Phage-based Diagnostic Platforms for Rapid Detection of Bacterial Pathogens

Fast-Track proposals will be accepted.
Direct to Phase II proposals will be accepted.

Number of anticipated awards: 2-3

Budget (total costs):

Phase I: \$225,000 for up to one year

Phase II: \$1,500,000 for up to 3 years

Background:

Resistance of bacterial pathogens to antibiotics is rapidly increasing, both in hospital environments and community settings, and it has become a national priority to find product-based solutions to this serious medical problem. Consequently, there is an urgent need for rapid, highly sensitive, easy-to-use, cost-effective clinical diagnostics that can identify bacterial pathogens and determine antibiotic susceptibility. Such diagnostic platforms have the potential to impact antibacterial resistance by helping physicians to determine the most effective treatments for infected individuals and thereby reduce the use of broad-spectrum antibiotics. In addition, these platforms may also support more efficient stratification of patients for clinical trials. Bacteriophages in particular offer many desirable characteristics which make them well-suited as a platform for rapid bacterial diagnostics tests. They are easily produced, remarkably diverse and target bacteria with exquisite specificity. The use of bacteriophage may also allow for detection of bacterial pathogens directly from clinical samples and potentially eliminate the need for primary culture methods. Assays utilizing phage detection in combination with drug testing offer the potential not only for pathogen identification but also for rapid determination of antibiotic susceptibility profiles critical for appropriate treatment decisions in the clinic.

Project goal:

The goal of this project is to leverage bacteriophages or their relevant biochemical components as tools for the development of rapid diagnostic platforms to detect bacterial pathogens that cause serious infections in humans. Responsive proposals must address bacteria [recently classified by the Centers for Disease Control and Prevention \(CDC\) as antibiotic resistance threats](#). Because drug resistance is key to the threat posed by these pathogens, bacteriophage-based diagnostic platforms that can both identify the pathogens, as well as provide an assessment of antibiotic susceptibility, are preferred.

Phase I activities can include but are not limited to:

- Detailed characterization of specific bacteriophages, or relevant biochemical components, that demonstrate utility for detecting clinically-relevant bacterial pathogens.
- Determination of diagnostic sensitivity and selectivity sufficient to meet the needs of the intended clinical application.
- Development of a prototype device that can identify one or more target pathogens and their antibiotic susceptibility in a spiked specimen matrix that represents the intended clinical application.

Phase II activities can include but are not limited to:

- Demonstration that prototype device detects, with sufficient sensitivity and selectivity, a representative sampling of bacterial pathogens found in the clinic.
- Demonstration of feasibility for determining antibiotic susceptibility using well-characterized clinical isolates of target pathogen(s).
- Development of standardized plan for manufacturing of components.
- Validation of diagnostic device prototype with blinded clinical samples.
- Development of a product development plan for achieving regulatory approval and demonstrating clinical utility for bacteriophage-based detection system.

This SBIR will not support:

- The design and conduct of clinical trials (see <http://www.niaid.nih.gov/researchfunding/glossary/pages/c.aspx#clintrial> for the NIH definition of a clinical trial). For clinical trial support, please refer to the [NIAID SBIR Phase II Clinical Trial Implementation](#)

[Cooperative Agreement program announcement](#) or the NIAID Investigator-Initiated Clinical Trial Resources [webpage](#).

NATIONAL INSTITUTE ON DRUG ABUSE (NIDA)

NIDA's mission is to advance science on the causes and consequences of drug use and addiction and to apply that knowledge to improve individual and public health.

This solicitation invites proposals in the following areas:

161 Virtual Reality Tools to Enhance Evidence Based Treatment of Substance Use Disorders

Fast Track is **not** allowed.

Direct to Phase II is **not** allowed.

Information about Phase II is provided for planning purposes only.

Number of Anticipated Awards: 2-3

Budget (total cost):

Phase I: \$150,000 for 6 months.

Phase II: For planning purposes, this may be sought with an estimated award of \$1,000,000 for two years to test clinical outcome of IT approaches to augment standard treatment in a patient population in comparison with stand treatment alone. Further, Phase II will include a description of the path toward clinical adoption of this VR based IT approach.

Background:

There are numerous existing evidence-based behavioral treatment approaches for substance use disorders. A significant proportion of patients who receive treatment using evidence-based behavioral therapies relapse, suggesting that additional adaptations are needed to enhance the effectiveness of these therapies. Technology driven approaches (e.g., cell phone based applications, text messaging interventions, ecological momentary assessment (EMAs)) to improving evidence-based treatments have shown some success.

Virtual reality is unique among other technological enhancements in that it can recreate some elements of the social situations and physical environments that typically trigger relapse, allowing patients to practice skills they will need when they encounter such situations in real life. The potential for VR to enhance treatment effects has been demonstrated in domains outside of substance use (e.g., Manzoni et al., 2015¹). In addition to the potential to increase the potency of interventions by allowing patients to practice skills in realistic virtual settings, VR also has the potential to extend access to treatment outside of clinical settings, this could increase the frequency of treatment for patients and could be particularly beneficial for patients who live in rural areas or who have other health or financial barriers that make it difficult for them to get to appointments on a regular basis.

The ultimate goal is to have VR-enhanced treatments facilitate improved treatment outcomes as well as make treatment more accessible.

Numerous evidence-based substance abuse treatments may lend themselves to virtual reality adaptation. Examples may include:

- Cognitive Behavioral Therapy variations
- Contingency Management
- Motivational Interviewing/Motivational Enhancement Therapy variations
- Multisystemic Therapy
- Multidimensional Family Therapy
- The Matrix Model
- 12-Step Facilitation Therapy
- Behavioral Therapy

Project Goals:

Develop Virtual Reality (VR) IT approach to be used to improve behavioral treatment approaches for substance abuse disorders with the following elements:

- Complete initial development and proof-of-concept for VR-enhanced evidence-based substance abuse treatment that takes advantage of the unique abilities to VR. This may include, but is not limited to, presenting a variety of virtual stimuli and environments that might illicit or inhibit drug seeking behavior or relapse using widely available commercial VR platforms (e.g., Oculus Rift, PlayStation Morpheus, HTC Vive, Samsung Gear VR).
- Complete initial efficacy/effectiveness testing of the VR-enhanced treatment to demonstrate impact on meaningful clinical outcomes.
- Obtain and document feedback that may include surveys, focus groups, user testing from relevant stakeholders who would be involved in implementing VR-enhanced treatments into substance abuse clinical treatment. This includes, but is not limited to, patients who would use the VR-enhanced treatment, clinicians who might use VR-enhanced therapy as part of their practice in private practice and larger clinical settings, and payers. This feedback should identify any challenges or barriers to implementing VR-enhanced therapy in both clinical settings as well as its potential to extend treatment outside of clinical settings (e.g., HIPPA privacy requirements, obstacles to reimbursement, patient safety concerns, etc.).

Make modifications that incorporate input received from the above surveys, focus groups and user testing.

Phase I Activities and Expected Deliverables:

Technical Requirements

- Seek feedback from a panel of health care professionals who are potential end users (e.g. therapists who are using the EBT in clinical practice) on what features and functions these professionals would most like to see and most likely convince them to employ this VR-enhanced approach.
- Assemble a team of professionals to develop a proof-of-concept VR-enhanced evidence-based substance use treatment for patients with substance use disorders. The adapted intervention must be capable of implementation on an existing commercially available consumer VR system (e.g., Oculus Rift, PlayStation Morpheus, HTC Vive, Samsung Gear VR) that use head mounted displays. At a minimum, it is expected that this proof-of-concept system would yield at least 1-2 hours of interactive content. The final amount of content should be determined by the EBP that is being adapted. Furthermore, documentation accompanying the proof-of-concept should indicate how the VR-enhanced intervention would be used to modify the existing EBP across the full treatment course indicated by the existing EBP (i.e., number of sessions, length of sessions, sequence of content, etc.).
- Conduct exploratory research with relevant stakeholders to understand the implications of HIPPA standards, data security and other considerations that would be required for clinical use (e.g., insurance reimbursement, etc.).
- Ensure that the VR system balances the need for high quality graphics to enhance user engagement, while also ensuring that the intervention could be implemented via widely available commercial technologies. Widely available technologies include consumer-grade laptop or desktop computers, tablet-based computers and/or smartphones.
- Collect quantitative and qualitative data on patient reactions to VR-enhanced treatment, including, but not limited to, ratings of graphics quality, immersive qualities, engagement, functionality, usability, acceptability, physical reactions (e.g., dizziness), interactivity, etc. Diverse patient perspectives should be solicited, and specific attention paid to features that could be easily modified to enhance the tailoring of the intervention and to enhance cultural relevance of the intervention.
- Examine clinician reactions to VR-enhanced proof concept including, but not limited to potential for inclusion in existing clinical workflow, expected patient engagement, expected clinical value, etc.
- In this phase of the research, testing for complete therapeutic outcomes is premature. However, for a treatment to work, it must produce change. Therefore, potential positive impact on the patient, which can include

biological, psychological, and/or therapeutic outcomes, should be measured. These data will be critical in determining if this project will move forward.

¹ Manzoni et al., VR-enhanced CBT for obesity treatment: A randomized Control Study with Year Follow-up:
<http://www.ncbi.nlm.nih.gov/pubmed/26430819>

162 Analytical Tools and Approaches for (Multidimensional) Scholarly Research Assessment and Decision Support in the Biomedical Enterprise.

Number of Anticipated Awards: 2-3.

Fast-Track proposals and Direct to Phase II proposals will be accepted.

Budget (total costs):

Phase I: \$225,000 for 6 months

Phase II: \$1,500,000 for 2 years

Fast-Track budget may not exceed \$1,725,000 and Fast-Track duration may not exceed 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.

Contemporary science evaluates and is also a subject to evaluation. Research assessment is increasingly becoming an integral part of any scientific activity. Among the reasons for such attention is the increasing demand by the public and government to demonstrate cost-benefit measures of the research programs within the institutions, especially those that are publically funded. Policy makers now explicitly expect science to demonstrate its value to society. Another reason is the current economical atmosphere where budgets are strained and funding is difficult to secure, making the ongoing, diverse and thorough assessment of an immense importance for the progression of scientific and research programs. The current consummate availability of and ability to collect and analyze large scale datasets also contributes to the increased interest in research assessment. While a decade ago, scientific evaluation relied mainly on citations and publications counts, most of which were done manually, today this data is not only available digitally but can also be triangulated with other data types. For example, publications and citations counts can be triangulated with collaborative indicators, text analysis and econometric measures producing multi-level view of an institution, program or an individual. Research funders begin to expect not only publications but also other indicators to be given as the proposed outputs and outcomes of research in proposals, signaling that other forms of scholarly products and novel metrics may play an important part in research evaluation. Appropriately, in the 2016-2020 Strategic plan, NIH announced the intent to take greater leadership in developing and validating the methodologies that are needed to evaluate scientific investments and to use transparent, scientific approaches in decision making.

The RFP solicits the research and development of advanced and sophisticated analytical models, tools and metrics to enhance the professional evaluation and decision making in life sciences management and administration. Those metrics must be developed to be embraced broadly by the life science community, be readily understandable by non-scientists and grounded in outcomes that are highly valued by the general public, funders and the policy makers. It is envisioned that, if proven, those metrics will be used by the NGOs/disease foundations, advocacy groups, research funders, policy makers and by the academic institutional bodies (e.g. promotion committees).

Examples of the projects may include, but not limited to:

- Studies to define and validate the metrics specifically measuring how virtuous the research is (quality, transparency, reproducibility, integrity and potential for translation/application).
- Studies to compare/investigate the relationship between traditional metrics, like text citations and expert evaluations, and webometrics/altmetrics, like social media usage analysis.

- Tools and approaches to quantify relationships between publications and registered products (drugs, devices, diagnostics, etc.), to help increase public appreciation of the societal value of life science discoveries, to provide instructive insights for policy makers, to guide funding decision making and path selection that would accelerate progress towards cures.
- Application of advanced empirical methods to altmetrics: large-scale studies assessing the reliability, validity and context of the metrics.
- Analytical approaches answering the question of how can research -productive scientists be identified, clustered, and configured for optimal research synergies.
- Sophisticated technologies to accurately analyze the demographics of research users, e.g. scholars or non-scholars, career stage, what was the actual research product they used and why, etc.
- Sophisticated approaches and tools that, based on bibliometrics or otherwise, would enable the meaningful nomination of research studies for replication.
- Sophisticated approaches and tools for the standardized evaluation of evidence in large numbers of biomedical research documents (project progress reports, research manuscripts, etc.)
- For student education, building the models of good and bad scientific behavior with demonstration of the possible consequences of both.
- Products that track a variety of scholarly activities such as teaching and service activities correlating them with the lecture attendance and popularity status of the reading lists
- Approaches to directly compare or intelligently combine the metrics (biblio- or alt-) and peer review
- Studies to investigate the new forms of impact measurements that are broader, speedier and more diversified than traditional metrics

CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

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

The CDC's National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP) carries out a variety of activities that improve the nation's health by preventing a range of chronic diseases such as arthritis, cancer, diabetes, heart disease, obesity and stroke, while promoting health and wellness in the areas of reproductive health, oral health, nutrition and physical activity. The Center's activities include supporting states' implementation of public health programs; public health surveillance; translation research; and developing tools and resources for stakeholders at the national, state, and community levels.

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

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

038 Improve Contextual Awareness using Social Network Data

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: up to \$150,000 for up to 6 months

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Background

Public health activities within the chronic disease realm have predominantly relied on survey data to gather information on disease prevalence, behavioral models, risk populations, risk probability, and disease progression. Surveys are subject to a number of known limitations, e.g., respondents' reluctance to participate, social desirability biases, lag time between questionnaire design, data collection and availability, and intermittent coverage of important topics due to associated implementation costs.

Chronic disease control experts and policy makers lack access to real time data and efficient tools to provide contextual awareness to the surveys that are implemented for chronic disease surveillance and program management. The implications of not having a timely and broader understanding of the environment/community affects the representativeness and demographic specificity of the assessment and the data used to drive policy and interventions.

This proposal seeks to develop an analytics platform that can be leveraged by both public health and clinical care to build a cohort around a given chronic indicator (e.g., Tobacco use) by harnessing web and social network data (e.g., Twitter, Facebook, Search data etc.). This national cohort can be utilized to provide specific insights both longitudinally and prospectively to help investigators reveal largely assumption-free insights via systematic generation of hundreds of possible outcomes rather than an arbitrary priority selection of a few outcomes. The approach can also potentially support traditional surveillance by serving as a guiding tool for vetting the inclusion and exclusion of survey questions.

Project Goal

CDC seeks to support the development of an analytics platform that harnesses web and social network data and delivers novel surveillance capabilities for chronic disease indicators. The proposal seeks to build large nationally representative cohorts of social network users for each indicator by key characteristics (e.g., demographics, activity, etc.) that are systematically inferred from user profiles, tweets, posts, and search behaviors. The project will employ

appropriate informatics tools and techniques to extract and infer traits among the data and allow the creation of cohorts that are reflective of regional U.S. Census estimates. These cohorts can then be analyzed to gain insights and answer a diverse set of questions for national, subnational, and demographic-specific prevalence estimates. Further analysis could help identify co-occurring themes and potentially answer the questions “*How many*” and “*Why?*” for any given indicator.

Phase I Activities and Expected Deliverables

- Conduct a review of the data access and use policy of Twitter, Facebook and Search engine data
- Conduct a preliminary study to determine applicable social network data streams and public health indicators
- Identify appropriate informatics solutions (e.g., natural language processing algorithms) to access, monitor, and extract data
- Develop a prototype analytics platform with “Cohort builder” function and demonstrate the creation of least one nationally representative cohort in the chronic disease domain

Impact

The overall goal is to leverage innovative health technologies to improve health outcomes and subsequently quality of life for individuals living with chronic disease. An analytics platform using social data can more efficiently provide deeper insights into health behaviors as they are occurring and improve policy development as well as delivery of interventions. By harnessing the data produced by social events and interventions, programs can be evaluated as they are implemented, hypothetically generating real-time feedback to maximize effectiveness. Web and social network data can be an important source for identifying new hypotheses and can greatly impact the future direction and investments of the center. The cohort builder and the cohort analysis capabilities will provide benefits to chronic disease surveillance and program management practices. Access to social behavior data in real time will help to drive:

- a contextual awareness to the survey, i.e., know your population
- development/modification of survey questions to improve survey data quality
- ability to monitor changes associated with program interventions between surveys

Commercialization Potential

The analytics platform can immediately operate on a subscription based revenue model from public health and clinical care. Any organization can diversify to support other healthcare initiatives (e.g., Community Health Needs Assessment, etc.) as revenue domains. Information technology companies, government, health systems, health information exchange entities, health care providers, and public health systems are a few of the potential markets.

NATIONAL CENTER FOR EMERGING ZOOBOTIC 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). 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, better health for humans and animals and an improved our environment can be attained.

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

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

014 Multiplexed Digital Counting of Single Molecules for Advanced Molecular Diagnosis

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: up to \$150,000 for up to 6 months

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Background

This topic proposal will evaluate the methodological limitations and benefits of direct highly multiplexed digital quantification (HMDQ) of molecules present in samples used in the diagnosis of infectious diseases. Although many multiplexed, quantitative assays have been described for infectious diseases, they suffer from several limitations: 1) Mixed infections are often not detected because only specific agents that are suspected to be present, based on clinical or epidemiological considerations, are tested. 2) Many tests also require multiple controls for quantitation making them difficult to do in a conventional multiplex format. 3) Most platforms are suitable for antigen detection or for nucleic acid detection and use different approaches that are difficult to do simultaneously and do not provide absolute quantitation. 4) Finally, multiplexed assays are often limited in the number that can be performed so that different targets from the same agent or different genotypes cannot be assessed during the initial screen. For example, it is estimated that as many as nine bacterial, viral, and parasitic agents may be present in ticks during feeding and because many of these are pathogenic for humans, domestic animals, or companion animals, it is not uncommon to find co-infections in hosts. The tick vector (*Ixodes scapularis*) of Lyme disease alone is estimated to cause more than 300,000 cases annually but this vector can also transmit *Anaplasma phagocytophilum*, *Babesia* sp., *Bartonella*, *Ehrlichia muris* subsp *euclairensis* and several viruses. The mosquito vector of Zika virus can also transmit several important human viral diseases including dengue and chikungunya virus. Many of the vector-borne diseases present a wide range of symptoms that are often confused with other diseases and co-infections are particularly difficult to recognize. Mixed vector-borne infections present significant diagnostic difficulties for physicians, even when a primary disease agent is recognized, especially as some co-infecting agents require very different therapeutic agents and/or the agents are resistant to those treatments.

Project Goals

The goals of the proposed research are to rapidly, simultaneously, and cost-effectively detect and accurately quantify multiple antigen (protein, carbohydrate) and nucleic acid (DNA, RNA) target molecules used in the primary diagnosis of vector-borne infectious diseases caused by viruses, bacteria, and parasites. The technology should ultimately incorporate innovations which enable large numbers of clinical samples and pools of vectors to be analyzed. The platform must incorporate an open architecture enabling the user to augment or change the specific target molecules as diagnostic and epidemiological interests for emerging vector-borne infectious diseases change (e. g., new agents or genetic types or alternative diagnostic targets are identified). Given the increasing number of studies attempting to relate specific host molecular changes (miRNA, cytokine and other effector molecule gene expression) to specific infectious diseases, the platform must be compatible with performing assays for these biomarkers. The platform and methodology employed must also be compatible with FDA approvals for clinical diagnostic assays for both infectious agents and host biomarkers.

Specific Project Goals:

- Develop assays suitable for use with pools of different vectors and obtain quantitative data from assays.
- Develop assays suitable for use with clinical samples obtained from different vector-borne diseases and obtain quantitative data from assays.
- Expand the range of assays available and move toward commercialization of a subset of those assays.

Phase I Activities and Expected Deliverables:

- To demonstrate the accurate and simultaneous detection and quantitation of at least 10 (3 viral, 4 bacterial, 3 parasitic) vector-borne disease agents found in pools of ticks and mosquitos (assays and associated data). Commercial reagents or in-house generated reagents may be utilized but the targets must include both antigens and nucleic acids and both types of pools.
- To demonstrate the accurate and simultaneous detection and quantitation of at least 10 (3 viral, 4 bacterial, 3 parasitic) disease agents found in clinical samples originating from 5 different vector-borne diseases transmitted by both ticks and mosquitos (assays and associated data). Commercial reagents or in-house generated reagents may be utilized but the targets must include both antigens and nucleic acids and at least two types of clinical samples (e.g., biopsy tissue, blood, urine). Commercial reagents or in-house generated reagents may be utilized.

Impact

One significant impact of this technology would be to avoid the bias introduced by PCR amplification of nucleic acids from various diagnostic samples where sparse amounts of target DNA limit the laboratorians' ability to detect it. Bias is introduced by the amplification method, the presence of molecules that interfere with amplification or which provide incorrect products. The ability to directly detect and count DNA, RNA, and protein molecules could greatly increase the speed in which samples are analyzed, the accuracy of the results obtained, and provide the ability to compare relative counts of different types of molecules in the same clinical sample and at different time points during the infection to monitor the patient's response. A highly multiplexed assay system has the capacity to improve QC in standardizations by increasing the numbers of controls, and can detect multiple mixed co-infections and contaminants simultaneously. This approach can significantly improve the quality of outbreak investigations and is a greatly superior methodology for complex diagnostic samples.

Commercialization Potential

Numerous companies have developed multiplexed platforms for detection of biomolecules. These include microarrays of various types (for both nucleic acid and proteins), flow cytometry, qPCR and ddPCR approaches, as well as second (Next Generation) sequencing platforms. Microscopy and direct optical mapping methods can also be highly multiplexed. Some of these approaches have been commercialized in the cancer diagnostic field. These advances are thus heavily covered by commercial and university patents. Companies successful in achieving the goals outlined above should be able to develop strong commercial markets given the number of cases of arbovirus (West Nile, dengue, Zika), rickettsial, parasitic (e. g., malaria, Chagas), and other bacterial etiological agents of interest (e.g., Lyme disease, plague, tularemia).

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 I, 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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