

**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 2018-1

Closing Date: October 20, 2017, 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 20, 2017, 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 at this time. Other Topics allow for ‘Fast Track’ submissions, which include both a complete Phase I proposal and a complete Phase II proposal. For more information on the three-phase program and the Fast Track process, refer to Section 2.

TOPIC NUMBER	PHASE I PROPOSAL ALLOWED?	FAST TRACK ALLOWED? (A Phase I proposal and a Phase II proposal submitted simultaneously)	TOPIC TITLE
NIH/NCI 370	Yes	Yes	Targeted Therapy for Cancer- and Cancer Therapy-Related Cachexia
NIH/NCI 371	Yes	Yes	Drugs to Exploit the Immune Response Generated by Radiation Therapy
NIH/NCI 372	Yes	Yes	Development and Validation of Non-Mouse Reagents to Enable Preclinical Development of Novel Therapeutics
NIH/NCI 373	Yes	No	Tools and Technologies for Monitoring RNA Modifications
NIH/NCI 374	Yes	Yes	Novel Approaches for Local Delivery of Chemopreventive Agents
NIH/NCI 375	Yes	Yes	Diagnostic Imaging for Cancer Immunotherapies
NIH/NCI 376	Yes	Yes	Imaging-Based Tools for Longitudinal and Multi-Dimensional Mapping of the Tumor and Its Microenvironment
NIH/NCI 377	Yes	Yes	Bridging the Guideline Implementation Gap: Clinical Decision-Support to Improve Cancer Symptom Management
NIH/NCI 378	Yes	Yes	Mobile Application for Surveillance of Post-Radiation Therapy Health-Related Quality of Life
NIH/NCI 379	Yes	Yes	Software Enabling Data Integration from Wearable Sensors to Generate Novel Analytics for Cancer Patients
NIH/NCI 380	Yes	Yes	Computer Aided Decision Support for Radiation Oncology
NIH/NCI 381	Yes	No	Development of Artificial Intelligence (AI) Tools to Understand and Duplicate Experts’ Radiation Therapy Planning for Prostate Cancer
NIH/NHLBI 103	Yes	Yes	Devices for Transcatheter Surgery
NIH/NHLBI 104	Yes	Yes	Tapered Guidewires for Transcatheter Electrosurgery
NIH/NHLBI 105	Yes	No	Reagent Development for Small Cell Number ChIC-seq

TOPIC NUMBER	PHASE I PROPOSAL ALLOWED?	FAST TRACK ALLOWED? (A Phase I proposal and a Phase II proposal submitted simultaneously)	TOPIC TITLE
NIH/NIAID 050	Yes	Yes	Methods Improving HIV Protein Expression: Cell Substrate and Protein Purification
NIH/NIAID 051	Yes	Yes	Inhaled Delivery of Clofazimine (CFZ) – An Important Anti-tuberculosis Drug
NIH/NIAID 052	Yes	Yes	High-Throughput Assay Platform for Quantifying Latent HIV Reservoirs
NIH/NIAID 053	Yes	Yes	Effective Targeted Delivery of RNA-based Vaccines and Therapeutics
NIH/NIAID 054	Yes	Yes	Adjuvant Discovery for Vaccines and for Autoimmune and Allergic Diseases
NIH/NIAID 055	Yes	Yes	Adjuvant Development for Vaccines and for Autoimmune and Allergic Diseases
NIH/NIAID 056	Yes	Yes	Reagents for Immunologic Analysis of Non-mammalian Models
NIH/NIAID 057	Yes	Yes	Development of Sample Sparing Assays
NIH/NIAID 058	Yes	Yes	Bioinformatics tools to make data FAIR (Findable, Accessible, Interoperable, and Re-usable)
NIH/NIAID 059	Yes	Yes	Diagnostics to Enable Malaria and Neglected Tropical Diseases (NTDs) Elimination
NIH/NIAID 060	Yes	Yes	Computational Software Development to Advance Translational Research for Infectious Diseases
NIH/NIAID 061	Yes	Yes	Induction of Mucosal Immune Response to Parenterally Delivered Vaccines
NIH/NIAID 062	Yes	Yes	Novel Vaccine Technologies and Strategies to Promote Sustained Vaccine Efficacy
NIH/NIDA 163	Yes	Yes	Digital Markers for Marijuana Intoxication
NIH/NIDA 164	Yes	No	Development of Portable Neuromodulatory Devices for the Treatment of Substance Use Disorders
CDC/CGH 009	Yes	No	Improving Global Laboratory Diagnostic Capacity: Modular, End-user-assembled Biosafety Cabinets for Sustainable Biocontainment
CDC/NCCDPHP 039	Yes	No	Finding Human Carriers of Taeniasis to Prevent Neurocysticercosis Associated Epilepsy
CDC/NCCDPHP 040	Yes	No	Web-based Application to Enable Healthy Behaviors through Behavioral Design
CDC/NCEZID 015	Yes	No	Antifungal-containing Solution for Corneal Tissue Storage and Transport

TOPIC NUMBER	PHASE I PROPOSAL ALLOWED?	FAST TRACK ALLOWED? (A Phase I proposal and a Phase II proposal submitted simultaneously)	TOPIC TITLE
CDC/NCEZID 016	Yes	No	Bacterial Amplicon Subtyping
CDC/NCEZID 017	Yes	No	Identification of <i>Brucella canis</i> Seroreactive Proteins and Serology Assay Development
CDC/NCEZID 018	Yes	No	Multiplex Pan_lyssavirus/ β -actin Real-time RT-PCR Assays for Rabies Diagnostics
CDC/NCEZID 019	Yes	No	Tools for Combined Analysis of Optical Mapping and Sequencing Data
CDC/NCHHSTP 048	Yes	No	Development of a Benchtop Laboratory Platform for Amplicon Deep Sequencing
CDC/NCHHSTP 049	Yes	No	Risk Reduction Toolkit for Non-Prescription Syringe Sales in Community Pharmacies
CDC/NCIRD 033	Yes	No	Heat Stable Sabin-based Inactivated Polio Vaccine

All firms that are awarded Phase I contracts originating from this solicitation will be eligible to participate in Phases II and III. Awarding Components (see Section 2.7) 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 Awarding Component instructions. The details on the due date, content, and submission requirements of the Phase II proposal will be provided by the Awarding 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. 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.

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.](#)"

2.2 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 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 be funded by non-Federal sources of capital, or may be funded by follow-on non-SBIR Federal funding agreements.

The competition for SBIR Phase I and Phase II awards satisfies the competition requirements of the Competition in Contracting Act. Therefore, for an agency that wishes to fund an SBIR Phase III project, 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).

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 significantly 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 a contractual 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

This solicitation will not accept Direct Phase II proposals. The congressional authority for Direct to Phase II proposals has expired.

2.5 I-Corps™ at NIH

The following NIH/CDC awarding components are offering the opportunity for companies performing Phase I SBIR contracts to further develop the project’s commercialization strategy by applying for participation in the I-Corps™ at NIH program:

- **All NIH awarding components** (NCI, NHLBI, NIAID, and NIDA), **CDC NCCDPHP**, and **CDC NCEZID**.

Any offeror submitting a proposal to a Topic falling under the above awarding components may include potential participation in the I-Corps™ at NIH program within its Phase I proposal.

The I-Corps™ at NIH program is designed to complement activities within the scope of a Phase I SBIR award. This opportunity is specifically aligned with the statutorily mandated purpose of the SBIR program to “increase private sector commercialization of innovations derived from Federal R/R&D, thereby increasing competition, productivity and economic growth.” 48 CFR 1819.7301.

The I-Corps™ at NIH program is selective, with each NIH/CDC cohort consisting of up to 24 companies, split amongst current grant and contract SBIR Phase I award recipients throughout the NIH and CDC. For a firm fixed price option amount not to exceed \$50,000 (in addition to the price for performing the base research project), companies selected to participate in this program will perform additional requirements and develop additional deliverables which will ultimately provide the resources to submit a refined Commercialization Plan within the Final Report for an SBIR Phase I award, meaning that I-Corps™ at NIH participation runs concurrently with the performance of the SBIR Phase I research.

Participants must assemble a three-member I-Corps™ team that will work collaboratively to complete the program’s required activities and assignments. Applicants should designate teams consisting of the following 3 members/roles:

- Chief-Level Corporate Officer
(CEO of the SBIR awardee company strongly preferred)
- Industry Expert
(internal, such as a Business Development Manager or Board Member, or external, such as a consultant or mentor with the [National Innovation Network](#))

- Program Director/Principal Investigator (PD/PI)
(or, in the case that PD/PI is also the CEO, an additional technical/scientific expert)

To successfully complete the I-Corps™ at NIH Program, the entire I-Corps™ team must be deeply committed and dedicated to the time-intensive curriculum. Each team member should plan to spend at least 20 hours per week on I-Corps™ activities for the full duration of the 8-week program. In-person attendance of all 3 team members is mandatory for a 3-day immersion ‘kickoff’ workshop and a 2-day closing workshop, location to be determined (within the United States), where team members will give presentations as well as participate in lectures and training sessions. There will also be weekly webinar sessions and requirements to get “out of the lab” and gather information by conducting at least 100 discovery interviews with potential customers, strategic partners, and other third-party stakeholders.

The program teaches researchers how to gain a clearer understanding of the value of their inventions in the marketplace, and ultimately how to advance their technologies from the research lab into the commercial world, helping to accelerate the commercialization of new products and services derived from NIH/CDC Phase I SBIR contract awards.

See <https://sbir.cancer.gov/programseducation/icorps> for further information on this program. Example timelines for the selection process and for course components may be viewed here, although specific dates are subject to change: <https://sbir.cancer.gov/programseducation/icorps/cohortcurriculum>.

Application Process

The first step in the I-Corps™ at NIH application process is submitting an additional, separate “Appendix C – Contract Pricing Proposal,” in your Business Proposal. Specify “I-Corps” in the “Title of Proposal” field. This separate budget must not exceed \$50,000 in total direct costs – indirect costs may not be included. Of that amount, \$20,000 must go towards covering workshop registration fees, which should be listed in field 4.e. OTHER of Appendix C. Remaining budget should be allocated as appropriate to cover personnel time for the I-Corps™ team members – at least 20 hours per week for 8 weeks for the 3 team member roles discussed above – as well as travel costs to participate in the in-person workshops and conduct on-site customer development interviews within the U.S.

Dates, times, and locations for NIH/CDC 8-week cohorts in 2019 have not yet been finalized. The Government will notify companies with the I-Corps™ contractual option once these determinations have been made. For the purpose of preparing a budget only, assume a cohort from April 1, 2019 to May 24, 2019 with travel to Los Angeles, California for a workshop April 2-5, 2019 and travel to Bethesda, Maryland for a workshop May 23-24, 2019.

Companies who submit this initial budget for consideration may have an option included in their SBIR Phase I contract for I-Corps™ participation – however, this option is not a guarantee of funding unless and until the Government exercises the option at a later date. The Government may exercise the option in the event that the company is ultimately selected for I-Corps™ participation and funds are available.

The second step in the I-Corps™ application process will take place several months into Phase I project performance, when the Government will notify companies with the I-Corps™ contractual option and allow them the opportunity to prepare a brief application to be considered for I-Corps™ selection, subject to availability of funds. The estimated deadline for this application is early January 2019 and the application will consist of components such as those discussed below:

- *Executive Summary of Predicate SBIR/STTR Phase I Contract and Team (1 page only)*
- *I-Corps™ Team and Project Plan (up to 5 pages)*
 - *I-Corps™ Team*
Description of the I-Corps™ team; indication of commitment to meet time-intensive requirements; discussion of team’s willingness to modify/refine the overall commercialization strategy based on knowledge gained during the course of the I-Corps™ Program.

- *Potential Commercial Impact*

Description of what has led team to believe that a commercial opportunity exists for the project; profile of typical customer; description of the customer's need that the proposed innovation will meet and how the customer is currently meeting that need; discussion of competitive advantage offered by the proposed product/service; discussion of how much a customer would pay for the solution.

- *Project Plan*

Description of the current stage of development for the product/service and what objectives will be achieved by the end of the Phase I project; description of next steps the company will take to advance the project toward commercialization.

Finally, after NIH/CDC reviews written I-Corps™ applications, it will conduct phone interviews to determine which companies will be invited to join the I-Corps™ cohort. The NIH/CDC awarding component selection committee will consider the ability of the proposed I-Corps™ effort to increase the overall success of the Phase I research project. (Specific criteria will be discussed in the notification provided by the Government containing finalized application due dates and cohort participation dates.)

If a company is selected, the I-Corps™ option in the contract may be exercised (pending availability of funds), increasing funding to the contract and incorporating I-Corps™ program participation requirements and associated deliverables into the contract, including:

- In-person participation in all Opening Workshop lectures/sessions;
- 3 team presentations at the Opening Workshop;
- Participation in weekly faculty office hour meetings;
- Participation in 6 Webex sessions;
- Completion of at least 100 customer discovery interviews;
- In-person participation in all Closing Workshop lectures/sessions
- Final Lessons Learned team presentation; and,
- Team presentation of final video.

Information obtained through the above I-Corps™-related efforts must be incorporated into the Commercialization Plan component of the Phase I Final Report.

2.6 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. Phase II contract awardees are eligible to apply for Phase IIB grants offered by those participating NIH ICs. The Phase II contract must be completed prior to award of a Phase IIB grant, although the Phase II contract need not be completed prior to application. Phase IIB Competing Renewal grant awards 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. Prospective applicants are **strongly encouraged** to contact NIH staff prior to submitting an application. 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](#) and the [NHLBI Small Market Award](#). 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 webpage for Small Business Grants: <https://www.ninds.nih.gov/Funding/Small-Business-Grants>. Contact Stephanie Fertig, M.B.A., at 301-496-1779 or fertigs@ninds.nih.gov for additional information.

2.7 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 Heart, Lung, and Blood Institute (NHLBI)

National Institute of Allergy and Infectious Diseases (NIAID)

National Institute on Drug Abuse (NIDA)

Centers for Disease Control and Prevention (CDC) Components:

Center for Global Health (CGH)

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

National Center for Emerging Zoonotic and Infectious Diseases (NCEZID)

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

National Center for Immunization and Respiratory Diseases (NCIRD)

3 DEFINITIONS

3.1 General Definitions

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

8(a) 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, awardees and consultants must establish written guidelines indicating the conditions of payment of consulting fees. Consultants may also include firms that provide paid professional advice or services.

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

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

Covered Small Business Concern. A small business concern that:

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

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 Personnel. The principal investigator/project manager and any other person considered to be essential to work performance.

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.

Proprietary Information. Information that constitutes a trade secret or other confidential commercial or financial information.

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.

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 21 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:

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

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: <https://www.federalregister.gov/documents/2016/04/15/2016-08810/national-institutes-of-health-nih-office-of-science-policy-osp-recombinant-or-synthetic-nucleic-acid>.

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.

Based on rare and unique circumstances, deviations from these performance requirements may occur, and must be approved in writing by the funding agreement officer after consultation with the agency SBIR Program Manager/Coordinator.

4.3 Benchmarks for Progress towards Commercialization

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 (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. The HHS Phase II to Phase III Commercialization Benchmark is as follows:

Companies that have received more than 15 Phase II awards across all federal SBIR/STTR agencies over the past ten (10) years 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 have received more than 15 Phase II awards across all federal SBIR/STTR agencies over the past ten (10) years must, prior to application submission, 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 not be eligible to receive new Phase I or Fast Track awards for a period of one year. Information on the Phase II to Phase III Commercialization Benchmark is available at SBIR.gov.

4.4 Multiple Principal Investigators

The NIH 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."

4.5 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.

4.6 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](#). 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.

4.7 Conflicts of Interest

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

4.8 Market Research

Base SBIR award funding will not support any market research or 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. However, refer to Section 2.5 I-Corps™ at NIH and Section 4.20 State Assistance and Technical Assistance for potential opportunities for specialized supplemental funding to support commercialization efforts.

For purposes of the SBIR program, “market research” is the systematic gathering, recording, computing, and analyzing of data about problems relating to the sale and distribution of the subject of the research project. It includes various types of research, such as the size of potential market and potential sales volume, the identification of consumers most apt to purchase the products, and the advertising media most likely to stimulate their purchases. However, “market research” does not include activities under a research plan or protocol that require a survey of the public as part of the objective of the project to determine the impact of the subject of the research on the behavior of individuals.

4.9 Research Involving Human Subjects

The HHS regulations “Protection of Human Subjects” (45 CFR part 46, administered by OHRP) define a human subject as a living individual about whom an investigator conducting research obtains: data through *intervention* or *interaction* with the individual **OR** identifiable *private information*.

Notice to Offerors of Requirements of 45 CFR Part 46, Protection of Human Subjects, HHSAR 352.270-4(a), Alternate I (December 2015)

- a. The Department of Health and Human Services (HHS) regulations for the protection of human subjects, 45 CFR part 46, are available on the Office for Human Research Protections (OHRP) Web site at: <http://www.hhs.gov/ohrp/index.html>. These regulations provide a systematic means, based on established ethical principles, to safeguard the rights and welfare of human subjects participating in research activities supported or conducted by HHS.
- b. The regulations define a human subject as a living individual about whom an investigator (whether professional or student) conducting research obtains data or identifiable public information through intervention or interaction with the individual, or identifiable private information. In most cases, 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. 45 CFR part 46 does not directly regulate the use of autopsy materials; instead, applicable state and local laws govern their use.
- c. Activities which involve human subjects in one or more of the categories set forth in 45 CFR 46.101(b)(1)-(6) are exempt from complying with 45 CFR part 46. See <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>.
- d. Inappropriate designations of the noninvolvement of human subjects or of exempt categories of research in a project may result in delays in the review of a proposal.
- e. In accordance with 45 CFR part 46, offerors considered for award shall file an acceptable Federal-wide Assurance (FWA) of compliance with OHRP specifying review procedures and assigning responsibilities for the protection of human subjects. The FWA is the only type of assurance that OHRP accepts or approves. The initial and continuing review of a research project by an institutional review board shall ensure that: The risks to subjects are minimized; risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result; selection of subjects is equitable; and informed consent will be obtained and documented by methods that are adequate and appropriate. Depending on the nature of the research, additional requirements may apply; see <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.111> for additional requirements regarding initial and continuing review. HHS regulations for the protection of human subjects (45 CFR part 46), information regarding OHRP registration and assurance requirements/processes, and OHRP contact information is available at the OHRP Web site (at <http://www.hhs.gov/ohrp/assurances/index.html>).
- f. Offerors may consult with OHRP only for general advice or guidance concerning either regulatory requirements or ethical issues pertaining to research involving human subjects. **ONLY** the contracting officer may offer information concerning a solicitation.

- g. The offeror's proposal shall document that it has an approved or active FWA from OHRP, related to the designated IRB reviewing and overseeing the research. When possible the offeror shall also certify the IRB has reviewed and approved the research. If the offeror cannot make this certification at the time of proposal submission, its proposal must include an explanation. Never conduct research covered by 45 CFR part 46 prior to receiving certification of the research's review and approval by the IRB. If the offeror does not have an active FWA from OHRP, the offeror shall take all necessary steps to obtain an FWA prior to the deadline for proposal submission. If the offeror cannot obtain an FWA before the proposal submission date, the proposal shall indicate the steps/actions the offeror will take to obtain OHRP approval prior to conducting research covered by 45 CFR part 46. Upon obtaining FWA approval, submit the approval notice to the Contracting Officer.

4.10 Good Clinical Practice Training for NIH Awardees Involved in NIH-Funded Clinical Trials

All NIH-funded investigators and staff who are involved in the conduct, oversight, or management of clinical trials should be trained in Good Clinical Practice (GCP), consistent with principles of the International Conference on Harmonisation (ICH) E6 (R2). GCP training may be achieved through a class or course, academic training program, or certification from a recognized clinical research professional organization. GCP training should be refreshed at least every three years to remain current with regulations, standards and guidelines. The Contractor shall provide completion of training documentation to the Contracting Officer's Representative (COR). The GCP training also may be obtained through NIAID GCP Learning Center at: <https://gcplearningcenter.niaid.nih.gov/Pages/default.aspx>.

Investigator: The individual responsible for the conduct of the clinical trial at a trial site. If a clinical trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

Clinical Trial Staff: Individuals, identified by the investigator, who are responsible for study coordination, data collection and data management. Clinical trial staff may also be called the research coordinator, study coordinator, research nurse, study nurse or sub-investigator.

4.11 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>.

4.12 Care of Vertebrate Animals

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

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

4.13 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 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.

4.14 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 in accordance with the Awarding Component's processes. The written request should be sent to the Awarding Component 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.

4.15 Phase I Award Information

Number of Phase I Awards. The Topic Description indicates the number of Phase I contract awards anticipated by the Awarding 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).

4.16 Phase II Award Information

Number of Phase II Awards. The number of Phase II awards made, through Fast Track proposals or through other transition to Phase II methods subsequent to Phase I completion, depend upon the results of the Phase I 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 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 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).

4.17 Registrations and Certifications

Registration in the System for Award Management (SAM) – Required Prior to Award

Before a contract award can be made, proposing firms must be registered in the System for Award Management (SAM) at <https://www.sam.gov>. The registration should reflect "Purpose of Registration: All Awards" and not "Purpose of Registration: Federal Assistance Awards Only."

SAM allows firms interested in conducting business with the federal government to provide basic information on business capabilities and financial information. It is in the firm's interest to visit SAM and ensure that all the firm's data is up to date to avoid delay in award. Confirmation of your company's Data Universal Numbering System (DUNS) number is necessary to verify your email address in SAM. For information on DUNS, see: <https://fedgov.dnb.com/webform>.

Proposals do not need to include proof of SAM registration – however, proposals should note the company's DUNS number, so that the Government may verify active SAM registration at any time.

SBA Company Registry – Required Prior to Proposal Submission (Include Proof of Registration in Business Proposal)

All applicants to the SBIR and STTR programs are required to register at the [SBA Company Registry](#) **prior to proposal 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 (see above) 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.

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 the 9-digit number reflects your firm’s SBC Control ID.

A copy of the completed SBA Company Registration for your organization must be submitted as part of your Business Proposal.

Funding Agreement Certification & Life Cycle Certifications – Required Prior to Award and During Contract Life Cycle

The SBA SBIR/STTR Policy Directive requires the collection of certain information from firms at time of award and during the award life cycle through use of the SBIR Funding Agreement Certification and the SBIR Life Cycle Certification, which can be viewed here: https://grants.nih.gov/grants/forms/manage_a_small_business_award.htm.

The 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 Certification is 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, and may also be required at any other time that has been identified and incorporated into the contract delivery schedule.

These certifications do not need to be included in your original proposal.

4.18 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.

4.19 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 multiple NIH/CDC SBIR solicitations and funding opportunity announcements. The only exception is that a grant application is allowed to be submitted after a contract proposal has been evaluated and is no longer being considered for award.

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. The small business concern must make appropriate disclosures within Appendix A and Appendix C.

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.

4.20 Reporting Matters Involving Fraud, Waste, and Abuse

Anyone who becomes aware of the existence or apparent existence of fraud, waste and abuse in NIH funded programs is encouraged to report such matters to the HHS Inspector General's Office in writing or through the Inspector General's Hotline. The toll-free number is **1-800-HHS-TIPS (1-800-447-8477)**. All telephone calls will be handled confidentially. The website to file a complaint on-line is: <http://oig.hhs.gov/fraud/hotline/> and the mailing address is:

US Department of Health and Human Services
Office of Inspector General
ATTN: OIG HOTLINE OPERATIONS
P.O. Box 23489
Washington, D.C. 20026

4.21 State Assistance and Technical Assistance

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 which is made possible by the efficiencies of scale accomplished through providing this service through the Government.

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](#) for how to include this in your Pricing Proposal. If the cost of the proposed technical assistance provider is determined to be appropriate and allowable, this cost will be in addition to the base SBIR award budget established in the appropriate Topic description in [Section 12](#). 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 awarded.

Technical assistance is limited to services 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.

4.22 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 (SAM) before the award of a contract.

Payments on fixed price contracts may be made based on the satisfactory completion, receipt and acceptance of contract deliverables. Payments on cost-reimbursement contracts may be made pursuant to receipt of proper invoices of allowable costs incurred which may be submitted no more frequently than on a monthly basis unless otherwise authorized by the contracting officer.

Advance payments may be requested, and approved on a case-by-case basis, and are 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.

4.23 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 at the beginning of the “Content of the Technical Element” section 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.”

4.24 Identification and Marking of SBIR Technical Data in Contract Reports and Deliverables

After award, to preserve the SBIR data rights of the awardee, the legend (or statements) used in the SBIR Data Rights clause included in the SBIR contract must be affixed to any submissions of technical data developed under that SBIR contract. If no Data Rights clause is included in the SBIR contract, 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. **Technical Progress Reporting.** Contractors will be required to submit periodic technical progress reports throughout the period of performance, to be specified by the Awarding Component. On fixed-price contracts, payments may be tied to delivery and acceptance of these technical progress reports. For all contracts, final payment will not be made until all reports and deliverables included in the contract have been delivered and accepted by the Government.

If reports are required to be submitted in electronic format, they must be compliant with Section 508 of the Rehabilitation Act of 1973. Additional information about testing documents for Section 508 compliance, including guidance and specific checklists, by application, can be found at: <http://www.hhs.gov/web/508/index.html> under "Making Files Accessible."

For NCI, the Contractor shall include the applicable PubMed Central (PMC) or NIH Manuscript Submission reference number when citing publications that arise from its NIH funded research.

- b. **Inspection.** Work performed under the contract is subject to Government inspection and evaluation at all reasonable times.
- c. **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.
- d. **Basic Information Systems Security.** The Contractor shall utilize defined security controls to provide at least a minimum level of protection for covered contractor information systems. See [FAR clause 52.204-21 Basic Safeguarding of Covered Contractor Information Systems](#) for applicability and specific requirements.
- e. **Default.** The Government may terminate the contract if the contractor fails to perform the work contracted.
- f. **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.
- g. **Disputes.** Any dispute concerning the contract which cannot be resolved by agreement shall be decided by the Contracting Officer with right of appeal.
- h. **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.
- i. **Salary Rate Limitation.** None of the funds appropriated 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 2017, Executive Schedule, Level II of the Federal Executive Pay Scale is \$187,000.**
- j. **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.

- k. **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.
- l. **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.
- m. **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.
- 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 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 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. For NIH, this peer review panel of experts will be composed of nongovernment personnel. For CDC, this panel may 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 a given 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. Reviewers will be instructed to comment on the compliance of a proposal with the following policies, if applicable:

- 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. **Proposals that are determined to be Technically Unacceptable by a majority of the peer review panel will not be considered further for award.** A contract may be awarded only if the proposal has been recommended as Technically Acceptable by the peer review panel. However, *funding for any/all technically acceptable proposals is not guaranteed.* See [Section 6.4 – Award Decisions](#) for other considerations. For NIH only, the program staff of the Awarding Component will conduct a second level of review, subsequent to the peer review panel.

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 determined 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, measurable 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 	25%

FACTORS FOR PHASE I PROPOSALS	WEIGHT
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.)	
2. The potential of the proposed research for technological innovation.	25%
3. The potential of the proposed research for commercial application - whether the outcome of the proposed research activity will likely lead to a marketable product or process considering the offeror's proposed methods of overcoming potential barriers to entry in the competitive market landscape.	20%
4. The qualifications of the proposed Principal Investigators, Project Directors, 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 (those included in Fast Track submissions and those subsequently submitted by contractors who are awarded a Phase I contract under this solicitation) will be evaluated based on the criteria outlined below – subfactors are considered to be of equal importance:

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, measurable 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.) 	25%
2. The potential of the proposed research for technological innovation.	25%
3. The potential of the proposed research for commercialization, considering the offeror's Commercialization Plan, the offeror's record of successful commercialization for other projects, commitments of additional investment during Phase I and Phase III from private sector or other non-SBIR funding sources, and/or any other indicators of commercial potential for the proposed research.	25%

FACTORS FOR PHASE II PROPOSALS	WEIGHT
4. The qualifications of the proposed Principal Investigators, Project Directors, supporting staff and consultants, and the appropriateness of the leadership approach (including the designated roles and responsibilities, governance, and organizational structure).	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

The Awarding Component will make awards to the offerors who provide the best overall value to the Government, considering the following:

- Ratings resulting from the scientific/technical panel 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 August 25, 2017. 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 15, 2017** at 2:00 PM Eastern Daylight Time. This informational webinar will discuss this solicitation, including the electronic contract proposal submission (eCPS) website that must be used to respond to this solicitation.

Offerors may register for the webinar at: <https://attendee.gotowebinar.com/register/1195433406128202754>. 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). There are NO exclusions to the page limit. 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 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

To aid the Government in the efficient receipt and organization of your proposal files, please follow the following file naming conventions:

- a. The language entered into the 'Proposal Name' field in eCPS for your proposal submission should 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.

An example is provided below:

- Phase I_XYZ Company_ NCEZID_Topic_014

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 should 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 and Fast Track proposals are different and are outlined below. Pay special attention to the requirements concerning Human Subjects and use of Vertebrate Animals if your project will encompass either item.

8.2 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 the following:

TECHNICAL PROPOSAL

Item 1: Technical Element

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

BUSINESS PROPOSAL

Item 2: Pricing Proposal (Appendix C)

Item 3: SBIR Application VCOC Certification, if applicable

(See [Section 4.6](#) to determine if this applies to your organization)

Item 4: Proof of Registration in the SBA Company Registry

(Refer to [Section 4.17](#) for Directions)

Item 5: Summary of Related Activities (Appendix F)

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. Refer to Appendix A and Appendix C.

8.4 Phase II Proposal Instructions (NIH Only – For Fast Track Submissions)

A complete Phase II proposal (as part of a Fast Track submission) consists of the following:

TECHNICAL PROPOSAL

Item 1: Technical Element

- Technical Proposal Cover Sheet (Appendix D)
- Table of Contents
- Abstract of the Research Plan, (Appendix B)
- Content of the Technical Element
- Draft Statement of Work (Appendix E)
- 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 4.6](#) to determine if this applies to your organization)

Item 4: Proof of Registration in the SBA Company Registry

(Refer to [Section 4.17](#) for Directions)

Item 5: Summary of Related Activities (Appendix F)

Phase II proposals for this solicitation will only be accepted for Topics that allow for Fast Track proposals. Refer to the table in [Section 1](#) to see which Topics are allowing Fast Track 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. If submitting a proposal reflecting Multiple Principal Investigators/Project Directors (PIs/PDs), the individual designated as the Contact PI should be entered here.

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

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

For Phase II proposals, complete the form identified as Appendix D and use it as the first page of the proposal. No other cover sheet should be used. For the

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

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

For the “Project Title” field on each of these cover sheets, select a title that reflects the substance of the project. Do not use the title of the Topic that appears in the solicitation.

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.

8.8 Content of Technical Element (Item 1)

NOTE: Prior to preparing the Content of the Technical Element, applicants should refer to the specific research Topic in Section 12 to tailor the proposed research plan to the description, goals, anticipated activities, and budget set forth for the specific Topic.

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 PI/PD Leadership Plan (NIH Only).** For proposals designating multiple PIs/PDs, a leadership plan must be included. A rationale for choosing a multiple PI/PD 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 PIs/PDs and other collaborators.

If budget allocation is planned, the distribution of resources to specific components of the project or the individual PIs/PDs 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, identified in the cost proposal, and supported by appropriate letters from each individual confirming his/her role in the project which must be included.
- 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. For facilities other than those of the applicant, a letter must be submitted with the proposal stating that leasing/rental arrangements have been negotiated and will be available for the use of the SBIR applicant.

List the most important equipment items already available for this project, noting location and pertinent capabilities of each. Title to equipment purchased with Government funding by the SBIR awardee in relation to project performance vests upon acquisition in the Federal Government. However, the Government may transfer such title to an SBIR awardee upon expiration of the project where the transfer would be more cost-effective than recovery of the property. Any equipment and products purchased with Government funds shall be American-made, to the extent possible.
- 11) **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.

- a) **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](#).
- b) **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](#).

(B) Research Plan for Phase II proposals (including the Phase II Proposal of a Fast Track submission)

- 1) **Anticipated Results of the Phase I** - For Fast Track proposals: Briefly discuss and summarize the objectives of the Phase I effort, the research activities to be carried out, and the anticipated results.
- 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, 4.12, 8.10, 8.11, and 8.14](#) 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 – Limited to 12 pages.** Be succinct. There is no requirement for offerors to use the maximum allowable pages allotted to the Commercialization Plan. Provide a description in each of the following areas:
- a) **Value of the SBIR Project, Expected Outcomes, and Impact.** Describe, in layperson's terms, the proposed project and its key technology objectives. Clarify the need addressed, specifying weaknesses in the current approaches to meet this need. In addition, describe the commercial applications of the research and the innovation inherent in this proposal. Be sure to also specify the potential societal, educational, and scientific benefits of this work. Explain the non-commercial impacts to the overall significance of the project. Explain how the SBIR project integrates with the overall business plan of the company.
 - b) **Company.** Give a brief description of your company including corporate objectives, core competencies, present size (annual sales level and number and types of employees), history of previous Federal and non-Federal funding, regulatory experience, and subsequent commercialization, and any current products/services that have significant sales. Include a short description of the origins of the company. Indicate your vision for the future, how you will grow/maintain a sustainable business entity, and how you will meet critical management functions as your company evolves from a small technology R&D business to a successful commercial entity.
 - c) **Market, Customer, and Competition.** Describe the market and/or market segments you are targeting and provide a brief profile of the potential customer. Tell what significant advantages your innovation will bring to the market, e.g., better performance, lower cost, faster, more efficient or effective, new capability. Explain the hurdles you will have to overcome in order to gain market/customer acceptance of your innovation.

Describe any strategic alliances, partnerships, or licensing agreements you have in place to get FDA approval (if required) and to market and sell your product

Briefly describe your marketing and sales strategy. Give an overview of the current competitive landscape and any potential competitors over the next several years. (It is very important that you understand and know the competition.)

- d) **Intellectual Property (IP) Protection.** Describe how you are going to protect the IP that results from your innovation. Also note other actions you may consider taking that will constitute at least a temporal barrier to others aiming to provide a solution similar to yours.
- e) **Finance Plan.** Describe the necessary financing you will require, and when it will be required, as well as your plans to raise the requisite financing to launch your innovation into Phase III and begin the revenue stream. Plans for this financing stage may be demonstrated in one or more of the following ways:
 - 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.
- f) **Production and Marketing Plan.** Describe how the production of your product/service will occur (e.g., in-house manufacturing, contract manufacturing). Describe the steps you will take to market and sell your product/service. For example, explain plans for licensing, internet sales, etc.
- g) **Revenue Stream.** Explain how you plan to generate a revenue stream for your company should this project be a success. Examples of revenue stream generation include, but are not limited to, manufacture and direct sales, sales through value added resellers or other distributors, joint venture, licensing, service. Describe how your staffing will change to meet your revenue expectations.

Offerors are encouraged to seek commitment(s) of funds and/or resources from an investor or partner organization for commercialization of the product(s) or service(s) resulting from the SBIR contract. Your Phase III funding may be from any of a number of different sources including, but not limited to: SBIR firm itself; private investors or “angels”; venture capital firms; investment companies; joint ventures; R&D limited partnerships; strategic alliances; research contracts; sales of prototypes (built as part of this project); public offering; state finance programs; non SBIR-funded R&D or production commitments from a Federal agency with the intention that the results will be used by the United States government; or other industrial firms.

- 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.

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):

- 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.
- 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, such as the examples below. 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.

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 solicitation.

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 **include 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:
 - Avian influenza virus (highly pathogenic)
 - *Bacillus anthracis*
 - Botulinum neurotoxin
 - *Burkholderia pseudomallei*
 - Ebola virus
 - Foot-and-mouth disease virus
 - *Francisella tularensis*
 - Marburg virus
 - Reconstructed 1918 influenza virus
 - Rinderpest virus
 - Toxin-producing strains of *Clostridium botulinum*
 - Variola major virus
 - Variola minor virus
 - *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/IDC 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 4.21 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 in Appendix A, 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.

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 4.23.

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.

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)	29-45	Scientific and Technical Merit Review: March-May 2018 Anticipated Award Date: August-September 2018
National Institutes of Health (NIH) National Heart, Lung, and Blood Institute (NHLBI)	3-4	Scientific and Technical Merit Review: February-April 2018 Anticipated Award Date: July-September 2018
National Institutes of Health (NIH) National Institute of Allergy and Infectious Diseases (NIAID)	20-37	Scientific and Technical Merit Review: March 2018 Anticipated Award Date: August 2018
National Institutes of Health (NIH) National Institute on Drug Abuse (NIDA)	7-8	Scientific and Technical Merit Review: March 2018 Anticipated Award Date: August 2018
Center for Disease Control and Prevention (CDC) Center for Global Health (CGH)	1-2	Scientific and Technical Merit Review: May-June 2018 Anticipated Award Date: August 2018
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 2018 Anticipated Award Date: August 2018
Centers for Disease Control and Prevention (CDC) National Center for Emerging Zoonotic and Infectious Diseases (NCEZID)	5	Scientific and Technical Merit Review: May-June 2018 Anticipated Award Date: August 2018
Center for Disease Control and Prevention (CDC) National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (NCHHSTP)	2	Scientific and Technical Merit Review: May-June 2018 Anticipated Award Date: August 2018
Centers for Disease Control and Prevention (CDC) National Center for Immunization and Respiratory Diseases (NCIRD)	1	Scientific and Technical Merit Review: May-June 2018 Anticipated Award Date: August 2018

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
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NATIONAL HEART, LUNG, AND BLOOD INSTITUTE (NHLBI)

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NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES (NIAID)

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NATIONAL INSTITUTE ON DRUG ABUSE (NIDA)

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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
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Darlene Forrest, M.A. (Contractor)
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Gwen Barnett, M.P.H.
Deputy Director
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CENTER FOR GLOBAL HEALTH (CGH)

Theresa Routh-Murphy
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NATIONAL CENTER FOR CHRONIC DISEASE AND HEALTH PROMOTION (NCCDPHP)

Julio Lopez
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E-mail: JLopez3@cdc.gov

NATIONAL CENTER FOR EMERGING ZOOBOTIC AND INFECTIOUS DISEASES (NCEZID)

Priscilla Turner
Contracting Officer
Centers for Disease Control and Prevention
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Fax: (770) 488-2024
E-mail: PBTurner@cdc.gov

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

Priscilla Turner
Contracting Officer
Centers for Disease Control and Prevention
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E-mail: PBTurner@cdc.gov

NATIONAL CENTER FOR IMMUNIZATION AND RESPIRATORY DISEASES (NCIRD)

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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, 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 facilitate the transition of SBIR Phase II projects to the commercialization stage. The specific requirements for the previously offered Phase IIB Bridge Award can be reviewed in the full RFA announcement: <https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-17-024.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 Award grants. 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:

370 Targeted Therapy for Cancer- and Cancer Therapy-Related Cachexia

Fast-Track proposals will be accepted.

Number of anticipated awards: 2-3

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

Cachexia is characterized by a dramatic loss of skeletal muscle and adipose tissue mass, which cannot be reversed by nutritional intervention. More than half of all cancer patients experience cachexia, and it is estimated that nearly one-third of cancer deaths can be attributed to cachexia. Patients suffering from cachexia are often so frail and weak that walking can be extremely difficult. Cachexia occurs in many cancers, usually at the advanced stages of disease. Cancer cachexia is most prevalent in gastric, pancreatic, and esophageal cancer (80%), followed by head and neck cancer (70%), and lung, colorectal, and prostate cancer (60%).

Despite cachexia's impact on mortality and data strongly suggesting that it hinders treatment responses and patients' abilities to tolerate treatment, no effective therapies have been developed to prevent or hamper its progression. Even for patients able to eat—appetite suppression or anorexia is a common cachexia symptom—improved nutrition often offers no respite.

Overall, cachexia is characterized into three prominent stages, namely pre-cachexia, cachexia, and refractory cachexia. Pre-cachexia is characterized by some metabolic and endocrine changes, but weight loss is minimal. In cachexia, the patient undergoes more prominent weight loss, anorexia, muscle mass depletion, and reduced muscle strength. At this point, weight loss can be somewhat countered by health supplements and corticosteroids, but improved muscle function has not been achieved. In refractory cachexia, there is severe body weight, muscle, and fat loss; the reversal of weight loss is negligible even with the dietary supplements.

Over the last few years, researchers have begun to better understand the underlying biology of cancer- and cancer therapy-related cachexia. Findings from several studies point to potential therapeutic approaches, and a number of clinical trials of investigational drugs and drugs approved for other uses have been conducted or are under way.

Project Goals

The goal of this SBIR contract topic is to provide support for the development of targeted agents, including small molecules and biologics, to prevent or treat cachexia related to cancer and/or cancer therapy, including chemotherapy and/or radiotherapy. Proposals submitted in response to this topic must focus on cancer indications with the highest prevalence of cancer- and cancer therapy-related cachexia. Any route of administration is acceptable, but it must be kept in mind that once cachexia has developed, absorption in patients may be impaired.

To apply for this topic, offerors should:

- Identify a therapeutic target and explain in detail the mechanism by which their drug will exhibit efficacy in preventing or treating cancer- or cancer treatment-related cachexia.
- Provide preliminary data or cite literature to support the role of the target in the development of cancer- or cancer treatment-related cachexia.
- Demonstrate ownership of, or license for, at least one lead agent (e.g., compound or antibody) with preliminary data showing that the agent hits the identified target.
- Possess experience with well-validated *in vitro* assays and *in vivo* models.
- The scope of work proposed may include structure activity relationships (SAR); medicinal chemistry for small molecules, antibody, and protein engineering for biologics; formulation; animal efficacy testing; pharmacokinetic, pharmacodynamic, and toxicological studies; as well as production of GMP bulk drug and clinical product. These data will establish the rationale for continued development of the experimental agent to the point of filing an investigational new drug application (IND).

Activities not supported by this topic:

Proposals involving supplements and food products will not be considered.

Phase I Activities and Deliverables

- Demonstrate *in vitro* efficacy for the agent(s) in appropriate models.
- Conduct structure-activity relationship (SAR) studies, medicinal chemistry, and/or lead biologic optimization (as appropriate).
- Perform animal toxicology and pharmacology studies as appropriate for the agent(s) selected for development.
- Perform animal efficacy studies in an appropriate model of cancer- or cancer treatment-related cachexia. Include controls to preclude drug-drug interactions (e.g., the drug for cachexia should not decrease efficacy or increase toxicity for the cancer drug).
- Develop a detailed experimental plan necessary for filing an IND or an exploratory IND (for potential SBIR phase II award).

Phase II Activities and Deliverables

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

371 Drugs to Exploit the Immune Response Generated by Radiation Therapy

Fast-Track proposals will be accepted.

Number of anticipated awards: 2-3

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

Tumor irradiation promotes recruitment of immune activating cells into the tumor microenvironment, including antigen presenting cells that activate cytotoxic T-cell function. However, tumor irradiation can also recruit immunosuppressive cells into the tumor microenvironment. Local irradiation can also impact tumor growth at a distance from the irradiated tumor site, known as the abscopal effect. This effect is potentially important for tumor control and is mediated through ceramide, cytokines, and the immune system.

Several factors can influence the ability of radiation to enhance immunotherapy, including a) the dose of radiation (IR) per fraction and the number of fractions; b) the total dose of IR; and c) the volume of the irradiated tumor tissue. However, the impact of these variables is not well understood. Inducing anti-tumor, cellular-mediated immune responses has been the subject of some pre-clinical tumor regression studies and is being applied in immune-modulatory clinical trials using antibodies against molecules that suppress immune responses such as PD1, PDL1, and CTLA4 or immune agonists such as OX40, CD27, GITR, 4-1BB, TNFR receptors, ICOS, and VISTA. Overall, discovery of checkpoint protein functional control of T-cells in tumor microenvironment led to the development of checkpoint blockade therapies and many checkpoint inhibitors including Nivolumab, Pembrolizumab, and Atezolizumab, which have been approved by the FDA for several indications. Several clinical trials testing combination of radiation with check point inhibitors are underway and have resulted in mixed results. Furthermore, many of these combination trials lack robust, pre-clinical scientific rationale, raising queries if such checkpoint agents augment the immune modulating effects of radiation. Hence, more agents that can augment immune activation or inhibit immune suppression induced by standard conventional 2 Gy fractions, (3-8 Gy) hypofractionation, and high-dose hypofractionated (>10 Gy) radiotherapy are warranted.

Project Goals

The broad goal of this Topic is to develop agents (cellular therapies, antibodies, small molecules, or miRNA/siRNA/CRISPR-CAS9 based approaches) that can augment (immune stimulation) or negate (immune suppression) one or more of the immune modulation events induced by radiation discussed above. IR can include conventional clinically relevant radiation, hypofractionated radiation, and high-dose hypofractionated radiation. Ionizing radiation (RT) causes changes in the tumor microenvironment that can lead to intra-tumoral as well as distal immune modulation (i.e., so-called abscopal phenomenon). Tumor-associated antigens (TAAs) are released by irradiated dying cancer cells triggering danger signals such as heat-shock protein (Hsp), HMGB1, and calreticulin (i.e., “eat-me” signal for phagocytes). These TAAs and cell debris are eaten by phagocytes such as macrophages, neutrophils, and dendritic cells for antigen processing and presentation. At the same time, RT can induce increased expression of tumor antigens and MHC class I molecules on tumor cells. Consequently, activated antigen presenting cells (APCs) migrate to the draining lymph node, further mature upon encountering T helper cells, and release interferons (IFNs) and IL-12/18 to stimulate Th₁ responses that support the differentiation and proliferation of antigen-specific CTLs. Activated antigen-specific CTLs traffic systemically from the draining lymph node to infiltrate and lyse in primary as well as distal tumors. Concomitantly, tumor irradiation can also recruit immunosuppressive cells into the tumor microenvironment. Further, expression of certain negative stimulatory molecules on T-cells and tumor cells (e.g., CTLA-4, PD-1, PDL1) are induced by RT and can curtail the activation of T-cells, leading to an immune suppressive environment. Other immune suppressive function of radiation can occur through induction IL-10 and TGF- β . Augmentation or inhibition of radiation induced immune activation and suppression could enhance anti-tumor effects.

Activities not supported by this topic:

Immune modulating agents that are already being tested in combination with radiation in clinical trials will not be supported. Immune modulating agents that augment or negate immune functions **in the absence of radiation** will not be supported.

Phase I Activities and Deliverables

- Selection of cancer type(s), organ site(s), immune modulation agent(s), and radiation dose & fractions, with adequate justification.
- Proof of concept animal (e.g., mice or rat) studies demonstrating augmentation or inhibition of radiation-induced immune activation or suppression respectively with the combination of radiation and the agent.
 - Demonstrate augmentation of immune activation in irradiated environment with appropriate standard markers showing an increased influx of positive effector immune cells (e.g., T-cells, macrophages, dendritic cells, etc.) in the tumor micro environment.
 - Demonstrate negation of immune suppression in irradiated environment with standard appropriate markers showing reduction in the influx of negative effector immune cells (e.g., neutrophil, T-reg, and MDSCs) in the tumor micro environment.
- Proof of concept animal (e.g., mice or rat) studies demonstrating tumor regression in a syngeneic contra-lateral tumor model whereby regression is observed in both the irradiated primary tumor as well as distal non-irradiated tumor when the agent is combined with radiation.

Phase II Activities and Deliverables

- Perform absorption, distribution, metabolism, and excretion (ADME) of agents with bioavailability and efficacy studies in appropriate animal models with adequate justification. The models chosen may be syngeneic rodent models, humanized rodent models, or canine models and should demonstrate:
 - Improved efficacy, both immune modulation and tumor regression, compared to radiation or agent alone.
 - Radiation sensitizing effects on tumors using standardized *in vivo* radiation regrowth delayed assays.
 - Comparative (i.e., similar or lower) toxicity compared to the agent or radiation alone.
- Perform IND-enabling GLP safety toxicology studies in relevant animal model(s) following FDA guidelines.
- For offerors that have completed advanced pre-clinical work, NCI may support pilot human trials.

372 Development and Validation of Non-Mouse Reagents to Enable Preclinical Development of Novel Therapeutics

Fast-Track proposals will 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 preclinical development of cancer therapeutics, including the recent trend and focus on cancer immunotherapies, is evolving from the traditional use of mouse models to the use of other animal models including canine, rat, and minipig. Each of these non-mouse models carries its own advantages and abilities to increase the clinical relevance of the model as compared to mouse models. Yet, the wide use of these models for preclinical validation of novel therapeutics is limited by multiple factors including the availability of analytically validated reagents, such as antibodies, and aptamers, for each model system.

While this topic is not limited to the development of canine reagents, canine reagents are of particular interest. Canine models may be particularly useful for the development of novel therapeutics, as canines have intact immune systems that can be used to study the interactions of therapeutics with the immune system. Canine models include companion dogs with spontaneous cancer. It has been shown that canines metabolize drugs similarly to humans (unlike mice), are amenable to serial biologic sample collections, and have comparable tumor biology. Importantly, canines have been shown to respond to human cancer therapeutics. Canine models would be especially valuable for the testing of immunotherapies, as the availability of fully immune competent mouse models is quite limited. While canines are more expensive than mice, canine trials are not nearly as expensive as human trials as the trials can be completed much faster due to shorter progression-free intervals and overall survival times.

A commercial supplier of reagents resulting from this topic is advantageous, as it could provide both the analytical validation for each reagent and a long-term source, as compared to academic labs that may produce reagents for each set of studies. The need for animal model-specific, analytically validated reagents includes a wide range of reagents and antibodies that would enhance the ability to test therapeutics within that animal model. For example, analytically validated canine reagents demonstrated to be both renewable and reproducible would both expand the suite of validated assays amenable to canine studies and provide a long-term commercial source of reagents for follow-up studies. This topic is in line with the Cancer Moonshot Blue Ribbon Panel's Recommendation to support a Cancer Immunotherapy Translational Science Network.

Project Goals

The development and ultimate commercialization of analytically validated, non-mouse reagents will facilitate more robust preclinical evaluation of novel therapeutics. Currently, there are several hundred active combination clinical trials involving at least one immunotherapeutic, which is partially a result of the lack of clinically predictive model systems. Reagents developed under this topic are likely to facilitate the use of additional clinically relevant animal models. Thus, a *short-term goal* of this topic is the creation of a set of reagents that will enable additional preclinical testing of novel therapeutics. In addition, the development of reagents for clinical testing in companion animals (such as canines) will facilitate additional market opportunities and impact of newly developed therapeutics. Thus, the long-term goal of this contract topic is to enable better demonstration of the utility of novel therapeutics for administration in both humans and companion animals. While reagents that enable the use of models for the testing of immunotherapeutics are of particular interest, proposals to develop reagents for the testing of other therapeutic approaches, such as chemotherapy and radiation approaches, will be considered if a strong rationale is provided for the need of such reagents.

Materials developed under this topic may include, but are not limited to, reagents for a wide variety of preclinical assays for target validation, characterization of immune response, mass cytometry, and pharmacodynamic assays. Potential offerors should demonstrate the current need and potential utility of newly developed reagents. The targets and applications of newly developed reagents must be targets and applications that have relevance to the potential clinical efficacy, toxicity, or mechanism of action of newly developed therapeutics. Reagents that will enable immune-relevant assays in non-mouse models, which are not currently possible and/or predictive in mouse models, are of particular interest.

The offerors should provide all relevant controls, reference standards, protocols, and SOPs. In the Phase I, the offerors should develop and validate an appropriate number of reagents and should provide justification for the choice of the number developed (e.g., novelty, utility, and complexity). Analytical validation and characterization of the reagent(s) should include, as appropriate, but not limited to: purity, concentration, storage conditions, reference standards, specificity, linearity, and limits of detection (LOD).

Proposals should demonstrate the broad utility of the developed reagents and assays, as the reagents' utilities should extend beyond one specific researcher/research project. Proposals should identify the potential utility of the assay(s) and how it addresses an unmet need. Demonstration of potential utility should include a description of which therapeutics would be the focus of the reagents/assays developed through this topic. Quantitative milestones that can be used to evaluate the utility of the reagents should be clearly defined and justified.

Phase I Activities and Deliverables

- Analytically validate and characterize the reagent(s) for a number of parameters including, as appropriate, but not limited to: purity, concentration, storage conditions, reference standards, specificity, linearity, limits of detection (LOD), range, accuracy, and precision.
- Develop pertinent controls and reference standards.
- Conduct tests to characterize the developed reagents to ensure rigor and reproducibility:
 - Reagents designed for *in vitro* assays: Proposals should demonstrate likelihood of obtaining pertinent non-mouse samples, and projects must include feasibility testing of the characterization test. Veterinary schools are a potential source of canine tumor/matched normal tissue samples.
 - Reagents designed for *in vivo* assays: Proposals should demonstrate the rationale for feasibility testing *in vivo*, and projects should include sufficient characterization to suggest proof of concept. In Phase I, it is not required to conduct *in vivo* studies.
- Provide a proof-of-concept SOP for the reagents and assays. The SOP should include necessary information on the required equipment, operating parameters, sample preparation, standards control solution preparation, procedure, system suitability, calculations, data reporting, and statistics.
- Demonstrate renewability and reproducibility of the developed reagents.

Phase II Activities and Deliverables

- Scale-up production of the reagents to produce sufficient quantities for proof of concept studies.
- Refine the assays to CLIA-grade, as appropriate.
- Establish quality control measures and carryout critical reagent supply chain audits.
- Demonstrate proof-of-concept and compare to currently available assays as a means of validating the proposed reagents.
- Provide a complete and final SOP based on the studies conducted in Phase II.

373 Tools and Technologies for Monitoring RNA Modifications

Fast-Track proposals 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 \$1,500,000 for up to 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. This topic is in line with the Cancer Moonshot Blue Ribbon Panel’s Recommendation to support Development of New Enabling Cancer Technologies.

Project Goals

As discussed at a workshop hosted by the NCI Division of Cancer Biology on ‘[RNA Editing, Epitranscriptomics, and Processing in Cancer Progression](#),’ and at other meetings, 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 may include, but are not limited to:

- 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.
- Products that would enable the *in vitro* or *in vivo* imaging of modified RNA molecules.
- Assay systems or reagents that facilitate the discovery, detection, or quantitation of modified messenger RNAs and/or circular RNAs.
- Well-validated antibodies, affinity reagents, or affinity-based assay kits for detection, quantitation, or immunoprecipitation of modified RNAs. *Note, however, that antibodies for N6 Methyladenosine (M6A) would be considered low priority.*
- 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.
- 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 the proposed 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 compare the tool or technology to existing approaches if applicable.
- Demonstrate 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, and equipment required for use.
- Provide justification 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.
- Provide proof-of-concept data demonstrating the monitoring of the specific RNA modification(s) in relevant cell or animal models with the potential to benchmark data across a variety of cancer models.

Phase II Activities and Deliverables

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

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, or *in vivo* animal models of cancer).
- Refine SOPs to allow for user friendly implementation of the tool, technology, or product by the target market.

374 Novel Approaches for Local Delivery of Chemopreventive Agents

Fast-Track proposals will be accepted

Number of anticipated awards: 3-5

Budget (total cost 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 clinical value of an agent is reflected by both its efficacy and its toxicity. In the chemoprevention space, where agents are administered to a relatively healthy (albeit high-risk) population, the intention is to minimize toxicity. Most chemopreventive agents require administration over long periods of time. This limit on toxicity presents a major challenge in the development of chemopreventive agents with acceptable benefit risk ratios.

Our ability to identify populations at higher risk of developing cancer has significantly improved over the past decade. For example, women with Hereditary Breast and Ovarian Cancer syndrome (HBOC) are at increased risk of developing breast and ovarian cancer, and potentially other cancers (e.g., pancreatic); individuals with Lynch syndrome are at increased risk of developing multiple cancer types including colorectal, endometrial, ovarian, and gastric cancer. We are also able to detect

cancer at earlier stages and often as precancerous lesions. Multiple studies have shown that these individuals at high risk for cancer or with precancerous lesions could benefit from chemoprevention approaches. A small number of chemopreventive agents have found some degree of success in the clinic, including tamoxifen and raloxifene for breast cancer prevention, and aspirin and celecoxib for colorectal cancer prevention. However, the systemic toxicities of these agents have limited their widespread use and acceptability.

Local agent delivery is an important strategy to reduce toxicity of chemopreventive agents, while maintaining clinical benefit. Local delivery of an agent can be performed by a physician or self-administered by an individual, which overcomes some of the access barriers that exist in healthcare. A localized chemoprevention approach is ideal in high risk individuals or individuals with premalignant diseases, as the agent can be applied locally to provide high drug concentrations at specific locations from where early disease would originate, while limiting systemic toxicity.

Project Goals

The goal of this topic is to advance the development and/or application of local delivery devices or formulations for chemoprevention. The technology should be designed for effective delivery of agent to a specific organ while minimizing systemic toxicities. Acceptable toxicities will depend on the agent and target population. Toxicity should not exceed minimal grade 2 local toxicities, while short term local grade 3 toxicity may be acceptable in some populations. The proposed local delivery device/formulation may utilize any technology or agent capable of meeting the goals of this topic. Examples of local administration include topical (for oral, breast, skin or cervical cancers), inhalant (for lung or esophageal cancers), or digestive (for esophageal, stomach, or colorectal cancers). Proposals for development of local delivery devices or formulations via other administration routes or for other cancer types are also encouraged.

The activities that fall within the scope of this contract solicitation include development and application of local delivery formulations or devices. Examples of appropriate activities include pre-clinical toxicity and efficacy studies in appropriate animal models, acceptability studies, and initial first-in-human testing. A local delivery approach for FDA approved chemoprevention agents or for novel chemoprevention agents may also be developed. For novel chemoprevention agents, significant reduction in cancer incidence in suitable cancer prevention animal models should be demonstrated. Phase II clinical trials and beyond are not appropriate for this mechanism; investigators are encouraged to seek support for these studies from alternative NCI programs.

Phase I Activities and Deliverables

- Select cancer type(s), organ site(s), chemoprevention agent(s), and method(s) of local delivery with adequate justification.
- Demonstrate that the chemoprevention agent is:
 - Stable in local formulation and/or when incorporated with the local delivery device/technology.
 - Released at the organ(s) of interest when incorporated into a local delivery device/technology.
- Perform preliminary proof-of-concept of the local delivery approach in a suitable animal model and demonstrate:
 - Accumulation/presence (>90% higher concentration) of the agent at the organ/tissue of interest than in the circulation.
 - At least 90% reduction in agent concentration in the blood compared to systemic delivery / administration.
 - Efficacy of the agent with relevant standard tests based on MOA of the agent (e.g., proliferation assay, apoptosis assay)
 - Significant reduction in toxicity with the local approach compared to systemic administration; relevant organ observed toxicity could be used with appropriate justification

Phase II Activities and Deliverables

- For agent(s) (or their metabolites) with known chemoprevention effect when administered systemically (FDA approved):
 - Demonstrate efficacy in suitable animal model(s)
 - Perform ADME, bioavailability and efficacy studies of the local delivery approach in suitable animal model(s) and demonstrate:

- at least same level of agent concentration at the organ/tissue of interest compared to systemic delivery/administration.
 - at least 90% higher concentration of the agent in the organ of interest than in the circulation.
 - at least 90% reduction in agent concentration in the blood compared to systemic delivery/administration.
 - at least same level of efficacy demonstrated with appropriate standard tests reflecting the MOA of the agent (e.g., proliferation assay, apoptosis assay) compared to systemic delivery/administration.
- Perform maximum tolerated dose (MTD) and/or biological active dose study and demonstrate superior therapeutic index using local approach compared to systemic administration with adequate justification.
 - Toxicity should not exceed minimal grade 2 systemic toxicities while short term local grade 3 toxicity may be acceptable in some populations.
- IND-enabling studies
 - Develop and execute an appropriate regulatory strategy; schedule pre-IND meeting with the FDA.
 - Perform IND-enabling GLP safety toxicology studies in relevant animal model(s) following FDA guidelines.
- For novel (non-FDA approved) chemoprevention agent(s):
 - Demonstrate efficacy in suitable animal model(s)
 - Perform ADME and bioavailability and efficacy studies of the local delivery approach in suitable animal model(s) and demonstrate:
 - reduction of oncogenic molecular/cellular characteristics reflecting the MOA of the agent (e.g., proliferation assay, apoptosis assay).
 - at least 50% reduction in cancer incidence following local administration of the chemoprevention agent in suitable cancer prevention animal model(s).
 - at least 90% higher concentration of the agent in the organ of interest than in the circulation.
 - at least 90% reduction in agent concentration in the blood compared to systemic delivery/administration.
 - Perform maximum tolerated dose (MTD) and/or biological active dose study and demonstrate superior therapeutic index using local approach compared to systemic administration with adequate justification.
 - Toxicity should not exceed minimal grade 2 systemic toxicities while short term local grade 3 toxicity may be acceptable in some populations.
 - Perform IND-enabling safety toxicology studies in relevant animal model(s) to warrant a type B or type C meeting with the FDA.
- For offerors that have completed advanced pre-clinical work, NCI may support pilot human trials.

375 Diagnostic Imaging for Cancer Immunotherapies

Fast-Track proposals will be accepted.

Number of anticipated awards: 3-4

Budget (total costs, per award):

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

Phase II: up to \$2,200,000 for up to 2 years

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

Summary

Immunotherapies have emerged as one of the promising approaches for cancer treatment by exploiting patients' own immune systems to specifically target tumor cells. However, it has been recognized that responses often occur in only a subset of patients in any given immunotherapy. This treatment is also associated with drug toxicity (e.g., cytokine storm) and high cost. As this treatment modality continues to evolve, a significant clinical question that needs to be addressed is to determine which patients would benefit from immunotherapies. In addition, there is increasing need for newer methods to evaluate the efficacy and potential toxicities of the treatment, and monitor cancer patients' prognosis.

Diagnostic imaging is routinely used to: 1) stratify patients for cancer treatment; and, 2) monitor and provide reliable predictive and/or prognostic information for a specific treatment. With the rapid advancement of imaging technologies, particularly molecular imaging technology development, this technique provides detailed visualizations and measurements of biologic processes taking place inside the body at molecular, cellular, and genetic levels. It offers capability to assess not only changes in a patient's tumor size, but also changes in molecular expression and cellular activity. Diagnostic imaging provides nearly real-time information about tumor target expression levels, potentially allowing physicians to predict which patients may respond to therapies. In addition to patient stratification, diagnostic imaging of therapeutic targets may provide insight into the efficacy and toxicity of the cancer treatment and overall disease progression.

The purpose of this initiative is to provide much needed support for the development of diagnostic imaging technologies to identify patients who are likely to respond to cancer immunotherapies, evaluate the efficacy and potential toxicities of the treatment, and/or monitor cancer patients' prognosis. The cancer immunotherapies for this topic will include the ones that either have been approved by the FDA, or are still under clinical development. This topic is intended specifically to address cancer immunotherapies that depend upon eliciting an immune response. Projects that do not meet this requirement will not be funded. For example, a monoclonal antibody based therapy that exerts a direct antitumoral effect either by neutralizing the antigen or by activating signaling pathways within the target tumor cells, but does not elicit an immune response for its clinical application, is not considered an immunotherapy and would not be funded. It should be noted that technologies that map the tumor and/or its microenvironment to predict response to immunotherapy should submit the proposal to the topic, "Imaging-Based Tools for Longitudinal and Multi-Dimensional Mapping of the Tumor and its Microenvironment." The "Diagnostic Imaging for Cancer Immunotherapies" topic is in line with the Cancer Moonshot Blue Ribbon Panel's Recommendation to support Development of New Enabling Cancer Technologies.

Project Goals

The goals of the project are to develop a diagnostic imaging technology to identify patients who are likely to respond to cancer immunotherapies, evaluate the efficacy and potential toxicities of the treatment, and/or monitor cancer patients' prognosis. The imaging modality could be one of the following, but is not limited to: optical imaging, PET, SPECT, or MRI. Molecular markers of interest could include but are not limited to: cell surface receptors, immune cells, cellular infiltrates, enzymes, DNAs, or RNAs. The technology development should be platform driven. For example, the procedure for the diagnostic imaging that targets immunotherapy for breast cancer or its subtype should be easily applied for other cancer types/subtypes, such as colon cancer or prostate cancer. To apply for this topic, offerors need to outline and indicate the clinical question and unmet clinical need that their diagnostic imaging will address. Offerors are also required to use validated imaging targets. This solicitation will not support efforts for imaging biomarker discovery.

The long-term goal of this contract topic is to enable small businesses to bring novel modalities of fully developed diagnostic imaging for cancer immunotherapies to the clinic and the market.

Phase I Activities and Deliverables

Phase I activities should generate scientific data confirming the clinical potential of the proposed molecular diagnostic imaging for cancer immunotherapies. The Phase I research plan must contain specific, quantifiable, and testable feasibility milestones.

Expected activities may include:

- Demonstrate proof-of-concept for the development of a diagnostic imaging technology to identify patients who are likely to respond to immunotherapies, and/or evaluate efficacy and toxicities of immunotherapy, and/or monitor tumor prognosis under immunotherapy using the imaging technology.
- Quantify sensitivity and specificity of the imaging technology.
- Conduct preliminary biosafety study for the imaging technology.
- Present Phase I results and future development plan to NCI staff.

Phase II Activities and Deliverables

Phase II should follow the development plan laid out in the Phase I, and should further support commercialization of proposed diagnostic imaging for cancer immunotherapies. The Phase II research plan must contain specific, quantifiable, and testable milestones.

Expected activities may include:

- Complete all pre-clinical and/or clinical experiments according to the development plan.
- Demonstrate capability of diagnostic imaging to: 1) identify whether cancer animal models and/or human patients respond to cancer immunotherapies; and/or, 2) evaluate efficacy and toxicities of cancer immunotherapies in animal models and/or human patients; and/or, 3) monitor tumor prognosis in animal models and/or human patients under cancer immunotherapies.
- Demonstrate high sensitivity and specificity of the imaging technology in animal models and/or human patients.
- Demonstrate high reproducibility and accuracy of the imaging technology in animal models and/or human patients.
- Determine biosafety of the imaging technology with animal or human toxicology studies.
- If warranted, initiate FDA approval process for the candidate imaging technology.

376 Imaging-Based Tools for Longitudinal and Multi-Dimensional Mapping of the Tumor and its Microenvironment

Fast-Track proposals will 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

Evolution of cancer is complex: from the early lesion to the development of primary tumor to widespread metastasis, numerous and complex interactions occur among normal and malignant cells, as well as their microenvironment. Studies on cancer progression and treatment have mostly focused on molecular underpinnings and pathways associated with these interactions at a single point in time under the assumption of a homogenous cell population. Within the last decade, researchers have found that tumor and its environment (TME) consist of a multitude of cell types. It's believed this heterogeneity contributes to unpredictable tumor behaviors and poses significant therapeutic challenges. We have limited knowledge in how the characteristics and interactions of a tumor and TME change in time during tumor progression and cancer treatment.

Tracking and understanding the dynamic evolution of heterogeneous cell populations and molecular characteristics within the tumor and its microenvironment (TME) would add significant knowledge on cancer progression and could lead to the development of novel therapeutics and more efficacious treatment strategies. The TME has an abnormal vasculature, stromal components, and immune cells, which are embedded in an extracellular matrix (ECM). The TME, which plays a critical role in tumor initiation, malignant progression, and metastasis and response, has been shown to hamper drug delivery and contribute to drug resistance. For this reason, research efforts and discoveries focusing on both tumor-killing and TME-remediation can synergistically improve cancer treatment efficacy. Concurrently, administration of anti-angiogenic or antifibrotic agents during chemotherapy has been shown to improve therapeutic outcome by curtailing TME-imposed barriers

to drug delivery to tumor sites. Over the recent years, immunotherapies utilizing checkpoint inhibitors to modulate the immune components of tumor cells and TME have been approved for multiple cancer types, and more are currently undergoing clinical trials; however, immunotherapies are only effective in a restricted group of patient populations.

The evaluation of tumor and TME at the molecular and cellular level is often based on histopathological analysis of tumor biopsies. However, these methods are invasive and lack spatial and temporal information; thus, the ability to use tumor and TME-associated molecular and cellular signatures for tumor prediction, diagnosis, prognosis, and therapy response are rather limited. Techniques capable of temporal *in vivo* molecular characterization and cell mapping of the tumor and its TME, in its physical location and over time, can accelerate lead compound identification, assist in patient stratification, monitor therapeutic response and modulate therapy accordingly.

Recent advances in **imaging** techniques are enabling assessment of tumor and 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 pre-malignant, tumor and 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 tumor or TME-associated molecular targets has been used in pre-clinical and clinical settings. All these *in vivo* methods are valuable tools to spatiotemporally examine the targeting efficiency and associated molecular events, and provide insight into the normalization of tumor and TME and its effect on anticancer drug delivery. 'Bio-activatable' delivery vehicles allow for controlled drug delivery, which is activated only by the change of tumor and TME parameters. However, most of these studies are pre-clinical, and the imaging modalities have mostly been limited to pre-clinical studies.

Dynamic or longitudinal evaluation of the molecular characteristics and cell populations in tumor and its TME within an individual patient is an effective and personalized strategy for early detection of cancer, the prognosis of tumor progression as well as prediction of treatment outcome. To accelerate research and translational efforts focused on dynamic profiling of tumor and TME in real time, the National Cancer Institute (NCI) requests proposals for the development of clinically viable *in vivo* technologies that can enable enhanced mapping of human tumors. This topic is in line with the Cancer Moonshot Blue Ribbon Panel's Recommendation to support Generation of Human Tumor Atlases.

Project Goals

Tumor diagnosis at an 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 tumor response to treatment is essential to prevent the use of ineffective treatment options and allow alternative treatment options. As such, the ability to characterize the dynamic changes in tumor and TME at the molecular and cellular levels in an individual patient for early diagnosis and during treatment is critical. 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 **goal** of this topic is to develop non-invasive, *in vivo* imaging-based platforms that can repeatedly generate three-dimensional molecular and cellular maps of the tumor and its TME at different time points for diagnosis and treatment prediction/response. With the emergence of promising immunotherapies, technologies and molecular imaging approaches to track immune response to immunotherapies are of particular interest. The proposed technology should be focused on interrogating one or more of the following tumor and TME parameters across time via *in vivo* imaging techniques with cellular resolution. The proposed imaging technology should provide three-dimensional information at any given time point. Potential molecular, cellular and physiological parameters to be measured may include but are not limited to the following:

- Gene expression profiles
- Protein expression profiles
- Maps of invading immune cell types in response to immunotherapy
- Maps of various cell types and subtypes in tumor or TME
- Tissue oxygenation profiles
- Vasculature and stromal structures
- Tissue integrity and/or pH
- Maps of enzymatic activities

This contract topic is agnostic to the imaging modality proposed. 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, optical, photoacoustic and ultrasound. Novel or currently existing imaging agents or probes (targeting certain molecular or cellular signatures) may be developed and optimized to enable molecular, cellular, and physiological measurements. The goal of the topic is to develop imaging tools for tumor and TME in the clinic; hence, the tools developed need 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 funded. Examples of inappropriate proposals 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), chemical constructs or linkers that are inherently toxic or immunogenic, and agents/probes that focus on molecular targets that do not have human equivalent. Image-based companion diagnostics that do not incorporate mapping of the tumor or TME are not appropriate for this topic and may better address the topic “Diagnostic Imaging for Cancer Immunotherapies.”

Phase I Activities and Deliverables

Phase I activities should generate scientific data to confirm clinical potential of the proposed agent and imaging capability with cellular resolution. Expected activities and deliverables should include but are not limit to:

- Optimize detection scheme to demonstrate *in vitro* signal specificity and correlate signals to molecular target concentrations measured using conventional assays.
- 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.
- Demonstrate feasibility in generating maps of measurable parameters as a function of time.
- If new molecular targets are proposed, demonstrate specific binding/targeting capabilities of the agent/probe to the molecular target (tumor and/or TME target).
- Determine optimal dose and detection window through proof-of-concept small animal studies with evidence of systemic stability and minimal toxicity.
- Benchmark experiments against current state-of-the-art methodologies. For successful completion of benchmarking experiments, demonstrate a minimum of 5x improvement against comparable methodologies.

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 *in vivo* clearance, tumor accumulation, *in vivo* stability, bioavailability, and the immunogenicity / toxicity of imaging agents or probes.
- Demonstrate high reproducibility and accuracy of the imaging agents or probes in multiple relevant animal models.
- Demonstrate superiority over currently available imaging tools in image resolution.
- Demonstrate that sensitivity of proposed imaging agents or probes is sufficient to detect *in vivo* perturbation.
- Demonstrate sensitive maps of measurable parameters as a function of time.
- Perform toxicological studies.
- Demonstrate clinical utility.
 - For diagnosis, demonstrate that the probes can detect tumors at early stages and demonstrate superiority to current diagnosis methods.
 - For predictive/decision, 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, 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.

377 Bridging the Guideline Implementation Gap: Clinical Decision-Support to Improve Cancer Symptom Management

Fast-Track proposals will be accepted.

Number of anticipated awards: 1-2

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

Uncontrolled symptoms during and following cancer treatment have been associated with emotional distress; diminished functional status and health-related quality of life; treatment delays, discontinuation, and non-adherence; and unplanned hospitalizations and emergency room visits. The evaluation and management of symptoms in cancer care, including multiple co-occurring symptoms (e.g., pain, depression, and insomnia), is complex.

A plethora of evidence-based clinical practice guidelines (CPG) for managing cancer-related symptoms have been developed by national organizations that include the Oncology Nursing Society (ONS), American Society of Clinical Oncology (ASCO), Multinational Association for Supportive Care in Cancer (MASCC), National Comprehensive Cancer Network (NCCN), European Society for Medical Oncology (ESMO), American Cancer Society (ACS), and the National Cancer Institute (NCI). However, implementation of these guidelines in practice has to-date been limited and haphazard, and the available guidelines are not offered to clinicians in a readily actionable format. Sifting through the options contained in multiple guidelines and determining the best approach for a specific patient takes more time than clinicians typically have available. Electronic decision-support would help to bridge this guideline implementation gap, and would allow for rapid dissemination into practice of both new guidelines and guideline updates.

Clinical Decision Support (CDS) is a health information technology designed to directly aid in clinical decision-making. CDS matches the characteristics of individual patients to a computerized knowledge base, and generates patient-specific assessments and recommendations. CDS provides clinicians and other stakeholders with pertinent knowledge and person-specific information, intelligently filtered, and delivered at appropriate times in clinical workflow to enhance health and healthcare delivery (Osheroff et al. JAMIA 2007; 14 (2), 141-145). The overall goal of CDS-Sx is to support health professionals in delivering personalized, evidence-informed, guideline-based clinical decision-making to improve the evaluation and management of cancer-related symptoms.

NCI Blue Ribbon Panel (BRP) Implementation Science Working Group Report urged an immediate strategic investment to provide *actionable decision support that accelerates the implementation of evidence-based cancer symptom management guidelines*. CDS for symptom management addresses recommendations made by the National Academy of Medicine (NAM), National Quality Forum, and the Coalition to Transform Advanced Care for improvements in symptom management and palliative care across the cancer continuum.

This topic requests proposals to create a system of computable algorithms to improve oncology clinicians' evaluation and management of common cancer-related symptoms, leveraging nationally endorsed, evidence-based CPGs. The algorithms would be delivered within a CDS that also includes a small set of well-curated resources for patient self-management support, ICD-10 coding, and other features to streamline clinician workflow and support coordinated interdisciplinary symptom management such as templated progress notes and referral pathways. The algorithms will be constructed such that the sequence of evaluation and management activities is triggered by patient-reported outcomes (PRO) data derived from a variety of contemporary PRO measurement systems (e.g., PRO-CTCAE, PROMIS, and NCCN symptom indices) and would offer decision support relevant across the cancer continuum from treatment to survivorship and end-of-life. At commercial scale, the CDS would allow for information to be exported into an electronic health record. This topic is in line with the Cancer Moonshot Blue Ribbon Panel's Recommendation to support Symptom Management Research.

Project Goals

Despite the plethora of evidence-based cancer CPGs for cancer symptom management, implementation is inconsistent in practice. There are few commercially available decision-support systems that provide guideline-based recommendations in interpretable and actionable ways to healthcare providers at the point-of-care. NCI investment in the development of CDS for symptom management has been sparse.

The overall objective is to develop an electronic, rule-based, clinical decision-support system for symptoms (CDS-Sx) that leverages national CPGs to improve the evaluation and management of symptoms during and following cancer treatment.

This objective will be accomplished by:

- *Creating and validating software-ready computable algorithms* for evaluation and management of eight common cancer-related symptoms that have associated national CPGs for cancer symptom management.
 - Computable algorithms will be iteratively developed by panels comprising clinical experts and experts in rule-based CDS system design, leveraging nationally endorsed symptom management guidelines, and aligned to an existing data standard to ensure interoperability with downstream systems.
 - Algorithms will be tailored to different levels of symptom severity and interference, as well as to other clinical and demographic factors such as concurrent symptoms (e.g., depression in the setting of pain and fatigue), disease site, treatment type, age, concurrent medications, comorbid conditions, and allow tailoring to patient goals and preferences.
 - Options for site-specific customization of the algorithms, particularly with respect to resources available at the practice site (e.g., referrals to specialized consult teams) will be included.
 - Included with the algorithm will be resources for patient self-management support; ICD-10 codes to facilitate billing for symptom management services; and features to streamline clinician workflow and support interdisciplinary symptom management, such as templated progress notes and referral pathways.
 - Branching logic within the algorithms should allow for tailoring to different places on the cancer continuum from treatment to survivorship and end-of-life.
- *Designing a clinical-decision support software system* to deliver the algorithms to clinicians at point-of-care
 - The system will allow for the entry and encoding of the CPGs in a user-friendly manner.
 - The system will present the clinical decision workflow to the clinician using straightforward medical language in an intuitive web-based graphical user interface (GUI) on a tablet, desktop, or laptop computer.
 - The system may be developed using existing software applications that are configured and/or integrated to achieve the desired functionality, or it may be developed as a custom application. However, if the offeror proposes development of a custom application, offeror must provide compelling justification for doing so versus configuration of off-the-shelf solution(s).
 - At commercial scale, the CDS-Sx should have the capacity to interoperate with EHR systems commonly used in oncology settings (e.g. data extractable in HL7CDA or similar format) and be compliant with applicable FDA regulatory guidance for CDS software.
- *Conducting iterative cycles of usability testing, CDS-Sx refinement, and user acceptance testing*, with a multidisciplinary panel of clinicians, cancer patients and survivors. Clinicians should reflect the breadth of settings where cancer care is delivered, including specialty care, community-based, home-based, and primary care settings.

Activities not supported by this topic:

Applications that do not leverage national practice guidelines, do not incorporate iterative development of the computable algorithms by expert panels, and approaches that do not address the complexities of cancer symptom management (e.g. co-occurring symptoms) will be not be considered for funding.

Activities and Deliverables

Expected CDS-Sx system functionalities include:

- Presentation of the CPG content in an intuitive user interface that fits into the clinician workflow.

- Graphical user interface with branching logic that allows for the clinician to quickly select responses and arrive at clear and specific clinical guidance for patient evaluation and management.
- Ability to make both minor and major revisions to the CDS-Sx system, such as adding new symptom management guidelines, or updating content when guidelines are revised, through the user interface and without changes to software code.
- Ability for clinician to print patient self-management materials or send them via email or text message.

Phase I Activities and Deliverables:

- Establish a project team with expertise in the areas of clinical decision-support, cancer symptom management, cancer care delivery, knowledge translation and implementation science, human factors engineering, and software design.
- Develop a replicable consensus-based methodology to synthesize and transform evidence-based guideline recommendations from their narrative prose formulation into algorithms for symptom assessment and treatment, converting the content into computable language, decision-points, and logic flows. Algorithms should reflect health IT standards, including Health Level 7 (HL7) and the Clinical Quality Framework (CQF) Initiative (<http://cqframework.info>).
- Develop algorithms for evidence-based evaluation and management of two symptoms (specifically, constipation and fatigue) that reflect the anticipated spectrum of algorithm complexity with respect to the number of decision nodes and separate pathways, based on prior research. Algorithms for evaluation and management should be evidence-based, and should leverage symptom management guidelines and patient self-management support materials that are offered and updated regularly by organizations such as ONS, ASCO, NCCN, AHRQ, ACS, ESMO, and NCI-PDQ. Algorithms should reflect recommendations for specific pharmacological and behavioral interventions, including recommendations to initiate medications or explicit adjustments for medication doses, laboratory tests, supportive care referrals, and behavioral self-care suggestions. The curation of guideline materials into the algorithms should include an approach to annotate the material to convey the source(s) of the evidence, and to address any intellectual property issues. Algorithms must clearly address the complexities of cancer symptom management (e.g., algorithms must integrate with one another to address multiple co-occurring symptoms, and must consider the multiple factors that may aggravate and/or alleviate symptoms).
- Identify the approach and specific standards (e.g., CDISC, SDTM, and ICD) for standardization and encoding of data points in the algorithms to provide for computability and interoperability with downstream systems. At commercial scale, the CDS-Sx would allow for information to be exported into the electronic health record in a standard format to strengthen documentation, support metrics of care quality and value, and document re-evaluation of symptoms and intensification of management as warranted.
- Formalize CDS-Sx design considerations, including proposing novel features for CDS that enhance usability in busy practice settings.
- Curate patient self-management support material for inclusion.
- Demonstrate the algorithm development and curation methodology using two common symptoms (constipation and fatigue).
- Pilot test the CDS-Sx algorithms with a multidisciplinary panel of clinicians (including physicians, nurse practitioners, physician assistants, registered nurses, social workers, psychologists, and physical therapists). While the pilot test group need not be large, it should reflect the breadth of settings where cancer care is delivered including specialty care settings, comprehensive cancer centers, community-based cancer settings, and primary care. Refine the prototype algorithms in an iterative manner based on results of pilot testing.
- For the CDS-SX:
 - Specify the user requirements for the system.
 - Provide an analysis of available open source, off-the-shelf (OTS) software systems, including options developed in the academic setting such as SEBASTIAN (Lobach et al 2016; JMIR Med Inform; 4 (4), e36) in terms of their suitability for use, and customization and integration requirements.
 - Recommend a design approach (i.e., custom development, integration of OTS software, or a combination).
 - Specify the technical design for the electronic CDS system, including:

- Technical specifications (e.g., web-based system that operates on desktop, laptop, and tablet computers)
 - Integration points and approach
 - System flow/technical diagrams
- Provide a final recommendation about selection of an OTS electronic CDS, and the budget and timelines required for any customization.
- Develop a wireframe prototype that outlines system flow and blocks of data that will appear in the UI. This is not meant to be a working prototype (i.e., no actual software coding is expected). Rather, this is part of the preliminary system design.
- Present Phase I findings and technical recommendations and design that demonstrates feasibility of building the CDS-Sx within the specified timeframes and budget of Phase II to the NCI.

Phase II Activities and Deliverables:

- Using the methodology developed in Phase I, create the assessment and management algorithms for six (6) additional symptoms (specifically pain, insomnia, nausea/vomiting, diarrhea, dermatologic toxicities, and psychological distress [anxiety and depression]).
- Specify detailed functional and non-functional requirements for the system.
- Specify technical requirements (add more detail to specification created in Phase I).
- Maintain a traceability matrix that details the relationship between user, functional, and technical requirements.
- Using the wireframe developed in Phase I build a production system CDS-Sx using an agile methodology.
- Develop test scripts for functional and user testing.
- Prior to usability testing, validate the accuracy of the CDS-Sx recommendations against the algorithms; identify and correct any logical inconsistencies or non-agreement in the symptom evaluation and management recommendations generated using the CDS-Sx employing test cases that include simulated patient data targeting boundary conditions for each decision node and multiple branches in the algorithm's decision logic. Documentation of successful tests must be provided.
- Conduct preliminary usability testing with a small, diverse group of early adopter clinicians to test CDS-Sx in their clinic settings and to provide feedback to be used to iteratively improve the design, UI, and workflow.
- Conduct usability testing with a multidisciplinary panel of clinicians (i.e., including physicians, nurse practitioners, physician assistants, registered nurses, social workers, psychologists, and physical therapists), cancer patients, and survivors. The clinician testing group should reflect the breadth of settings where cancer care is delivered including specialty care settings, comprehensive cancer centers, community-based cancer settings, and primary care settings.
- Conduct final user acceptance testing with a diverse group of end-user clinicians. The sample for end-user testing should also be diverse with respect to practice site and patient population served (e.g., diverse tumor sites, radiation, medical and surgical oncology, and active treatment and survivorship), and should include clinicians in comprehensive cancer centers, community-based settings, home-based care, and primary care settings.
- Create standardized data extract (e.g., HL7 C-CDA or CDA/Progress Note) that can be imported/integrated into existing EHR solutions (e.g., Epic).
- Present Phase II findings and demonstrate the technology to an NCI evaluation panel via webinar.
- In the first year of the Phase II contract, provide the program and contract officers with letters of commercial interest.
- In the second year of the Phase II contract, provide the program and contract officials with a letter(s) of commercial commitment.
- Create a dissemination/publication plan that outlines potential presentations at national meetings and publications resulting from this scientific development work.

378 Mobile Application for Surveillance of Post-Radiation Therapy Health-Related Quality of Life

Fast-Track proposals will be accepted.

Number of anticipated awards: 3-4

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 goal of this topic is to develop mobile applications for reporting toxicities after radiation therapy, either alone or in combination with other modalities in accordance with Patient Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE). Cancer survivorship is expected to improve over the next decade. Radiotherapy plays a major role in improving survival. However, cancer registries do not collect information on treatment-related toxicities; treatment-related adverse effects after radiation therapy are not being reported accurately. Therefore, mobile apps in accordance with PRO-CTCAE provided to patients for reporting of treatment-related toxicities with an interface to hospital-managed patient databases are needed. Such mobile apps would allow early reporting of toxicities by patients to their physicians, by which clinicians could intervene to provide appropriate treatment and better designs in future patient-centric clinical trials. These mobile apps will be made available for patients' use at radiation oncology academic research centers and radiation oncology clinics around the world. This need, when filled, will ultimately help improve treatment outcomes.

Project Goals

Improvements and access to treatments around the world will result in improved survival of cancer patients. Radiotherapy, alone or in combination, plays a major role in the treatment of cancer. Currently, treatment decisions in radiotherapy/radiochemotherapy are primarily defined by disease stage, tumor location, volume, and patient co-morbidities, together with normal tissue tolerance for surrounding organs. As there are variations in sensitivities of individual patients and tumors to radiation, a substantial number of patients suffer from severe to life-threatening adverse 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 lungs and cognitive decline, which are irreversible and progressive.

Consider: 1) Treatment-related toxicities are not being reported accurately and/or adequately by patients; 2) existing cancer registries often do not capture such information; 3) clinicians often underestimate the toxicity burden among patients; and 4) there is a post-treatment health-related quality-of-life (HRQOL) discordance among patients and clinicians. In this context, PRO-CTCAE, which is a patient-centric approach necessary for reporting adverse effects, is gaining importance.

Smartphone apps have become valuable tools in health care management for many diseases, but none addresses improving patients' HRQOL after radiotherapy/radiochemotherapy. A mobile app that interfaces with hospital managed patient databases, and collects and archives toxicity data will allow clinicians to interact with their patients early to provide personalized care. Further, increasingly granular data driven by patient reports will also help clinicians to design better future clinical trials with active patient participation (patient-centric) in radiation oncology. The goal is to develop a mobile app for reporting toxicities for use with iOS and Android platforms.

In Phase I the contractor will define project needs and develop requirements by "mind-mapping" (i.e., collecting information to develop ideas and concepts via creative, logical, and hierarchical means towards the specific goal of developing mobile apps for surveillance of post-treatment toxicities) expert opinions on radiation therapy-induced normal tissue toxicities in accordance with PRO-CTCAE. Treatment-related toxicities will depend on patient profile, organ/site, disease stage, tumor type, treatment, volume, location, and patient co-morbidities. Contractors may address toxicities related to the treatment of a specific organ/site or inclusive of all organ/sites. Project documentation, proposed functionalities, specifications, and technical documents are essential. Activities will also include designing the application, coding, framing, developing screens, and delivering a prototype app on iOS and/or Android platforms, and then conducting a small-scale usability test with at least 25 cancer patients.

Phase II activities will include further development, refinement, and validation of the app. Specifically, these activities are refinement of coding, based on Phase I usability testing, interfacing with databases, and integration of analytics (e.g., tracking

download numbers; identifying, reporting, and eliminating bugs; requesting features; etc), as well as introducing additional features. Such additional features may include developing a module for social networking among patients and their families to develop a support structure and assist clinicians in designing patient-centric clinical trials. Contractors must validate the product with an expanded “large-scale test” with the appropriate radiation therapy patient groups of interests and identify potential customers for marketing. The number of patients required for validation should be determined in consultation with a biostatistician and proposed to NCI by the offeror.

Activities not supported by this topic:

Any proposal that does not address specific goals of addressing normal tissue toxicity induced by radiation therapy alone or in combination with other treatment modalities will not be considered for funding.

Phase I Activities and Deliverables:

Develop application requirements and proto-type in iOS and/or Android platforms.

- Establish a project team, including expertise in: mobile app development, radiation oncology specific to the treatment of at least one anatomical tumor location/site, and relevant adverse effects related to a specific tumor site or all sites. Demonstrate verifiable 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 essential.
- Conduct a focused workshop with appropriate key opinion leaders (consisting of no more than 12 experts) to deliver a definitive list of reportable normal tissue toxicities in accordance with PRO-CTCAE. The list should attribute toxicities based on pre-defined patient profiles, a specific disease site or multiple sites, disease stage, tumor and treatment type, treatment volume, patient co-morbidities, etc.
- In consultation with NCI, develop requirements for mobile application(s).
 - The app must be able to assist clinicians to better design patient centric future clinical trials.
- Deliver project documentation – functionalities, specifications, and technical documents.
- Create application design, framing, screens, and coding.
- Deliver product requirement documentation to NCI.
- Develop a prototype mobile application on the iOS and/or Android platforms.
- Design app to address potential users including radiation oncology/cancer clinics, academic/research/clinical centers, individuals within healthcare systems, health insurance companies and health IT departments.
- Perform small scale usability testing with at least 25 cancer patients.

[Note: The offeror may be required to be meet compliance with HIPAA privacy act policies.]

Phase II Activities and Deliverables

Develop and refine applications for use in iOS and/or Android platforms.

- Refine coding, interface with databases, and introduce features and functionalities.
- Refine the prototype based on Phase I usability and internal testing results.
- Integrate analytics (to track downloads, identify bugs, opportunities to improvise, etc.).
- Introduce and refine features, and eliminate bugs.
- Validate the product with an expanded testing with a larger cohort for adverse effects related to the treatment of a specific tumor site or all tumor sites.
- Product features could also allow social networking to develop support structure among patients and their families based on patient-reported symptoms.
- Provide letters of interest from potential customers.
- Provide letters of commitment to purchase the product from customers.

- Provide letter of acceptance of the product by the iOS and/or Android platforms.
- The offeror will be required to meet compliance with HIPAA privacy act, IT security, and compliance policies.

379 Software Enabling Data Integration from Wearable Sensors to Generate Novel Analytics for Cancer Patients

Fast-Track proposals will 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 wearable and external sensing platforms since 2015, by the consumer health market, has paved the way for similar platforms to act as objective measures for continuous, out of clinic, cancer research and patient assessment. The passive, continuously measured data streams generated by current or future physical and chemical/biological sensors will allow direct/indirect measures of cancer progression and its symptoms. Increased out-of-clinic patient and clinician engagement via these tools will allow more precise delivery of cancer care during treatment, as well as during cancer remission. Ultimately, these passive sensing platforms of digital biomarkers will afford clinicians: 1) more objective metrics of response to therapeutics; 2) control and auto-reporting of symptoms and their fluctuations; 3) monitoring of side-effects of experimental or standard of care therapies; and, 4) more ecologically valid clinical endpoints, all decreasing assessment burden via increased continuity of physiological measurement sampling and patient context, outside of the standard clinical visit.

Near real-time analytical capabilities, such as these devices offer, represent an opportunity to measure population based statistics from large cohorts of cancer patients from a myriad of devices currently available or being developed. From vital signs, activity, or non-invasive patch based measures of biochemistry from bodily fluids to external monitoring of environment, these tools will offer a more complete picture of patient performance status, fatigue, other symptoms, cachexia, and patient monitoring (e.g., drug metabolism, toxicity, adherence, or side effects) during clinical trials, in convenient small form factors with the ability to auto-report these data for research purposes or informed clinical assessment of patients outside of the clinic.

In order to ascertain the potential of these tools for more precise delivery of cancer care and patient monitoring, much clinical cancer research must be performed to understand sensor measurement versus cancer progression and patient context outside of the clinic. As much of the power of these technologies lies in their ability to offer a granularity not seen before in patient specific data, the research to advance this to the clinical setting will rely on either existing commercial tools already or research grade platforms not yet translated. Moreover, as any one wearable sensor-specific parameter will unlikely allow for both patient physiology and context in which the measurement was taken, multiple devices and subsequent parameters will be necessary to enable commercialization of more targeted and specific devices for clinical cancer care or assessment.

There is a considerable need for scalable informatics tools that allow automated data aggregation, integration, and machine learning algorithms that can pull from disparate data sets across device vendors and have the flexibility to add new measures as they are developed. Furthermore, a central software platform that could obtain wearable, implantable, or external device data and uniformly compare/contrast/couple data streams to understand physiology versus patient context with respect to time will advance this unique approach to aid cancer patients, clinician assessment, and clinical trial design. This topic is in line with the Cancer Moonshot Blue Ribbon Panel's Recommendation to support Symptom Management Research.

Project Goals

The goal of this solicitation is to advance the development, and subsequent commercialization, of scalable informatics tools and resources for their broad adoption across the burgeoning clinical cancer research applications that continuous, passive monitoring of multiple biological parameters via wearable platform technologies are beginning to be used. A limitation to their current use in cancer research is that device manufacturers and platform technology developers do not utilize identical data sets/standards, and no resources are available to easily assess large multiparameter data sets via traditional

bioinformatics methods. As such, the primary focus of this contract topic is on data agnostic informatics tools and resources that can be adopted easily in the cancer research communities for cohort studies involving their monitoring platform(s) of choice to understand their specific research problem/patient cohort of choice. Informatics *tools* include mobile apps for sensor data retrieval; computer software tools and platforms to aggregate, integrate and organize data streams from multiple devices; and machine learning-based informatics platforms for subsequent interpretation of integrated data streams derived from a myriad of continuous passive monitoring devices that could be used by cancer researchers. The informatics *resources* include sensor 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 overall scope of the topic includes the entire spectrum of passive continuous monitoring devices being commercialized or developed, extending from wearable sensor platforms and implantable devices to external monitoring devices for all phases of cancer clinical research. Offerors will be expected to propose well-designed project plans with clearly defined milestones that will eventually lead to commercially viable solutions for: 1) sustained development and evolution of passive continuous monitoring platform informatics tools and resources; and, 2) their broad adoption in clinical cancer research.

Activities not supported by this topic:

- Tools that do not allow the integration and subsequent interpretation of a myriad of current wearable sensor platforms, simultaneously, or that rely solely on inertial sensing type wearables.
- Tools that are not scalable to future wearable, implantable or external out of clinic monitoring tools.
- Tools that do not 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.

Phase I Activities and Deliverables

- Establish a project team including proven expertise in: sensor technology for physiological monitoring, wireless sensor integration with mobile devices, secure wireless transport of health data using standards based protocols, secure cloud computing models, bioanalytical technologies, epidemiology, biostatistics / bioinformatics, and systems architecture.
- Provide a report including a detailed description and/or technical documentation of proposed:
 - Development of bioinformatic methods or algorithms (e.g., machine learning, etc.) for wearable sensor data integration across data inputs from diverse wearable bio-/sensor platforms, including harmonization of data of the same biometric from different vendor device platforms;
 - Evaluation of wide range of wearable, implantable, and external sensors platforms that would be of legitimate use for out of clinic patient monitoring and/or understanding disease/symptom progression (e.g., therapy-induced fatigue, patient performance status, cachexia, experimental therapeutic side effects or toxicity, etc.) vs. the myriad of potential physical and / or physiological factors;
 - Database structure for the proposed system's chem-/bio-/physical sensor based data inputs and metadata requirements;
 - Database formats that support the import and export of individual datasets and coalesced datasets, store structured data from different sources of wearable sensor data, and are readily used for data integration and QC protocols;
 - Specific approach to QC;
 - Technology compatibility matrix for Phase I and Phase II wearable sensor data sources by platform, sensor type, sensor technology, and differing device data streams as well as and back-end server systems to be developed;
 - Data visualization, feedback, and reporting systems for population or clinical monitoring and research applications;
 - Data integration approaches to leverage multiple data input streams;
 - Data types for exchange of physiological-metrics between mobile platforms and secure servers;
 - Data standards for transfer and importation of individual wearable sensor data and storage of individual and coalesced wearable sensor data;
 - Transparent, documented, and non-proprietary bio-/informatic methods; and

- Description of additional software and hardware required for use of the tool.
- Provide wireframes and user workflows for proposed Graphical User Interface (GUI) and software functions that;
 - Support the import and export of individual datasets and coalesced datasets;
 - Implement, script, or automate all features and functions of the data integration tool(s); and
 - Conduct QC of coalesced datasets.
- Develop a functional prototype system from planned Phase I compatibility matrix that includes:
 - Front-end mobile applications to facilitate and control the collection and transport of multiple wearable chem-/bio-/physical sensor data inputs and any associated metadata used within the system;
 - Integration with several wearable chem-/bio-/physical sensor;
 - Automated data screening algorithms and importation protocols for data transferred from the mobile application to the back-end server systems;
 - Software systems GUI (web- or computer-based);
 - Software tools as mobile and web applications;
 - Back-end user-interface controls for custom data integration and visualization for individual or group-level data; and
 - Finalize database formats and structure, data collection, transport, and importation methods for targeted data inputs.
- Present Phase I findings in a detailed report and demonstrate the final prototype to an NCI evaluation panel.

Phase II Activities and Deliverables

- Expand the informatic methods to include other research grade sensor data points or streams, in addition to already identified commercialized wearable sensor data, and demonstrate data integration across inputs from diverse sensor platforms.
- Demonstrate database integration capability to collect data from four different parameters and collected from three distinct wearable device platforms, as well as to be adaptable to at least 20 more current, or future, platforms designed for physiological or objective measurements of patients outside of the clinic.
- Participate in validation and scale-up between the offeror, NCI, and/or NCI-identified third party sources to access relevant input data types for the proposed project. Validation within established cohort studies with wearable sensor data (e.g., pre-identified analytes of use to monitoring of syndrome-specific therapeutics, patient fatigue, or similar cancer cachexia-specific physiological metric, etc.) will serve: 1) to train and validate the expanded bioinformatic methods; and, 2) to demonstrate the application of these methods through scalable software to automate complex data integration tasks for wearable sensor data sources.
- Beta-test and finalize front-end mobile applications developed in Phase I.
- Beta-test and finalize automated file transfer, screening, and database importation protocols and systems.
- Perform regression testing for both front-end and back-end system functions.
- Demonstrate usability of scalable software through the following:
 - Beta-test and finalize automated file transfer, database importation protocols, wearable biosensor data integration applications and reporting tools developed in Phase I;
 - Develop beta-test, finalize, and demonstrate the GUI; and
 - Demonstrate the software systems ability to integrate data from planned Phase II technology compatibility matrix data sources using automated algorithms and analytic methods.
- Conduct usability testing of the GUI elements of the sensor-specific data integration tool(s).
- Conduct usability testing of consumer/patient-facing mobile applications and any associated web portals and care team/researcher-facing user interface features including system management, analyses, and reporting applications.
- Develop systems documentation to support the software and informatic methods.

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

380 Computer Aided Decision Support for Radiation Oncology

Fast-Track proposals will 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

Radiotherapy, both with or without systemic therapy, is administered to over half a million patients annually in the United States alone. The decision regarding what kind of radiotherapy to employ (e.g., Intensity Modulated Radiation Therapy, Proton therapy, Stereotactic Body Radiation Therapy, etc.) and which, if any, drugs to add to radiotherapy for a patient are usually based upon rather crude criteria (e.g., age, TNM stage, histological grade, etc.) that frequently fail to accurately predict the outcome of the treatment administered. Better tools are needed to improve decision-making and thereby decreasing both over and under-treatment.

For more than two decades, almost every patient treated by radiotherapy in the United States has undergone a “treatment planning” CT scan; some patients also undergo MRI or PET scans in addition to CT scans. Recent advances in image analysis, pattern recognition, and data characterization enable high throughput extraction of quantitative imaging features from these images. This emerging field of imaging studies (“Radiomics”) allows us to quantify various tumor phenotypes that can be visualized non-invasively by analyzing numerous imaging features such as tumor shape, boundary features, tumor size, texture, uptake or density distributions, etc. These data can be combined with other patient data and be mined with sophisticated bioinformatics tools to develop models that may improve diagnostic, prognostic, and predictive accuracy.

Radiomic tools thus could be used with treatment planning CT and other scans to extract a treasure trove of information that by using the right tools/algorithms could help greatly improve decision making in radiotherapy. This topic is in line with the Cancer Moonshot Blue Ribbon Panel’s Recommendation to support Development of New Enabling Cancer Technologies.

Project Goals

Radiomic studies for lung cancer using CT and FDG PET images have shown that tumor image features and parameters can describe the nature of disease and predict patient outcomes. Other localized diseases such as brain, breast, kidney lung, liver, and esophageal cancers have also been analyzed with different imaging modalities such as FDG PET, CT, MRI, and ultrasound. Studies have shown that Radiomics has the potential to impact clinical care by contributing to cancer diagnosis, assessing tumor prognosis, assisting in biopsy decision and helping to select the right chemotherapeutic regimen. Computer aided diagnostic tools are being developed for diagnostic radiology but so far the tools for radiotherapy decision making remain sparse. Radiotherapy treatment prescription involves:

- 1) selecting the type of radiation (e.g., 3-dimensional conformal RT, Intensity modulated RT, Stereotactic body RT, Stereotactic radiosurgery, Proton RT, Carbon ion RT, Low dose rate brachytherapy, High dose rate brachytherapy, etc.);
- 2) selecting drugs that can enhance the effects of radiation on tumors (e.g., cisplatin, temozolomide, cetuximab, mitomycin, gemcitabine, etc.);
- 3) selecting drugs that can decrease the effects of radiation on organs-at-risk (e.g., amifostine, memantine, etc.); and,
- 4) selecting the total dose of radiation, the dose per fraction, the number of fractions of radiation, the sequencing of those fractions with the drugs, etc.

At present the radiotherapy prescription is too often “one size fits all” and based upon relatively rudimentary criteria such as age, TNM stage, and histological grade. Studies that explore the utility of radiomics have indicated that the use of image analysis tools will help refine and personalize cancer decision-making, thereby increasing tumor control and decreasing adverse effects. Furthermore, their use may facilitate more robust “mid-course corrections” (i.e., adaptive therapy), since CT

scanning for readjustment of radiotherapy treatment plans is often repeated during a course of radiotherapy on account of weight loss or tumor shrinkage.

The short-term goal of this contract topic is to develop new approaches and refine existing “radiomics” tools for radiotherapy treatment planning images to enable more accurate decision making support for radiation therapy treatment planning. These can include (but are not limited to) the following:

- Selection, extraction and qualification of imaging features.
- Integration with clinical, molecular and other “omics” data.
- Novel data mining and analysis methodologies to handle the enormous amount of data.
- Testing and validation of those tools in datasets from single-institutions, multi-institutional clinical trials and/or clinical practices).
- Testing differences in treatment plans and their outcomes using radiomics tools vs standard of care plans.

It is expected that the proposed innovation will be driven by clinical practice. Therefore, in addition to standard proposal components; the contract proposal must contain specific discussion of the target patient population and evidence of an existing clinical problem which is addressed by the proposed method. The proposal must also contain an analysis of competitive methods to address the same problem and an explanation of competitive technical advantages of the proposed algorithm. All Phase II or Fast-Track proposals MUST contain a section entitled “Regulatory Plan” that 1) demonstrates an understanding of the regulatory requirements for clearing the software device through the FDA, if appropriate; 2) details the company’s plan to meet the requirements, and 3) explains how the proposed work helps to meet these requirements. If regulatory approval is not expected to be required, the offeror must provide an extensive justification for this. The long-term goal of this program is to eventually commercialize an image analysis software toolkit for decision support in radiation oncology.

Activities not supported by this topic:

Development of algorithms for image acquisition and/or routine image processing tools is not appropriate for this topic and will not be considered for funding. Development of computer aided diagnosis/detection systems not intended for radiation oncology are also not appropriate and will not be considered for funding.

Phase I Activities and Deliverables

- Select radiomic features that are suitable for the proposed organ site and imaging modality (such as treatment planning CT) for improving treatment plans and/or their modification during therapy.
- Develop appropriate tools and algorithms to extract the features from the images, characterize the data and assess the stability of the features. These may be developed *de-novo* or adapted from sources such as Pyradiomics and other QIN developed tools, but with a focus on developing tools that would be more specific to radiation oncology. Combinations with other validated outcome measures (such as genomic and specific cancer type phenotype profiles) to make treatment planning more comprehensive are encouraged.
- Use the obtained radiomics data from treatment planning CTs (and other scans) to develop models for treatment plans and predict outcomes in radiation oncology.
- Test the models for differences in treatment plans and/or their outcomes using appropriate training data sets.
- The company must obtain feedback from radiation oncologists at a minimum of 3 different institutions regarding user specifications and clinical need. This input must be included as part of the technical specifications of the product.
- Testing and validation of the software tool on a small subset of clinical images to demonstrate feasibility.

Phase II Activities and Deliverables

- Validate the software using a validation data set.
- Perform the required clinical studies as required by FDA for approval as a stand-alone decision support tool or as a package.
- Present Phase II findings and demonstrate the final prototype to an NCI evaluation panel via webinar.

381 Development of Artificial Intelligence (AI) Tools to Understand and Duplicate Experts' Radiation Therapy Planning for Prostate Cancer

Fast-Track proposals 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 goal of this topic is to see if Artificial Intelligence (AI) technology can be used to improve treatment planning for prostate cancer by developing algorithms to “read” standard Computerized Tomography (CT) images in context with clinical information and recommend suitable treatment plan approaches. The resulting tool may aid radiation oncologists in reaching unbiased consensus treatment planning, help train junior radiation oncologists, update practitioners, reduce professional costs, and improve quality assurance in clinical trials and patient care. Treatment planning for radiation therapy has become increasingly complex with the advent of image-guided radiation therapy and charged particle therapy. A substantial amount of physician time and effort are required to contour key tumor and normal tissue structures. The process involves assessing the patient’s risk for disease progression based on tumor volume; histological grade and biomarkers (e.g., prostate specific antigen or other tests); and assigning one of three risk groups as defined in the National Comprehensive Cancer Network (NCCN) guidelines: low, intermediate, or high. See NCCN guidelines here: <https://www.tri-kobe.org/nccn/guideline/urological/english/prostate.pdf>. Radiation treatment will use external beam radiation with or without androgen deprivation. Imaging uses CT and often magnetic resonance imaging. Based on these, the physician and medical physicists plan the target volume to be treated, radiation dose, and normal tissue to be spared. In practice, treatment guidelines are established by consensus papers. However, proposed plans among even world renowned experts often differ. Thus, it may be possible to go beyond verbal consensus text and understand the rationale among expert “preferences” in treatment plans by using AI-based contextual image analysis that uses feature extracting algorithms and/or interactive machine learning to formulate treatment plan. Such an approach would provide an initial plan to the physician upon which to facilitate treatment planning, build consensus, and help understand expert thinking.

Project Goals

The goal of this contract topic is to develop and evaluate the concept that AI can be used to understand and duplicate experts’ radiation therapy planning. The purpose is to understand how human cognition performs in work, focused in the context of developing radiation therapy treatment plans, and then incorporate such an understanding into machine learning with the intent to automate treatment planning to reduce subjective biases, improve treatment quality, and reduce cost. This contract topic does not intend to achieve a breakthrough in AI technology. The objective is to integrate recent advances in treatment planning systems and machine learning to improve radiation therapy by eliminating repetitive, time-consuming, and subjective biases in treatment delivery. Subjective biases could result in normal tissue injury and compromise therapeutic benefit. Machine learning approaches may involve extraction of relevant features from “consensus image datasets” of expert medical teams and then applying them to train machines with an initial focus on prostate cancer. The broad and highly impactful goal is to improve the outcome for patients with prostate cancer. By developing knowledge-based planning solutions, it may be possible to provide a more standardized treatment at a significantly lower cost. This may facilitate quality assurance, possibly extending it to facilities with limited expert personnel and enabling the conduct of research by reducing the variability and potential arbitrariness and/or preference that individuals incorporate in their treatment design. The goal of this project is to encourage creative small businesses to design, develop, and build approaches to AI-based treatment planning systems to improve radiation therapy. Progress here could be applied to other disease sites.

Activities supported by this topic:

Proposals that develop AI software that only outlines tumor and normal tissues but does not select a treatment plan for the three risk groups will not be considered for funding.

Phase I Activities and Deliverables

- Establish a project team to develop an AI tool to understand and improve treatment planning for prostate cancer, comprising of cross disciplinary expertise. This cross disciplinary expertise will require proven expertise in AI, application development, radiation treatment planning for prostate cancer, IT experience in a healthcare setting, data security, HIPAA, and other laws and regulations to protect privacy and confidentiality of patient information.
 - Choose one expert radiation therapy planning team comprising of a physician and planners (i.e., a person who is knowledgeable in treatment planning with good understanding of the treatment planning system) and evaluate expert cognition process in developing treatment planning strategies for all three strata of patient risk groups (i.e., low, intermediate, and high based on NCCN guidelines).
 - Note: For Phase II, three independent teams will be required so that there can be comparison between expert teams using the same set of cases.
- Identify criteria used by an expert planner to develop each treatment plan for each risk group (i.e., low, intermediate, and high NCCN).
 - Based on the expert planning methods, develop an AI based planning process including feature extraction. Existing algorithms could be used for feature selection. Expected innovation is in using AI for treatment planning. Plan will use external beam radiation, fields to be determined by expert team, with or without androgen deprivation therapy per expert's discretion. Other forms of treatment will not be considered for this project.
- Design and develop computational algorithms/methods aimed at improving treatment planning for prostate cancer patients.
- Propose plan to develop, incorporate, and compare the AI methods with expert treatment planning methods and validate AI based treatment planning system.
 - There should be a minimum of 10 patients per risk group or a suitable number that the research team feels is sufficient for the AI algorithm to begin the initial planning. Provide justification for the selected number of patients. Retrospective de-identified data could be used for this purpose.
- Present AI concept to develop knowledge based radiotherapy treatment planning to NCI's SBIR Development Center and the Radiation Research Program.
- Design and deliver an AI approach to improve radiation therapy planning for prostate cancer to be tested in Phase II.
- Present an estimate of the number of training and validation sets that would be needed for each of the risk groups so that the AI results can provide a starting point for the planning team to refine the initial plan and determine the final course of treatment.
 - Establish a set of patient records for the three risk groups to be used in Phase II among the 3 expert teams.
- At a minimum, apply this technology to standard 3D CT datasets. Use of additional imaging is at the preference of the planning team.

Phase II Activities and Deliverables

- Refinement of algorithm based on the results of Phase I.
- Demonstration of utility of AI plan as the initial step to be reviewed and then modified by the planning team.
- Establish sufficient cases in each of the three treatment categories for the comparison among expert groups, based on Phase I deliverables.
- Expand to a minimum of three independent expert treatment planning teams and have each expert team plan the 3 risk groups. There will be 3 consensus reviews: a) comparing the plans among the 3 expert panels done by the "standard" hands-on approach; b) comparison of the 3 AI produced plans; and, c) an analysis of how the hands-on and AI based plans differ.
- Compare the consensus approach of the expert hands-on plans to the consensus among the AI plans to see where there was agreement or disagreement and see if this difference can be understood and rectified. This would enable the AI to refine its algorithm.

- Evaluate developed AI software to see if it can match the performance of the expert teams (each team would have 3 categories of patients). Examine differences and present plans to refine the performance of the AI.
- Expand types of data sets to include MRI or PET or other sources of data that would improve AI's performance. Establish external partnership(s) for future validation of method, as demonstrated with letters of intent from strategic partners.

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>

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.

103 Devices for Transcatheter Surgery

Fast-Track proposals will be accepted.

Number of anticipated awards: [1-2 Phase I, 1 Phase II]

Budget (total costs):

Phase I: \$400,000 for 12-18 months

Phase II: \$3,000,000 for 24-36 months

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

Summary

This solicitation will develop an ensemble of devices to enable a broad array of novel catheter treatments for structural heart disease in adults and children. These devices will deliver and secure sutures inside the beating heart without surgery and promise a dramatic impact on cardiovascular therapeutics.

Project Goals

The goals are to develop and test a collection of independent catheter devices for transcatheter electrosurgery procedures to treat adult and pediatric structural and congenital heart diseases without surgery. NHLBI has demonstrated the preclinical feasibility of such procedures including pledgeted suture annuloplasty, but commercially available tools are poorly suited for these applications in humans because of features including inadequate length, flexibility, radiopacity, and caliber. The devices are all variants of standard surgical tools specially adapted for application through flexible catheters under conventional imaging guidance including conspicuous sutures and pledgets, deflectable catheters for directing guidewires, knot pushers and lock devices to deliver and secure stitches under tension. Together this group of regulatory Class I or Class II tools would enable a wide range of novel but attainable non-surgical interventional cardiovascular procedures such as intracameral suture annuloplasty, valvular leaflet repair, and extraanatomic bypass.

Phase I Activities and Expected Deliverables

A phase I award would develop and test working prototypes in swine. The contracting intramural laboratory wishes to test the final prototypes in vivo, and offers one no-cost testing round to the contractor if desired.

Below is a list of individual devices which are part of the suite, along with specific requirements. The devices must be able to function alone or together as components of the multifunctional suite.

1. Radiopaque sutures

- a. Must be visible in vivo under fluoroscopy and echocardiography
- b. MRI compatible although a small susceptibility artefact may be desirable to impart visibility.

- c. Exhibits mechanical and biological properties (tensile strength, strength retention, tissue reaction/thrombogenicity) similar to a commercial comparator known to perform satisfactorily (*size O Ethibond EXCEL suture*). Smaller caliber alternatives may be considered with appropriate justification.
 - d. Preferred embodiments have different colors to each half, to simplify tying
 - e. Minimal length 240cm
 - f. Non-absorbable
 - g. Hemocompatible
2. Guidewire to suture ‘connector’
- a. A low-profile device that can securely connect a 0.014” coronary guidewire to the radiopaque suture (item #1) with smooth transition, to allow the operator to pull one end of the guidewire in order to exchange for the suture through and across tissues through catheter devices. The connector “transition” must allow safe and reliable traversal of fibrotic annular structures.
 - b. Must resist unlocking at high (>20N) forces
 - c. Novel docking or crimping or connecting solutions are welcome
 - d. May be integrated directly onto the suture.
 - e. A preferred solution can pass through a 0.038”-compatible catheter lumen
 - f. Hemocompatible
3. Catheter knot pusher
- a. A low-profile catheter device that can deliver a half-hitch or superior non-sliding suture along a transcatheter intracameral trajectory
 - b. Length at least 110cm
 - c. Must be able to pass through a fully deflected Abbott St Jude Agilis SML curl deflectable sheath 8.5Fr, and preferably would also pass curved coronary guiding catheters 8Fr to deliver a knot along two radiopaque sutures (item #1 above) and alongside one or more 0.014” guiding catheters
 - d. Must be designed to allow tension to be maintained on the rail suture during delivery of each hitch
 - e. A preferred embodiment would have a safety feature to enable the operator to loosen the knot.
4. Radiopaque felt or fabric pledgets
- a. Intended to allow sutures to apply focal tension to cardiovascular tissue without pull-through, including myocardium, annular tissue, and valvular leaflets
 - b. Must be visible in vivo under fluoroscopy and echocardiography. The visibility may be imparted focally using metal markers, or diffusely.
 - c. MRI compatible although a small susceptibility artefact may be desirable to impart visibility.
 - d. Must exhibit equivalent mechanical and biological properties to *Ethicon Teflon Pledgets, ref PCP-20*
 - e. Hemocompatible
5. Deflectable steering catheter
- a. Intended to guide at least one 0.014” guidewires traversing myocardial, annular, and leaflet tissue.
 - b. A preferred embodiment has a mechanism to deliver precisely a second traversing guidewire a known distance (4-10mm, preferably adjustable) defined proximity to the first traversing guidewire.
 - c. Preferred embodiments are deliverable through a 2.8mm inner diameter curved guiding sheath
 - d. Preformed with at least two embodiments: one fixed curved such as a multipurpose-curve catheter, another curved with a 180-to-235-degree retroflex curve catheter, to allow apposition to both sides of valve annulus from transvenous, transarterial, transseptal, and transapical access routes. Preferred embodiments are deflectable up to 235-degrees/
 - e. Must be conspicuous under fluoroscopy and under ultrasonography.
 - f. Mechanical properties: resembling coronary guiding catheters or deflectable guiding sheaths to allow delivery of two commercial rigid 0.014” effector guidewires (with mechanical characteristics resembling Asahi Astatato XS-20 guidewires).
 - g. Hemocompatible
6. Adjustable transcatheter suture lock
- a. Allows secure and permanent locking of the pledgeted suture under tension
 - b. Allows adjustment of tension, reversal or tension, and full retrieval after application
 - c. The design prevents loss of suture tension during application
 - d. Visible under X-ray and echocardiography
 - e. MRI compatible although a small susceptibility artefact may be desirable to impart visibility.
 - f. The lock delivery system need not be MRI compatible.
 - g. Biocompatible and hemocompatible

- h. Must fit through 8.5Fr Agilis sml curl deflectable sheath during full deflection and alongside one or more O sutures and one or more 0.014” guidewires
7. Transcatheter Suture cutter
- a. Must cut suture through an 8.5Fr Agilis sml curl fully deflected, alongside one or more 0.014” guidewires
 - b. Must have effector visible under X-ray and preferably also under ultrasound
 - c. Must effectively cut the accompanying sutures in this suite

Phase II Activities and Expected Deliverables

In addition to meeting all requirements for Phase I, a phase II award would allow commercial introduction of the suite of tools together or independently as 510(k) devices substantially equivalent to marketed predicate devices. If this is not feasible, the phase II deliverable would be all testing and regulatory development for the device to be used in human investigation in the United States, under Investigational Device Exemption, along with devices sufficient to test in 30 human subjects.

The contracting DIR lab offers to perform an IDE clinical trial at no cost to the awardee. Complete IDE documentation and license and a suitable supply of clinical materials would constitute the deliverable.

104 Tapered Guidewires for Transcatheter Electrosurgery

Fast-Track proposals will be accepted.

Number of anticipated awards: [1 Phase I, 1 Phase II]

Budget (total costs):

Phase I: \$200,000 for 12 months

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

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

Summary

The solicitation will support the small business development of specific guidewire devices to ease and simplify transcaval access to the aorta, to make the procedure available to a wider range of patients and operators.

Project Goals

The goals are to develop and commercialize specific tools to simplify transcaval access to the aorta. The tools are a tapered guidewire and a connector-switch to a common electrosurgery generator. These will greatly simplify transcaval access procedures, reducing the required operator skill, making the procedure more accessible to a wider array of patients and operators, and reduce the cost of the procedure.

Phase I Activities and Expected Deliverables

A phase I award would develop and test a suite of working prototypes in swine. The contracting intramural laboratory wishes to test the final prototype in vivo, and offers an earlier stage test to the contractor at no cost.

Below is a list of individual devices which are part of the suite, along with specific requirements. The devices must be able to function alone or together as components of the multifunctional suite.

8. Tapered transcaval guidewire
- a. Intended to cross a vascular or chamber wall with a 0.014” tip and then seamlessly transition to a rigid 0.35” shaft
 - b. Preferred embodiments have a long continuously tapered core, a lubricious and electrically insulating coating except at the tip.
 - c. Tip mechanical properties must resemble Asahi Astatto XS 20 guidewire
 - d. Shaft mechanical properties must resemble Cook Lunderquist guidewire

- e. Approximately distal 10cm is 0.014”, approximately next 20-30cm is tapered, remainder of wire has 0.035” outer diameter. Total length is 2.6-3m
9. Electrosurgical connector
- a. Serves to replace a Bovie electrosurgery pencil connector to a guidewire, otherwise accomplished using a forceps
 - b. Connects to the back end of a 0.014” and 0.035” guidewire, such as using a screw-type friction clamp
 - c. Connects to a conventional electrosurgery generator such as Medtronic Valleylab FX
 - d. Allows controlled actuation only of the “cutting” switch
 - e. A preferred embodiment allows a preset time-limit to individual actuations for each button press, such as 1-second timeout, before the button is again depressed.
 - f. A preferred embodiment also has a switch lockout to assure no inadvertent actuation

Phase II Activities and Expected Deliverables

In addition to meeting all requirements for Phase I, a phase II award would allow commercial introduction of the suite of tools together or independently as 510(k) devices substantially equivalent to marketed predicate devices. If this is not feasible, the phase II deliverable would be all testing and regulatory development for the device to be used in human investigation in the United States, under Investigational Device Exemption, along with devices sufficient to test in 30 human subjects.

The contracting DIR lab offers to perform an IDE clinical trial at no cost to the awardee. Complete IDE documentation and license and a suitable supply of clinical materials would constitute the deliverable.

105 Reagent Development for Small Cell Number ChIC-seq

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

Number of anticipated awards: 1

Budget (total costs):

Phase I: \$150,000 for 1 year

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

Summary

This solicitation is for the development of conjugates between specific antibodies or protein A with micrococcal nuclease (MNase) to be used for genome-wide epigenetic mapping. They will be used to identify genome-wide epigenetic changes during normal development and pathological conditions, requiring only a few hundred primary or patient cells.

Project Goals

The project goal is to develop reagents that can be used for mapping genome-wide epigenetic changes during normal development and disease process in rare primary and patient cells. Because conjugating proteins could result in inactivation of the proteins, it will be important to achieve efficient conjugation between antibodies and MNase while reserving the activities of both.

Phase I Activities and Expected Deliverables

Specific deliverables are:

- Conjugates between 10 different histone modification antibodies and MNase; one milligram specific antibody per histone modification (antibodies include H3K4me1, H3K4me2, H3K4me3, H3K27ac, H3K27me3, H2A.Z, H3K9ac, H3K9me3, H3K36me3, histone H3).
- Conjugates between 40 transcription factor antibodies and Mnase; one milligram specific antibody per transcription factor (antibodies for transcription factors include RNA Pol II, Brd4, BRG1, GATA3, Eomes, T-bet, ETS1, RORg,

and other general and sequence-specific factors that will be decided by the Contracting officer Representative (COR) on the resultant contract.

- Conjugates between Protein A and MNase (10 milligrams)

It is critical that the developer provide evidence to show that the antibodies in the conjugates are still specific and as active as non-conjugated antibody using Western and ChIP assays. It is critical that the MNase in the conjugates is still as active as non-conjugated MNase using chromatin digestion assay. It is critical that the free individual proteins (un-conjugated) in the final products are less than 5% of all protein components.

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 <https://www.niaid.nih.gov/research/role>.

050 Methods Improving HIV Protein Expression: Cell Substrate and Protein Purification

Fast Track proposals will be accepted

Number of anticipated awards: 3-4

Budget (total costs):

Phase I: \$300,000/year for up to 2 years

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

Background

Despite the widespread use of GMP-established pharma cell substrates (e.g., CHOs, 293 etc.) in development of recombinant HIV Env protein antigens, critical bottlenecks still exist in their use for large-scale, high-yield GMP manufacturing; yields often are on the order of mg/L compared to mAbs at gm/L. Some of the limitations relate to their intrinsic incapacities to metabolically produce high levels of stable properly folded, properly glycosylated recombinant HIV Env protein, often times requiring extensive clonal screening to identify the rare high-level producer clone. These constraints have a cascading effect in increasing the overall cost and time for production of HIV vaccine antigens from millions of dollars and years of upstream and downstream process development. As such, there is an urgency to evaluate alternative strategies/technologies capable for developing highly productive cellular substrates suitable for high yield GMP manufacturing of HIV antigens and reduced product development lead times. Traditional downstream purification processes for HIV Env purification are equally plagued with similar inefficiencies either requiring expensive lectins or multi-step purification cycles resulting in low yields. Alternative approaches to HIV Env purification are needed to improve yields and expedite the overall purification process and costs.

Project Goals

The objective is to evaluate and modulate the molecular pathways involved in regulating and enhancing HIV envelope/antigen expression in mammalian cell lines and to accelerate development of purification platforms in a CGMP manufacturing setting. Key areas of support will include, but are not limited to, the following:

Phase I activities may include the following non-CGMP activities:

- Exploration of methodologies to improve HIV Envelope protein expression in mammalian cell substrates. The following approaches may include: alteration of codon usage, improvements in expression cassettes including the use of novel selection markers or other selection approaches, evaluation of Env mRNA sequence
- Exploration of methodologies to improve of existing cell substrates by removal of deleterious proteases, targeting of genes involved in glycosylation, improved secretion or other post-translational modifications that enhance yield and/or stability, or removal of endogenous retroviruses.
 - Methodologies to improve HIV Env expression or cell substrates can include traditional gene modification approaches as well as novel technologies such as siRNA and/or CRISPR/Cas9 gene targeting.
- Development of strategies to accelerate phase appropriate manufacturing including transient transfection or stable cell pool approaches for HIV Env GMP manufacture
- Improvement of HIV envelope downstream protein purification methodologies including affinity purification approaches or other strategies.

Phase II activities may include the following CGMP activities:

- CGMP development of the improved Cell Substrates explored in Phase I, including additional IND-enabling characterization studies, development of technical reports, generation of MCB, etc
- CGMP Process Development of the improved Downstream purification methodologies developed in Phase 1, including technical reports, development of scale-up approaches, etc.

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

Fast Track proposals will be accepted

Number of anticipated awards: 2-3

Budget (total costs):

Phase I: \$300,000/year for up to 2 years

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

Background

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

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

Project Goal

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

Phase I activities

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

Phase II activities

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

052 High-Throughput Assay Platform for Quantifying Latent HIV Reservoirs

Fast-Track proposals will be accepted

Number of anticipated awards: 1-2

Budget (total costs):

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

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

Background

One of the most significant hurdles to overcome in evaluating strategies to cure HIV infection is the lack of a simple method for quantifying changes in the size of the latent reservoir of replication-competent HIV in resting CD4+ memory T cells in individuals on highly effective antiretroviral therapy. Most of the HIV DNA in these cells represents defective virus; less than 0.01% of highly purified resting CD4 cells harbor replication-competent provirus. As a result, PCR-based methods tend to over-estimate the size of the reservoir and do not correlate with the number of cells producing functional virus in a viral outgrowth assay. However, viral outgrowth assays are labor-intensive and require large volumes of blood.

Project Goal

The goal of this project is to design a high-throughput assay platform that can be used to reproducibly quantify changes in the size of the replication-competent latent HIV reservoir in resting CD4+ memory T cells isolated from individuals on highly effective antiretroviral therapy. Applicants must provide a plan for validating the assay by demonstrating correlation with quantitative viral outgrowth assays (QVOA) and/or functional non-induced HIV proviruses using cells isolated from virally suppressed HIV+ individuals on optimized antiretroviral therapy.

Phase I activities

- Development of technologies for detecting replication-competent latent proviruses
- Validation of detection methods using standardized controls
- Optimization of sensitivity to detect low-frequency latently infected cells
- Demonstration of correlation with replication-competent provirus vs. defective provirus

Phase II activities

- Further optimization of the assay platform technology and validation of assay reproducibility
- Increased throughput
- Comparison of assay to other methods published in the literature
- Testing of clinical samples from diverse cohorts of HIV+ individuals with varying levels of residual viral reservoirs
- Comparison of blood vs. tissue samples from virally suppressed individuals
- Modification of assay to detect latent HIV in humanized mouse models and latent SIV in nonhuman primate models in the context of optimized antiretroviral therapy
- Use of assay to demonstrate changes in the size of the latent HIV/SIV reservoir in response to an intervention

053 Effective Targeted Delivery of RNA-based Vaccines and Therapeutics

Fast-Track proposals will be accepted.

Number of anticipated awards: 1-2

Budget (total costs):

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

054 Adjuvant Discovery for Vaccines and for Autoimmune and Allergic Diseases

Fast-Track proposals will be accepted.

Number of anticipated awards: 1-3

Budget (total costs):

Phase I: \$300,000/year for up to 2 years

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

Background

The goal of this program is to support the screening for new vaccine adjuvant candidates against infectious diseases or for tolerogenic adjuvants for autoimmune or allergic diseases. Traditionally, adjuvants are defined as compounds that stimulate innate and/or adaptive immune responses. The goal of this program is to support the discovery of novel vaccine adjuvants as well as adjuvants with tolerogenic properties. For the purpose of this SBIR, vaccine 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.” Tolerogenic adjuvants are defined as compounds that promote immunoregulatory or immunosuppressive signals to induce non-responsiveness to self-antigens in autoimmune diseases, or environmental antigens in allergic diseases.

Currently, only three adjuvants have been approved for clinical use as components of vaccines in the United States - aluminum hydroxide/aluminum phosphate (alum); ASO4, a combination of 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 FLUAD influenza vaccine for people age 65 years and older. The gaps that need to be addressed by new adjuvants include improvements to existing efficacious vaccines (*e.g.*, the acellular pertussis vaccine), and development of vaccines: for emerging threats (*e.g.*, Ebola outbreaks); for special populations that respond poorly to existing vaccines (*i.e.*, elderly, newborns/infants, immunosuppressed patients); or to treat/prevent immune-mediated diseases (*e.g.*, allergic rhinitis, asthma, food allergy, autoimmunity, transplant rejection). Recent advances in understanding innate immunity have led to new putative targets for vaccine adjuvants and for allergen immunotherapy. Simultaneously, progress is slowly being made in the identification of *in vitro* correlates of clinical adjuvanticity which allows the design of *in vitro* screening assays to discover novel adjuvant candidates in a systematic manner.

The field of tolerogenic adjuvants is still in its infancy. No compounds have been licensed yet in the US and immune-mediated diseases continue to be treated mostly with broadly immunosuppressive drugs or long-term single or multi-allergen immunotherapy. In contrast to drugs, tolerogenic (or immunomodulatory) adjuvants would interfere with immune responses to specific antigens through a variety of mechanisms which include the induction of regulatory T cells, or by changing the profile of the pathogenic lymphocyte response (*e.g.*, Th1/Th2/Th17, etc). The combination of tolerogenic adjuvants with allergen immunotherapy should aim at accelerating tolerance induction, increasing the magnitude of tolerance and decreasing the duration of treatment.

Project Goal

The objective of this program is to support the screening for new adjuvant candidates for vaccines against infectious diseases or for autoimmune and allergic diseases; 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 vaccine- or tolerogenic 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 lead 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

055 Adjuvant Development for Vaccines and for Autoimmune and Allergic Diseases

Fast-Track proposals will be accepted

Number of anticipated awards: 1-3

Budget (total costs):

Phase I: \$300,000/year for up to 2 years

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

Background

Adjuvants stimulate innate and/or adaptive immune responses. For the purpose of this SBIR, vaccine 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”. Tolerogenic adjuvants are defined as compounds that promote immunoregulatory or immunosuppressive signals to induce non-responsiveness to self-antigens in autoimmune diseases, or environmental antigens in allergic diseases. Currently, only three adjuvants have been approved for clinical use 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 FLUAD 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 to treat/prevent immune-mediated diseases (e.g., allergic rhinitis, asthma, food allergy, autoimmunity, transplant rejection). The field of tolerogenic adjuvants is still in its infancy. No compounds have been licensed yet in the US and immune-mediated diseases continue to be treated mostly with broadly immunosuppressive drugs or long-term single or multi-allergen immunotherapy. In contrast to drugs, tolerogenic or immunomodulatory adjuvants would interfere with immune responses to specific antigens through a variety of mechanisms which include the induction of regulatory T cells, or by changing the profile of the pathogenic lymphocyte response (e.g., Th1 to Th2 or vice versa). The combination of tolerogenic adjuvants with allergen immunotherapy should aim at accelerating tolerance induction, increasing the magnitude of tolerance, and decreasing the duration of treatment.

Project Goal

The goal of each 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 infectious pathogens, or for autoimmune or allergic diseases. For this solicitation, a combination-adjuvant is defined as a complex exhibiting synergy between individual adjuvants, such as: overall enhancement or tolerization of the immune response; potential for adjuvant-dose sparing to reduce reactogenicity while preserving immunogenicity or tolerizing effects; or broadening of effector responses, such as through target-epitope spreading or enhanced antibody avidity. The adjuvant products supported by this program may be studied and further developed toward human licensure with currently licensed or new investigational vaccines, and/or may be developed as stand-alone immuno-stimulatory or immuno-regulatory 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 or tolerize immune responses synergistically and/or additively
- 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 or tolerizing efficacy of a lead adjuvant:vaccine
- Analysis of vaccine efficacy through the use of a combination adjuvant and studies to evaluate the safety profile of the combination adjuvant:vaccine-formulation

Phase II Activities

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

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

This SBIR will not support:

- The further development of an adjuvant that has been previously licensed for use with any vaccine
- The conduct of clinical trials (see http://osp.od.nih.gov/sites/default/files/NIH%20Definition%20of%20Clinical%20Trial%2010-23-2014-UPDATED_0.pdf 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 or tolerogenic activity themselves
- The discovery, development and/or optimization of an immunogen component of a vaccine

056 Reagents for Immunologic Analysis of Non-mammalian Models

Fast-Track proposals will be accepted

Number of anticipated awards: 1-3

Budget (total costs):

Phase I: \$300,000/year for up to 2 years

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

Background

This Funding Opportunity Announcement (FOA) is intended to address the limited availability of reagents (e.g., antibodies, proteins, ligands) for the identification and discrimination of immune cells of non-mammalian models (e.g., arthropods, amphibians, fish, nematodes, marine echinoids). Non-mammalian models are easily tractable model systems to study basic, conserved immune defense pathways and mechanisms. For example, characterization of the *Drosophila* Toll signaling pathway facilitated the discovery of mammalian Toll-Like Receptors (TLR), which helped to launch the field of innate immunity. Non-mammalian models can be much more easily adapted to high-throughput screening formats than mammalian organisms. *Caenorhabditis elegans* has been used for whole organism high-throughput screening assays to identify developmental and immune response genes, as well as for drug screening. Many non-mammalian species are natural hosts for human pathogens and share many conserved innate immune pathways with humans, such as the Nf- κ B pathway in mosquitoes, the intermediate hosts for *Plasmodia* parasites. Results from such studies can guide research in mammalian systems and provide insights into immune responses against pathogens transmitted to humans. Work leading towards a better understanding of immune regulation within non-mammalian models has been constrained by the limited availability of antibodies and other immune-based reagents for the use in scientific studies.

Project Goal

Development and validation of reliable antibodies against non-mammalian immune cell markers or other reagents that allow for the identification and tracking of primary immune cells.

Phase I Activities include, but are not limited to:

- Identification of protein targets (immune cell markers, receptors with immune function)
- Development of antibodies/reagents that allow for the identification and/or discrimination between primary immune cells from non-mammalian species

Phase II Activities include, but are not limited to:

- Validation of antibodies/reagents
- Screening for cross-reactivity with related molecules on other non-mammalian species and/or mammalian immune cells
- Scale-up production

This SBIR will not support:

- Development of antibodies/reagents against immune markers on mammalian cells
- Development of antibodies/reagents against markers on cells not involved in immune responses

057 Development of Sample Sparing Assays

Fast-Track proposals will be accepted.

Number of anticipated awards: 1-3

Budget (direct costs):

Phase I: \$300,000/year for up to 2 years

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

Background

The NIAID's Division of Allergy, Immunology and Transplantation (DAIT) supports a wide range of research programs spanning basic immunology, translational and clinical research on protective immunity and immune-mediated diseases, including autoimmune and primary immunodeficiency diseases, allergic diseases, graft-versus host disease (GVHD) and allograft rejection in organ, tissue and cell transplantation. Major constraints encountered in designing mechanism of action studies are related to limited quantity of biological specimens available for study and the paucity of robust, validated, miniaturized assays that can reliably and reproducibly assess immune function, disease state or effects of therapy. The restricted amounts of tissue, cells and fluids that can be collected from adult, pediatric or immunocompromised patients are often inadequate for the application of conventional assays that interrogate immune function. Novel, multi-parameter, sample sparing assays are needed to obtain maximal biologic information from limited amounts of biological materials.

Project Goal

The goal of this proposal is to accelerate commercial development of novel, standardized sample sparing assays that improve monitoring of the immune system using limited amounts of biological sample. Sample sparing immune assays of interest may include, but are not limited to monitoring or assessments of the following:

- Antigen-specific immune responses
- Distinct immune cell populations
- T-cell and B-cell regulatory networks
- Innate immune responses
- Markers of T-cell turnover and homing to lymphoid tissue
- Cytokine and signaling networks
- Gene and protein expression and regulation
- Mucosal inflammatory and innate immune response

Technologies that address novel sample preparation or cell isolation processes are also included in the areas of interest for this announcement.

The sample sparing assays developed through this funding opportunity must address challenges, gaps or unmet needs in the study of human immune responses and provide clear advantages over existing assays.

Phase I Activities

Depending on the developmental stage of the sample sparing assay the offeror may choose to perform one or more of the following:

- Preliminary studies performed in a suitable animal model or in human samples to evaluate the assay feasibility (scientific and technical)
- Establish assay's quality of performance, assay reproducibility and validation
- Define process controls
- Establish potential for commercialization

Phase II Activities

- Further technology developments and assay improvements
- Development and validation of prototype platforms
- Development of quality control program to enable longitudinal measurements in compliance with Good Clinical Laboratory Practice

This SBIR will not support:

- Any phase clinical trial
- Identification of new biomarkers
- Validation of biomarker candidates
- Proposals focused exclusively on animal studies and animal disease models. Animals may be used in assay development phase but all assays must be validated using primary human samples
- Development of assays using established cell lines without validation in primary human samples
- Virus-induced cancers
- Studies that do not fall within NIAID mission

058 Bioinformatics tools to make data FAIR (Findable, Accessible, Interoperable, and Re-usable)

Fast-Track proposals will be accepted.

Number of anticipated awards: 1-2

Budget (total costs):

Phase I: \$300,000/year for up to 2 years

Phase II: \$1,000,000/year 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 the immunology research community for data sharing, knowledge dissemination, standard development and integrative analyses:

- ImmPort (<https://immport.niaid.nih.gov/>): a unique resource for public data sharing of clinical immunology and research studies
- 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 the ITN's clinical studies and specimen bio-repository

- IEDB (<http://www.iedb.org/>): a bioinformatics resource that offers easy searching of experimental data characterizing antibody and T cell epitopes 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 are freely available, their usage becomes limited to specific domains because the data representations (the internal method used to represent the type of data) stored in the repository for search, retrieval and presentation tools are specific to the individual repository. There is a growing need for informatics tools and approaches that make it easy for researchers to make data Findable, Accessible, Interoperable and Reusable (FAIR). Tools that facilitate this integration can contribute to transparency and reproducibility and ultimately accelerate research.

Project Goal

The goal of this project is to support the development of new and/or improved methods that make data FAIR in order for popular search engines to index and provide relevant search results for research data sets that are available for public use. These tools will complement the capabilities of more specialized search interfaces or services such as those provided by DAIT-funded data repositories.

Phase I Activities

Phase I activities must include performing a gap analysis of the above-mentioned databases according to the FAIR principles and developing informatics tools to address the identified gaps. The offeror may choose to develop tools with one or more of the following functionalities:

1. Novel approaches to make data more findable by utilizing information that includes but is not limited to data, metadata, associated literature, and text.
2. Approaches that extract information about features of the data and make it FAIR so a search engine can find it.
3. Approaches that perform quality control by verifying ontology mapping, conformance to data description standards or other pre-processing steps involved in making data FAIR.

Phase II Activities

1. Improve stability, scalability, and usability of the informatics tools prototyped during Phase I.
2. Add functionalities and capacities to these systems based on research community's needs.

059 Diagnostics to Enable Malaria and Neglected Tropical Diseases (NTDs) Elimination

Fast-Track 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

Malaria and Neglected Tropical Diseases (NTDs) disproportionately affect the poorest people in developing countries. The World Health Organization disease burden reduction targets for 2030 include global elimination of leprosy, lymphatic filariasis, trachoma, onchocerciasis, and human African trypanosomiasis (HAT), and a reduction in the malaria mortality rate by 90%. Impressive progress is being made towards these goals. For example, malaria incidence rates fell 37% globally between 2000 and 2015; an 80% reduction in new HAT cases was seen between 2000 and 2014, and 18 countries have been able to stop preventative chemotherapy for lymphatic filariasis, as have eight countries for trachoma. However, we currently lack diagnostic tools with optimal sensitivity and specificity for use in the elimination and post-elimination phases. For example, microscopy and available rapid diagnostic tests (RDTs) have been largely adequate for malaria control but lack the sensitivity to detect asymptomatic infections. In the case of HAT, current diagnostic methods are limited by sensitivity and

reproducibility, and the lumbar puncture method is invasive and less than ideal. For these diseases slated for elimination, there is a pressing need for new diagnostic tools that can detect subclinical infections that serve as a disease reservoir and contribute to onward transmission. Such diagnostics would be intended for use in active-infection-detection interventions such as mass-screen-and-treat, targeted mass-drug-administration, post-elimination surveillance and for detecting cases in low-prevalence areas.

Project Goal

The goal of this project is to develop a low-cost, diagnostic platform with appropriate sensitivity and specificity for the detection of subclinical malaria or select NTD infections (leprosy, lymphatic filariasis, trachoma, onchocerciasis, HAT) for use in disease elimination campaigns in resource-limited settings. The final product should demonstrate the necessary sensitivity and specificity to reliably detect asymptomatic infections that are outside the limits of detection of currently available diagnostics.

Phase I Activities can include but are not limited to:

- Development of a prototype point-of-care diagnostic device that can identify one or more target pathogens in low biomass infections.
- Determination of the sensitivity, specificity and other performance characteristics (e.g. time to result, limit of detection, test stability) of the diagnostic.
- Initial testing on laboratory isolates.

Phase II Activities can include but are not limited to:

- Development of well-defined test platform under good manufacturing practices (GMP).
- Scale up and production for multi-site evaluations using clinical isolates.
- Product development strategy for regulatory approval and demonstration of clinical application.

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](#).

060 Computational Software Development to Advance Translational Research for Infectious Diseases

Fast-Track proposals will be accepted.

Number of anticipated awards: 3-4

Budget (total costs):

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

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

Background

There is a critical need to develop new and improved vaccines and therapeutics for high priority pathogens such as influenza, *Mycobacterium tuberculosis* (Mtb), and HIV. Research investments in sequencing these pathogens have resulted in an explosion of publicly available genomic data, creating a need for intuitive and efficient software tools to analyze massive amounts of data and enable prediction and/or identification of new targets and control strategies for treatment and prevention. This solicitation will support software development in two specific and separate areas (one area per proposal):

1. **Non-Coding RNA:** Although non-coding RNAs (ncRNAs) have been identified as promising biomarkers and therapeutic targets for a number of human diseases, translational efforts in the infectious disease field are largely lacking. A critical barrier to translation is our lack of understanding of the functional roles of ncRNAs in infectious disease. The development of software packages to analyze existing ncRNA data sets will assist researchers in

identifying the most promising ncRNAs for future mechanistic studies, helping to overcome this barrier and move the field forward from discovery to translation.

2. **Influenza vaccines:** Public databases now contain genomic sequences for tens of thousands of influenza viruses as well as associated *in vitro*, *in vivo*, and in some cases clinical data. Engaging the software industry in the development of predictive software linking genetic sequencing information with other types of data such as antigenicity, protein structure, viral fitness and/or vaccine efficacy, is anticipated to bring a new dimension to the annual influenza vaccine strain selection process and vaccine development, decreasing the likelihood of vaccine strain mismatch and leading to more effective influenza vaccines.

Project Goal

The goal of this project is the development of computational software that provides sensitive tools to enable translational research on high priority infectious disease pathogens by analyzing massive amounts of existing data. Use of novel cognitive computational strategies that combine large complex data sets and machine learning algorithms is encouraged to translate information into knowledge that can help drive more informed decision-making. The scope of software development is limited to two priority areas:

- Analyzing large-scale ncRNA data to identify expression patterns associated with influenza, Mtb, or HIV infection and/or disease progression to guide future mechanistic and translational studies (e.g., algorithms/analytics that enable target prediction/identification, structure analysis, functionality determination, quantification of ncRNA expression levels, etc.).
- Predicting influenza virus evolution to improve vaccine strain selection and vaccine efficacy.

Phase I activities can include but are not limited to:

- Develop a functional software prototype.
- Demonstrate capability of the software to: (1) analyze large-scale ncRNA data to identify expression patterns associated with influenza, Mtb, or HIV infection and/or disease progression (Area 1); or (2) link influenza genetic sequencing information with other types of data such as antigenicity, protein structure, viral fitness and/or vaccine efficacy to predict influenza virus evolution and improve vaccine strain selection and vaccine efficacy (Area 2).

Phase II activities can include but are not limited to:

- Evaluate, revise, and enhance the software prototype.
- Perform beta testing of the software with relevant end users.
- Incorporate user feedback from beta tests.
- Develop user support and instructional guides to facilitate commercialization.

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](#).
- Use of novel or non-publicly available datasets to develop and demonstrate the utility of the computational software and tools.

061 Induction of Mucosal Immune Response to Parenterally Delivered Vaccines

Fast-Track proposals will be accepted

Number of anticipated awards: 2-3

Budget (total costs):

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

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

Background

For a wide range of pathogens, the first contact between the pathogen and the human host occurs at a mucosal surface, such as the gastrointestinal tract. Ideally, vaccines against enteric infections would elicit protective immunity at both systemic and mucosal compartments. Non-living, subunit, or conjugate vaccines given parenterally may induce systemic responses, but generally elicit less-than-optimal responses, if any, in mucosal tissues. Oral administration of such vaccines is not practical because the acidic stomach environment may degrade the antigen, which then requires increased amounts of vaccine to reach the target, inductive site. One strategy to overcome this limitation is to include components that elicit mucosal immunity when formulating parenteral vaccines. Mucosal adjuvants, such as bacterial toxins or toxin derivatives, induce homing receptor expression on T cells and B cells that leads to their migration to intestinal mucosal compartments and, thus, ultimately elicits protective immunity. Examples of enteric infections for which vaccine candidates are under development include Enterotoxigenic *E. coli*, *Shigella* spp., *Salmonella* spp., *Campylobacter jejuni*, *Clostridium difficile*, *C. botulinum*, and enteric viruses (e.g., norovirus or rotavirus), and the addition of mucosal adjuvants to their formulation may enhance vaccine immunogenicity and efficacy. Thus, the overall goal of this topic is to formulate parenterally delivered enteric vaccines that will elicit mucosal immune responses in addition to systemic immune responses.

Project Goals

- To determine the best vaccine:adjuvant formulation(s) of current enteric vaccine candidate(s) that induce immune responses at both mucosal and systemic compartments;
- To characterize systemic and mucosal immune responses to parenterally-delivered enteric vaccine candidates;
- To encourage collaboration between academic institutions and small business entities to determine the optimal formulation for such vaccines.

Phase I activities may include but are not limited to:

- Identification of enteric vaccine candidate(s) and relevant adjuvant(s) that may be delivered parenterally to mice and that induce systemic and intestinal immune responses;
- Performance of preliminary studies in mouse model with various vaccine:adjuvant combinations to determine immunogenicity and optimal dose;
- Development of *in vitro* assays to evaluate immune responses, including functional assays using mucosal and systemic samples;
- Selection of at least two vaccine:adjuvant combinations for further studies; each vaccine must target a different enteric disease.

Phase II activities may include but are not limited to:

- Confirmation of preliminary results obtained during Phase I with the selected vaccine:adjuvant combinations;
- Additional testing of lead vaccine candidate(s) for progress towards IND-enabling studies, including but not limited to testing to improve safety, efficacy, and QA/QC;
- Pilot lot cGMP manufacturing of the vaccine candidate(s);
- Formulation, stability, and toxicology studies, as appropriate, for later stages in the vaccine product development pathway.

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 SBIR phase II clinical trial support, see the [NIAID SBIR Phase II Clinical Trial Implementation Cooperative Agreement program announcement](#).
- Platform development such as vehicle or delivery systems.

062 Novel Vaccine Technologies and Strategies to Promote Sustained Vaccine Efficacy

Fast-Track proposals will be accepted.
Number of anticipated awards: 2-3

Budget (total costs):

Phase I: \$450,000 for up to 2 years

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

Background

There is an unmet need to improve vaccine performance to combat malaria and pertussis, which are considered significant public health threats. Recent advances in the field of malaria vaccine development have led to the achievement of significant milestones. Several malaria vaccines are now in late stage development or are being considered for widespread deployment. However, these vaccine candidates have only been shown to provide short-term protection, suggesting a need for further improvement. Similarly, widely accepted acellular vaccines for pertussis are showing waning protection, resulting in outbreaks of pertussis, a disease that was previously thought to have been controlled. Knowledge about immunological memory and correlates of vaccine protection is constantly evolving; newly available vaccine delivery tools, strategies, and formulations are currently being optimized with prototype antigens to develop vaccines with enhanced protective immunity. This contract topic aims to leverage the new knowledge and tools, and calls for the development of novel vaccine technologies and strategies that promote sustained vaccine efficacy against malaria or pertussis.

Project Goals

- To identify or develop novel vaccine technologies, such as delivery platforms or formulations, that induce long-term protection against malaria or pertussis;
- To develop new vaccines or vaccine strategies using technologies that induce long-term immunity and sustainable efficacy against malaria or pertussis.

Phase I activities can include but are not limited to:

- Identification and evaluation of novel formulations (e.g., adjuvants, adjuvant systems), delivery platforms (e.g., viral vectors), or vaccine strategies (e.g., novel prime-boost regimens) to induce long-term immunity or surrogate markers for long-term protection;
- Development of *in vitro* surrogate assays to evaluate induction of long-term immunity or protection using phenotypic markers;
- *In vivo* proof-of-concept studies to demonstrate sustainable protection in appropriate animal models.

Phase II activities can include but are not limited to:

- Additional testing and process development of the lead technologies and/or vaccine candidate(s) in the product development pathway leading to IND-enabling studies, including but not limited to testing to improve safety, efficacy, and QA/QC;
- Further definitive preclinical testing in non-human primate models;
- Pilot lot cGMP manufacturing, as appropriate, for further refinement of the vaccine candidate(s);
- Stability and toxicology studies, as appropriate, for later stages of the vaccine product development pathway.

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 SBIR phase II clinical trial support, see the [NIAID SBIR Phase II Clinical Trial Implementation Cooperative Agreement program announcement](#).
- Technology development using prototype antigens other than known or newly identified protective antigens for malaria and pertussis.

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 involves:

- Strategically supporting and conducting basic and clinical research on drug use (including nicotine), its consequences, and the underlying neurobiological, behavioral, and social mechanisms involved.
- Ensuring the effective translation, implementation, and dissemination of scientific research findings to improve the prevention and treatment of substance use disorders and enhance public awareness of addiction as a brain disorder.

This solicitation invites proposals in the following areas:

163 Digital Markers for Marijuana Intoxication

Number of Anticipated Awards: 3-4.

Phase I and Fast-Track proposals will be accepted. Fast-Track proposals include Phase I and Phase II activities.

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 2 years 6 months.

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

Objective

This RFP solicits the research and development of digital markers for detection of acute marijuana intoxication. In the content of this solicitation the digital markers are described as smart phone-based diagnostic test data or real time, data-driven signals. The proposed digital markers must be created on Apple Inc.'s ResearchKit or/and Android ResearchStack frameworks. Both frameworks are open-source software platform which make it easy for researchers and developers to create mobile applications (apps) for specific biomedical research questions by circumventing the development of custom code. Mobile app development on custom platforms will not be funded. Then, the offerors are expected to test the apps clinically and validate the embedded digital markers. It is envisioned that the developed and validated digital markers will be consolidated into novel digital health tools for use in clinical research and law enforcement procedures.

Background

As marijuana is being medically and recreationally legalized in many states, there is a growing concern over marijuana intoxication. A major public health concern is the increased risk of marijuana-impaired driving, because the number of individuals testing positive for marijuana constituents and the proportion who was involved in traffic fatalities doubled in the three years. According to the 2017 report issued by the Governors Highway Safety Association (GHSA) and the Foundation for Advancing Alcohol Responsibility, drugs are now involved in more fatal U.S. crashes than alcohol alone, and marijuana-impaired driving significantly contributes to this trend. However, currently there is no quantitative biologic test that can accurately determine whether an individual is acutely impaired following marijuana consumption.

When marijuana is absorbed, the concentration of tetrahydrocannabinol (THC), one of the psychoactive marijuana constituents, decreases rapidly in the blood stream due to the distribution through the hepatic metabolism and absorption into fat cells. Over time, THC is slowly released back into the bloodstream and subsequently excreted in the urine. The rapid and variable absorption and release of THC into the blood stream makes it difficult to correlate the level of THC with impairment in chronic marijuana users. In addition, due to the multiple marijuana species, there are over 100 marijuana metabolites. These metabolites can be detected in the blood, however, they have been not associated with the psychoactive effects of marijuana use. This translates into unreliable blood tests for marijuana detection which have high rate of false positive results. One alternative is a saliva-based screening tool. The oral fluid is easy to collect, non-invasive, and is associated with recent cannabis intake. Unfortunately, recent studies have shown that the saliva-based tests have a two- to five-fold greater

variability than the blood tests, and the level of marijuana detection is also not precise. In the absence of a quantitative, bio-specimen-based test for marijuana intoxication and psychomotor impairment, the Diagnostic and Statistical Manual IV (DSM V) test remains the only diagnostic gold standard used by drug recognition experts and mental health professionals.

Using digital parameters of person's psychomotor impairment in the response to the marijuana consumption may represent more reliable and correlative approach for diagnostics. To test this hypothesis, the National Institute on Drug Abuse (NIDA) plans to support the identification, development, testing and validation of digital markers for detection of psychomotor impairment due to marijuana intoxication. To increase the project efficiency and to increase interoperability and sustainability of the research tools produced as the result of this solicitation, NIDA requests that the proposed markers be developed and clinically validated using mobile applications created on Apple Inc.'s ResearchKit or Android ResearchStack frameworks. Both frameworks are open-source and allow researchers and developers to easily create biomedical apps by circumventing the development of custom code. Due to the availability of these pre-coded platforms, NIDA will limit the costs directly associated with the app design to no more than \$50,000 per project (with the maximum of \$30,000 for the Phase I and \$20,000 for the Phase II). Mobile app development on custom platforms will not be funded. The majority of proposed work should be focused on testing objective digital variables in response to marijuana intoxication-associated impairment and correlate those digital variables with one of more existing or (novel) biomarkers, imaging technologies and DSM V test results. Offerors are expected to have in-house capabilities or the established practice or experience to detect THC in biological specimens and quantify the level of the cognitive/psychomotor impairments in human subjects.

The app features may leverage and integrate with the internal sensors, compatible add-apters and external hardware to monitor the measurable markers of marijuana intoxication. Examples of the app features may include, but not limited to, accelerometer, microphone, gyroscope, facial or eye pupil's changes recognition software, glucometers, inhalers, skin voltage sensor, heart rate sensor, other existing and newly developed sensors.

In the future, the clinical studies using the validated apps may be more cost-efficient than the analogous ones using physiological biomarkers. The Fast Track projects may include consolidation of the validated markers into novel digital health technologies/tools to be used in the future outside of the research purposes. It is envisioned that the final app/tool will meet the FDA device class II designation.

The developed products could have enormous impact meeting a critical, unmet need for clinical research and law enforcement procedures.

Phase I Activities and Expected Deliverables

Develop a mobile application prototype and test its feasibility to measure psychomotor impairment following marijuana consumption. Conduct research on selection of the digital markers of marijuana intoxication.

Technical Requirements

1. Identify and describe selected digital markers. Customize the variables to be highly specific to the detection of marijuana-dependent dysfunction. Present the conceptual framework of the selected digital markers.
2. Develop a prototype of mobile application software using ResearchKit or/and Android ResearchStack frameworks with integration of digital markers. Create a video of the app prototype to clearly demonstrate the app functionality. Develop the white paper describing the app built upon the proposed markers and the design of the "proof-of-concept" study.
3. Conduct the "proof-of-concept" study testing feasibility and usability of digital biomarkers to detect marijuana intoxication
 - a. Obtain IRB approval for clinical studies.
 - b. Enroll healthy volunteers for the pilot clinical study and screen them for eligibility.
 - c. Demonstrate the capability of the app in the pilot clinical study. NIDA requests that the offerors should use NIDA Drug Supply Program to obtain marijuana or TCH for this clinical research. <https://www.drugabuse.gov/researchers/research-resources/nida-drug-supply-program>
 - d. Determine the feasibility by achieving reproducible, highly sensitive measurements of the cognitive/psychomotor impairment.
 - e. Compare the digital data with clinical standards (biological specimens or imaging technologies) and DSM V tests.

Phase II Activities and Expected Deliverables

Test and validate the mobile application to measure cognitive and psychomotor impairment at marijuana intoxication.

Technical Requirements

1. Revise and improve software in response to the needs identified in the Phase I. Optimize the digital variables as needed. Complete the enhanced software design based on the final system requirement document.
2. Determine efficiency and sensitivity of the digital markers to quantitatively measure the cognitive/psychomotor impairment at a known doses of THC.
3. Determine the app performance by demonstrating of the linear range, detection limits, and specificity.
4. Validate the digital biomarkers with a large cohort of marijuana users using clinical standards (biological specimens or imaging technologies) and DSM V test. Determine the residual effects of recent marijuana intake vs cumulative effects of chronic use vs poly-substance abuse (including alcohol and stimulants). Expand the statistical data and determine sensor accuracy and precision levels. Verify the diagnostic specificity, sensitivity and reproducibility.
5. Test the digital biomarkers for confounding effects of a) pre-existing cognitive and educational deficits; b) co-morbidity with other psychiatric disorders, and c) medications for drug abuse or other neurologic disorders. Validate objectivity and reliability.
6. Conduct the efficiency survey with professionals representing the target end-users. Collect survey's feedback and analyze the data.
7. Prepare the plan to address FDA-regulations if a Health IT Tool is to be used in the future outside of the research purposes.
8. Prepare strategy for implementation and dissemination.

164 Development of Portable Neuromodulatory Devices for the Treatment of Substance Use Disorders

Number of anticipated awards: 4

Budget (total costs, per award including F&A and fee):

Phase I: \$225,000 for 8 months

Phase II: \$1,500,000 for 1 year

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

NIDA strongly suggests that proposals adhere to the above project period. NIDA may not fund proposals with budgets exceeding the above amounts and project periods.

Summary

The National Institute on Drug Abuse (NIDA) has an interest in assisting people to overcome substance use disorders (SUDs) and to achieve and maintain sustained recovery. There are effective pharmacological and behavioral treatments for some substance use disorders, however not all individuals respond to treatment and long-term success rates tend to be low. Following the approval of neuromodulatory devices for the treatment of mental health disorders such as depression, obsessive compulsive disorder and neurological disorders such as Parkinson's disease, there is a growing interest to apply neuromodulatory technologies to SUDs. Studies that examine the effects of neuromodulation on nicotine, alcohol and cocaine use have suggested that this technology may have a significant potential for therapeutic use in SUDs. However, further work is needed to build upon these preliminary research studies that use prototypic neuromodulatory technologies. Limited data are available that describe the relationship between changes in brain circuitry and behavioral responses, the types of SUD behavioral activities responsive to neuromodulation, the number of treatments needed to establish and maintain behavioral responses, or the duration and persistence of such responses. For example, the current data suggest that for the therapeutic effects of rTMS and tDCS to have any lasting effect, repeated treatments and thus repeated clinic visits are needed. Current constraints to the therapeutic use of neuromodulatory devices lies in the size, cost, and complexity of current generation tools. The lack of portability of neuromodulatory devices and need for repeated daily clinical treatment increases patient costs and hinders the studies required to improve the development and ultimate acceptance of these modalities. In order to accelerate the portability of neuromodulatory device research, NIDA is seeking SBIR proposals to develop portable neuromodulation devices that by their flexibility of use will be able to extend the current research and provide novel tools to evaluate the use of neuromodulation for SUD treatment.

Project Goals

To build on established well-controlled, published empirical studies by developing commercially viable portable neuromodulatory devices for the treatment of SUDs. Successful awardees will develop new or convert existing neuromodulatory technologies used for other indications to treat SUDs, in a manner that will facilitate wide application and enhance market penetration. The technologies should translate peer-reviewed academic research studies using prototypic neuromodulatory technologies into FDA-approvable commercial products.

- The portable neuromodulatory devices produced should demonstrate similar efficacy to modulate brain circuitry, as validated by neuroimaging to that of prototypic devices as reported in the literature
- The portable neuromodulatory device should be oriented towards specific SUD-related indications
- In addition to being efficacious, devices should be safe and practical given cost/benefit considerations
 - Examples include transcranial magnetic stimulation, direct current stimulation, and vagal stimulation, while development of new invasive technologies (e.g., deep-brain stimulation), might be more difficult to justify in terms of risk/reward ratio and likely patient acceptability.

The Phase I contract proposal must include:

- Go/no-go decision tree with quantitative, not subjective milestones
- Objective measures that examine both the delivered dosage/treatment duration and the proposed mechanisms of action of the portable neuromodulatory device. Studies should include validated empirically established comparators.
- Studies designed to address all project-specific questions of feasibility.
- Detailed discussion of potential pitfalls, side effects and safety issues associated with the technology and how these concerns are to be mitigated.
- Device development plan with the appropriate regulatory authorities at the FDA and provide a regulatory pathway in the contract application.

Phase I Activities and Expected Deliverables

This phase focuses on characterizing the neuromodulatory device and parameters of the device, including:

- Building a prototypic and appropriately-sized functional device; demonstrate feasibility
- Ensuring the portable neuromodulatory device includes a refractory period or other suitable mechanism to safeguard from overuse of the device.
- Showing bio-equivalency based on prototypic measure and demonstrate device capability, for example, by comparing the effects using imaging or other techniques (fMRI, EEG, etc).
- Complete initial safety studies
- Complete a proof-of-concept clinical trial
- The Contractor will design a clinical study to assess the feasibility and acceptability of the device. The study should have a minimum of 15 enrolled participants. If desired, NIDA may provide assistance with the study design and finding clinical partners.
- A milestone on the acceptability of integrating portable devices with pharmacotherapies or behavioral therapies to maximize treatment efficacy, functional and/or clinical outcomes will be required
- Following determination of milestone acceptability by NIDA, a 1-week outpatient study will be conducted. This study is to evaluate 1) measures of acceptability including retention of the portable device, 2) measures of discomfort, 3) portability, and 4) durability. This study should have a minimum of 24 enrolled participants

Phase II Activities and Expected Deliverables

Phase II involves clinical studies on the effects of the portable neuromodulatory device to the user and device usability. NIDA is required to review the clinical protocols prior to study initiation.

- Lab test of device followed by improvement finalization
- A test on SUD with a minimum of 15 enrolled participants. If desired, NIDA may provide assistance with the study design and finding clinical partners.
- File an IDE, Complete IDE-enabling studies, and retesting of device in a Phase I condition
- Detailed commercialization plan, including cost analysis, market strategy to extend treatment effects and reduce relapse, device sales and reimbursement possibilities

Planned Timing of Awards

- The Phase I report will be due exactly 11 months after the date of issuance of the Phase I contract.
- No extensions will be granted for Phase I.

CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

CDC's Mission: [CDC](#) works [24/7](#) to protect America from health, safety and security threats, both foreign and in the U.S. Whether diseases start at home or abroad, are chronic or acute, curable or preventable, human error or deliberate attack, CDC fights disease and supports communities and citizens to do the same.

CDC increases the health security of our nation. As the nation's health protection agency, CDC saves lives and protects people from health threats. To accomplish our mission, CDC conducts critical science and provides health information that protects our nation against expensive and dangerous health threats, and responds when these arise.

CDC Role:

- Detecting and responding to new and emerging health threats
- Tackling the biggest health problems causing death and disability for Americans
- Putting science and advanced technology into action to prevent disease
- Promoting healthy and safe behaviors, communities and environment
- Developing leaders and training the public health workforce, including disease detectives
- Taking the health pulse of our nation

Those functions are the backbone of CDC's mission. Each of CDC's component organizations undertakes these activities in conducting its specific programs. The steps needed to accomplish this mission are also based on scientific excellence, requiring well-trained public health practitioners and leaders dedicated to high standards of quality and ethical practice.

CENTER FOR GLOBAL HEALTH (CGH)

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

CGH's Web site: <http://www.cdc.gov/globalhealth/index.html>

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

009 Improving Global Laboratory Diagnostic Capacity: Modular, End-user-assembled Biosafety Cabinets for Sustainable Biocontainment

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

Number of anticipated awards: 1 - 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

A protective space with negative pressure and air flow is necessary for safe manipulation of human specimens that may contain of communicable pathogens. Use of biosafety cabinets (BSCs) with HEPA filtration is the best method to protect both laboratory workers from exposure and potential infection and the surrounding environment from contamination. Biosafety cabinets are readily accessible in the global north, but are expensive, and require continuous maintenance to ensure their effective removal of pathogens from lab spaces. In many countries where dangerous pathogens are endemic, there is limited infrastructure and resources to purchase such equipment. Further, laboratories in resource-poor countries have limited space and may lack technical expertise to maintain BSCs. Annual inspection of filters as well as airflow speed and pressure is required for certification and safe use of BSCs.

Project Goals

To offer sustainable biocontainment to global laboratories by developing an inexpensive cabinet with modular components that are easy to assemble, disassemble and transport.

Phase I Activities and Expected Deliverables

To engineer the BSC cabinet modules so that all motor parts and filters are easily accessible and can be replaced or repaired by laymen as needed. Modular BSC cabinets will be designed with robust, multi-membrane filter components that are durable and easy to maintain.

For Successful Phase I Awardees ONLY (Expected Phase II Deliverables)

During Phase II of this project, the modular BSCs will be piloted in three or more laboratories of varying infrastructure, funding and capabilities (local/rural, state/exurban, national/urban) as well as in a field situation.

Ease of assembly and use: Instructional materials and necessary tools will be provided to pilot labs; hands-on training will be provided if needed. BSCs will be used once assembled, then dismantled, moved and reassembled. Ideally, assembly training required will be nominal, and assembly/disassembly time will be less than one hour.

Quality testing (Field): Test materials (small particulates, glow dust) will be used to ensure quality of filtration in polluted and unhygienic locations. Air flow pressure will be measured and compared before and after contamination with particulates.

Repair and maintenance: Instructions and tools required for repair (motor, filter change, etc.) will be provided to lab designees. Adjustments to protocols and modules will evolve as needed to simplify field maintenance.

Impact

The availability of a portable BSC that can be maintained with minimal experience and expense will enable more rapid detection of infections at their source, thereby preventing larger clusters of disease and epidemics. The modular BSC will be cost-saving in that specimens can be tested at source laboratories without the need for transport to city reference labs. Further, the modular BSC will reduce time to diagnosis, as specimens can be tested closer to the point of care, thereby reducing morbidity and mortality. Finally, the modular BSC will protect laboratory staff and environments, reducing unnecessary illness and increasing biosafety and biosecurity practices.

Commercialization Potential

There is a need for this product, since 1) International labs with some infrastructure and funding require a product like this in order to meet minimal safety and quality standards, and 2) International labs with little infrastructure and funding cannot safely handle human specimens from potentially infected persons without this product.

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:

039 Finding Human Carriers of Taeniasis to Prevent Neurocysticercosis Associated Epilepsy

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

Number of anticipated awards: 1

Budget (total costs):

Phase I: up to \$150,000 for up to 12 months

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

Background

Cysticercosis is a neglected parasitic infection targeted for priority public health action. Cysticercosis is caused by larval cysts of the tapeworm *Taenia solium* (*T. solium*) acquired by eating pork tapeworm egg-contaminated food or through accidental self-infection due to poor personal hygiene of subjects with taeniasis (the harboring of adult worm stage in the gastro-intestinal tract). When these cysts infect the brain (neurocysticercosis), they can result in seizures. Neurocysticercosis (NCC) is the leading cause of adult onset epilepsy in the developing world, accounting for about 29% of epilepsy cases in endemic areas (Nash 2014). In areas with large U.S. immigrant populations, up to 10% of emergency room seizure patients had NCC (Ong et al., 2012). NCC is reportable in 6 U.S. southwest border states. NCC related hospital costs in California exceeded \$17 million (Crocker et al., 2012). Globally, human cysticercosis poses the highest burden for disability-adjusted life years (DALYs) associated with food-borne infection (Torgerson et al., 2015). A fecal-oral-transmitted disease, cysticercosis can be spread by people directly or indirectly through food contamination. Infected persons often are unaware of their infection or of the potential risks regarding transmission (Sorvillo et al., 2011).

As humans are the only reservoir of *T. solium*, finding subjects with taeniasis is critical to control and eliminate *T. solium* related diseases. Current laboratory tools to detect infected cases are inadequate. Developing a valid point-of-care (bedside medical diagnostic) test for taeniasis coproantigen can support efforts to control and eliminate *T. solium*. This test could be used to screen subjects at high risk for taeniasis, potentially preventing spread of infection by food handlers, within households, and among other community members, thereby reducing epilepsy burden.

Currently, finding taeniasis carriers relies on either microscopy, by polymerase chain reaction (PCR), and/or detection of taeniasis coproantigen in the stool in the enzyme-linked immunosorbent assay (ELISA) platform. Microscopy is not sensitive and cannot differentiate between *T. saginata* and *T. solium*. PCR for detection of *T. solium* performs well but cannot be used in the field or for monitoring effects of treatment of subjects with taeniasis. The Taeniasis coproantigen ELISA-based platform detects current, active case of taeniasis and could quantify the amount of antigens in the stool.

Unfortunately, the current ELISA-based platform also cannot be used in the field and more importantly, uses polyclonal antibodies against *T. saginata* which makes it not species-specific and increases batch-to-batch variation. Public health officials need a better test reagent that is species-specific and avoids batch-to-batch variation.

By developing a taeniasis coproantigen assay, we could screen subjects at high risk for taeniasis, especially food handlers, to improve US food safety and to prevent neurocysticercosis in the US population. Globally, the availability of a point-of-care test for taeniasis coproantigen would support the effort to control and eliminate *T. solium*.

Project Goals

To develop a human taeniasis coproantigen detection assay using capture reagents that are species-specific and heat-stable and have minimal batch-to-batch variation.

Phase I Activities and Expected Deliverables

1. Find monoclonal antibodies/aptamers that will bind to *T. solium* adult worm extracts but not to Phosphate buffered saline or normal stool samples
2. Submit to CDC 5 monoclonal antibody clones or 5 aptamers (sequences and aptamer products) that bind with high affinity to *T. solium* adult worm extracts but NOT to normal stool samples
3. Submit to CDC a detailed report of the strategy and the analysis of the monoclonal antibodies or aptamers which include the sequences of the 5 aptamers selected

For Successful Phase I Awardees ONLY (Expected Phase II Deliverables)

1. Develop an ELISA using those monoclonal antibodies or aptamers with the expected deliverable: an ELISA kit with monoclonal antibodies or aptamers that could differentiate human taeniasis positive stool samples from negative samples with a sensitivity of 95% and a specificity of 95%.
2. Develop a dipstick test to determine if a stool sample is positive or not with the expected deliverable: A dipstick assay with a quantitative results based on fluorescence that could be read by a mobile phone reader.
3. Conduct heat stability study for the all developed assays with the expected deliverable: a test with self-life of 1 year at 4 C.

Impact

Availability of a species-specific taeniasis coproantigen ELISA assay will improve the service of the CDC Reference Diagnostic Laboratory in helping states and clinicians to detect, treat, and monitor the effects of treatment for a patient with taeniasis. The point-of-care test will benefit US public health by finding patients with taeniasis, the source of transmission. Globally, availability of the taeniasis coproantigen rapid test will allow program managers to find and treat patients with taeniasis and eventually, eliminate taeniasis and reduce global epilepsy burden.

Commercialization Potential

The ELISA kit could be sold to state public health laboratories, and the point-of-care test could be sold to all interested parties.

040 Web-based Application to Enable Healthy Behaviors Through Behavioral Design

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

Number of anticipated awards: 1

Budget (total costs):

Phase I: up to \$150,000 for up to 12 months

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

Background

Nutrition, Physical Activity, and Obesity are key objectives for Healthy People 2020. A 2015 executive order directed federal agencies to apply behavioral insights to improve the effectiveness and efficiency of government programs and the CDC's 2017 Food Service Guidelines for Federal Facilities encourage the use of behavioral design strategies to make healthier foods and beverages easier for consumers to choose. However, little guidance exists to help public health professionals (such as public health departments) and private and public sector building operations (such as food service and vending operators) apply behavioral design strategies in order to enable healthier dietary or physical activity behaviors. Tools such as the Sustainable Facilities Tool (sftool.gov) and USDA's [Smarter Lunchroom](#) tool provides

initial guidance but lack the necessary breadth and detail in operationalizing behavioral design approaches toward dietary or physical activity practices.

Building and design firms recognize that nearly all aspects of their work will influence the occupant's or user's experience and behavior, however, they neither have the expertise nor inclination to consider health as a primary outcome. These firms do recognize the value of health and potential return on investment (ROI) to their clients and thus, are willing and interested to incorporate health-enabling design. This can be assisted by the translation of evidence from numerous fields, such as psychology, community design, and public health, into guidance on how our experience and behaviors are affected by our environment. Although this remains an unmet ideal, the field can be moved forward via tools that translate and operationalize evidence-based strategies that alter the human experience with the built environment for the advancement of public health.

This SBIR contract seeks to build a web-based platform that assists the architecture and design community to incorporate behavioral design strategies in the built environment to enable healthy behaviors. The proposed tool will also allow users to provide direct feedback into the platform, in order to add to the evidence-base on behavioral design's practical applications, and to create best practices through platform modification.

Ultimately, the goal is for health to be a normative consideration and outcome in the design and construction of the places we live, work, and play. This platform will:

1. Assist and enhance changes within the food environment, making healthier choices easier or more likely for consumers
2. Support environmental changes that enable and encourage safe and convenient opportunities for physical activity at the building, neighborhood and community level

Project Goals

1. Translate concepts and aspects introduced in the Health, Behavioral Design, and Built Environment White Paper, published in March 2017 by the National Collaborative on Childhood Obesity Research (NCCOR) (<http://www.nccor.org/wp-content/uploads/2017/03/nccor-behavioral-design-whitepaper-final.pdf>) to operationalize behavioral design strategies to enable healthy behaviors. Translation of concepts and aspects will initially take the form of checklists and toolkits for each setting (i.e., worksites, assisted-living facilities) and venue (i.e., vending machines, cafeterias).
2. Design and build a web-based tool that demonstrates how each concept/aspect of the environment and resulting human experience can be modified to enable healthier behaviors (i.e., dietary choices, physical activity, and social interaction/cohesiveness).

Phase I Activities and Expected Deliverables

Phase I (0-12 mos)

1. Collaborate with an innovative design/architectural firm that can use architectural modelling, design thinking, and industry insights to layout a basic web-platform assisting those in the building and design community to understand the potential health impacts of their work. The contract partner will need expertise in behavioral science and how space, time, material, and information can influence behavior.
2. Develop checklists and guide (i.e., toolkits) for application for each setting and venue, with subject matter expert input (i.e., nutrition and PA scientists).
3. Create a framework to guide design choices by how they influence behaviors or actions with health outcomes.

For Successful Phase I Awardees ONLY (Expected Phase II Deliverables)

1. Design a user-interface that allows architects, designers, and public health professionals to construct, understand, and interact with the specified environment (e.g., setting and venue).
2. Apply and operationalize behavioral design aspects/concepts, as described for example in the White Paper Figure 4, to the platform.
3. Test and make modifications to the web-based tool as necessary.
4. Allow users to share success stories and practice-based evidence, in order to advance and improve the evolving application. This can be accomplished via web based collaborative methods (sharing).

Impact

Improvement of food and physical activity environments can lead to many positive long-term health, social, and economic outcomes, including:

- reductions in chronic disease and early death
- increased productivity
- decreased absenteeism
- reduced healthcare costs
- improvements in mental health and cognition
- prevention of falls
- reduction of health inequities
- reduced stress
- improved sleep
- increased life satisfaction

Commercialization Potential

There are numerous methods to commercialize these concepts, particularly the web-based tool emerging from Phase a successful Phase I & II. For example, fee-based access by design and architecture firms can be part of the pay-to-play version of this interface and can enable advanced features such as saving projects, networking within business or between businesses and clientele, or interfacing with other design software. However, the most simple income generating method for this project is to connect the various aspects of this work with the materials providers that enable it to work and allow them to advertise. For example, building and design materials and machinery of all kinds and the companies that specialize in their installation [e.g., paint, glass, flooring, lighting systems, HVAC systems, etc] can use this tool to target products to specific projects and needs. Design, building, and planning firms will all be interested in advertising their services on such a website.

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:

015 Antifungal-containing Solution for Corneal Tissue Storage and Transport

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

Number of anticipated awards: 1

Budget (total costs):

Phase I: up to \$150,000 for up to 12 months

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

Background

Endophthalmitis is a rare, but severe infectious complication of corneal transplant surgery (keratoplasty) that requires prolonged treatment with intraocular antimicrobial drugs and results in vision loss for over half of patients. Post-keratoplasty endophthalmitis incidence has more than doubled from 2007 to 2014 according to adverse event surveillance conducted by the Eye Bank Association of America, and fungi (primarily *Candida* yeast) caused the majority of cases. Moreover, the proportion of post-keratoplasty fungal endophthalmitis is increasing and CDC has received several recent reports of fungal endophthalmitis clusters associated with corneal tissue banks and corneal surgery centers. The predominant *Candida* yeast etiology among post-keratoplasty fungal endophthalmitis cases suggests that donor skin and gastrointestinal flora are a possible source of contamination, and that corneal tissue handling and storage after donor extraction might allow transmission of fungal contaminants to recipients. Currently, the main corneal tissue storage and transport solution used in the United States does not contain an antifungal drug, and may provide a permissive environment for donor contaminant fungi to grow.

Project Goals

The specific research aim is to develop a liquid solution for corneal tissue storage and transport that contains an antifungal drug that inhibits growth of contaminant fungi for at least 14 days following donor tissue extraction. The solution must be usable in compliance with current corneal tissue storage, evaluation and transport procedure guidance and regulations.

Phase I Activities and Expected Deliverables

The primary activity is formulation of a liquid solution that serves the purpose of currently available products, and that contains an effective antifungal that is safe for use and non-damaging to corneal tissue.

Monthly Deliverables:

- Assemble list of viable antifungals (e.g., Amphotericin B) and design *in vitro* and *in vivo* studies to demonstrate effectiveness against *Candida* and other fungi, optimize antifungal concentration, and demonstrate that the product does not adversely affect corneal tissue quality and health.
- Present preliminary data on efficacy and safety, showing effective antifungal properties without compromise of corneal tissue health and quality.
- Present data supporting optimized antifungal and ingredient concentrations, and advanced evidence of product suitability for further development and ultimate regulatory evaluation.

Impact

A corneal storage and transport solution containing safe and effective antifungals could reduce morbidity, vision loss and healthcare expenditures due to post-keratoplasty fungal endophthalmitis, and could reduce the recent increase in fungal endophthalmitis incidence. Previously, a product currently on the market was reformulated to include antibiotics effective against bacteria, and surveillance data indicated a subsequent decrease in bacterial endophthalmitis although causality was not established. We speculate that adding an antifungal may result in similar effects for fungal endophthalmitis, preventing these devastating and sight-threatening eye infections.

We expect many stakeholders will benefit from this product going to market. Eye banks, which harvest donor corneas where contamination might occur, will have an added layer of security by storing tissue in antifungal-containing media immediately after harvest, which will prevent pathogenic fungi from growing. In addition, the Eye Bank Association of America, which collects and reports on adverse events linked to corneal transplants, has been advocating for a product like this for several years in an effort to reduce the increasing trend in fungal endophthalmitis. Finally, this product would be a straightforward win for a small business; corneal storage solution is universally used and required by those who work with and transplant corneal tissue and the urgent need for reduced risk of fungal contamination during the corneal harvest-storage-transplant process is currently unmet by any other product on the market.

Commercialization Potential

Successfully developed and marketed to surgeons, this product will have significant commercial potential as there is currently no similar competing product available to corneal surgeons in the United States. The primary target market for this product will be corneal surgeons who perform corneal transplants (keratoplasties), as well as eye banks who procure corneal storage media and must respond to the demands of their clients (corneal surgeons).

016 Bacterial Amplicon Subtyping

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

Number of anticipated awards: 1

Budget (total costs):

Phase I: up to \$150,000 for up to 12 months

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

Background

Recently, culture-independent diagnostic tests (CIDTs) have been introduced into the diagnostic test market and are rapidly being adopted by clinical laboratories. These assays are attractive to physicians and patients as they are rapid and can simultaneously test patient specimens for multiple pathogens. However, CIDTs pose a challenge for public health and hospital infection control settings because they do not yield the isolates which are necessary for generating a molecular fingerprint to track a patient strain for infection control purposes or public health disease surveillance. For example, PulseNet, a national subtyping network of over 80 labs nationally and over 80 international laboratories, tracks foodborne outbreaks and currently relies on isolates for generating molecular fingerprints for foodborne bacterial surveillance for over 90,000 isolates.

In response to these new challenges, this proposal aims to develop new molecular fingerprinting techniques that can be used with specimens such as stool. The assay approach will rely on PCR amplification of informative regions and sequencing of amplicons using short read technology such as the Illumina platforms. An algorithm for the identification of heterogeneous regions for isolate subtyping and design of conserved flanking primers is necessary for the development of these assays, but are currently not available commercially or in the open source community. Providing an algorithm for development of these primers, or the primers generated from the algorithm, would be of great use to the public health community and could be used in both public health laboratories nationally and internationally as well as infection control groups in a health care setting.

Project Goals

The offeror will provide an innovative bioinformatics algorithm in their software platform that allows the user to design amplicons that can be sequenced to determine the subtype of a pathogen. Specifically, the software must identify

heterogeneous regions which are useful for strain typing and also flanked by conserved sites suitable for primers. The resolution of strain subtyping must be equivalent to current WGS-based subtyping techniques for isolates and can distinguish isolates associated with an outbreak from background cases. The algorithm must include an option to measure and adjust the amount of heterogeneity so that the user may decide how much is needed for subtyping. The software must identify these regions either automatically (defining subgroups naturally) or allow the user to pre-define the groups or subtypes for which the primers will be designed and include the ability to consider Illumina or other sequencing adapters and multiplex barcodes when testing for primer-to-primer interactions. Ideally, the software must be packaged so that it could work directly with existing infrastructure such as high-performance computing (HPC) resources.

Phase I Activities and Expected Deliverables

The contractor will design the algorithm to meet the above specifications and perform in silico validation of amplicons. The contractor will use epidemiologically relevant sequence data from the relevant pathogen groups for testing their algorithm and will be expected to provide preliminary results upon completion of phase I. The results must include primers, fasta files for amplicons, in silico PCR results, annotated bedgraphs and coverage histograms.

For Successful Phase I Awardees ONLY (Expected Phase II Deliverables)

In Phase II, the contractor will further refine the algorithm and primers based on laboratory results. The contractor will also evaluate the usefulness of the software for developing assays for generating molecular fingerprints of pathogens. At the completion of Phase II, the contractor will provide a stand-alone license for a single copy of the software which is a compiled, command-line binary that runs on the high performance computing clusters and standalone Linux workstations installed with Ubuntu; sample configuration files and documentation must be included in the binary install. With this software, the developers must create training documentation that instructs the user in how to operate the software to generate primers in conserved regions that flank heterogeneous regions and generate the output outlined in the Activities and Expected Deliverables section above.

Impact

This novel bioinformatics approach would enable public health professionals to identify phylogenetically informative regions and design rapid PCR subtyping approaches that detect and subtype pathogens directly from disease state stool and other specimen types. In addition, this approach will significantly improve assay development strategies by incorporating multiple steps to assay design into a single, streamlined platform. Furthermore, the assays that are developed will be deployed in public health labs worldwide, allowing for continued surveillance of these pathogens and the identification of outbreaks in the absence of cultures.

Commercialization Potential

Currently there are no software programs on the market that design primers around heterogeneous regions in bacterial genomes for a sequencing-based subtyping workflow. The addition of this product to the subtyping market is necessary now that CIDT tests are being more widely used not just for identifying pathogens associated with foodborne infections but also febrile illnesses, respiratory illnesses, and other disease types. Due to the rapid adoption of CIDTs in the health sector, the design of novel and innovative approaches for subtyping directly from specimens is needed within the public health surveillance community. With the product the awardee designs, subtyping can begin with the same specimen on which a CIDT test is performed, rather than the isolate which can take several days to weeks to culture. By being able to more rapidly subtype pathogens, outbreaks are detected sooner which means the public can be alerted to health threats sooner and more lives saved. This software product or the primers designed using this product would be of interest to public health professionals and those in the health care sector that need to identify related illnesses through subtyping to detect and stop outbreaks.

017 Identification of *Brucella canis* Seroreactive Proteins and Serology Assay Development

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

Number of anticipated awards: 1

Budget (total costs):

Phase I: up to \$150,000 for up to 12 months

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

Background

Several species of the genus *Brucella*, Gram-negative, facultative intracellular coccobacilli, cause brucellosis in animals and humans. Whereas the zoonotic potential of *Brucella melitensis*, *B. abortus*, and *B. suis* is well known, and manifests itself in a disease burden of more than 500,000 annual human cases worldwide, the extent to which *B. canis* is transmitted from infected dogs to humans is unclear. Human brucellosis infections are difficult to diagnose and difficult to treat. There is no human vaccine available in the United States. *B. melitensis*, *B. abortus*, and *B. suis* are Select Agents, with a low infectious dose, which makes brucellosis one of the most frequent laboratory-acquired infections. Serological assays are a critical tool for diagnosis of brucellosis and for monitoring exposed personnel for evidence of infection. However, there are currently no *B. canis* serological tests available to detect and measure the humoral immune response in humans.

Brucella strains such as *B. melitensis*, *B. abortus*, and *B. suis* have an O-specific polysaccharide as part of the outer membrane lipopolysaccharide and are designated as “smooth” strains. In contrast, other strains such as *B. canis*, *B. ovis*, and the live attenuated bovine vaccine strain *B. abortus* RB51, are missing the O-specific polysaccharide from the outer membrane lipopolysaccharide and are designated as “rough” strains. The lack of this specific lipopolysaccharide means that standard *Brucella* serological assays do not work for “rough” strains. The identification of specific antigens of rough *Brucella* strains is a prerequisite for the development of serological assays.

Project Goals

The goal of this project is to develop assays for detection of antibodies against rough *Brucella* strains such as *B. canis* and bovine vaccine strain *B. abortus* RB51, which are known human pathogens. Presently, we are not able to offer serological diagnosis to infected patients, or monitoring to exposed individuals.

Phase I Activities and Expected Deliverables

Phase I: Screen entire proteome of *Brucella* species using sera from canine and human infections to identify specific *B. canis* and *B. abortus* RB51 antigens that are recognized by antibodies. If successful, antigens (e.g., proteins) identified in Phase I will be used in Phase II to develop a diagnostic serologic assay.

For Successful Phase I Awardees ONLY (Expected Phase II Deliverables)

Develop optimized serodiagnostic assays with high specificity and sensitivity based on the Phase I analysis of the humoral immune response to *B. canis*. Current *Brucella* serology assays lack specificity and sensitivity and are not able to detect infection by rough strains such as *B. canis*. Depending on data from Phase I, combinations of antigens could be used to detect infection by both smooth and rough strains.

Impact

At present, we are unable to gauge the burden of *B. canis* human infections or risk associated with exposure to *B. canis* infected animals because we have no diagnostic tools for serological surveillance. We are also not able to measure the antibody response in potentially exposed occupational risk groups such as veterinarians, physicians, clinical microbiologists, dog breeders, dog kennel and animal shelter workers, and in pet owners whose dogs develop *B. canis* infection. Comprehensive screening of the *B. canis* proteome for specific antigenic targets would allow for development of serological methods to detect and respond to human exposure cases and strengthen public health in the US and globally by gaining insight into *B. canis* dog-to-human transmission patterns and risk factors.

Commercialization Potential

The worldwide burden of brucellosis has been estimated at 500,000 cases/year; however, this is likely underestimated due to the lack of optimal diagnostics. All presently available assays to detect host antibody responses to exposure and infection by smooth *Brucella* strains are lacking specificity and sensitivity. Inactivated whole cell preparations or LPS extracts serve as crude capture antigens with high levels of cross-reactivity. There are no serology assays available for detection of human antibody responses against rough *Brucella* strains. There is a critical need to find specific, immunogenic markers whose epitopes can be analyzed, synthesized and developed into optimized serological diagnostic assays. Development and use of

such assays would be of interest to public health laboratories, private diagnostic laboratories, and academic brucellosis researchers.

018 Multiplex Pan_lyssavirus/ β -actin Real-time RT-PCR Assays for Rabies Diagnostics

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

Number of anticipated awards: 1

Budget (total costs):

Phase I: up to \$150,000 for up to 12 months

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

Background

Rabies, caused by *Rabies virus* (RABV) and related lyssaviruses, is one of the most deadly zoonotic diseases responsible for up to 70,000 estimated human deaths worldwide each year. Rapid and accurate laboratory diagnosis of rabies is essential for timely administration of post-exposure prophylaxis in humans and control of the disease in animals. Currently, only the direct fluorescent antibody (DFA) test is recommended for routine rabies diagnostics. DFA is a rapid and sensitive method, but its accuracy depends on the quality of brain tissue, availability of high-quality anti-rabies diagnostic conjugates, accessibility to a fluorescence microscope and, most importantly, an experienced diagnostician. Reverse Transcription-Polymerase Chain Reaction (RT-PCR)- based diagnostic methods have been widely adapted for the diagnosis of other viral pathogens, but there is currently no widely accepted rapid real-time RT-PCR assay for the detection of all lyssaviruses. The CDC rabies molecular diagnostic team has developed and validated a new multiplex real-time RT-PCR assay named LN34, which uses a combination of degenerate primers and probes along with probe modifications to achieve superior phylogenetic breadth, while maintaining sensitivity and specificity. The primers and probes of the LN34 assay target the highly conserved non-coding leader region and part of the nucleoprotein (N) coding sequence of the lyssavirus genome to maintain assay robustness. The probes were further modified by locked nucleotides to increase their melting temperature to meet the requirements for an optimal real-time RT-PCR assay. The LN34 assay was able to detect all rabies-causing variants in a validation panel that included representative RABV isolates from most regions of the world and 13 additional lyssavirus species. The LN34 assay was successfully used for both ante-mortem and post-mortem diagnosis using over 200 clinical samples as well as field derived surveillance samples. An algorithm of using the LN34 assay for rabies diagnostics has been developed based on the international validation data. The algorithm also comprised of a beta-actin real-time RT-PCR assay to measure the quality of the sample tested. This combined assay represents a major improvement over previously published rabies-specific PCR or RT-PCR assays because of its ability to universally detect RABV and other lyssaviruses, its high throughput capability and its simplicity of use, which can be quickly adapted in a laboratory to enhance the capacity of rabies molecular diagnostics. The LN34 assay provides an alternative approach for rabies diagnostics, especially in rural areas and rabies endemic regions that lack the conditions and broad experience to run the standard DFA assay. Nevertheless, the cost of the assay will be an important factor for its adaptation both in US (rabies surveillances test more 100,000 samples each year) and developing countries. We are looking for a products to further combined the LN34/beta-actin real-time RT-PCR assays and reduce the reaction volume to simplify the assay cost and set-up.

Project Goals

1. Develop a reaction kit combining the LN34/beta-actin real-time RT-PCR assays into a single reaction.
2. Select enzymes and reaction volumes to further reduce the cost for the assay.
3. Develop a dry-bead format and optimize the reaction conditions for diagnostic laboratories.

Phase I Activities and Expected Deliverables

1. Utilize artificial positive control RNA and rabies-negative brain samples to optimize the multiple assay combining LN34/beta-actin real-time RT-PCR assays (end of the 4th month).
2. Test low cost enzymes to further reduce the cost of the reaction kit, develop a dry-bead format for the reaction kits to improve the stabilities of the reaction kits (end of the 6th month).
3. Optimize the reaction in a low volume format to further reduce the cost of the reaction (end of the 6th month)

For Successful Phase I Awardees ONLY (Expected Phase II Deliverables)

1. Large-scale production of the optimized real-time RT-PCR reaction kits and the start of large scale validation of these kits in multiple laboratories where both CLIA samples and field collected samples will be tested. The validation data must lead to the development of a standardized algorithm of using this assay for rabies diagnostics.
2. Based on the validation data through multiple laboratories, a standardized commercial kit will be optimized and finalized at the end of 24 months. A widely available and utilized new PCR-based rabies diagnostic assay will enhance rabies diagnostics and surveillances, and make a key contribution to the goal of canine rabies eradication by 2030.

Impact

A PCR-based rabies diagnostic is expected to be recommended later this year as multiple research and validation data for using PCR-based rabies diagnostics are highly supportive. Laboratories in the US and in most developing countries have real-time PCR capability and have the expertise required for conducting real-time PCR assays for the diagnosis of viral infections and, therefore, for rabies molecular diagnostics.

Successful commercialization of a real-time PCR-based rabies diagnostic will further improve the rabies diagnostic capacities in many laboratories domestically and internationally. An assay that can detect highly variable rabies viruses and other lyssaviruses can be used in areas endemic to both rabies viruses and other lyssaviruses and will enhance clinical rabies diagnostics and surveillance.

Commercialization Potential

This new multiplex assay should be able to detect all the available rabies virus variants and other lyssaviruses. It can be used for rabies diagnostics domestically and around the world, especially in regions with both canine rabies and lyssaviruses. Development of this assay could represent a significant advancement compared to previously published PCR-based rabies diagnostics assays, which only detected a limited number of rabies variants or limited other lyssaviruses.

019 Tools for Combined Analysis of Optical Mapping and Sequencing Data

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

Number of anticipated awards: 1

Budget (total costs):

Phase I: up to \$150,000 for up to 12 months

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

Background

Next generation sequencing (NGS) is used to determine the genetic sequence of pathogens. For public health laboratory surveillance activities, a high quality genome sequence is required to serve as a comparator or “reference sequence.” To generate the highest quality reference genome sequence requires the use of optical mapping (OM) to resolve sequence inversions and identify the ends of chromosomes. An optical map is like a restriction enzyme map for the entire genome. Currently, OM data and NGS data are assembled using separate software systems. However, no tool exists that can fully integrate all types of NGS data and OM data for graphical display. The few tools that do exist are limited in their functionality and visualization capabilities. This is especially problematic when working with large genomes with tens of thousands of data points that can take multiple days to analyze.

Project Goals

Although OM is currently used as a quality control tool for NGS assemblies, if an efficient tool were available to combine both datasets, optical mapping data could be used to accelerate or automate genome assemblies. Development of a tool would allow users to integrate optical mapping and sequencing data from any platform, thereby reduce investigation response time and increase sequence data quality.

Phase I Activities and Expected Deliverables

The project goal is to create a user-friendly graphical interface that can assemble, combine, and compare OM and NGS data generated from any platform. This tool will automatically scale optical maps based on NGS assemblies and should scale well with larger multi-chromosome genomes. Algorithms will be developed to match NGS assemblies to optical maps, scaffold sequencing reads using optical maps, and perform quality filtering for both sequencing reads and optical mapping reads. The tool will also have standard report generation and data export capabilities. All methods should be callable via a RESTful API. The tool will have access/group control, and users in the same group will be able to share data.

Month	Deliverable
1	Import OM and NGS data from any platform
2.5	Develop algorithms to scaffold sequence data using optical mapping data
4	Develop algorithms to compare optical maps with NGS assemblies
6	Develop graphical interface and reporting

For Successful Phase I Awardees ONLY (Expected Phase II Deliverables)

Updates and added features to the tool and algorithms will be driven by advancements in OM and NGS technologies. Possible updates to the tool in Phase II include integration of long read NGS data to be used for scaffolding, automated misassembly prediction algorithms, collaboration capabilities, and improved graphics and usability.

Month	Deliverable
9	Integrate long read NGS data for scaffolding
12	Develop misassembly prediction algorithms
15	Increase collaboration capabilities
18-24	Optimize commercialization potential

Impact

By developing a software tool that can visualize all types of optical mapping and NGS data, bioinformaticians can more effectively analyze sequencing data for various customers. Algorithms developed for this project could also be applied to future analytical tools. Further, this tool could be distributed to customer laboratories so that researchers can fully interrogate or reanalyze their own sequence assemblies, which is technically difficult at this time.

Commercialization Potential

The genome sequencing market is expected to grow to \$20 billion by 2020. As this market grows and the complexity sequencing analysis increases, there will be broad demand for data analysis and visualization tools. The product market will only be as large as the overlap of both the sequencing and optical mapping markets (maximum \$1B), but the technology developed for analyzing and visualizing sequencing data can be applied to new analytical tools for the larger market. In the future, we envision suites of tools for performing multivariable analysis of genomic sequencing data.

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

The National Center is committed to our vision of a future free of HIV/AIDS, viral hepatitis, STDs, and TB. NCHHSTP is responsible for public health surveillance, prevention research, and programs to prevent and control HIV and AIDS, other STDs, viral hepatitis, and TB. CDC's National Center for HIV, Viral Hepatitis, STD, and TB Prevention's (NCHHSTP) Strategic Plan Through 2020 articulates a vision, guiding principle, and overarching goals and strategies through 2020 to influence and enhance our programs. The three overarching goals highlighted in this plan are to decrease:

- Incidence of infection,
- Morbidity and mortality, and
- Health disparities.

Every year, millions of Americans are infected with HIV, viral hepatitis, STDs, or TB and tens of thousands die from their infection. Most of these infections share commonalities, from modes of transmission to demographic, social, and economic conditions that increase risk. As a prevention leader, NCHHSTP focuses on high impact prevention and control efforts to reduce incidence, morbidity, mortality, and health disparities due to these infections.

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

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

048 Development of a Benchtop Laboratory Platform for Amplicon Deep Sequencing

Fast-Track proposals 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

Molecular identification of infectious agents most commonly requires nucleic acid extraction, PCR amplification, and sequencing. Despite the availability of automated platforms, most standard laboratory protocols rely on manual procedures. Importantly, exposure to infectious materials during manual processing is a major safety concern, particularly when processing highly infectious agents. Moreover, manual processing affects reproducibility of testing, reduces throughput and increases sample processing time; as a consequence, time to accurate identification is delayed. Manual processing also introduces an increased risk of contamination which may confound results by the amplification of contaminating nucleic acids many fold during PCR processing. Thus, the implementation of a fully automated, closed platform is highly desirable for the efficient molecular identification of infectious agents, including hepatotropic viruses and other enteric, airborne and blood-borne pathogens. The CDC Division of Viral Hepatitis has designed and built an automated platform for the construction of DNA libraries from clinical samples in a compact fashion suitable for amplicon deep sequencing using the popular MiSeq instrument. Whereas capable of high throughput sample processing, this workstation is expensive and has a relatively large footprint. These characteristics impose limitations for the commercialization of a workstation suitable for smaller laboratories and clinical facilities. Thus, there is an important, and increasingly growing need for significantly smaller, ideally benchtop, comprehensive workstations capable of performing the same compound processes at a considerably reduced cost, yet exhibiting comparable biosafety standards and quality results. Whereas a number of units are commercially available for each of the individual steps of the compound process, there are no existing platforms capable of performing the entire process from A to Z in an automated, compact manner.

Project Goals

The aim of this proposal is to develop and evaluate a new, small footprint, benchtop automated nucleic acid extraction, amplification and sequencing system that fundamentally improves laboratory safety and quality control (QC). This platform consolidates all manual laboratory operations related to next-Generation Sequencing into a single compact process performed automatically by a single workstation in a small footprint, ideally at a reduced cost. The workstation should be

capable of being used in support of clinical testing, surveillance programs and outbreak investigations conducted by clinical and public health laboratories using NGS, which recently became a mainstay technology for the detection of pathogen drug resistance and transmission networks enabling public health interventions and management of patients in clinical settings. The workstation should be capable of performing RNA/DNA extraction from clinical samples, RT-PCR, nested PCR/tagging, amplicon clean up, quantification and pooling, resulting in DNA libraries ready for amplicon deep sequencing using the MiSeq platform. Whereas assembling workstations by integrating existing liquid handling robotic stations with stand-alone thermal cyclers, spectrophotometers and cappers/decappers (for specimen aliquoting) is possible, the resulting process is prone to all of the negative characteristics of manual processing outlined above. The goal of this project is to devise a new, affordable instrument that can perform all necessary functions starting from receipt of biological samples (such as whole blood, plasma, serum, stool, sputum and other) to construction of DNA libraries. This novel platform would be expected to significantly reduce constraints for established complex molecular next-generation sequencing-based methods. It should also contribute to strengthening quality control and biosafety in clinical and public health laboratories. This workstation will be capable of preparing DNA libraries for different pathogens and will require no manual steps except for the initial setup of the instrument for loading reagents/kits and clinical specimens. The unit is expected to be sufficiently flexible to accommodate different laboratory protocols. It should be readily adaptable to: (1) generate DNA libraries for the MiSeq illumina; (2) handle biological specimens such as whole blood, plasma and serum; (3) handle variable numbers of specimens from low to medium throughput; (4) use specific/customized reagents and kits for different pathogens. Availability of various preloaded programs for specific processing of specimens from different pathogens is also desirable. In such cases, user input should allow the incorporation of specific conditions (pathogen, number of samples, etc.) into the workstation controller to allow specific conditions from run to run. Substantial modifications and new programs must be registered in the workstation for quality control management in clinical and public health laboratories. Handling of laboratory protocols by the workstation should be highly reproducible and accurate to comply with clinical test requirements and automatic reporting on conducted tests should be outputted and available to managers and accounts with elevated privileges.

Phase I Activities and Expected Deliverables

During Phase I, the unit design and industrial diagrams with the final layout will be generated. Computer modeling of the final design is required for testing virtual laboratory protocols and fine tuning of individual processes and steps. The workstation is expected to perform the entire laboratory protocol starting from clinical samples to the NGS library within a few hours (between 8-12 hours) without any user intervention. It will be easily programmable, accommodate different specimen types (whole blood, plasma, and serum), variable numbers of specimens and sample volumes. It will be controlled by computer programs, which may be initiated manually or automatically using barcoded reagent kits. For enhanced QC, workstation data will be used to automatically detect instrument errors and control instrument maintenance.

For Successful Phase I Awardees ONLY (Expected Phase II deliverables)

For Phase II, full development and assembly of the pilot workstation is expected. It is important that the company awarded the contract demonstrate feasibility of performing all of the required steps to convert the prototype into a full-fledged platform. As aforementioned, the workstation is expected to be suitable for processing clinical samples for identification of pathogens. The platform will be extensively tested for its performance using serum panels specifically developed from specimens collected from individuals infected with hepatitis C viruses. Once developed, the workstation is expected to be thoroughly evaluated for use with other pathogens as well. Robustness of the automated workstation will be evaluated in comparison with currently established laboratory gold standards. Each step of the process will be assessed for reproducibility, accuracy, sensitivity, specificity, potential for cross-contamination, yield, time-to-run, safety, and throughput. Another criterion is the long-term stability of performance during continuous use. A full biosafety evaluation of the unit will have to be performed. Assessment of aerosols and user exposure will be conducted. Safety guidelines and recommendations will be put forward. This unit is expected to have a large market for state health laboratories and clinical laboratories, as well as reference laboratories worldwide.

Impact

Implementation of the workstation allows for continuous monitoring and evaluation of data, minimizing human errors and significantly improving accuracy of clinical testing and surveillance. It will significantly reduce hands-on time and exposure to infectious materials, thus fundamentally improving safety of laboratory work. The instrument is expected to have a broad use in public health and clinical laboratories. It is expected that the workstation will significantly improve quality of testing and accelerate sample processing for the identification of infectious agents and for outbreak investigations and molecular surveillance of different infectious agents. Both clinical and public health laboratories are expected to benefit from a commercially available fully automated, inexpensive, benchtop workstation for performing NGS. It will significantly reduce

complexity of the laboratory process for technical personnel in clinical and public health laboratories, while cardinally improving throughput and reproducibility of testing, reducing contamination, and keeping the cost per tested specimen low. Availability of the workstation makes massive and complex genetic testing as defined by Advanced Molecular Detection affordable and attainable for many laboratories in the United States and worldwide, fundamentally improving outbreak investigations, public health surveillance, and the identification and treatment of infectious diseases.

Commercialization Potential

The laboratory workstation is expected to have a very large market owing to a significant and rapidly growing need for complex genetic identification and testing of infectious agents for patient management in clinical settings (drug and antibiotic resistance) and for devising public health interventions to control viral and bacterial diseases. Each clinical and public health laboratory that is expected to conduct genetic testing and identification but lacks equipment and personnel capable of handling the demands of NGS is a potential customer. Integration of liquid handling platforms with many instruments is currently used to manage such tasks. However, a prohibitive cost, large footprint and complexity of the integrated assemblies reduce their application. A single, affordable, standalone instrument with a small footprint, specifically designed for performing all laboratory procedures required for NGS of different pathogens in a completely automated, closed mode will be useful to many laboratories in the United States and worldwide.

049 Risk Reduction Toolkit for Non-Prescription Syringe Sales in Community Pharmacies

Fast-Track proposals 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

Persons who inject drugs (PWID) are at increased risk of acquiring HIV, hepatitis C virus (HCV), hepatitis B virus (HBV), and bacterial infections. Persons who inject drugs can substantially reduce their risk of getting and transmitting HIV, viral hepatitis and other blood borne infections by using a sterile needle and syringe for every injection. In many jurisdictions, persons who inject drugs can access sterile needles and syringes through syringe services programs (SSPs) and through pharmacies without a prescription (<http://lawatlas.org/>). The science shows that access to sterile syringes can reduce needle sharing and does not result in increased injection frequency, injection drug use, or unsafe disposal of syringes.

The National Alliance of State and Territorial AIDS Directors (NASTAD) and the Urban Coalition for HIV/AIDS Prevention Services (UCHAPS) published “Syringe Service Program Development and Implementation Guidelines for State and Local Health Departments” in 2012 (<http://www.uchaps.org/assets/NASTAD-UCHAPS-SSPGuidelines-8-2012.pdf>). These guidelines state that pharmacies and pharmacy organizations are a resource and strong ally for SSPs and describe a “Pharmacy Distribution Model” and “Pharmacy Voucher Program” as service delivery models for SSPs. Pharmacists are equipped to apply risk reduction strategies among PWID by selling non-prescription syringes, promoting safe injection practices, discussing safe syringe disposal, performing HIV and HCV testing, administering recommended immunizations (e.g., Tdap, hepatitis A, hepatitis B), providing counseling and education (e.g., sexually transmitted infections, HIV, HCV, HBV, substance abuse), assessing medications and adherence, and linking patients to appropriate healthcare. In addition, pharmacists counsel patients and family members on naloxone administration in order to address injection related opioid overdose concerns. A training program for implementation of a pharmacy-based statewide naloxone distribution program demonstrated that promotion and distribution of materials along with training resulted in increased dispensing of naloxone (Morton KJ, *J Am Pharm Assoc* 2017 <https://doi.org/10.1016/j.japh.2017.01.017>)

Pharmacists are legally allowed to sell sterile needles and syringes in most areas of the United States; in fact, other than through SSPs, pharmacies are essentially the only option for a person to access a sterile syringe legally. As an example of the magnitude of the syringe sales in pharmacies, a 2015 survey of nearly 80% of the more than 1,000 community pharmacies in Massachusetts, where there is no limit on the number of syringes that can be sold, found that 97% of community pharmacies reported selling nonprescription syringes. They also reported median sales per store of 75 per week which translates into nearly 100,000 nonprescription syringes sold statewide per week (Stopka TJ, *J Am Pharm Assoc* 2017 <https://doi.org/10.1016/j.japh.2016.12.077>).

Syringe access programs provide a framework, typically developed by a state or local health department, within which non-prescription syringe sales (NPSS)-specific guidance for HIV prevention counselling, pharmacist and pharmacy staff education, syringe disposal or referrals are provided. To date, three states, Minnesota, New York and California have established pharmacy-based syringe access programs. These programs can serve as a model for the establishment of similar services in areas with injection drug use and low SSP coverage. However, in most pharmacies, NPSS is left to the discretion of the pharmacist. Education and tools are needed to support pharmacists in the delivery of risk reduction services to lower risk behaviors, facilitate safe disposal of syringes, and provide referrals for substance abuse treatment.

Project Goals

The primary goal of this project is to develop a toolkit for pharmacies to implement risk reduction services targeting PWID who access syringes through pharmacies. Pharmacists should be provided training and tools to implement pharmacy-based syringe programs and risk reduction services in order to improve the health of their local communities through the prevention of blood-borne pathogens, safe syringe disposal, testing for HIV and HCV with rapid point-of-care tests, linking to clinical care providers, mental health care providers, SUBSTANCE ABUSE PROVIDERS and other services. The training curriculum can be developed for on-line use or for in-person use (e.g. to be delivered at pharmacy conferences or meetings) and should be designed such that Continuing Pharmacy Education (CPE) accreditation can be attained by pharmacists and pharmacy technicians. The final development of the on-line or in-person training and accreditation can be secured during Phase II.

Phase I Activities and Expected Deliverables

Develop a prototype for a pharmacy-based syringe program and toolkit to implement risk reduction services for pharmacy-based risk reduction services associated with NPSS. Tools can include products that provide safer methods for injection and for safe syringe disposal. For example, risk reduction materials may include commercially available products provided to PWID such as alcohol swabs, sterile filters for needles, sterile ‘works,’ and a portable sharps container. The toolkit should include pamphlets that describe safe injection and safe syringe disposal and a list of referrals tailored to the local area developed in conjunction with the local health department. The toolkit should be packaged in a manner that facilitates distribution from the pharmacy either from a counter or a private consultation room. The toolkit should be designed so it will be affordable to potential customers which may include pharmacies, health departments, or commercial companies that sell sterile needles, sharps containers, or other products used for safe injections. The design may be tiered such that different customers may purchase individual components that meet their needs. The offeror may propose development of new materials to support safe injection, risk reduction, and safe syringe disposal (e.g., a new sterile filter to attach to commercially available syringes that will be easy to use and acceptable to PWID). The offeror should develop a training curriculum to implement a prototype for a platform for pharmacists and pharmacy staff to implement the toolkit for pharmacy-based risk reduction services associated with NPSS to PWID within the usual customary practice of their business process. The offeror should propose a pilot of the training curriculum and prototype in several pharmacies in one jurisdiction that would benefit from enhanced NPSS for PWID. The training and prototype should accommodate the laws and regulations for pharmacy syringe sales in that jurisdiction. The pilot should quantify the number of PWID clients served with the toolkit, numbers of syringes dispensed, and a variety of other metrics for monitoring and evaluation as outlined from the publication from the National Alliance of State and Territorial AIDS Directors (NASTAD) and the Urban Coalition for HIV/AIDS Prevention Services (UCHAPS) guidelines on “Syringe Service Program Development and Implementation Guidelines for State and Local Health Departments” <http://www.uchaps.org/assets/NASTAD-UCHAPS-SSPGuidelines-8-2012.pdf>). Other metrics may be proposed as well.

Impact

If pharmacies are provided with toolkits, they can collaborate with state and local health departments, insurers, syringe-service programs, and other healthcare facilities to provide linkage and continuity of care, testing for blood-borne pathogens, and other risk reduction services for PWID in order to address public health concerns. Pharmacists can be a vital resource for prevention of transmission of blood-borne pathogens among PWID if they are given the appropriate tools.

Commercialization Potential

- Pharmacists and pharmacy technicians can obtain proprietary continuing education and/or certificate programs that may be paid for by the individual pharmacist or technician or paid for by a pharmacy company.

- Pharmacies, health departments, insurers or other organizations can purchase materials for a pharmacy-based syringe services program that may include web-based materials, printed materials, and a package of materials to be distributed along with syringes at the time of sale to support risk reduction (e.g., disposal container, alcohol swabs, materials needed for clean injections, sterile filters for needles).
- Pharmacies, health departments, insurers or other organizations can purchase newly developed products to support safe injection (e.g., a new filter to attach to syringes).

NATIONAL CENTER FOR IMMUNIZATION AND RESPIRATORY DISEASES (NCIRD)

The mission of the National Center for Immunization and Respiratory Diseases (NCIRD) is the prevention of disease, disability, and death through immunization and by control of respiratory and related diseases. NCIRD balances its efforts in the domestic and global arenas as well as accommodates the specific needs of all populations at risk of vaccine preventable diseases from children to older adults.

NCIRD's web site: <http://www.cdc.gov/ncird/>

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

033 Heat Stable Sabin-based Inactivated Polio Vaccine

Fast-Track proposals 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

Current inactivated polio vaccine (IPV) products are sensitive to both freezing and elevated temperatures and therefore must be shipped and stored between 2°C and 8°C, a requirement that imposes financial and logistical challenges in their global distribution. This results in significant wastage of vaccine in the current formulations since multi-use vials must be discarded at the end of an immunization session and cannot be returned to the refrigerator for later use. Because IPV cannot be lyophilized in its current formulation, the vaccine cannot be dry-preserved.

Inactivated polio vaccine products based on the attenuated Sabin poliovirus strains have been developed as an alternative to the inactivated virulent strains used in conventional IPV, and such products have been licensed for use in several countries. Whereas stabilization of vaccines can be achieved in a partially dried state for a limited amount of time (several days) when stored at room or higher temperatures (i.e., 37°C), long-term stabilization of the vaccine requires arresting molecular mobility to stop the degradation processes during storage. Drying polio vaccines can be very damaging if performed in the absence of protective fillers such as simple sugars like sucrose.

Alternative preservation methods that increase vaccine stability at high temperatures could reduce shipping costs, improve cold chain logistics, and reduce vaccine wastage in the field.

Project Goals

Proposals are solicited for the development of a heat-stable, Sabin-based inactivated polio vaccine administered by needle and syringe. Heat stability is defined as no loss in antigenicity (as measured by standard vaccine potency tests) and no reduction in immunogenicity (as measured in accepted animal models for IPV potency) following heat challenge.

Phase I Activities and Expected Deliverables

1. Develop a formulation and process for dry-preserving polio vaccines.
2. Generate a Sabin-IPV by inactivating dry-preserved oral polio vaccine (OPV).
3. Assess heat stability by in vitro potency tests, at the following storage conditions:
 - a. 1 hour at 70°C
 - b. 1 month at 37°C
 - c. 1 month at 25°C
 - d. 3 months at 37°C
 - e. 3 months at 25°C
4. Prepare vaccine formulations for in vivo IPV potency assay using Wistar rat model.

For Successful Phase I Awardees ONLY (Expected Phase II Deliverables)

1. Optimize formulation and processing parameters for heat stable Sabin-IPV.
2. Production scale up for heat stable Sabin-IPV and generation of GMP lots.

Impact

A heat stable Sabin-IPV could increase vaccine availability by reducing storage and transport costs, as well as reducing vaccine wastage. This would potentially allow vaccines to be transported to areas of the United States and in the developing world where using icepacks or coolers to transport vaccines is challenging. A heat stable vaccine technology could significantly impact the progress of polio eradication as well as immunization programs for other vaccine preventable diseases.

Commercialization Potential

A heat-stable Sabin-IPV would most likely be licensed to vaccine manufacturers. Polio vaccine manufacturers produce and distribute vaccines to prevent polio in the US and globally to support the Global Polio Eradication Initiative.

13 APPENDICES

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

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 A PHASE I AND A PHASE II PROPOSAL

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 A PHASE I AND A PHASE II PROPOSAL

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 A PHASE II PROPOSAL

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 A PHASE II PROPOSAL

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 A PHASE I AND A PHASE II PROPOSAL

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 A PHASE II PROPOSAL

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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