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 2022-1

Closing Date: October 28, 2021 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 28, 2021, 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/SBA_SBIR_STTR_POLICY_DIRECTIVE_OCT_2020_v2.pdf to read the SBIR/STTR Policy Directive issued by the Small Business Administration for further information.

Table of Contents

1 INTRODUCTION

The National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) invite small business concerns (SBCs) 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.

Coronavirus Disease 2019 (COVID-19) (INFORMATION ONLY): Information for NIH Applicants and Recipients of NIH funding, including funding opportunities specific to COVID-19, can be found at Coronavirus Disease 2019 (COVID-19): Information for NIH Applicants and Recipients of NIH Funding. Information for CDC Applicants and Recipients of CDC funding, including funding opportunities specific to COVID-19, can be found at Financial Resources | CDC. This is a rapidly evolving situation and NIH/CDC will provide updated guidance and information as it becomes available.

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. Some Topics allow for only a Phase II proposal to be submitted, through the 'Direct to Phase II' process. Some Topics allow for 'Fast Track' proposals, which include both a Phase I proposal and a Phase II proposal. For more information on the SBIR program, including the Fast Track and Direct to Phase II processes, refer to Section 2.

TOPIC NUMBER	PHASE I ALLOWED?	FAST TRACK ALLOWED? (A Phase I proposal and a Phase II proposal submitted simultaneously)	DIRECT TO PHASE II ALLOWED? (Includes only a Phase II Proposal)	TOPIC TITLE
NIH/NCATS 022	Yes	No	No	Technological Development and Validation of Remote Measures for Use in Clinical Trials in Individuals with Rare Diseases
NIH/NCI 430	Yes	Yes	Yes	Development of Senotherapeutic Agents for Cancer Treatment
NIH/NCI 431	Yes	Yes	Yes	Cancer Treatment Technologies for Low-Resource Settings
NIH/NCI 432	Yes	No	Yes	Synthetic Biology Gene Circuits for Cancer Therapy
NIH/NCI 433	Yes	Yes	Yes	Developing Unbiased Medical Technologies to Reduce Disparities in Cancer Outcomes
NIH/NCI 434	Yes	Yes	Yes	Ultra-Fast Dose Rate (FLASH) Radiation Detectors and Safety Systems
NIH/NCI 435	Yes	Yes	No	Devices to Treat Secondary Lymphedema Following Cancer Treatment
NIH/NCI 436	Yes	Yes	No	New Technologies to Analyze Extra-Chromosomal DNA in Cancer
NIH/NCI 437	Yes	No	Yes	3D Spatial Omics for Molecular and Cellular Tumor Atlas Construction
NIH/NCI 438	Yes	No	No	Understanding Cancer Tumor Genomic Results: Technology Applications for Community Providers
NIH/NCI 439	Yes	No	Yes	Advanced Sample Processing Platforms for Downstream Single-Cell Multi-Omic Analysis

TOPIC NUMBER	PHASE I ALLOWED?	FAST TRACK ALLOWED? (A Phase I proposal and a Phase II proposal submitted simultaneously)	DIRECT TO PHASE II ALLOWED? (Includes only a Phase II Proposal)	TOPIC TITLE
NIH/NCI 440	Yes	Yes	Yes	Cancer Prevention and Diagnosis Technologies for Low-Resource Settings
NIH/NCI 441	Yes	Yes	Yes	At-Home Screening for Hepatitis C Virus
NIH/NCI 442	Yes	No	No	Quantitative Biomarkers as Medical Device Development Tools for Cancer
NIH/NCI 443	Yes	Yes	Yes	Development of Computer-Aided Diagnosis Tools for Upper and Lower Gastrointestinal Tract Cancer Prevention
NIH/NCI 444	Yes	No	No	Evaluation Datasets as Medical Device Development Tools for Testing Cancer Technologies
NIH/NCI 445	Yes	Yes	Yes	Advanced Manufacturing to Speed Availability of Emerging Autologous Cell-based Therapies
NIH/NIA 004	Yes	Yes	Yes	Improving CNS Gene Delivery Systems for AD/ADRD Therapy Development
NIH/NIA 005	Yes	No	No	Geroscience-based Chronic Wound Treatment Product Development
NIH/NIA 006	Yes	Yes	No	The Development of Mechanism-based Adult Stem Cell Treatments to Combat Aging Pathologies
NIH/NIAID 101	Yes	Yes	No	Novel Platforms for Delivery and/or Expression of HIV Env Immunogens for HIV Vaccines
NIH/NIAID 102	Yes	Yes	No	Genetically Engineered Mice for Pre-clinical Evaluation of HIV Vaccine Candidates
NIH/NIAID 103	Yes	Yes	No	Development of Diagnostics to Differentiate HIV Infection from Vaccine Induced Seropositivity
NIH/NIAID 104	Yes	Yes	Yes	Adjuvant Discovery for Vaccines and for Autoimmune and Allergic Diseases
NIH/NIAID 105	Yes	Yes	Yes	Adjuvant Development for Vaccines and for Autoimmune and Allergic Diseases
NIH/NIAID 106	Yes	Yes	Yes	Production of Adjuvants Mimics
NIH/NIAID 107	Yes	Yes	Yes	Reagents for Immunologic Analysis of Non-mammalian and Underrepresented Mammalian Models
NIH/NIAID 108	Yes	Yes	No	Development of Rapid POC Diagnostics for Treponema pallidum

TOPIC NUMBER	PHASE I ALLOWED?	FAST TRACK ALLOWED? (A Phase I proposal and a Phase II proposal submitted simultaneously)	DIRECT TO PHASE II ALLOWED? (Includes only a Phase II Proposal)	TOPIC TITLE
NIH/NIAID 109	Yes	Yes	No	Development of Monoclonal Antibody-mediated Interventions to Combat Malaria
NIH/NIAID 110	Yes	Yes	No	Point of Care (POC) Diagnostics for Antimicrobial Resistant (AMR) Enteric Bacterial and Parasitic Pathogens
NIH/NIAID 111	Yes	Yes	No	Data Science Tools for Infectious and Immune-mediated Disease Research
NIH/NIAID 112	Yes	Yes	No	Digital Tools Against Misinformation About Infectious Disease Treatments and Vaccines
CDC/NCBDDD 020	Yes	No	No	Open-Source and User-Friendly Record Linkage/De-duplication Tool
CDC/NCCDPHP 044	Yes	No	No	Algorithmic Database Food Product Tool to Align Food Service with Guidelines
CDC/NCEZID 028	Yes	No	No	Development Rapid, Portable, Point-of-Care C. auris Diagnostic
CDC/NCEZID 029	Yes	No	No	Product to Inactivate and Stabilize Wastewater Samples for Shipping and Transport
CDC/NCHHSTP 052	Yes	No	No	Electronic Health Record Algorithm to Identify Persons with HIV Not in Care
CDC/NCHHSTP 053	Yes	No	No	Simultaneous Detection of Molecular and Serological Markers via Next-Generation Sequencing
CDC/NCIRD 035	Yes	No	No	Nanoparticle-based Multi-Antigen Influenza Vaccine that Induces both Antibody and Cell-Mediated Immune Responses

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 provide additional non-SBIR funding. 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 October 1, 2020. 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 Phased Program

The SBIR program consists of 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

Phase III refers to work that derives from, extends, or completes an effort made under prior SBIR/STTR Funding Agreements, but is funded by sources other than the SBIR/STTR programs. Each of the following types of activity constitutes SBIR/STTR Phase III work: (i) Commercial application of SBIR/STTR funded R/R&D that is financed by non-Federal sources of capital. (ii) SBIR/STTR-derived products or services intended for use by the Federal Government, funded by non-SBIR/STTR sources of Federal funding. (iii) Continuation of SBIR/STTR work, funded by non-SBIR/STTR sources of Federal funding including R/R&D. For HHS SBIR/STTR projects, Phase III is primary financed by non-Federal sources of capital.

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 project beyond the Phase II, it is sufficient to state for purposes of a Justification and Approval pursuant to FAR 6.302-5 that the project 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 small business concern is treated as other Phase I awardees are in regards to submitting a Phase II proposal in accordance with Section 1.0, "Introduction."

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

2.4 Direct to Phase II Proposals (NIH Only)

If a Topic notes that Direct to Phase II proposals will be accepted, a small business concern that has already performed Phase I stage-type research through other, non-SBIR/STTR funding sources may submit a Phase II only proposal. Direct to Phase II awards allow a small business concern that has already built a technology prototype and tested its feasibility (i.e., completed Phase I type R&D) to move directly into Phase II type R&D that tests the functional viability of the prototype according to scientific methods and potential for commercial development. Refer to the table in Section 1.0 "Introduction" and Section 12.0 "Research Topics," for notation of Topics allowing Direct to Phase II proposals.

2.5 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** (NCATS, NCI, NIA, and NIAID), as well as **CDC/NCEZID and CDC/NIOSH (**National Institute of Occupational Safety and Health).

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 $55,000 (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 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 $55,000 in total direct costs – indirect costs may not be included. Of that amount, $22,000 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 2022 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 spanning April to May in 2022 with travel to Los Angeles, California for a three day workshop in April and travel to Bethesda, Maryland for a two day workshop in May.

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 2022 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 and Commercialization Readiness Pilot (CRP) Program (INFORMATION ONLY)

Phase IIB Competing Renewal Awards: 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, including those requiring regulatory approval or development complex instrumentation, clinical research tools, and behavioral interventions. NIH ICs that accept Phase IIB applications, either through the Omnibus SBIR/STTR grant funding opportunity announcements or other specific funding opportunity announcements, are listed in the PHS 2020 SBIR/STTR Program Descriptions and Research Topics for NIH, CDC, and FDA. Additional requirements and instructions (e.g., submission of a letter of intent) are available in the specific IC research topics section and in the NIH Targeted Funding Opportunities that allow Phase IIB applications.

Commercialization Readiness Pilot (CRP) Program: Some NIH ICs offer Phase II SBIR/STTR awardees the opportunity to apply for the Commercialization Readiness Pilot (CRP) Program. The goal of the CRP is to facilitate the transition of previously funded SBIR/STTR Phase II/IIB projects to the commercialization stage by providing additional support for later stage technical assistance and, in some cases, research and development (R&D) not typically supported through Phase II or Phase IIB grants or contracts, often because they are normally outsourced to CROs. NIH ICs that accept CRP applications accept them through specific CRP funding opportunity announcements listed in NIH Targeted Funding Opportunities.

2.7 Awarding Components

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

National Institutes of Health (NIH) Components:

National Center for Advancing Translational Sciences (NCATS)

National Cancer Institute (NCI)

National Institute on Aging (NIA)

National Institute of Allergy and Infectious Diseases (NIAID)

Centers for Disease Control and Prevention (CDC) Components:

National Center on Birth Defects and Developmental Disabilities (NCBDDD)

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

National Center for Emerging Zoonotic and Infectious Diseases (NCEZID)

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

National Center for Immunization and Respiratory Diseases (NCIRD)

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 (SBC) 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 award, SBIR Phase II award, or follow-on non-SBIR Federal funding agreement.

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. Innovation encompasses the full commercialization pathway.

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 follow-on 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 note 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**.**

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. NIH defines a clinical trial as a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

If the answers to **all** four questions below are **yes**, the study meets the definition of a Clinical Trial:

- Does the study involve human participants?
- Are the participants prospectively assigned to an intervention?
- Is the study designed to evaluate the effect of the intervention on the participants?
- Is the effect that will be evaluated a health-related biomedical or behavioral outcome?

See Appendix H.1 Instructions, Human Subjects and Clinical Trials Information Form, Section 1.4. Clinical Trial Questionnaire, for further information and references for understanding this definition. Appendix H.1. is located in Section 13 – Appendices of this solicitation.

Human Subjects. The HHS regulations "Protection of Human Research 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.

See Appendix H.1 Instructions, Human Subjects and Clinical Trials Information Form, Section 1.3. Exemption Number, for additional guidance. Appendix H.1. can be located in Section 13 – Appendices of this solicitation.

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 award dollars.

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 be considered on a case by case basis. Deviations must be approved in writing by the funding agreement officer after consultation with the agency SBIR Program Manager/Coordinator.

4.3 SBIR/STTR Performance Benchmarks for Progress towards Commercialization

In accordance with Section 4 of the SBIR/STTR Policy Directive, and as required by the SBIR/STTR Reauthorization Act of 2011, the following two performance benchmarks have been established for companies participating in SBIR programs.

Companies will not be eligible to **submit a proposal** for a **new SBIR/STTR project** for a period of one year from the time that SBA issues a determination of failure to meet a performance benchmark. A company that fails to meet a performance benchmark may continue working on its current or ongoing SBIR/STTR projects, including submitting a proposal to transition a Phase I award to a Phase II award.

For more information on benchmark requirements, refer to https://www.sbir.gov/performance-benchmarks and/or the SBIR/STTR Policy Directive referenced on the first page of this solicitation.

Phase I to Phase II Transition Benchmark

All companies that have received 20 or more SBIR/STTR Phase I awards, throughout all federal agencies, over the past five (5) fiscal years excluding the most recently completed fiscal year, must have transitioned to SBIR/STTR Phase II on at least 25% of those awards.

Companies can view their transition rate and verify compliance on https://www.sbir.gov/. When logging in, the Phase I to Phase II transition rate will be displayed in the welcome screen.

Phase II to Phase III Commercialization Benchmark

All companies that have received more than 15 SBIR/STTR Phase II awards, throughout all federal agencies, over the past ten (10) fiscal years excluding the two most recently completed fiscal years, must show an average of at least $100,000 in revenues and/or investments per Phase II award, or, must have received a number of patents resulting from the SBIR/STTR work equal to or greater than 15% of the number of Phase II awards received during the period.

Companies can view their commercialization data and verify compliance on https://www.sbir.gov/ and viewing the Company Registry.

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 4.16 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 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's point of contact 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.

4.10 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).

4.11 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).

4.12 Registrations and Certifications

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

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.

Representation Regarding Certain Telecommunications and Video Surveillance Services or Equipment.

All offerors must complete and submit FAR Provisions 52.204-24 and 52.204-26 as part of your Business Proposal, which are attached and incorporated as Solicitation APPENDICES I.1. and I.3.

4.13 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.

4.14 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.

4.15 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/report-fraud/ 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

4.16 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 and Business Assistance

NIH offers distinct technical assistance programs to NIH SBIR and STTR Phase I and Phase II awardees. These programs offer specialized, strategic business training and provide access to a vast network of industry experts 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. Awardees that utilize their own technical assistance provider and include those costs in their budget will not have access to the centralized NIH technical assistance programs.

You may request up to $6,500 per year for a Phase I and up to $50,000 per Phase II project (across all years) for assistance. You may request up to these amounts for each Phase in a Fast-Track application.

Note for CDC offerors*: CDC does not participate in the NIH Technical and Business Assistance Program. If you are a CDC offeror and 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 $6,500 per year for a Phase I and up to $50,000 per Phase II project (across all years) for assistance.*

Refer to Section 8 for how to include this in your Pricing Proposal. 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 and business assistance services, such as access to a network of scientists and engineers engaged in a wide range of technologies, product sales, IP protections, market research, market validation, development of regulatory plans, manufacturing plans, 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.

4.17 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).

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 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.

4.18 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."

4.19 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

Upon award of a contract, the contractor will be required to make certain legal commitments through acceptance of Government contract clauses. This Section discusses which clauses will be included in a contract resulting from this solicitation, if applicable to the project being proposed.

5.1 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.

5.2 CARE OF LIVE VERTEBRATE ANIMALS, HHSAR 352.270-5(b) (December 2015)

a. Before undertaking performance of any contract involving animal-related activities where the species is regulated by the United Sates 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). (End of clause)

5.3 Animal Welfare

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 PROTECTION OF HUMAN SUBJECTS, HHSAR 352.270-4(b) (December 2015)

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. (End of clause)

5.5 Required Education in the Protection of Human Research Participants

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 .

The information below is a summary of the NIH Policy Announcement:

The Contractor shall maintain the following information: (1) a list of the names and titles of the principal investigator and any other individuals working under the contract who are responsible for the design and/or conduct of the research; (2) the title of the education program(s) in the protection of human subjects that has been completed for each named personnel and; (3) a one sentence description of the educational 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.

Prior to any 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 following written information to the Contracting Officer: the title of the education program and a one sentence description of the program that has been completed by the replacement.

5.6 Inclusion of Women and Minorities in Research Involving Human Subjects

NIH-conducted and supported clinical research must conform to the NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research in accord with Public Health Service Act sec. 4928 U.S.C. sec 289a-2. The policy requires that women and members of minority groups and their subpopulations must be included in all NIH-conducted or supported clinical research projects involving human subjects, unless a clear and compelling rationale and justification establishes to the satisfaction of the relevant NIH Institute/Center (IC) 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 IC Director, based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research.

All investigators proposing research involving human subjects should read the UPDATED "NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research, Amended November 2017," 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 .

The Contractor must submit the results of valid analyses by sex/gender and race/ethnicity to Clinicaltrials.gov for all NIH-conducted or supported applicable NIH-defined Phase III clinical trials. This requirement does not apply to NIH-defined Phase III trials not considered to applicable clinical trials under 42 CFR Part 11. The Contractor must report applicable NIH-defined Phase III clinical trials involving research subjects of all ages, including foreign awards and domestic awards with a foreign component. The Contractor must specify outcomes on sex/gender and race/ethnicity, as required based on prior evidence, and as explained in the NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research.

Note: Applicable clinical trials are required to be registered in ClinicalTrials.gov not later than 21 calendar days after the enrollment of the first participant. Results information, including the results of the valid analyses by sex/gender and race/ethnicity, from those trials must be submitted not later than one year after the trial's primary completion date. Submission of results information can be delayed in certain circumstances for up to two additional years for trials of products regulated by the FDA that are unapproved, unlicensed, or uncleared or for trials of products for which approval, licensure, or clearance of new use is being sought

5.7 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).

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.

5.8 Clinical Trial Registration and Results Information Submission

The Contractor conducting clinical trials, funded wholly or partially through the NIH extramural and intramural programs, shall ensure that its NIH-funded clinical trials are registered at, and summary results information is submitted to, www.clinicaltrials.gov for public posting. See NIH Guide Notice NOT-OD-16-149 dated September 16, 2016.

All NIH-funded clinical trials shall be registered and results information submitted to www.clinicaltrials.gov regardless of study phase, type of intervention, or whether they are subject to the regulation 42 CFR Part 11. Clinical trials subject to the regulation are called "applicable clinical trials."

The Contractor must submit a plan with its proposal to meet the regulatory requirements of the dissemination of information of NIH-funded Clinical Trials. This plan should be uploaded to Section 4.7, Dissemination Plan, of Appendix H.3. – Study Record, which can be found in Section 13 – Appendices. The Contractor and investigators are required to comply with all terms and conditions of award, including following their acceptable plan for the dissemination of NIH-funded clinical trial information.

The Contractor must register all NIH-funded clinical trials in www.clinicaltrials.gov not later than 21 calendar days after the enrollment of the first participant. Results information from those trials must be submitted not later than one year after the trial's primary completion date. Submission of results information can be delayed in certain circumstances for up to two additional years for trials of products regulated by the FDA that are unapproved, unlicensed, or uncleared or for trials of products for which approval, licensure, or clearance of a new use is being sought. The Contractor shall include the trial registration number (NCT number) in the Technical Progress Report covering the period in which registration occurred, and as a standalone notification to the Contracting Officer within ten (10) calendar days of the registration. Each NIH-funded clinical trial must have only one entry in ClinicalTrials.gov that contains its registration and results information.

The Contractor shall include a specific statement in all informed consent documents relating to posting of clinical trials information to www.clinicaltrials.gov . The responsibilities of the Contractor will fall within one of the following three categories:

1. If the NIH-funded clinical trial is an applicable clinical trial under the regulation and the Contractor is the responsible party, the Contractor will ensure that all regulatory requirements are met.
2. If the NIH-funded clinical trial is an applicable clinical trial under the regulation but the Contractor is not the responsible party, the Contractor will coordinate with the responsible party to ensure that all regulatory requirements are met.
3. If the NIH-funded clinical trial is not an applicable clinical trial under the regulation, the Contractor will be responsible for carrying out the tasks and meeting the timelines described in regulation. Such tasks include registering the clinical trial in ClinicalTrials.gov and submitting results information to ClinicalTrials.gov.

Failure to comply with the terms and conditions of the award may provide a basis for enforcement actions. Identifying clinical trial record as non-compliant in ClinicalTrials.gov may lead to termination, consistent with 45 CFR 75.371 and/or other authorities, as appropriate. If the NIH-funded clinical trial is also an applicable clinical trial, non-compliance with the requirements specified in 42 USC 282(j) and 42 CFR Part 11 may also lead to the actions described in 42 CFR 11.66.

The Contracting Officer may take one or more of the following enforcement actions, if the Contractor fails to provide evidence of compliance within 30 days.

- Temporary withhold payments pending correction of the deficiency;
- Disallow all or part of the cost of the activity or action not in compliance;
- Wholly or partly suspend or terminate the contract award;
- Initiate suspension or debarment proceedings as authorized under 2 CFR part 180 and HHS awarding regulations at 2 CFR part 376;
- Withhold further awards for the project and program;
- Take other remedies that may be legally available.

5.9 Single Institutional Review Board (sIRB)

For Institutional Review Board (IRB), the Contractor shall use the single Institutional Review Board (sIRB) of record for multi-site research. All domestic sites participating in multi-site studies involving a non-exempt human subjects research funded wholly or partially by the National Institutes of Health (NIH) shall use a sIRB to conduct the ethical review required by the Department of Health and Human Services regulations for the Protection of Human Subjects at 45 CFR Part 46 and the NIH Policy on the Use of Single Institutional Review Board for Multi-Site Research . Any IRB serving as the sIRB of record for NIH funded research shall be registered with the HHS Office for Human Research Protections (OHRP) and shall have membership sufficient to adequately review the proposed study.

The Contractor shall provide to the Contracting Officer a properly completed "Protection of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption", Form OMB No. 0990-0263 certifying IRB review and approval of the research that encompasses all sites of performance.

Contractor shall provide to the Contracting Officer sIRB information and data in a timely manner as necessary to meet the policy and/or regulatory requirements of the Protection of Human Subjects at 45 CFR Part 46.

Exceptions to the NIH Single IRB Policy

The Contractor may request an exception in the following instances:

1. Sites for which Federal, state, or tribal laws, regulations or policies require local IRB review (policy-based exceptions);
2. *Other exceptions*, to be determined by NIH if there is a compelling justification; and
3. Time Limited Exception: ancillary studies to ongoing research without a sIRB- new multi-site non-exempt human subjects' ancillary studies, that would otherwise be expected to comply with the sIRB policy, but are associated with the ongoing multi-site parent studies, will not be required to use a sIRB of record until the parent study is expected to comply with the sIRB policy.

Policy-based exceptions and time limited exceptions are automatically granted when identified in the sIRB Plan.

Other exceptions must be reviewed by NIH sIRB Exceptions Review Committee (ERC) and are expected to be granted rarely. *Other exceptions* when Offeror believes that one or more research sites should be exempt from use of the single IRB of record to conduct local IRB review based on compelling justification-

a. Offerors should request an exception in the sIRB plan attachment within the contract proposal, by uploading an attachment to Field 3.2 in the **Appendix H.3 Study Record**, which is itself an attachment to the **Appendix H.2 Human Subjects and Clinical Trials Information form**.

b. Offerors must include the name of the site(s) for which an IRB other than the sIRB of record is proposed to review the study for the sites(s).

c. Offerors must substantiate their exception request with sufficient information that demonstrates a compelling justification for *other exceptions* to the sIRB policy. The rationale should include why the sIRB of record cannot serve as the reviewing IRB for the site(s), and why the local IRB is uniquely qualified to be the reviewing IRB for the specific site(s).

- For instance, the justification may consider ethical or human subjects protections issues, population needs, or other compelling reasons that IRB review for the site(s) cannot be provided by the single IRB of record.

d. Note that the proposed budget in the proposal must reflect all necessary sIRB costs without an approved *other exception.* The Offerors should not assume that an *other exception* will be granted when considering what sIRB costs to include in the budget.

5.10 Research Involving Recombinant or Synthetic Nucleic Acid (Including Human Gene Transfer Research)

All research projects (both NIH-funded and non-NIH-funded) involving recombinant or synthetic nucleic acid molecules that are conducted at or sponsored by an entity in the U.S. that receives any support for recombinant or synthetic nucleic acid research from NIH shall be conducted in accordance with the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (*NIH Guidelines*) available at: http://osp.od.nih.gov/biotechnology/nih-guidelines). All NIH-funded projects abroad that include recombinant or synthetic nucleic acid molecules must also comply with the *NIH Guidelines* .

The *NIH Guidelines* stipulate biosafety and containment measures for recombinant or synthetic nucleic acid research, which is defined in the *NIH Guidelines* as research with (1) molecules that a) are constructed by joining nucleic acid molecules and b) can replicate in a living cell, i.e. recombinant nucleic acids, or (2) 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 (3) molecules that result from the replication of those described in (1) or (2). The *NIH Guidelines* apply to both basic and clinical research. Specific guidance for the conduct of human gene transfer studies appears in Appendix M of the *NIH Guidelines* .

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 research or a requirement for the Contracting Officer to approve any or all recombinant or synthetic nucleic acid molecule projects under this contract. This includes the requirement for the institution to have an Institutional Biosafety Committee (IBC) registered with the NIH Office of Science Policy that complies with the requirements of the *NIH Guidelines* . Further information about compliance with the *NIH Guidelines* can be found on the NIH Office of Science Policy website available at: http://osp.od.nih.gov /.

5.11 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.

5.12 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 follow-on non-SBIR Federal funding agreement) 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 follow-on non-SBIR Federal funding award is issued within or after the Phase II data rights protection period and the follow-on non-SBIR Federal funding award refers to and protects data developed and protected under the Phase II award, then that data must continue to be protected through the award 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 or II of the SBIR Program, or follow-on non-SBIR Federal funding award, as described in section 4 of the SBIR Policy Directive. The scope and extent of the SBIR technical data rights applicable to follow-on non-SBIR Federal funding 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.

5.13 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

5.14 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 2021, Executive Schedule, Level II of the Federal Executive Pay Scale is $199,300.

5.15 Other Contract Requirements

The outline that follows is illustrative of the types of generally-applicable 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. **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.

j. **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.

k. **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.

l. **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.

m. **Equal Opportunity.** The contractor will not discriminate against any employee or applicant for employment because of race, color, religion, sex, or national origin.

n. **Equal Opportunity for Veterans.** The contractor will not discriminate against any employee or applicant for employment because he or she is a disabled veteran.

o. **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.

p. **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.

q. **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.

r. 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**.**

s. **Patent Infringement.** The contractor shall report each notice or claim of patent infringement based on the performance of the contract.

t. **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.

u. **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.

v. **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.

w. **Dissemination of False or Deliberately Misleading Information.** The Contractor shall not use contract funds to disseminate information that is deliberately false or misleading.

x. **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.

y. **Gun Control.** The contractor shall not use contract funds in whole or in part to advocate or promote gun control.

z. **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.

aa. **Prohibition on Contracting for Certain Telecommunications and Video Surveillance Services or Equipment**. Contracts resulting from this solicitation will include FAR clause 52.204-25, attached and incorporated as Solicitation APPENDIX I.2.

ab. **Subcontracts for Commercial Items**. Contracts resulting from this solicitation will include FAR clause 52.244-6 (Jul 2021), which can be referenced here.

ac. **Service Contract Reporting Requirements**. Contracts with an estimated total value of $500,000 or greater resulting from this solicitation will include FAR clause 52.204-14, which can be referenced here.

6 METHOD OF EVALUATION

All proposals will be evaluated and judged on a competitive basis. 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

Using the technical evaluation criteria specified below, a panel of experts knowledgeable in the disciplines or fields under review will evaluate proposals for scientific and technical merit. For NIH, this peer review panel will be composed of experts from outside the Awarding Component, in accordance with 42 CFR 52h. For CDC, this panel may be composed of internal governmental scientific and technical experts. 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.

Reviewers will also be instructed to comment on the compliance of a proposal with applicable HHS, NIH, and CDC policies, such as those listed below. If the Government is interested in funding a proposal, but a concern is noted with one of these policies, the offeror company will be afforded the opportunity to address the concerns through negotiation and proposal revisions. If the offeror company is not able to submit a proposal revision that is found acceptable in terms of these policies, then the proposal may not be considered further for award.

- 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

For NIH Awarding Components:

For NIH Awarding Components, the peer review technical evaluation panel will also determine whether each proposal is technically acceptable, meaning that it demonstrates sufficient technical understanding and capabilities to perform the technical objectives set forth in the solicitation. If a proposal is not found Technically Acceptable by a majority of the peer review panel members, then the proposal cannot be considered further for award, pursuant to 42 CFR 52h.

NIH program staff of the Awarding Component will conduct a second level of review of all proposals found Technically Acceptable by the peer review panel. NIH program staff will take into consideration all factors set forth in Section 6.4 Award Decisions. Note: *A determination of technical acceptability does not mean that the proposal will result in an award, it only means that the NIH Awarding Component is able to consider the proposal for award.*

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 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 technical evaluation;
- 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.

6.3 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. a. Identification of clear, measurable goals (*i.e.*, 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.e.*, 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 – whether the end product or technology proposed would offer significant advantages over existing approaches, methodologies, instrumentation, or interventions currently utilized in research or clinical practice.	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, and the appropriateness of the leadership approach (including the designated roles and responsibilities, governance, and organizational structure).	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.

6.4 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 a. Identification of clear, measurable goals (*i.e*., 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.e.*, 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 – whether the end product or technology proposed would offer significant advantages over existing approaches, methodologies, instrumentation, or interventions currently utilized in research or clinical practice.	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 II from private sector or other non-SBIR funding sources, and/or any other indicators of commercial potential for the proposed research.	25%
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.

7 PROPOSAL SUBMISSION

7.1 Questions

Offerors with questions regarding this solicitation must submit them in writing to the Contracting Officer point of contact identified in Section 10 of this solicitation for the Awarding Component that is responsible for the Topic of interest to the offeror. To ensure that the Government has sufficient time to respond, questions should be submitted by **September 3, 2021**. The Government may issue an amendment to this solicitation which publishes its responses to questions submitted. 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 12, 2021 at 1:00 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://nih.zoomgov.com/webinar/register/WN_4WI8-pyGQ46Gy8-lXX007Q. Following registration, a confirmation e-mail will be sent containing information about joining the webinar.

Presentation material from this webinar shall be posted on beta.SAM.gov 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.

The Human Subjects and Clinical Trials Information form and its attachments (Appendix H.2., and, if applicable, Appendix H.3.) are excluded from these page limits. This is the only exclusion. The Human Subjects and Clinical Trials Information form and its attachments (Appendix H.2., and, if applicable, Appendix H.3.) are to be submitted separately from the rest of the Technical Proposal. There is a field in the eCPS proposal submission website that is specifically identified for upload of the Human Subjects and Clinical Trials Information Form and its attachments, separate from the Technical Proposal.

Besides the Human Subjects and Clinical Trials Information form, the Technical Proposal shall not exceed the page limits stated above, inclusive of all pages, cover sheet, tables, CVs, resumes, references, pictures/graphics, appendices, attachments, etc. Page margins must be at least one inch on all sides (with the exception of forms provided as appendices to this solicitation). 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). 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/ 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/howtosubmit. Offerors may also reference Frequently Asked Questions regarding online submissions at https://ecps.nih.gov/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 3 parts: Technical Proposal, Human Subjects and Clinical Trials Information Form, and Business Proposal.

   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 Human Subjects and Clinical Trials Information Form shall consist of Item 2, as described in Section 8.12. A link to this form is found in Section 13 Appendices. **This form – Appendix H.2. – is required for every proposal submission.** If your proposal does not involve Human Subjects or Clinical Trials, you must still note this on the form and submit the form. If applicable, Appendix H.3. – Study Record must be attached to Appendix H.2., as described in the Instructions set forth in Appendix H.1.

The Business Proposal shall consist of Items 3, 4 (if applicable), 5, and 6, 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
Human Subjects and Clinical Trials Information Form:	XYZ Company_NIAID_TOPIC_033_HumanSubjectsForm.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
Human Subjects and Clinical Trials Information Form:	XYZ Company_NCIRD_TOPIC_031_ HumanSubjectsForm.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

Item 2: Human Subjects and Clinical Trials Information Form and Attachments (Appendix H.2 and, if applicable, H.3)

BUSINESS PROPOSAL

Item 3: Pricing Proposal (Appendix C)

Item 4: SBIR Application VCOC Certification, if applicable
(See Section 4.6 to determine if this applies to your organization)

Item 5: Proof of Registration in the SBA Company Registry
(Refer to Section 4.17 for Directions)

Item 6: 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

A complete Phase II proposal (either as part of a FAST TRACK or Direct to Phase II) 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)

Item 2: Human Subjects and Clinical Trials Information Form and Attachments (Appendix H.2 and, if applicable, H.3)

BUSINESS PROPOSAL

Item 3: Pricing Proposal (Appendix C)

Item 4: SBIR Application VCOC Certification, if applicable
(See Section 4.6 to determine if this applies to your organization)

Item 5: Proof of Registration in the SBA Company Registry
(Refer to Section 4.17 for Directions)

Item 6: Summary of Related Activities (Appendix F)

Phase II proposals for this solicitation will only be accepted for Topics that allow for Fast Track proposals Direct to Phase II proposals. Refer to the table in Section 1 to see which Topics are allowing Fast Track or Direct to Phase II proposals.

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

8.5 Technical Proposal Cover Sheet (Item 1)

For Phase I Proposals, complete the form identified as Appendix A and use it as the first page of the proposal. No other cover sheet should be used. 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 (including Direct to Phase II Proposals and the Phase II Proposal of a Fast Track submission), complete the form identified as Appendix D and use it as the first page of the proposal. No other cover sheet should be used. 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

Consider whether a list describing abbreviations or providing significant definitions would be helpful to reviewers, and if so, include such a list at the beginning of your Research Plan.

Discuss the following elements in the order indicated:

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) **Detailed Approach and Methodology.** 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.
   - Address the points discussed in the Section 8.9 Enhancing Reproducibility through Rigor and Transparency.
   - If a project involves vertebrate animals, include a Vertebrate Animals Section, as discussed in Section 8.10 Research Involving Vertebrate Animals.
   - If Section 8.11 Dual Use Research of Concern is applicable to your project, address it here.

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) **Innovation.** Discuss how the end product or technology being developed would offer significant advantages over existing approaches, methodologies, instrumentation, or interventions on the market currently being utilized in research or clinical practice, such as meaningful improvements in quality, capability, cost, speed, efficiency, etc.

7) **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. Describe the strategy for protecting your innovation (such as status of and/or potential for intellectual property or market exclusivity, etc.).

8) **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.

9) **Subcontractors/Consultants.** Identify all investigator/collaborators by name and organization. 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) **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.

11) **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.

12) **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 Direct to Phase II Proposals and the Phase II Proposal of a Fast Track submission)

Consider whether a list describing abbreviations or providing significant definitions would be helpful to reviewers, and if so, include such a list at the beginning of your Research Plan.

Discuss the following elements in the order indicated:

1) Anticipated Results of the Phase I/ Phase I-like Effort –

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.

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

2) **Detailed Approach and Methodology** - Provide an explicit detailed description of the Phase II approach. This section should be the major portion of the proposal and must clearly show advancement in the project appropriate for Phase II. Indicate not only what is planned, but also how and where the work will be carried out. List all tasks in a logical sequence to precisely describe what is expected of the contractor in performance of the work. Tasks should contain detail to (1) establish parameters for the project; (2) keep the effort focused on meeting the objectives; (3) describe end products and deliverables; and (4) describe periodic/final reports required to monitor work progress under the contract.

- Address the points discussed in the Section 8.9 Enhancing Reproducibility through Rigor and Transparency.
- If a project involves vertebrate animals, include a Vertebrate Animals Section, as discussed in Section 8.10 Research Involving Vertebrate Animals.
- If Section 8.11 Dual Use Research of Concern is applicable to your project, address it here.

3) **Innovation -** Discuss how the end product or technology being developed would offer significant advantages over existing approaches, methodologies, instrumentation, or interventions on the market currently being utilized in research or clinical practice, such as meaningful improvements in quality, capability, cost, speed, efficiency, etc.

4) **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.

5) **Subcontractors/Consultants**. Identify all investigator/collaborators by name and organization. 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 form each individual confirming his/her role in the project must be included.

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.

   If budget allocation is planned, the distribution of resources to specific components of the project or the individual PDs/PIs should be delineated in the Leadership Plan. In the event of an award, the requested allocations may be reflected in Contract Award.

7) **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.)

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.** The Phase II portion of Fast-Track proposals and all Direct Phase II proposals must include a Commercialization Plan. 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 commercialization 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 non-SBIR follow-on 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 follow-on non-SBIR funding may be from any of a number of different sources including, but not limited to: SBIR firm itself; private investors or "angels"; venture capital firms; investment companies; joint ventures; R&D limited partnerships; strategic alliances; research contracts; sales of prototypes (built as part of this project); public offering; state finance programs; non SBIR-funded R&D or production commitments from a Federal agency with the intention that the results will be used by the United States government; or other industrial firms.

Fast-Track proposals that do not contain all parts described above will be redirected for Phase I consideration only.

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 the information below within the Detailed Approach and Methodology section of the technical proposal:

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 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 titled "Vertebrate Animals Section" within the Detailed Approach and Methodology section of the technical proposal**:**

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

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. 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. This information should be addressed in the Technical Proposal section on Vertebrate Animals.

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.

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.

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.

8.11 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.

8.12 Human Subjects and Clinical Trials Information Form

All proposal submissions must include Appendix H.2 – Human Subjects and Clinical Information Form.
Attachments must also be included if applicable, based on the nature of your project.

Please review **Appendix H.1. - INSTRUCTIONS, HUMAN SUBJECTS AND CLINICAL TRIALS INFORMATION FORM,** found in Section 13 – Appendices, which is the last page of this solicitation.

Then, download and complete **Appendix H.2. – HUMAN SUBJECTS AND CLINICAL TRIALS INFORMATION FORM,** found in Section 13 – Appendices, which is the last page of this solicitation. This form must be included in every proposal.

If your project involves Human Subjects, even if the project is exempt from Federal Regulations, then completion of Appendix H.2. will also require **Appendix H.3. – STUDY RECORD**, which is an attachment to Appendix H.2., and can be found in Section 13 – Appendices, which is the last page of this solicitation.

Through these forms, each proposal must address the Human Subjects Research, Inclusion, and Clinical Trials policies which are included in this solicitation, as applicable to your project.

If there is not a specific place identified within Appendix H.2. or Appendix H.3. for a particular issue concerning Human Subjects protection, Inclusion, or Clinical Trials policies discussed in this solicitation, include your response as an attachment in the "Other Requested Information" field on the Human Subjects and Clinical Trials Information form.

8.12.1 Human Specimens and/or Data

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. There is a field in the Human Subjects and Clinical Trials Information form to attach this explanation. To help determine whether your research is classified as human subjects research, refer to the Research Involving Private Information or Biological Specimens flowchart.

8.12.2 Human Subjects Research with an Exemption from Federal Regulations

If **all** of your proposed human subjects research meets the criteria for one or more of the 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. This exemption justification must be attached to the Human Subjects and Clinical Trials Information form using the **"Other Requested Information"** field.

8.12.3 Protection of Human Subjects

A. Notice to Offerors of Requirements, Protection of Human Subjects, HHSAR 352.270-4(a) (December 2015)

- 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.
- 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.
- 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 .

- 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.
- 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).
- 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.
- 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 human subjects work beginning. Upon obtaining FWA approval, submit the approval notice to the Contracting Officer. (End of provision)

Proof of an approved or active FWA should be attached to the Human Subjects and Clinical Trials Information form using the **"Other Requested Information"** field.

B. Instructions to Offerors Regarding Protection of Human Subjects

If the proposal is for research involving non-exempt human subjects, offerors must address the following human subjects protections issues in an attachment uploaded to the "**Section 3.1. Protection of Human Subjects**" field in the **Study Record** form that is an attachment to the **Human Subjects and Clinical Trials Information** form.

Note: under each of the following points below, the offeror should indicate whether the information provided relates to the primary research site, or to a collaborating performance site(s), or to all sites.

a. Risks to the subjects

- Human Subjects Involvement, Characteristics, and Design
  - Briefly describe the overall study design in response to the solicitation.
  - Describe the subject population(s) to be included in the study; the procedures for assignment to a study group, if relevant; and the anticipated numbers of subjects for each study group.
  - 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.
- Study Procedures, Materials, and Potential Risks
  - Describe all planned research procedures (interventions and interactions) involving study subjects; how research material, including biospecimens, data, and/or records, will be obtained; and whether any private identifiable information will be collected in the proposed research project.
  - For studies that will include the use of previously collected biospecimens, data or records, describe the source of these materials, whether these can be linked with living individuals, and who will be able to link the materials.
  - Describe all the potential risks to subjects associated with each study intervention, procedure or interaction, including physical, psychological, social, cultural, financial, and legal risks; risks to privacy and/or confidentiality; or other risks. Discuss the risk level and the likely impact to subjects.
  - Where appropriate, describe alternative treatments and procedures, including their risks and potential benefits. When alternative treatments or procedures are possible, make the rationale for the proposed approach clear.

b. Adequacy of Protection Against Risks

- Recruitment and Informed Consent:
  - Describe plans for the recruitment of subjects and the procedures for obtaining informed consent. Include a description of the circumstances under which consent will be sought and obtained, who will seek it, the nature of the information to be provided to prospective subjects, and the method of documenting consent. When appropriate, describe how potential adult subjects' capacity to consent will be determined and the plans for obtaining consent from a legally authorized representative for adult subjects not able to consent. The informed consent document for the Contractor and any collaborating sites should be submitted only if requested elsewhere in the solicitation. Be aware that an IRB-approved informed consent document for the Contractor and any participating collaborative sites must be provided to the Government prior to patient accrual or participant enrollment.
    - For research involving children: If the proposed studies will include children, describe the process for meeting HHS regulatory requirements for parental permission and child assent (45 CFR 46.408). See the HHS page on Research with Children FAQs and the NIH page on Requirements for Child Assent and Parent/Guardian Permission.
    - If a waiver of some or all of the elements of informed consent will be sought, provide justification for the waiver.
- Protection Against Risk:
  - Describe the procedures for protecting against or minimizing potential risks, including risks to confidentiality, and assess their likely effectiveness.
  - Discuss provisions for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects where appropriate.
  - In studies that involve interventions, describe the provisions for data and safety monitoring of the research to ensure the safety of subjects.
- **Vulnerable Subjects, if relevant to your study** – 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. 'Prisoners' includes all subjects involuntarily incarcerated (for example, in detention centers).
  - Pregnant Women, Fetuses, and Neonates or Children - If the study involves vulnerable subjects subject to additional protections under Subparts B and D (pregnant women, fetuses, and neonates or children), provide a clear description of the risk level and additional protections necessary to meet the HHS regulatory requirements.
    - HHS' Subpart B - Additional Protections for Pregnant Women, Fetuses, and Neonates
    - HHS' Subpart D - Additional Protections for Children
    - OHRP Guidance on Subpart D Special Protections for Children as Research Subjects and the HHS 407 Review Process

c. Potential Benefits of the Proposed Research to the Subjects and Others

- Discuss the potential benefits of the research to the subjects and others.
- Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to subjects and others.
- Describe treatments and procedures that are alternatives to those provided to the participants by the proposed research, where appropriate.
  - Note: Financial compensation of subjects should not be presented as a benefit of participation in research.

d. Importance of the Knowledge to be Gained

- Discuss the importance of the knowledge gained or to be gained as a result of the proposed research.
- Discuss why the risks to subjects are reasonable in relation to the importance of the knowledge that may reasonably be expected to result.
  - Note: If a test article (investigational new drug, device, or biologic) is involved, name the test article and state whether the 30-day interval between submission of offeror's certification to the Food and Drug Administration (FDA) and its response has elapsed or has been waived and/or whether the FDA has withheld or restricted use of the test article.

Collaborating Site(s)

When research involving human subjects will take place at collaborating site(s) or other performance site(s), the offeror must provide

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

8.12.4 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 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 . 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 the following information as an attachment to the Human Subjects and Clinical Trials Information form **"Other Requested Information"** field:

(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" at: http://phrp.nihtraining.com . This course is also available in Spanish under the title "Protección de los participantes humanos de la investigación" at: http://pphi.nihtraining.com . You may take the tutorials on-line or download the information in PDF form at no cost. The University of Rochester has made its training program available for individual investigators. Completion of this program will also satisfy the educational requirement. The University of Rochester manual, entitled, "Protecting Study Volunteers in Research," can be obtained through Centerwatch, Inc. at: http://store.centerwatch.com/c-29-training-guides.aspx .

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.

8.12.5 Inclusion of Women and Minorities in Research Involving Human Subjects and Inclusion of Children in Research Involving Human Subjects

For all proposals including clinical research, attach a discussion of Inclusion into Field "2.4. Inclusion of Women, Minorities, and Children" on the **Appendix H.3 Study Record Form**, which is an attachment to the **Appendix H.2 Human Subjects and Clinical Trials Information Form**. Organize your attachment into two sections: first "Inclusion of Women and Minorities," then "Inclusion of Children." Refer to both the instructions below, as well as the instructions set forth in Section 2.4 of **Appendix H.1 Instructions, Human Subjects and Clinical Trials Information Form.** Note: You will also have to complete an Inclusion Enrollment Report (IER).

Your Inclusion discussion may include multiple Inclusion Enrollment Reports for each study proposed. The Inclusion Enrollment Report is embedded into the **Appendix H.3 Study Record Form**. To access the Inclusion Enrollment Report, click the button "Add Inclusion Enrollment Report" at the end of "Section 2 – Study Population Characteristics" within the **Appendix H.3 Study Record Form**. The Study Record form is itself an attachment to the **Appendix H.2 Human Subjects and Clinical Trials Information Form.**

Inclusion of Women and Minorities in Research Involving Human Subjects

NIH-conducted and supported clinical research must conform to the NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research in accord with Public Health Service Act sec. 4928 U.S.C. sec 289a-2. The policy requires that women and members of minority groups and their subpopulations must be included in all NIH-conducted or supported clinical research projects involving human subjects, unless a clear and compelling rationale and justification establishes to the satisfaction of the relevant NIH Institute/Center (IC) 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 IC Director, based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research.

All investigators proposing research involving human subjects should read the UPDATED "NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research, Amended November 2017," 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

Information Required for ALL Clinical Research Proposals

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

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

The proposal must include the following information:

- A description of the subject selection criteria
- The proposed dates of enrollment (beginning and end)
- A description of the proposed outreach programs for recruiting women and minorities as subjects
- A compelling rationale for proposed exclusion of any sex/gender or racial/ethnic group
- The proposed sample composition using the Inclusion Enrollment Report.

NOTE : *For all proposals, complete the Inclusion Enrollment Report, and use ethnic and racial categories, in accordance with the Office of Management and Budget (OMB) Directive No. 15, which may be found at* :http://whitehouse.gov/omb/fedreg_notice_15.

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

In addition to the above requirements, solicitations for **NIH defined Phase III clinical trials** require that: a) all proposals and/or protocols provide a description of plans to conduct analyses, as appropriate, to detect significant differences in intervention effect by sex/gender, racial/ethnic groups, and relevant subpopulations, if applicable; and b) all contractors to report annually cumulative subject accrual, and progress in conducting analyses for sex/gender and race/ethnicity differences. See the NIH Guide for definitions of Significant Difference and NIH-Defined Phase III Clinical Trial:
http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm .

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

- Plans to conduct valid analysis to detect significant differences in intervention effect among sex/gender and/or racial/ethnic subgroups when prior studies strongly support these significant differences among subgroups,

  OR

- Plans to include and analyze sex/gender and/or racial/ethnic subgroups when prior studies strongly support no significant differences in intervention effect between subgroups,

OR

- Plans to conduct valid analyses of the intervention effect in sex/gender and/or racial/ethnic subgroups (without requiring high statistical power for each subgroup) when the prior studies neither support nor negate significant differences in intervention effect between subgroups.

If you are awarded a contract under this solicitation, you will use the **Cumulative Inclusion Enrollment Report** for reporting during the resultant contract.

Inclusion of Children in Research Involving Human Subjects

It is NIH policy that children (as defined in this solicitation) 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.

All offerors proposing research involving human subjects should read the "NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects" which was published in the NIH Guide for Grants and Contracts on March 6, 1998 and is available at the following URL address: https://grants.nih.gov/grants/guide/notice-files/not98-024.html . Offerors should also read the update to this Policy, changing the NIH definition of 'child,' which is available at the following URL address: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-010.html .

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

When children are included, the plan also must include a description of: (1) the expertise of the investigative team for dealing with children at the ages included; (2) the appropriateness of the available facilities to accommodate the children; and, (3) the inclusion of a sufficient number of children to contribute to a meaningful analysis relative to the purpose/objective of the solicitation.

Justifications for Exclusion of Children

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

- The objective of the solicitation is not relevant to children.
  - There are laws or regulations barring the inclusion of children in the research to be conducted under the solicitation.
  - The knowledge being sought in the research is already available for children or will be obtained from another ongoing study, and an additional study will be redundant. You should provide documentation of other studies justifying the exclusion.
  - A separate, age-specific study in children is warranted and preferable. Examples include:
    - The relative rarity of the condition in children, as compared with adults (in that extraordinary effort would be needed to include children); or
    - The number of children is limited because the majority are already accessed by a nationwide pediatric disease research network; or
    - Issues of study design preclude direct applicability of hypotheses and/or interventions to both adults and children (including different cognitive, developmental, or disease stages of different age-related metabolic processes); or
    - Insufficient data are available in adults to judge potential risk in children (in which case one of the research objectives could be to obtain sufficient adult data to make this judgment). While children usually should not be the initial group to be involved in research studies, in some instances, the nature and seriousness of the illness may warrant their participation earlier based on careful risk and benefit analysis; or

- Study designs aimed at collecting additional data on pre-enrolled adult study subjects (e.g., longitudinal follow-up studies that did not include data on children);
- Other special cases justified by the offeror and found acceptable to the review group and the Institute Director.

Definition of a Child

For the purpose of this solicitation, a child is defined as an individual under the age of 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 21) may differ in the age at which their own consent is required and sufficient to participate in research under State law.

8.12.6 Data and Safety Monitoring in Clinical Trials

A “Data and Safety Monitoring Plan” attachment is required for all NIH-defined Clinical Trials (- see the definition section of this solicitation for reference). For human subjects research that does not involve a clinical trial: Your study, although it is not a clinical trial, may have significant risks to participants, and it may be appropriate to include a data and safety monitoring plan. If you choose to include a data and safety monitoring plan, you may follow the content criteria listed below, as appropriate. This plan should be attached in Field “3.3 Data and Safety Monitoring Plan,” on the **Appendix H.3 Study Record Form**, which is an attachment to the **Appendix H.2 Human Subjects and Clinical Trials Information Form**.

All offerors are directed to the full text of the NIH Policies regarding Data and Safety Monitoring and Reporting of Adverse Events that are found in the NIH Guide for Grants and Contracts Announcements at the following web sites:

http://grants.nih.gov/grants/guide/notice-files/not98-084.html
http://grants.nih.gov/grants/guide/notice-files/not99-107.html
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html

All offerors receiving an award under this solicitation must comply with the NIH Policy cited in these NIH Announcements and any other data and safety monitoring requirements found elsewhere in this solicitation.

The following is a brief summary of the Data and Safety Monitoring and Adverse Event Reporting Requirements.

Data and Safety Monitoring is required for every clinical trial. Monitoring must be performed on a regular basis and the conclusions of the monitoring reported to the Contracting Officer's Representative (COR).

The type of data and safety monitoring required will vary based on the type of clinical trial and the potential risks, complexity and nature of the trial. A plan for data and safety monitoring is required for all clinical trials. A general description of a monitoring plan establishes the overall framework for data and safety monitoring. It should describe the entity that will be responsible for the monitoring, and the policies and procedures for adverse event reporting. Phase III clinical trials generally require the establishment of a Data Safety Monitoring Board (DSMB). The establishment of a DSMB is optional for Phase I and Phase II clinical trials.

The DSMB/Plan is established at the time the protocol is developed and must be approved by both the Institutional Review Board (IRB) and the Government and in place before the trial begins. If the protocol will be developed under the contract awarded from this solicitation, a general description of the data and safety monitoring plan must be submitted as part of the proposal and will be reviewed by the scientific review group (Technical Evaluation Panel, (TEP)) convened to evaluate the proposal. If the protocol is developed and is included as part of the submitted proposal, a complete and specific data and safety monitoring plan must be submitted as part of the proposal.

For any proposed clinical trial, NIH requires a data and safety monitoring plan (DSMP) that is commensurate with the risks of the trial, its size, and its complexity. Provide a description of the DSMP, 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, hospitalizations, and life-threatening events and Unanticipated Problems (UPs), will be managed and reported, as required, to the IRB, the person or group responsible for monitoring, the awarding IC, the NIH Office of Biotechnology Activities, and the Food and Drug

Administration.

- The individual(s) or group that will be responsible for trial monitoring and advising the appointing entity. Because the DSMP 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:
    - PD/PI: While the PD/PI must ensure that the trial is conducted according to the approved protocol, in some cases (e.g., low risk trials, not blinded), it may be acceptable for the PD/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 experts.
    - Data and Safety Monitoring Board (DSMB): a formal independent board of experts including investigators and biostatisticians. NIH requires the establishment of DSMBs for multi-site clinical trials involving interventions that entail potential risk to the participants, and generally, for all Phase III clinical trials, although Phase I and Phase II clinical trials may also need DSMBs. If a DSMB is used, please describe the general composition of the Board without naming specific individuals.

The NIH Policy for Data and Safety Monitoring at: http://grants.nih.gov/grants/guide/notice-files/not98-084.html describes examples of monitoring activities to be considered.

Organizations with a large number of clinical trials may develop standard monitoring plans for Phase I and Phase II trials. In this case, such organizations may include the IRB-approved monitoring plan as part of the proposal submission.

8.12.7 Plan for the Dissemination of Information of NIH-Funded Clinical Trial (ClinicalTrials.gov)

The Food and Drug Administration Amendments Act of 2007 (FDAAA) at: http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110.pdf ,Title VIII, expands the National Institutes of Health's (NIH's) clinical trials registry and results database known as ClinicalTrials.gov (http://www.clinicaltrials.gov/) and imposes new requirements that apply to certain applicable clinical trials, including those supported in whole or in part by NIH funds. FDAAA requires:

a. The registration of certain "applicable clinical trials" in ClinicalTrials.gov no later than 21 days after the first subject is enrolled; and

b. 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.

The "responsible party" is the entity responsible for registering and reporting trial results in ClinicalTrials.gov.

- Where the Contractor is the IND/IDE holder, the Contractor will be considered the Sponsor, therefore the "Responsible Party."
- Where there is no IND/IDE holder or where the Government is the IND/IDE holder, the Government will generally be considered the "Sponsor" and may designate the contractor's Principal Investigator (PI) as the "Responsible Party."
- For Multi-Center trials where there is no IND/IDE holder or where the Government is the IND/IDE holder, the "Responsible Party" will be designated at one site (generally the lead clinical site) and all other sites will be responsible for providing necessary data to the "Responsible Party" for reporting in the database.

Additional information is available at http://prsinfo.clinicaltrials.gov

When the proposal includes a clinical trial, offerors are required to submit a plan for the dissemination of NIH-funded clinical trial information in the proposal. This plan should be attached in Field "4.7 Dissemination Plan," on the **Appendix H.3 Study Record Form**, which is an attachment to the **Appendix H.2 Human Subjects and Clinical Trials Information Form**.

At a minimum, the plan must contain sufficient information to assure that:

1. The Contractor shall register and submit results information to ClinicalTrials.gov as outlined in the NIH policy on the Dissemination of NIH-Funded Clinical Trial Information and according to the specific timelines stated in the policy (this can be a brief statement);
2. Informed consent documents for the clinical trial(s) shall include a specific statement relating to posting of clinical trial information at ClinicalTrials.gov; and

3. The Contractor has an internal policy in place to ensure that clinical trials registration and results reporting occur in compliance with NIH policy on the Dissemination of NIH-Funded Clinical Trial Information requirements.

If the Offerors plan does not meet these minimum standards, or is otherwise not acceptable as determined by the Contracting Officer, the contract award cannot be issued until an approved plan has been submitted

8.12.8 Plan for Single Institutional Review Board (sIRB)

Offerors are required to submit a plan for Single Institutional Review Board (sIRB) for each protocol involving more than one domestic site. This plan should be attached in Field 3.2 on the **Appendix H.3 Study Record Form**, which is an attachment to the **Appendix H.2 Human Subjects and Clinical Trials Information Form**.

At a minimum, the plan shall set establish the following:

1. Participating sites will adhere to the sIRB Policy;
2. Sites and the sIRB will adhere to the communication plan described in the authorization/reliance agreement; and
3. If, in the case of a restricted award, a sIRB has not yet been identified, include a statement that the offeror will follow the sIRB Policy and communicate plans to select a registered IRB of record. This information must be provided to the Contracting Officer prior to initiating recruitment for a multi-site study.

The Offeror may request direct cost funding for the additional costs associated with the establishment and review of the multi-site study by the sIRB, with appropriate justification; all such costs must be reasonable and consistent with cost principles, in accordance with the Federal Acquisition Regulation (FAR) 31.202, Direct Costs and FAR 31.203, Indirect Costs.

EXCEPTIONS TO THE SINGLE INSTITUTIONAL REVIEW BOARD (sIRB) POLICY

Offerors may request an exception to the sIRB policy for one or more studies.

1. For sites for which Federal, state, or tribal laws, regulations or policies require local IRB review (policy-based exceptions):
    a. The Offeror shall identify any site that meets the requirements for the Single IRB policy but is required to have local IRB review because of a federal, state, or tribal law, regulation or policy; and
    b. The Offeror shall provide specific citation for policy-based exceptions.
2. Time Limited Exception: ancillary studies to ongoing research without a sIRB- new multi-site non-exempt human subjects' ancillary studies, that would otherwise be expected to comply with the sIRB policy, but are associated with the ongoing multi-site parent studies, will not be required to use the sIRB of record until the parent study is expected to comply with the sIRB policy. The Offeror shall provide the parent contract number to request an exception.
3. *Other exceptions* when Offeror believes that one or more research sites should be exempt from use of the single IRB of record to conduct local IRB review based on compelling justification:
    a. Offerors should request an exception in the sIRB plan attachment within the contract proposal, using Field 3.2 within **Appendix H.3 – Study Record**. Appendix H.3. – Study Record may be found in Section 13 – Appendices, which is the last page of this solicitation.
    b. Offerors must include the name of the site(s) for which an IRB other than the sIRB of record is proposed to review the study for the sites(s).
    c. Offerors must substantiate their exception request with sufficient information that demonstrates a compelling justification for *other exceptions* to the sIRB policy. The rationale should include why the sIRB of record cannot serve as the reviewing IRB for the site(s), and why the local IRB is uniquely qualified to be the reviewing IRB for the specific site(s).
        - For instance, the justification may consider ethical or human subjects protections issues, population needs, or other compelling reasons that IRB review for the site(s) cannot be provided by the single IRB of record.
    d. Note that the proposed budget in the proposal must reflect all necessary sIRB costs without an approved *other exception*. The Offerors should not assume that an *other exception* will be granted when considering what sIRB costs to include in the budget.

Post-Award Exception Requests

For any post-award changes that necessitate an exception request, such as the addition of a new domestic site that may be unable to use the sIRB Contractor shall contact their Contracting Officer (CO). For policy-based exceptions, the Contractor shall provide the

appropriate citation to verify the requirement for local IRB review for the newly added site(s) to the CO. For *other exceptions* , the Contractor shall provide compelling justification to the CO to be reviewed by the NIH Exceptions Review Committee (ERC) (see **Steps to Request an *Other Exception* to the sIRB Policy** above). For time limited exceptions, Contractor shall provide the parent contract number to the CO.

Notice of Approval or Disapproval of *Other Exception* Requests

The sIRB exception requests will be considered after peer review for proposals in the competitive range. All requests for *other exceptions* must be reviewed by the NIH ERC. The decision of NIH ERC is final. Offerors will be notified of the final decision by their CO prior to award. Approved exceptions will be incorporated as a term and condition in the contract award. Also, any exception requests submitted after award must be submitted to the CO and reviewed by the NIH ERC. No further revisions of the exception request will be accepted.

The award budget may need to be adjusted if an exception is granted.

8.12.9 Research Involving Recombinant or Synthetic Nucleic Acid Molecules (Including Human Gene Transfer Research)

All research projects (both NIH-funded and non-NIH-funded) involving recombinant or synthetic nucleic acid molecules that are conducted at or sponsored by an entity in the U.S. that receives any support for recombinant or synthetic nucleic acid research from NIH shall be conducted in accordance with the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines) (see http://osp.od.nih.gov/biotechnology/nih-guidelines). All NIH-funded projects conducted abroad that involve research with recombinant or synthetic nucleic acid molecules must also comply with the NIH Guidelines. In addition to biosafety and containment requirements, the *NIH Guidelines* 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 *NIH Guidelines*).

Prior to beginning any clinical trial involving the transfer of recombinant or synthetic nucleic acid molecules into humans, the trial must be registered with the NIH Office of Science Policy (OSP) and, if applicable, reviewed by the NIH Recombinant DNA Advisory Committee (RAC). If this contract involves a human gene transfer trial raising unique and/or novel issues, the trial may be discussed by the RAC in a public forum (see Appendix M-I-B of the *NIH Guidelines* for the specific criteria for the selection of protocols for RAC review and discussion). Approval of an Institutional Biosafety Committee (IBC) and the Institutional Review Board (IRB) are necessary before the Contracting Officer's Representative (COR) and Contracting Officer (CO) may approve the protocol prior to the start of the research. IBC approval may not occur until the protocol registration process with NIH is complete. If the trial is reviewed by the RAC, IBC approval may not occur before the RAC has concluded its review of the protocol and the protocol registration process with NIH is complete.

For human gene transfer research, Appendix M-I-C-4 of the NIH Guidelines requires any serious adverse events (SAEs) that are both unexpected and possibly associated with the human gene transfer product to be reported to NIH OSP and an 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 CO. SAE reports must also be submitted within their mandated time frames to the IRB, Food and Drug Administration (FDA), and, if applicable, the Health and Human Services (HHS) Office for Human Research Protections (OHRP). In addition, annual reports must be submitted to NIH OSP covering certain information about human gene transfer protocols. Further information about the content of these reports can be found in Appendix M-I-C-3 of the *NIH Guidelines* . Additional information on the requirements that pertain to human gene transfer can be found in a series of Frequently Asked Questions at: http://osp.od.nih.gov/office-biotechnology-activities/biosafety/institutional-biosafety-committees/faq .

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 research or a requirement for the CO to approve any or all recombinant or synthetic nucleic acid molecule projects under this contract. This includes the requirement for the institution to have an IBC registered with NIH OSP that complies with the requirements of the *NIH Guidelines* . Further information about compliance with the *NIH Guidelines* can be found on the NIH OSP web site: at: https://osp.od.nih.gov/biosafety-biosecurity-and-emerging-biotechnology/

8.12.10 Human Stem Cell Research

On March 9, 2009, the President issued Executive Order (EO) 13505: Removing Barriers to Responsible Scientific Research Involving Human Stem Cells. The NIH has published Guidelines on Human Stem Cell Research at: http://stemcells.nih.gov/policy/pages/2009guidelines.aspx. The Guidelines implement EO 13505 with regard to extramural NIH-funded human stem cell research, establish policy and procedure under which the NIH will fund such research, and help ensure that NIH-funded research in this area is ethically responsible, scientifically worthy, and conducted in accordance with applicable law.

To facilitate research using human embryonic stem cells, the NIH has established a Human Embryonic Stem Cell Registry ("the NIH Registry") that lists the human embryonic stem cells that are currently eligible for use in NIH-funded research. This registry is available at: http://grants.nih.gov/stem_cells/registry/current.htm. Proposed human embryonic stem cell line(s) must be on the NIH Registry at the time of proposal submission. Any possible changes to the proposed cell line must be discussed in the proposal. Offerors wishing to have Human Embryonic Stem Cell Lines added to the NIH Human Embryonic Stem Cell Registry must submit the request on Form NIH 2890 through the following website: http://hescregapp.od.nih.gov/NIH_Form_2890_Login.htm.

8.13 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** – SBIR offerors who propose a G&A/IDC rate of 40 percent of total direct costs or less will not be required to negotiate Final Indirect Rates with the NIH Division of Financial Advisory Services (DFAS), or other cognizant auditing agency. However, awarding Contracting Officers may require offerors to document how they calculated their IDC rate(s) in order to determine that these costs are fair and reasonable. Furthermore, the Division of Financial Advisory Services (DFAS) will retain the authority to require well-documented proposals for G&A/IDC rates on an *ad hoc* basis. If the SBC has a currently effective negotiated indirect cost rate(s) with a Federal agency, such rate(s) shall be used when calculating proposed G&A/IDC costs for an NIH proposal. (However, the rate(s) must be adjusted for IR&D expenses, which are not allowable under HHS awards.)

  SBCs are reminded that only actual G&A/IDC costs may be charged to projects. If awarded at a rate of 40 percent or less of total direct costs, the rate used to charge actual G&A/ID costs to projects cannot exceed the awarded rate unless the SBC negotiates an indirect cost rate(s) with DFAS.
- Offerors submitting proposals may include the amount of up to $6,500 per year for a Phase I and up to $50,000 per Phase II project (across all years) for technical assistance as discussed and outlined in Section 4.16 of the solicitation. Include a detailed description of the technical or business assistance that your vendor/s will provide, including the name of the vendor/s and the expected benefits and results of the technical or business assistance provided. A letter of support from the vendor describing their qualifications and services to be provided is recommended.
- **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.

8.14 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.

- Each proposal will be reviewed for compliance with the section 8 proposal requirements. A Phase I proposal submission must contain the documents required by Section 8.3., including a Technical Proposal that addresses all content set forth in Section 8.8(A). A Phase II proposal submission must contain the documents required by Section 8.4., including a Technical Proposal that addresses all content set forth in Section 8.8(B). In addition, each proposal will also be checked by NIH/CDC staff to ensure that the proposed research falls within the scope of the technical goals set forth in the Topic under which the proposal is submitted.

  Any proposal submission that fails to meet these material terms and conditions of the solicitation will be evaluated as noncompliant and will not be advanced to peer review.

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 Center for Advancing Translational Sciences (NCATS)	1-4	Scientific and Technical Merit Review: February-April 2022 Anticipated Award Date: July-September 2022
National Institutes of Health (NIH) National Cancer Institute (NCI)	42-70	Scientific and Technical Merit Review: March-May 2022 Anticipated Award Date: August-September 2022
National Institutes of Health (NIH) National Institute on Aging (NIA)	4-9	Scientific and Technical Merit Review: January-February 2022 Anticipated Award Date: August-September 2022
National Institutes of Health (NIH) National Institute of Allergy and Infectious Diseases (NIAID)	19-41	Scientific and Technical Merit Review: March 2022 Anticipated Award Date: August 2022
Center for Disease Control and Prevention (CDC) National Center on Birth Defects and Developmental Disabilities (NCBDDD)	1	Scientific and Technical Merit Review: March 2022 Anticipated Award Date: August 2022
Centers for Disease Control and Prevention (CDC) National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP)	1	Scientific and Technical Merit Review: March 2022 Anticipated Award Date: August 2022
Centers for Disease Control and Prevention (CDC) National Center for Emerging Zoonotic and Infectious Diseases (NCEZID)	2-4	Scientific and Technical Merit Review: March 2022 Anticipated Award Date: August 2022
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: March 2022 Anticipated Award Date: August 2022
Center for Disease Control and Prevention (CDC) National Center for Immunization and Respiratory Diseases (NCIRD)	1	Scientific and Technical Merit Review: March 2022 Anticipated Award Date: August 2022

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 CENTER FOR ADVANCING TRANSLATIONAL SCIENCES (NCATS)

Rieka Plugge
Contracting Officer
NIDA Office of Acquisition
Phone: (301) 827-7515
Email: rieka.plugge@nih.gov

NATIONAL CANCER INSTITUTE (NCI)

Cherie Wells
Contracts Analyst (Contractor)
Office of Acquisitions, OM, NCI
Phone: (240) 276-5405
E-mail: ncioasbir@mail.nih.gov

NATIONAL INSTITUTE ON AGING (NIA)

Karen Mahon
Contracting
Officer
Office of Acquisitions, NIDA/NIA
Phone: (301) 435-7479
E-mail: karen.mahon@nih.gov

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES (NIAID)

Charles H. Jackson, Jr.
Contracting Officer
Office of Acquisitions, DEA, NIAID
Phone: (240) 669-5175
Email: Charles.Jackson@nih.gov

CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

NATIONAL CENTER ON BIRTH DEFECTS AND DEVELOPMENTAL DISABILITIES (NCBDDD)

Sherrie Randall
Contracting Officer
Centers for Disease Control and Prevention Office of Financial Resources
Phone: (770) 488-2866
E-mail: IOM2@cdc.gov

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

Jerry Outley
Contracting Officer
Centers for Disease Control and Prevention Office of Financial Resources
Phone: (770) 488-2831
E-mail: JMO4@cdc.gov

NATIONAL CENTER FOR EMERGING ZOONOTIC AND INFECTIOUS DISEASES (NCEZID)

Kristopher Lemaster
Contracting Officer
Centers for Disease Control and Prevention Office of Financial Resources
Phone: (770) 488-2995
E-mail: ENE3@cdc.gov

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

Sherrie Randall
Contracting Officer
Centers for Disease Control and Prevention Office of Financial Resources
Phone: (770) 488-2866
E-mail: IOM2@cdc.gov

NATIONAL CENTER FOR IMMUNIZATION AND RESPIRATORY DISEASES (NCIRD)

Christina McMichael
Contracting Officer
Centers for Disease Control and Prevention Office of Financial Resources
Phone: (770) 488-2697
E-mail: WPN6@cdc.gov

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://nlm.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

NATIONAL INSTITUTES OF HEALTH

NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES (NCATS)

The NCATS mission is to catalyze the generation of innovative methods and technologies that will enhance the development, testing and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions. The SBIR and STTR programs support NCATS' mission to transform the translational science process so that new treatments and cures for disease can be delivered to patients more efficiently. These programs serve as an engine of innovation, offering grants, contracts and technical assistance to small businesses and research organizations focused on advancing translational research and technologies that will improve disease prevention, detection and treatment.

For more information on the NCATS SBIR/STTR programs, visit our website at: https://ncats.nih.gov/smallbusiness/about

Limited Amount of Award

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

NCATS Topics

This solicitation invites proposals in the following areas:

NIH/NCATS 022 - Technological Development and Validation of Remote Measures for Use in Clinical Trials in Individuals with Rare Diseases

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

Number of anticipated awards: 1 to 4

Budget (total costs, per award): Phase I: $325,000 for 9 months; Phase II: $2,000,000 for 2 years

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

Summary: The objective of this contract is to develop and validate digital health technologies for data capture that can be used to assess individuals with rare diseases in remote settings in a manner that is suitably sensitive and specific for use in clinical trials. Technologies should be reliable, secure, and easy to use to monitor study participants remotely.

Conducting clinical trials for both rare and common diseases involve many challenges, some of the most frequent of which include the identification, enrollment, and retention of study participants. Most clinical research trials, regardless of disease area, are conducted at large academic medical centers, and patients who do not live near the research centers are often unable to participate due to health challenges, financial challenges, and the difficulty committing to long-term trials that requires regular travel. It is also difficult to recruit a diverse cohort of patients for study, resulting in many study populations being homogenous and not broadly representative of the US population. Additionally, because the individual rare diseases each have only a few patients with the condition, participation from patients at multiple national and international sites will often be needed, and rare disease research community often faces the added challenge of meeting regulatory requirements for more than one international regulatory agency. Virtual, decentralized, remote or site agnostic trials may be used to include individuals in studies that previously would have been excluded.

In addition to these commonly encountered clinical trial challenges, rare diseases present additional complexities beyond those seen with many common conditions. For example, most rare diseases do not have clinical trial precedent and there are typically no validated outcome measures to assess treatment effects. Rare disease researchers often are, therefore, left to develop their own measures that have not been previously used or validated or they must modify existing measures developed for other disorders that may not provide the required sensitivity or specificity needed to accurately assess targeted outcomes. Data that is collected will also need to be seamlessly captured and integrated from multiple sources and be of sufficient quality to meet regulatory requirements.

Mobile technology offers the opportunity for remote participation and monitoring of study subjects, as well as remote and reliable data capture. This includes technologies that have not yet been widely incorporated into regulated clinical trials, such as wearables, ingestibles, implantables, and portables. Patient-reported outcomes (PROs), Observer-reported outcomes (ObsROs), Performance outcomes (PerfOs), Clinician-Reported outcomes (ClinROs) can also be collected using innovative technology. Development and use of these technologies have the potential to allow for broader and more diverse study populations for participation in clinical trials for rare diseases while simultaneously improving the quality of data capture and efficiency of the trials.

The Clinical Trials Transformation Initiative (CTTI), (funded in part, by the Food and Drug Administration through grant R18FD005292 and cooperative agreement U19FD003800 - https://www.ctti-clinicaltrials.org/projects/digital-health-technologies) has developed recommendations for the use of mobile technologies for data capture for use in clinical trials, and comprehensive guidelines for reducing barriers to participation. These recommendations, provided only for informational purposes, include mobile technology selection, data collection, analysis, and interpretation, data management, protocol design and execution, and FDA submission and inspection. In addition, CTTI recommendations state that as technologies are developed, it will be important to consider that end users will still need to 1) adhere to scientific principles currently in use across the clinical trials enterprise; 2) adhere to data quality principles, which are the same for clinical trials using mobile technologies for data capture and those using data collection approaches in the clinic; and 3) study participant engagement is critical in the design of trials that use mobile technologies for data capture.

Goals and Specific Objectives:

Technology developers, clinicians, researchers, and patients/patient groups will work collaboratively to develop validated digital health technologies specifically for outcomes data capture for clinical trials for rare diseases, and not for the purposes of recruitment, retention, or as the intervention itself. Digital health technologies may include clinical outcome assessments including new or modified: Patient-reported outcomes (PROs), Observer-reported outcomes (ObsROs), Performance outcomes (PerfOs), Clinician-Reported outcomes (ClinROs) and devices for gathering physiological data. The technology must be reliable, secure, and easy to use to monitor study participants remotely, either in the home or while participating in activities of daily living. The technology should also be appropriate for use in three or more different rare diseases, (e.g., tool to assess movement in neurodegenerative diseases, PRO for reporting level of pain).

Phase I Activities and Expected Deliverables:

Develop prototype digital health technologies specifically for outcomes data capture for clinical trials

1. Intended population
    a. Describe intended population(s)
        i. Rare diseases
        ii. Age group
2. Measurement Property
    a. Target measure – describe purpose of measure
        i. Reliability – describe test re-test reliability
        ii. Validity – describe content and construct validity
        iii. Sensitivity – describe the ability to detect change
        iv. Specificity – describe the ability to measure target
3. Technical Performance – For the digital health technology prototype describe and demonstrate:
    a. Measurement Performance across multiple environments
        i. Accuracy – The digital health technology must have agreement between the measurement and a known standard in the field
        ii. Precision – Describe and demonstrate agreement across multiple measurements for the device such that it is evident that variability in assessment is due to the measuring technology
        iii. Calibration-Describe the process of calibration.
        iv. Sampling Frequency- Describe the sampling process
        v. Resolution- Describe the amount of measurable change
        vi. Reliability -Describe the ability to yield consistent, reproducible estimates of true treatment effects
        vii. Data Processing – Describe the operations performed on a given set of data to extract the required information in an appropriate form
    b. Metadata- Sufficient and appropriate metadata is required to provide context for the data captured by mobile technologies, allow it to be readily interpreted, and determine its clinical meaningfulness
    c. Mobile Technology Communication and Data Transfer

        i. App Pairing – the connectivity and quality
        ii. Transfer to Data Gathering Platform – the transfer of individual participant data to a central server
4. Data Management Specifications
    a. Must be 21 CFR Part 11 Compliant
    b. Data Access
        i. Mobile Technology Manufacturer Access to Study Data – describe and demonstrate the process. Address security and consent issues
        ii. Sponsor Access to Study Data – describe and demonstrate what data will be provided to the end user (e.g., raw data, processed data, algorithms) and the data format.
        iii. Third Party Access to Study Data – describe procedures related to third party access to data (e.g., deidentified data from all users)
5. Safety Specifications
    a. Study Participant
    b. Data Security and Privacy
        i. Cybersecurity – describe and demonstrate steps taken to avert potential cybersecurity vulnerabilities
        ii. Privacy – describe and demonstrate policies, procedures, and technical approaches implemented to ensure Health Insurance Portability and Accountability Act (HIPAA) compliance
6. Human Factor Specifications
    a. Acceptability
    b. Tolerability
    c. Useability
    d. Appropriate for age of participant
7. Operational Specifications
    a. Firmware
    b. Failure Rate
    c. Battery life
8. Non-Performance specifications
    a. Cost
    b. Customer Service

- Provide cost estimates to develop a proof-of-concept digital health tool capable of meeting the specifications listed above.
- Present phase I findings and demonstrate the functional prototype system to an NCATS contracts and scientific team via webinar.
- Provide NCATS with all data and materials resulting from Phase I Activities and Deliverables

Phase II Activities and Expected Deliverables:

- Build a prototype that meets the Phase I specifications.
- Validate assessment method and technology in selected rare disease populations.
- Provide a test plan to evaluates all components of the digital health technology
- Demonstrate that the technology is scalable to potentially hundreds of pieces of instrumentation in a distributed fashion.
- Present Phase II findings and demonstrate the software system to an NCATS contracts and scientific team via webinar.
- Develop systems documentation where applicable to support the software and bioinformatic methods.
- In the first year of the contract, provide the program and contract officers with a letter(s) of commercial interest.
- In the second year of the contract, provide the program and contract officers with a letter(s) of commercial commitment.
- Provide NCATS with all data and materials resulting from Phase II Activities and Deliverables.

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.

Each proposal will be reviewed for compliance with the section 8 proposal requirements. If a proposal is submitted as a Phase I proposal, the submission must contain the documents required by section 8.3, including a Technical Proposal that addresses all content set forth in Section 8.8(A). If the proposal is submitted as a Phase II proposal, the submission must contain the documents required by section 8.4, including a Technical Proposal that addresses all content set forth in Section 8.8(B). In addition, each proposal will also be checked by NCI staff to ensure that the proposed research falls within the scope of the technical goals set forth in the Topic under which the proposal is submitted.

Any proposal submission that fails to meet these material terms and conditions of the solicitation will be evaluated as noncompliant and will not be advanced to peer review.

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 $4M 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-21-036.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. Offerors may propose clinical studies, as appropriate.

NIH/NCI 430 – DEVELOPMENT OF SENOTHERAPEUTIC AGENTS FOR CANCER TREATMENT

Fast-Track proposals **will be** accepted.

Direct-to-Phase II proposals **will be** accepted.

Number of anticipated awards: 3-5

Budget (total costs, per award):

Phase I: up to $400,000 for up to 12 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

Age is a well-recognized risk factor for cancer development; and older patients pose a growing healthcare challenge since they are prone to developing more aggressive and therapy-resistant tumors. A key biological contributor to aging and age-related diseases is cellular senescence and its associated secretory phenotype (SASP). Senescence is a complex cellular state characterized by stress-induced replicative arrest, heterochromatization and transcriptional reprogramming. While senescence and the SASP play important short-term beneficial roles in orchestrating tumor suppression by blocking the proliferation of damaged cells, it also contributes to long-term detrimental effects if not readily removed. The oncogenic and tumor aggressive effects of senescence are driven by the SASP-associated anti-apoptotic, pro-inflammatory and invasive cytokines, growth factors and matrix-degrading enzymes.

Aging tissues accumulate senescent cells; and the *in vivo* selective elimination of age-dependent/spontaneously emerging senescent cells is documented to delay tumor formation and deterioration of cardiac, renal and adipose tissue function. Furthermore, senescence is induced by a range of cancer treatments, including radiation, chemotherapy, and several targeted therapies. Therapy-induced senescence (TIS) and SASP-induced field cancerization may in turn promote invasive and metastatic phenotypes. In contrast, elimination of TIS cells is reported to reduce many side effects of cancer drugs in pre-clinical models, including bone marrow suppression, cardiac dysfunction, fatigue, and also reduce cancer recurrence.

A number of research groups and companies are developing senotherapeutics, agents that exploit senescent cells for therapeutic benefit. Senotherapeutics include senolytics, pharmacologic agents that eliminate senescent cells, and senomorphics, agents that suppress senescent phenotype without cell-killing. A variety of agents have been reported to have senolytic activity and have demonstrated promising results in animal models. Despite the progress, senotherapeutic agents are not represented in the NCI's SBIR portfolio and/or extensively tested as anti-cancer agents. Thus, the goal of this contract topic is to support small businesses developing senotherapeutics and catalyze the development of this class of drugs to improve outcomes for cancer patients

Project Goals

The purpose of this contract topic is to support the basic and pre-clinical development of senotherapeutic agents for use in research, neoadjuvant, adjuvant, or combination cancer therapy. Projects supported under this contract topic should extend the pre-clinical development of senotherapeutics as anticancer agent(s). Projects intending to enhance the efficacy of cancer therapies (including radiotherapy) or reduce the toxicities or the severity and duration of adverse effects by the use of senotherapeutics will also be supported. Such agents may include radiation-effect modulators and mitigators that reduce senescence associated side-effects. Responsive projects should have hit or lead compounds in hand, and offerors should use clearly defined parameters and accepted markers of senescence to define the population of senescent cells and senescent phenotypes being targeted by their agent(s).

Phase II projects should focus on IND-enabling pre-clinical studies. The scope of work may include further work on structure activity relationships (SAR); formulation; animal efficacy testing; pharmacokinetic, pharmacodynamic, and toxicological studies.

Phase I Activities and Deliverables:

Phase I projects should focus on the optimization of the senotherapeutic agent(s), or combinations, and demonstrate proof-of-concept by showing senolytic or senomorphic activity, and benefits in terms of efficacy and/or reduction of side effects when combined with appropriate cancer treatments (e.g. chemotherapy or radiotherapy) in human cancer-relevant animal models. Offerors should provide a justification and rationale for their choice of animal model(s) for the proof-of concept studies. The scope of work proposed may include structure activity relationships (SAR); medicinal chemistry for small molecules, antibody, and protein engineering for biologics; formulation. At the end of Phase I, in vivo efficacy should be demonstrated in an appropriate animal model.

- Demonstrate *in vitro* efficacy for the agent(s) in human cancer-appropriate models. Appropriate endpoints

include demonstration of enhanced anticancer activity in combination with other therapeutic approaches (e.g. chemotherapy or radiotherapy), or the reduction of cancer therapy side-effects.
- Conduct structure-activity relationship (SAR) studies, medicinal chemistry, and/or lead biologic optimization (as appropriate).
- Optimize formulation of senotherapeutic agent(s) (as appropriate).
- Perform animal efficacy studies in an appropriate and well-justified animal model of human cancer, for TIS, or aged mouse models that have accumulated senescent cells through aging and increased risk for cancer, and conduct experiments to determine whether senotherapeutic agent(s) confer benefits with respect to reduced side effects and/or cancer therapy efficacy.

Phase II Activities and Deliverables:

Phase II projects should focus on IND-enabling pre-clinical studies. The scope of work may include further work on structure activity relationships (SAR); formulation; animal efficacy testing; pharmacokinetic, pharmacodynamic, and toxicological studies.

- 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.
- Expand upon initial animal efficacy studies in an appropriate model for cancer therapy induced senescence and conduct experiments to determine whether senolytic agent(s) confer benefits with respect to mitigation of adverse side effects to normal tissues and/or enhanced cancer therapy efficacy.
- Perform other IND-enabling studies as appropriate for the agent(s) under development.

NIH/NCI 431 - CANCER TREATMENT TECHNOLOGIES FOR LOW-RESOURCE SETTINGS

Fast-Track Proposal **will be** accepted

Direct-to-Phase II proposal **will be** accepted

Number of Anticipated Awards: 3-5

Budget (total costs, per award):

Phase I: up to $400,000 for 12 months

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

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

Summary

Cancer is a leading cause of premature death in low-resource settings globally. Nearly two-thirds of the 7.6 million cancer deaths worldwide occur in low- and middle-income countries (LMICs). Gaps in access to cancer treatment present significant challenges in many global health settings, especially in rural areas with limited infrastructure, where most of the LMIC population lives.

Most of current cancer treatment technologies are not affordable in global low resource settings, and there is a need to develop cost-effective cancer treatment technologies. In addition, although treatment approaches exist in the US for most cancers, many examples of disparities in cancer outcomes exist for certain underserved populations, in both rural and urban settings. There are many factors thought to contribute to these disparate outcomes. We believe that novel treatment products that are affordable can improve cancer outcomes in LMICs and in underserved US populations.

This solicitation will provide funding opportunities for small business concerns (SBCs) to develop cost-effective and affordable cancer treatment technologies that target low-resource settings, both internationally and within the US. It will allow applications to focus on any specific cancer type, however four cancer types (histologies) are highlighted that are of particular interest because they are highly amenable to cancer treatment in low-resource settings. The four cancer types of interest are: cancers of the cervix, colon/rectum, esophagus, and oral cavity. These four cancer types are given a high priority because the introduction of low-cost technologies for cancer treatment is likely to have an especially strong impact to reduce the burden of these cancers in low-resource settings.

Project Goals

The goal of this solicitation is to encourages applications from SBCs to develop or adapt, apply, and validate existing or emerging technologies into low-resource setting-appropriate technologies for cancer treatment.

Projects proposed for this contract topic will require multidisciplinary efforts to succeed, and, therefore, all applicant teams must include expertise in oncology, engineering, global health, and healthcare delivery in low-resource settings. Products addressing cancers of the cervix, colon/rectum, esophagus, and oral cavity are particularly encouraged for this solicitation. However, applications may address any cancer type and may benefit from LMICs collaborators. When appropriate, the proposed project may focus on a specific cancer type (histology).

Scientific/Technical Scope

Applications submitted to this solicitation must propose to develop or adapt technologies into user-friendly, affordable products for treatment of cancers in a low-resource setting.

The proposed project must focus on a specific cancer type (histology) and must show preliminary evidence to deliver medical utility for improved cancer outcomes. Products addressing cancers of the cervix, colon/rectum, esophagus, and oral cavity are particularly encouraged for this solicitation. However, applications may address any single cancer type.

The proposals must include quantitative milestones and a way to document the clinical utility of the propose product within the specific low-resource healthcare system of interest. The proposed product must comply with the regulations and international standards/guidelines applicable to investigational medical products in the low-resource setting where the product will be used (examples are World Health Organization guidelines and local regulations in LMICs, and Good Laboratory Practice, Good Manufacturing Practice, FDA Investigational New Drug, and Investigational Device Exemption for US settings). All applicants should demonstrate familiarity with applicable regulatory requirements, while Phase II applications require in the commercialization plan to include a detailed regulatory strategy matched to the low-resource setting of the study.

Beyond the scope of this solicitation, it is anticipated (and encouraged) that the outcomes of successful SBIR projects will help attract strategic partners or investors to support the ultimate commercialization of the technology as a publicly available product or service.

Projects funded by this solicitation may include patient enrollment in foreign countries. Per SBIR policy, when there are special circumstances justifying the conduct of the proposed research outside the US within time and budget constraints (e.g. a high disease incidence that makes clinical validation more feasible and timely), agencies may approve performance of a portion of the SBIR R&D work outside of the US. In this case, applicants are required to include a statement in their applications on why these resources are not available in the US.

Technology areas of interest include, but are not limited to, the following:

- Affordable guided surgery
- Affordable immunotherapy
- Affordable tumor-infiltrating lymphocytes or adaptive cell cancer therapies
- Affordable photodynamic therapies
- Affordable technology for eradication of H. pylori infection
- Affordable and preferably mobile devices for cancer treatment such as tools that may facilitate standard minimally invasive cancer treatment modalities tools for cryotherapy, thermal ablation, radiofrequency ablation, laser therapy, low-power-density sonication, high-intensity focused ultrasound (HIFU) therapy that are appropriate to low-resource settings
- Devices to aid in delivery of cancer drugs
- Mobile "pop-up" cancer therapy lab
- Oncolytic viruses' therapies
- Mobile radiotherapy treatments
- Portable radiation equipment for therapy and assisting surgery
- Tools for information and communications technologies to enhance cancer data collection, sharing, or analysis for treatment of cancer

  Technologies that are generally not appropriate for this solicitation include the following:
- Devices that require extensive user training before they can be used
- Drug screening
- Experimental therapeutics modalities which are not approved in the US
- Technologies not affordable or can't be maintained in low resource settings

Expected Activities and Deliverables

Quantitative milestones are required for both Phase I and Phase II projects, regardless of whether they are combined in a Fast-Track application.

It should be noted that LMICs have limited healthcare budgets and often struggle to prioritize healthcare needs. Because of

the variation in healthcare systems among LMICs and US regions with underserved populations, applicants will need to consult with local partners and organizations (beginning before they submit their application) to develop plans for product design and testing that are suitable to the low-resource setting, including strategies for regulatory approval and reimbursement (if applicable) for the proposed product.

Examples of suitable consulting organizations are local hospitals, medical schools, charities, community groups, non-governmental organizations, and local governmental offices with expertise in the setting. A portion of contract fund can go to these organizations, standard SBIR outsourcing requirements apply.

Phase I Activities and Deliverables

- Develop a working prototype based on adaptation of existing technology, or development of new technology.
- Demonstrate the feasibility of the technological innovation for use in a low-resource setting (real or modeled), using a small number of biological samples or animals, where appropriate.
- Deliver to NCI the SOPs of the system for cancer treatment
- Develop a regulatory strategy/plan and timeline for seeking approval from the appropriate regulatory agency to market the product
- Provide a brief business plan, which is likely to require partnering with healthcare staff local to the low-resource setting of interest

Phase II Activities and Deliverables

- Continue the consultation with local healthcare delivery experts in the low-resource setting of study
- Adapt the prototype device or treatment technology developed in Phase I to the targeted low-resource setting
- Validate the device or treatment technology in the low-resource setting with a statistically significant number of animal and/or human samples, live animals, or human subjects (if animal work or human subjects are involved) for the proposed product in the low-resource setting of interest. Animal studies are optional and may not be needed for many products supported by this solicitation. Animal studies need only be proposed for products where intermediate testing in animals is thought to be necessary for regulatory approval, or necessary before an IRB will approve a follow-on human study.
- To the extent possible, benchmark the product against existing commercial products used to address the same healthcare need in developed countries and include a description of competitive landscape in the commercialization plan.

- Engage with FDA or the local state regulatory agency to refine the regulatory strategy
- In the first year of the contract, provide the Program and Contract officers with a letter(s) of commercial interest.
- In the second year of the contract, provide the Program and Contract officers with a letter(s) of commercial commitment, where appropriate.
- By the end of Phase II, engage with the appropriate regulatory agency (e.g., US Food and Drug Administration, World Health Organization) to seek and/or obtain marketing approval for the product that was developed.

NIH/NCI 432 - SYNTHETIC BIOLOGY GENE CIRCUITS FOR CANCER THERAPY

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

Direct Phase II proposal **will be** accepted

Number of anticipated awards: 3 - 5

Budget (total costs, per award):

Phase I: up to $400,000 for up to 12 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

Gene therapy has come of age over the past few years. One of the most promising anticancer approaches in the clinic is chimeric antigen receptor (CAR)-T cell therapy. However, the pioneering first-generation products now on the market for B-cell malignancies, that target a single cancer antigen, have major limitations. First, all normal B cells expressing CD19 are eliminated by the therapy meaning that normal B cell functions are lost. Second, patients may lose expression of the CD19 CAR-T target antigen, rendering the malignant tumor cells invisible to the immune system tasked with its

destruction. Third, the therapies can trigger toxicities that are hard to predict and control, such as cytokine release syndrome. By combining computer science logic with biology, scientists have developed synthetic gene circuit technologies to redirect genetic events within cells to enable the resulting therapies to sense and adapt to their environment, or be controlled to avoid the safety and efficacy pitfalls that limited first-generation products. For example, new CAR-T approaches involve the delivery to T cells of gene circuits based on Boolean logic that can produce tumor cell killing only when two (or more) cancer antigens are expressed on cancer cells but not on normal cells, preserving normal B cell function.

These synthetic gene circuits are assembled of DNA encoding RNA or protein that enable individual cells to respond and interact with each other to perform a function at the desired locations (e.g. within the tumor vs. whole body), targets (e.g. cancer cells vs. healthy neighboring cells), amount (e.g. therapeutic vs. toxic doses) and duration (e.g. shut down before significant side effect occurs). Key components include sensors that detect user-defined inputs, processors that make decisions in response to the inputs, and actuators that produce the desired output activities (payloads).

Synthetic gene circuits can be delivered into cells *ex vivo* as in the CAR-T case, or *in vivo* using any well-established gene transfer vectors. These gene circuit therapies can be programmed to distinguish cancer cells from normal cells and to activate therapeutic payload expression from inside tumors.

Project Goals

The goal of the topic is to stimulate the development of gene circuit therapies for cancer. Engineering of immune cells and/or cancer cells is encouraged, while other cell types are not excluded. The recent pioneering work in synthetic biology has shown the potential of overcoming current challenges in gene therapy by creating sophisticated gene circuits to distinguish between malignant and healthy cells and to efficiently kill the former without harming the latter. Unlike conventional small molecules or biologics, including most of the current gene therapies, gene circuit therapies can potentially sense multiple disease signals, integrate this information to make a decision to trigger sophisticated or combinatory therapeutic mechanisms. Alternatively, gene circuit therapies can also be controlled exogenously, therefore allowing precise control over timing, dose and location of the therapies.

The activities that fall within the scope of this solicitation include the development of the gene circuits designed and created using synthetic biology approaches into cancer therapies through engineering immune cells *ex vivo*, or by delivering directly into cancer cells in patients using viral or non-viral gene transfer approaches/vectors, including engineering of bacteria to specifically target cancer. The approach should also allow precise control over timing, dose, and location of the therapies. Examples of appropriate activities include to demonstrate that the gene circuit can be expressed in cancer cells *in vitro* and *in vivo*, with increased efficacy and decreased toxicity compared to currently available similar therapies or to standard of care. A system that does not have the potential to allow precise control of the therapeutics over timing, dose, and location as needed will not be responsive. Methodologies to create gene circuits without delivery will not be responsive. Animal studies establishing proof-of-concept efficacy in well-validated *in vitro* and *in vivo* models should be completed in Phase I. In Phase II the contractor is expected to perform a large-scale *in vivo* efficacy study, as well as other studies required for FDA IND submission.

Phase I Activities and Deliverables:

Establishing proof-of-concept efficacy and/or toxicity:

- Demonstrate *in vitro* sustained and controllable transgene expression with efficacy in appropriate cell lines and/or 3D models
- Demonstrate *in vivo* sustained and controllable transgene expression with efficacy in appropriate small animal models
- Conduct gene circuit optimization (as appropriate).
- Perform (optional) animal toxicology and pharmacology studies as appropriate.
- Demonstrate (optional) increased efficacy and/or decreased toxicity as compared with standard-of-care for the cancer indication in appropriate animal model(s).

Phase II Activities and Deliverables:

The offerors are encouraged, but not required, to meet FDA before the submission of a Phase II proposal. A detailed experimental plan necessary for filing an IND is expected in the Phase II proposal:

- Conduct properly powered efficacy studies, demonstrating benefits with statistical significance.
- Complete IND-enabling experiments and assessments according to the plan developed. The plan should be re-evaluated and refined as appropriate.
- Develop and execute an appropriate regulatory strategy. If warranted, provide sufficient data to file an IND or an exploratory IND for the candidate therapeutic agent.

- Demonstrate the ability to produce a sufficient amount of clinical grade material suitable for an early clinical trial.

NIH/NCI 433 – DEVELOPING UNBIASED MEDICAL TECHNOLOGIES TO REDUCE DISPARITIES IN CANCER OUTCOMES

Fast-Track proposals **will be** accepted.

Direct-to-Phase II proposals **will be** accepted.

Number of anticipated awards: 3-5

Budget (total costs, per award):

Phase I: up to $400,000 for up to 12 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

There is an urgent need to spur innovation in developing unbiased medical technologies to reduce disparities in cancer outcomes. Structural inequalities in health and medicine, including in cancer control, have garnered the attention of leading clinicians, researchers, and journals. One insidious symptom of, and contributor to, structural inequalities in cancer outcomes is biased medical technology.

For example, existing pulse oximeters overestimate oxygen saturation when used by people with darker skin, and particularly women of color. This is consequential for cancer, given that pulse oximeters are an important prognostic tool for lung cancer. Similarly, Black, Indigenous, or other People of Color (BIPOC) individuals are at risk of getting inaccurate readings from smartwatches and fitness trackers that monitor heartbeat, due to increasing inaccuracy in darker skin. This is consequential for cancer because activity guidelines for cancer prevention recommend the use of heart rate monitors. Algorithms and machine learning-informed artificial intelligence (AI) used to guide clinical cancer decisions are often adjusted for race/ethnicity (with no explanation or explanations based on outdated/biased data); such algorithms guide decisions in ways that direct greater resources to white patients, compared to BIPOC patients. Similarly, computer-aided cancer diagnostic tools (e.g., for medical imaging) may be biased because the datasets they are developed on are imbalanced with respect to race/gender. If underlying data informing algorithms, AI, and imaging reflect structural inequalities, these will perpetuate bias and widen existing cancer disparities. As such, there is a critical need to develop unbiased medical technologies to improve cancer disparities.

Project Goals

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

Proposals should identify existing, racially/ethnically biased medical technologies integral to cancer prevention and control; identify the mechanisms contributing to such bias (e.g., targeted development and testing, inability to work effectively with a variety of skin tones, biased data inputs or outcome measurements); and develop new, unbiased replacement technologies. Potentially biased technologies could be identified in the existing literature or by the applicant.

Activities that fall within the scope of this solicitation include development of unbiased medical technologies to replace existing bias in technologies that contribute to disparities in cancer control outcomes. Proposals should target existing technologies integral to cancer control and with demonstrated bias, including (but not limited to): pulse oximeters or other measures of blood oxygen to be used at home or in clinical settings; heart rate monitors to be used at home to guide appropriate intensity exercise for weight loss and maintenance; and algorithms and artificial intelligence (AI) designed to inform clinician decision making individualized to the patient, such as those used for diagnosis, prognostic prediction, distribution of medical resources, and assessment of patient-reported outcomes (including pain). Projects could also involve integration of large biomedical data sets containing genomic, proteomic, histological, and clinical information to develop

new technologies or algorithms, as prioritized in the Cancer Moonshot Blue Ribbon Panel. Activities can involve the development of any medical technology that could complement or replace existing, racially/ethnically biased technologies that are widely employed in the medical care system or recommended for at home use.

Phase I Activities and Deliverables:

- Establish a project team including personnel with training and research experience in the specific type of medical technology targeted, knowledge of the relevant area of cancer prevention and control, and expertise in structural inequalities/health disparities;
- Provide a report including a detailed description and/ or documentation of:
  - Existing racial/ethnic bias in the targeted medical technology;
  - The role of such biased technology in perpetuating or exacerbating disparities in cancer prevention and control;
  - Potential mechanisms underlying biases in the target medical technology;
  - Description of the technical strategy that would be used to correct the bias in the existing technology or develop a new technology that could replace the cancer prevention and control function of the target biased technology;
  - Analysis of the cost-effectiveness and ability to disseminate/ implement/ integrate technology into standard cancer prevention and control practices or healthcare settings;
  - A detailed plan of methods that will be used to validate and evaluate the acceptability of the new technology in performing requisite cancer prevention and control strategies among the racial/ ethnic group for whom the initially targeted technology produced biased results;
  - A detailed plan of methods that will be used to validate and evaluate the efficacy of the new technology in performing requisite cancer prevention and control strategies among the racial/ ethnic group for whom the initially targeted technology produced biased results;
  - A detailed plan of methods that will be used to examine the reliability of the new technology in performing requisite cancer prevention and control strategies among the racial/ ethnic group for whom the initially targeted technology produced biased results across time;
  - A plan for marketing and distribution of the novel medical technology after it has passed cost-effectiveness and efficacy/ acceptability tests described above;
  - Any original data collected to demonstrate the bias in the target technology; and
  - A list of all references and research informing the description and documentation outlined above.
- Develop a functional prototype of the newly developed technology;
- Provide preliminary evidence for potential efficacy for newly developed technology in reducing or eliminating bias;

Phase II Activities and Deliverables:

- Evaluate and document cost of and time to development of technology, compared to the existing biased technology;
- Scale the production of the technology, if necessary, to accommodate efficacy/acceptability research as described in the plan requested above;
- Conduct studies of acceptability, efficacy, and reliability, based on the detailed methodological plan outlined as described above;
- Prepare a report describing the cost-effectiveness and acceptability/efficacy/reliability findings;
- Execute marketing and dissemination/ implementation plan;
- In the first year of the contract, provide the program and contract officers with a letter(s) of commercial interest; and
- In the second year of the contract, provide the program and contract officers with a letter(s) of commercial commitment.

NIH/NCI 434 – ULTRA-FAST DOSE RATE (FLASH) RADIATION DETECTORS AND SAFETY SYSTEMS

Fast-Track proposals **will be** accepted.

Direct-to-Phase II proposals **will be** accepted.

Number of anticipated awards: 2-3

Budget (total costs, per award):

Phase I: up to $400,000 for up to 12 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

An important development in the field of radiation oncology is demonstration that ultra-fast dose rate (*also known as FLASH*) radiation therapy at the same delivered dose has fewer side effects than regular radiation therapy. This finding is under intense investigation globally and a race is underway to understand and subsequently implement this methodology in the clinic.

The current devices that measure radiation dose lack response times sufficient to adequately address ultra-fast dose rates of 40-120 Gy/second. This is especially problematic when the total prescribed dose may be only 8-20 Gy. Current medical practice dictates that radiation dose must be given within 20% of the prescription, or else be subject to a formal reportable *medical event*, as regulated by the United States Nuclear Regulatory Commission. In order to safely utilize FLASH radiobiology effects in the clinic, detectors need to be developed that can affordably extend dose rate capacities from 2-10 Gy/minute to 40-120 Gy/second. Additionally, the physical structure of the pulse must meet FLASH specifications.

Project Goals

The goal of this concept is to solicit proposals to advance the development and/or application of devices, to allow FLASH radiation therapy to be properly evaluated and ultimately translated into the clinic. In particular, ultra-fast radiation dose rate detectors, and related components are the focus of this topic solicitation. By prompting the development of new, commercialized, ultra-fast detectors and safety systems, this solicitation has the potential to facilitate validated translation of laboratory findings to patients in this new and exciting domain – that of FLASH radiation therapy.

The supported projects will focus on various devices and technologies to allow for measurement and evaluation of FLASH radiation delivery. The examples of the products are:

- Development of devices to measure and validate the time and pulse structure, fluence and other characteristics of the FLASH irradiation beam in both laboratory and clinic.
- Systems to record delivery rapidly and precisely enough to measure over or under dose delivery, and stop dose delivery if needed quickly enough to prevent delivery of dose causing a medical event.

Activities not responsive to announcement:

Tools that don't measure FLASH dose rate reproducibly; tools that cannot measure the time structure of flash radiation therapy; design approaches that don't account for scalability, interoperability or the need to be tested for daily validation in a non-destructive fashion; approaches that don't plan for using tools in diverse medical centers and IT systems; tools or devices unable to be validated and traced to NIST sources/dose definitions. For applications designing safety system, systems that cannot stop the beam fast enough to prevent more than 5% dose over/under the goal (prescribed) dose.

Phase I Activities and Deliverables:

- Project team: Establish a project team, including proven expertise in: sensor development, user-centered design, team communication and clinical workflows, ultra-high speed electronic safety systems, radiation hardening electronics engineering and testing, measurement and display of beam time structure in a FLASH environment for at least one and ideally multiple modalities (electron beam, proton beam, photon beam, and other hadron beams potentially), clinical radiation oncology and medical physics. Knowledge and design of medical electronic safety systems architecture, health IT interoperability, NIST traceability and related processes will be required.
- Design and build proof-of-principle prototype system to measure the time structure of FLASH beam delivery than can both sum dose and collect time structure data and allow the analysis of such data to confirm if it is with 5% of planned beam delivery immediately after treatment (within seconds but ideally much faster to allow use in a safety feedback system that could stop a beam during treatment). Appropriate controls with poor beam structure and inadequate dose rate should be implemented in the testing process. If a system is designed to shut off a delivery device that capability must be designed and tested in the prototype system.
- Demonstrate that the prototype has a high probability of development into a clinically-relevant radiation measurement tool and/or safety device component that has is able to work in the FLASH regime (40-120 Gy/s).
- Provide a report on the results of the first round of usability testing and any resultant modifications of the platform based on this user feedback.
- Present phase I findings and demonstrate the functional prototype system to an NCI evaluation panel via webinar to be summarized in a formal report.

Phase II Activities and Deliverables:

- Enhance, beta test, and finalize system, data standards and protocols for a platform that can measure FLASH beam deliveries with less than 1% variance between at least 5 prototype measurement devices by the end of year

1 of the Phase II contract.
- Enhance, beta test, and finalize system for clinical implementation.
- Provide a report that synthesizes feedback from all relevant categories of end-users (such as physicians, physicists, OEM engineers, and radiobiologists) and summarizes the modifications made to the platform after each round of usability testing.
- Provide a report specifying lessons learned and recommended next steps to implement the components in a commercial capacity.
- Provide a report detailing plans for implementation of technical assistance and delivery of the complete system including needed software and related API data, platform compatibility standards employed if any, and measures developed, including standard operating procedures for use, validation of measurements, and checking device performance.
- Develop systems documentation and user guides to facilitate commercialization.
- Present phase II findings and demonstrate the system via a webinar at a time convenient to the offeror and NCI program staff.
- In the first year of the contract (Phase II), provide the program and contract officers with a letter(s) of commercial interest.
- In the first year of the contract (Phase II), conduct a call with the FDA.
- In the second year of the contract, provide the program and contract officers with a letter(s) of commercial commitment.

Where cooperation with other equipment manufacturers is critical for implementation of proposed technology, company should provide evidence of such cooperation (through partnering arrangement, collaboration, or letters of intent) as part of the Phase II proposal.

NIH/NCI 435 – DEVICES TO TREAT SECONDARY LYMPHEDEMA FOLLOWING CANCER TREATMENT

Fast-Track proposals **will be** accepted.

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

Number of anticipated awards: 2-4

Budget (total costs, per award):

Phase I: up to $400,000 for up to 12 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

Lymphedema is a clinical expression of an impaired lymphatic circulation. Acquired lymphedema is most often the consequence of regionalized injury to lymphatic vessels as a consequence of trauma, infection, neoplasia, radiation damage, or surgical interventions, especially those that include lymphadenectomy. Secondary lymphedema following axillary lymph node dissection during surgery to remove malignant tissue is the most common cause of lymphedema in United States. Lymphedema is commonly associated with treatment for several types of cancers including breast cancer, melanoma, sarcoma, and gynecological cancers among others.

Early stage lymphedema begins as tissue swelling with sense of heaviness and discomfort in affected area. This is followed by transient non-tender pitting edema and development of leathery texture on the skin due to thickening and fibrosis. Without any interventions, non-pitting edema may develop which indicates irreversible stage of lymphedema. Skin in chronic lymphedema is prone to fissures, ulceration, and recurrent cellulitis. Lymphorrhea and Impetigo are also common at this stage. Frequency of acute inflammatory incidences, pain, skin deformities, and reduced hand usage in cases of lymphedema in the arm all lead to frustration, annoyance, anxiety, depression, poor psychological adjustment, and poor body image issues in patients suffering from secondary lymphedema. Lymphedema-related physical disabilities and psychological issues can cause severe limitations and negatively affect personal, work, and social lifestyles. Despite the debilitating physical, psychological, and financial consequences, little progress has been made for the treatment of lymphedema. Current lymphedema treatments mostly involve physiotherapeutic interventions such as massage to manually drain the lymph, multilayer bandaging, topical skincare, compression garments etc. with varying degree of success.

Project Goals

The goal of this contract topic is to support the development of technologies that prevent, reduce, or eliminate lymphedema

following removal or radiation of lymph nodes due to cancer in the upper body, i.e. neck, chest, arm(s), or thoracic cavity. These technologies will provide healthcare providers with solutions for preventing and treating lymphedema, which can cause a serious reduction in function and quality-of-life for patients following treatment for cancer.

Examples of technologies considered responsive to this solicitation include, but are not limited to; implantable devices capable of modulating the movement of lymph fluid to prevent lymphedema; innovative mechanical devices that can provide real time monitoring and compression throughout daily activities or sleeping hours, or other wearable devices incorporating highly innovative solutions to substantially improve control of lymphedema. The proposed technologies should provide either significant prevention of lymphedema in patients at high-risk of developing it or a long-term solution that reduces/eliminates lymphedema in patients that have the condition. While proposed technologies can have monitoring capability, the technology should include an integrated solution for the prevention or control of lymphedema. Priority will be given to technologies that aim to eliminate or nearly eliminate lymphedema.

Activities not responsive to announcement:

Proposals for new surgical techniques for lymph node transplant surgery, standard rehabilitation procedures (e.g., massages, techniques, or exercises) for managing lymphedema, or new tools that improve patient education of current rehabilitation procedures will not be considered responsive.

Phase I Activities and Deliverables:

- Develop a prototype of a device with appropriate specifications.
- Demonstrate preliminary proof-of-concept of the device in a suitable animal model or phantom model.
- Specify the quantitative technical and commercially relevant milestones that will be used to evaluate the success of the technology.
- Identify required specifications necessary to make the device clinic ready.
- Develop a regulatory strategy/plan and timeline that is necessary to file a regulatory application for the device.
- Implantable device specifications and regulatory plans must include a description of infection risk and plans to test and mitigate the risk of infection or spreading infection.
- Present phase I findings and demonstrate the functional prototype system to an NCI evaluation panel via webinar.

Phase II Activities and Deliverables:

- Build a device according to the specifications developed in Phase I.
- Optimize the device design and performance for a clinical setting, and demonstrate the feasibility of this novel device to function in the current clinical workflow and/or in a home setting for patient use.
- Demonstrate the safety and efficacy of the device in relevant animal models as required by FDA.
- Engage with FDA to refine and execute an appropriate regulatory strategy. If warranted, provide sufficient data to submit a regulatory application to obtain approval for clinical application.
- For offerors that have completed advanced pre-clinical work, NCI will support pilot human trials.
- Present phase II findings and demonstrate the system via a webinar at a time convenient to the offeror and NCI program staff.

NIH/NCI 436 – New Technologies to Analyze Extra-Chromosomal DNA in Cancer

Fast-Track proposals **will be** accepted.

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

Number of anticipated awards: 2-3

Budget (total costs, per award):

Phase I: up to $400,000 for up to 12 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

Numerous studies over the last several decades have reported on extrachromosomal circular DNAs (eccDNAs) that appear alongside coiled linear chromosomes in the cells of normal tissues. These DNAs are found in many eukaryotic species and have been observed in various forms including telomeric circles, small polydispersed DNA elements, and microDNAs. New research has revealed that cancer cells contain large numbers of a specific type of extrachromosomal DNA known

simply as 'ecDNA.' As compared to the other forms of DNA listed above, ecDNAs are relatively large (1-3 MB) and contain multiple full genes and regulatory regions. Recently, ecDNA has been increasingly recognized as a potent source of driver oncogene copy number amplification events in human tumors. ecDNAs are subject to non-Mendelian inheritance and can multiply rapidly while maintaining intratumoral genetic heterogeneity, which likely plays an important role in helping cancers to adapt, evolve and become resistant to treatment. Driver "undruggable" oncogenic targets, such as N-Myc, are subject to ecDNA driven amplifications, and other enzymes and oncogenic proteins responsible for drug resistance may also be transiently driven by such events. Recent interest in this emerging and important area of research is reflected in the latest round of Cancer Grand Challenges, a major collaborative funding initiative between the NCI and Cancer Research United Kingdom (CRUK), which identified as one of its new 2020 challenges, "Understand the biology of ecDNA generation and action, and develop approaches to target these mechanisms in cancer." Unfortunately, little is known about the genomic organization of ecDNA or the mechanisms that drive their formation, due in part to the challenges involved in their detection. ecDNAs can reintegrate into the genome and are distributed unequally to daughter cells during cell division, both of which contribute to the difficulty in their detection. Although recent advances in commercially available long-read sequencing platforms may play a role in addressing some of these challenges, many technology gaps still exist for the reliable analysis of ecDNAs, especially if limited samples are available. To keep pace with our rapidly evolving understanding of ecDNAs and their role in cancer, this contract topic aims to develop new tools that are critically needed to analyze ecDNA sequence, structure and regulation. This topic is agnostic as to specific technological approaches, which could involve optimizing ecDNA enrichment and purification, improving existing sequencing technologies, and/or developing new informatics tools. In the near term, technologies developed under this topic are expected to enable important basic research on ecDNA and cancer. Ultimately, such tools may also play a key role in revealing new therapeutic vulnerabilities in cancers that are currently intractable.

Project Goals

The goal of this contract topic is to spur the development of new and/or advanced analytical approaches that can support research into the mechanisms giving rise to ecDNA formation and organization, and its role in cancer. This solicitation seeks both completely new approaches, as well as "better, faster, cheaper" versions of existing technologies, to advance this field. Responsive proposals may include novel methods and/or reagents to selectively enrich, isolate, detect, and/or visualize ecDNA targets. Possible approaches that would be considered responsive to this solicitation include (but are not necessarily limited to):

- Biochemical approaches to selectively enrich or purify ecDNA
- Sequencing approaches that distinguish ecDNA from other forms of DNA
- Affinity reagents or other biochemical detection strategies specific for ecDNA
- Imaging probes that are specific for ecDNA targets
- IT approaches that allow novel data analysis to interpret/detect ecDNA

Phase I projects must demonstrate that the proposed technology/approach is capable of selectively detecting, analyzing and/or characterizing ecDNA in cancer-relevant biological systems (e.g., cancer cell lines). Offerors should conduct feasibility studies in cancer models for which there exists a sufficient understanding of the ecDNA biology to reliably interpret the results of the novel assay or technique. Phase I activities should focus on characterizing the relevant analytical parameters of the technique and should include target performance measures for key analytical parameters. Phase II activities should demonstrate the assay throughput, as well as the ability to analyze ecDNA in systems of increasing biological complexity (e.g., patient-derived xenografts, tumor tissue sections, human plasma). Phase II activities should demonstrate the ability of the proposed approach to detect temporal changes in ecDNA that are biologically relevant in human cancers (e.g., ecDNA biogenesis, replication, genomic organization, distribution to daughter cells). Offerors are encouraged, but not required, to conduct experiments in which changes in ecDNA can be monitored in a cancer-relevant model(s) following drug treatment or some other biological perturbation. Phase II activities should include other necessary validation activities to advance the technology as a commercially available research tool.

Activities not responsive to announcement:

Activities involving the detection of ecDNAs in non-cancer biological systems will be considered non-responsive to this announcement.

Phase I Activities and Deliverables:

- Demonstrate the ability to selectively analyze (e.g., enrich, purify, isolate, detect, image) ecDNAs found in cancer-relevant biological systems
- Provide a clear justification for the biological systems (e.g., cell lines) used for analytical validation; include a summary of what is currently known about the role of ecDNA in these systems and how this may impact the interpretation of the proposed validation experiments
- Demonstrate the specificity of the assay/technique to distinguish ecDNA from all other forms of cellular DNA in

the chosen cancer cells
- Fully characterize the relevant analytical parameters of the assay/technique including sensitivity, specificity, limit of detection, dynamic range, etc. (as appropriate)
- Describe target performance measures (i.e., quantitative milestones) for key analytical parameters, including the methods by which they will be assessed

Phase II Activities and Deliverables:
- Demonstrate the maximum throughput of the approach, and define appropriate measures of performance reliability for large-scale screening of cancer samples
- Demonstrate the ability to analyze ecDNA in systems of increasing biological complexity (e.g., patient-derived xenografts, tumor tissue sections, human plasma)
- Demonstrate the ability to use the proposed approach to detect temporal changes in ecDNA that are biologically relevant in human cancers (e.g., ecDNA biogenesis, replication, genomic organization, distribution to daughter cells)
- Offerors are encouraged, but not required, to demonstrate that the technique can be used to monitor biologically relevant ecDNA changes in a cancer-relevant model(s) following drug treatment or some other biological perturbation
- Conduct additional validation studies to advance the technology as a commercially available research tool, including manufacturing scale up, commercial partnerships, beta testing, etc. (as appropriate).

NIH/NCI 437 – 3D SPATIAL OMICS FOR MOLECULAR AND CELLULAR TUMOR ATLAS CONSTRUCTION

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

Direct-to-Phase II proposals **will be** accepted.

Number of anticipated awards: 3-5

Budget (total costs, per award):

Phase I: up to $400,000 for up to 12 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

Public large-scale molecular-level datasets have facilitated sophisticated secondary data analysis leading to new biological discovery. These data sources provide rich, multi-omic data on bulk or single-cell populations, but most measurements do not preserve the spatial relationships between tumor cells and thus limit the ability to discover important and targetable cell-cell and cell-microenvironment interactions. To address this shortcoming, several programs supported by NIH, NCI and beyond have undertaken the construction of spatiotemporal single cell resolution atlases of normal and diseased tissues.

Examples of technologies currently employed to build spatial atlases include multiplex microscopy and mass cytometry-based imaging modalities that provide information on multiple (10s-1000s) of biological molecules (genes, proteins, metabolites, etc) in a single two-dimensional thin tissue section. While imaging of sequential tissue sections provides a way to re-construct the three-dimensional (3D) tumor microenvironment, most high content imaging modalities require multiple rounds of tissue staining and manipulation that can be destructive to any one tissue section making it difficult to reconstruct accurate 3D views. Therefore, technologies that provide imaging workflows that deliver cellular to sub-cellular resolution omic-level data in three dimensions (i.e. in thick tissue resections or whole biopsy samples) are likely to more faithfully conserve the architectural or structural components within the tumor microenvironment that could be destroyed or altered during multiple rounds of tissue processing. It is possible that approaches such as light sheet microscopy could fill this need, but the current protocols for tissue clearing, multiple rounds of target labeling to facilitate highly multiplexed omics measurement, and subsequent image processing make the overall workflow for an individual tissue prohibitively slow (days to weeks) and difficult to employ in atlas building activities where a large number of normal and tumor maps is required for a representative normal tissue or tumor atlas.

Project Goals

The goal of this concept is to solicit proposals to advance the development and dissemination of imaging workflows capable of omics-level measurements in thick tissue resections or whole biopsy cores. Proposals should enable interrogation

in a manner that combines high resolution (preferably single-cell) omics level data (i.e. genomic, transcriptomic, proteomic, metabolomic, etc) with information about 3D native tumor architecture (i.e. extracellular matrix, vasculature, higher order structure, etc).

Proposals that are within scope of this solicitation may combine existing, new, or improved assay components into an improved imaging workflow. Examples of existing, new, or improved components include imaging technologies or modalities, tissue clearing methodologies, imaging probes and/or detection reagents, cyclic staining or targeting procedures, and/or unique combinations of imaging and multi-omic measurement platforms. A minimal workflow will provide a 3D view of multiplexed omics data without the need for reconstruction from 2D tissue slices. The ability to concurrently acquire additional information regarding native tumor architecture would be considered a strength (eg. second harmonic imaging or alternative technology). Offerors should benchmark their proposed workflow against current state-of-the-art imaging workflows and demonstrate a decrease in overall assay time while maintaining a similar or increased capacity for omic-scale analysis. Cellular or sub-cellular resolution imaging is a requirement.

It is anticipated that proposals may include the development of new algorithms, visualization tools, and analysis software to facilitate data handling, analysis and visualization of results. However, applications that are solely software-based are not within the scope of this solicitation.

Phase I Activities and Deliverables:

Phase I activities should generate data to confirm feasibility and potential of the technology(ies) to provide 3D images of high-resolution omics-level data in thick resections or whole biopsy cores by completing the following deliverables:

- Define the relevant use cases for the technology (i.e. what tissues can be used, what imaging resolution can be expected, what -omic measurement(s) will be completed).
- Generate proof-of-concept dataset using resection tissue or biopsy cores from solid human cancers or from a generally accepted mammalian cancer model (i.e. PDX, xenograft, GEMM) that demonstrates the ability to capture and visualize molecular omics measurements in 3D.
    - Offerors should specify quantitative technical and commercially-relevant milestones that can be used to evaluate the success of the technology versus current state-of-the-art 3D high resolution imaging platforms (i.e. light sheet microscopy).
    - Quantitative milestones may be relevant metrics (i.e. compared to benchmarks, alternative assays) or absolute metrics (i.e. minimum number of proteins or genes detected, metrics related to repeatability of the assay).
    - Metrics regarding total assay time (including tissue preparation, cyclic staining (if relevant), and imaging processing/analysis) should be included.
- Development of preliminary Standard Operating Procedures for system use, including a validated list of reagents for a specific tumor type.

Phase II Activities and Deliverables:

Phase II activities should support the commercialization of the system developed in Phase I and include the additional activities and deliverables:

- Demonstrate the ability to quantify the 3D native tumor architecture (i.e. extracellular matrix, vasculature, higher order structure, etc) in addition to the capabilities optimized in Phase I.
- Demonstrate reliability, robustness and usability for the purpose of generating large scale datasets for atlas building.
- Benchmark system performance (including total assay time) and functionality against commercially relevant quantitative milestones.
- Demonstrate utility across at least three solid tumor types (thick resections or whole biopsies).
- Show feasibility to be scaled up at a price point that is compatible with market success and will facilitate large-scale atlas-building activities.
- Publication of Standard Operating Procedures for system use, including a validated list of reagents for each of the three tumor types. Documentation for troubleshooting new tumor or tissue types to demonstrate the system can be utilized beyond the tumor types proposed.
- Provide a roadmap for development of a turnkey system.

NIH/NCI 438 – UNDERSTANDING CANCER TUMOR GENOMIC RESULTS: TECHNOLOGY APPLICATIONS FOR COMMUNITY PROVIDERS

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

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

Number of anticipated awards: 2-3

Budget (total costs, per award):

Phase I: up to $400,000 for up to 12 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

Next-generation sequencing (NGS)–based technology has lowered the cost of testing for genomic alterations in a patient's cancer and is now commercially available from many diagnostic laboratories. Due to increasing numbers of approved or investigational targeted therapies, cancer patients are more routinely undergoing tumor/somatic genetic testing at the time of diagnosis or progression. Although the decision to undergo tumor/somatic testing can have profound medical implications for patients, oncology providers traditionally have not been trained to interpret and communicate NGS results. Yet, they are increasingly advised by professional societies to consider NGS testing, and thus face the need to counsel patients about generated results. Published data indicate that the growing uptake of NGS in cancer care has left many oncology providers inadequately prepared to discuss the complex and potentially hereditary implications of such testing. Often, clinicians lack not only the expertise but also the time needed to counsel cancer patients about whether to undergo tumor/somatic testing, and the layered implications of test results. Tumor/somatic testing creates several added responsibilities for oncology providers such as guiding follow-up care - including clinical trial options - and facilitating communication within families. The need for assistance is particularly acute in low-resourced settings that lack access to geneticists, genetic counselors, tumor boards, or other such consultation. Indeed, clinicians in such lower resourced oncology settings face unique challenges discussing NGS testing with cancer patients. Tools, technologies and/or services are needed to help providers: (i) evaluate the benefits of somatic/tumor testing for their individual patients, (ii) understand and interpret test findings, including potential familial implications for suspected inherited cancer and (iii) communicate findings with their patients both before testing (to obtain truly informed consent) and after testing (to explain results). Such products must be integrated with current care models and be easily accessible to oncology providers given the time constraints of medical practice. These tools or technologies must distill complex genomic data so that oncology providers appropriately implement tumor/somatic genomic testing in the context of evolving National Comprehensive Cancer Network (NCCN) guidelines. They should also provide information in a legible format to facilitate patient comprehension and engagement in decision-making. Companies should incorporate provider and community input into the design of these products, to ensure utility and uptake.

Project Goals

The goal is to design and develop products such as tools, technologies, and/or services to: (i) inform oncology providers about tumor/somatic testing and current NCCN guidelines, (ii) help oncology providers evaluate the need for tumor/somatic testing for specific cancer patients, (iii) assist oncology providers with interpretation of tumor/somatic test results, including the impact of incidental germline findings, and (iv) help oncology providers communicate NGS results to their patients. Interpretation of NGS results must be personalized for individual patients. Products that cater to settings with limited or no access to genetic counselors, or on-site tumor boards, are encouraged. Products should: (i) identify strategies for enhancing provider understanding of cancer genomic test results; (ii) assist with provider communication of test results in a clear and lay-friendly manner, to aid both treatment and life planning decisions; (iii) inform providers about genetic counseling and clinical trial resources for their patients; (iv) offer remote technology applications such as video and telephone guidance; and (v) incorporate perspectives of populations experiencing disparities in cancer outcomes, such as minority and rural communities. In addition, contractors must evaluate, pilot and disseminate the product.

The product(s) should aim to accomplish as many of the following as primary goals:

- provide a resource for improving knowledge of somatic genetic testing for oncology health care providers;
- assist health care providers to evaluate patients and determine need of genetic testing;
- facilitate interpretation of somatic genetic test results (include noting germline findings vs. somatic findings and flagging germline variants for possible follow-up), using existing clinical guidelines, available resources and established standards to help health care providers understand medical and familial implications of test results;

- promote communication of genetic test results in a clear and lay-friendly manner, to assist with treatment or life planning decisions;
- explain to health care providers how and why information on variants of unknown significance may evolve over time and provide guidance about how to communicate this information to patients;
- provide a discussion guide to facilitate communications regarding genetic results with providers and related family;
- inform health care providers about genetic counseling resources they may provide to their patients;
- offer options for video and telephone guidance if a patient is located in a remote setting; and
- include and incorporate perspectives of populations experiencing disparities in cancer outcomes, such as minority, underserved and rural communities as well as identify and meet needs that would improve use and access for understanding cancer genomic test results.

Some recommended practices for product development include:

- Including patients' and families' perspectives in deciding when, whether and how to communicate specific genetic findings, and when to offer genetic counseling and confirmatory testing based on counseling. This could be accomplished using the principles and elements of a design thinking approach focused on designing the communication strategies for oncology care providers from the perspective of the patients, in an agile, iterative way.
- Considering a range of cancer treatment scenarios to elicit a broad range of provider needs that can inform tool development. This range includes pediatric, adolescent and young adult as well as adult cancer types.
- Assembling trans-disciplinary teams that include but are not limited to geneticists, genetic counselors, behavioral researchers, psychologists, oncologists as well as patient navigators, patient advocates, and user experience designers to inform development and validation of tools.
- Planning for pilot implementation testing of the tool in clinical or other applicable settings as the tool is developed.

The following would be considered out of scope:

- Methodologies of genetic counseling that do not focus on development of provider-facing tools
- Methods, reports, and tools that include only germline genetics/genomics
- Genetic testing services
- Reports and tools requiring genetic testing services be conducted by offeror

Phase I Activities and Deliverables:

The goal of Phase I is to design and develop tools, technologies, or products to 1) inform the user about the role of tumor (somatic) genetic testing and counseling in cancer research and treatment 2) aid understanding and interpretation of somatic genetic findings; 3) aid in effective communication of tumor (somatic) genetic test results.

- Establish a project team with expertise in the area of genetic counselling, software development, user-centric design, oncology, patient navigation as appropriate for this proposed project.
- Conduct or utilize formative/exploratory research during the trial period to identify barriers and facilitators faced by physicians in staying up to date regarding genetic testing best practices and regulations, understanding test results (and evolution of results as more is known about impact of specific genetic variants/somatic mutations), and accessing counseling resources based on currently available platforms for genetic counselling.
- Develop a prototype tool or technology based on formative research, to explain genetic tests and test result to physicians for them to provide to their patients. This could be a tool/technology for physicians, a communication tool for physicians to use, and/or a tool/technology to support remote genetic counseling or use of other educational resources. It should have a physician and counselor interface to meet the goals of genetic testing and counseling while maintaining confidentiality. Prototype must include -
    - The database structure for the proposed platform, user-interfaces, and metadata requirements;
    - Data visualization, data query functions, feedback and reporting systems;
    - Data adaptation for mobile application(s) if applicable;
    - Ability to generate lay-friendly reports of genetic testing results that health care providers may use and are understandable to patients;
    - Ability to continuously incorporate new information on genetic variants for physicians to update their patients as necessary (i.e. when it impacts clinical care or has familial implications).
- Identify at least one clinical setting where the tool may be used and integrated within a research or practice setting and develop process maps and algorithms to set up appropriate data flows and ensure privacy protections.
- Test the feasibility /usability of tool in a sample population of physicians and patients and providing written report and recommendations on the best practices for use of the tool in research and practice settings.

Deliverables for this Phase include:

- Prototype design
- Demonstration of the tool and practicality of use by patients, counselors and providers
- Provision of technical specifications as well as an operations/user guide for the tool
- Outline of metrics that can be used to assess the successful application of the tool

Phase II Activities and Deliverables

The goal of Phase II is to evaluate application of the tool as well as pilot and disseminate in an ongoing research project or community practice setting after procurement of needed human subjects and operational approvals. Finally, a plan for commercialization based on the pilot should be developed. In order to meet these goals, the offeror will

- Outline a plan to use the tool, technology, or product in practice settings.
- Enhance systems interoperability for deployment in diverse software environments and provider networks. Provide a report detailing communication systems architecture and capability for data reporting to healthcare providers, electronic health records, and health surveillance systems as appropriate for the proposed project.
- Refine prototype and scale up.
- Perform an evaluation of the interpretation of genetic results by comparing to gold standard guidelines for interpretation.
- Design and conduct a validation study including specifying study aims, participant characteristics (physicians and patients), recruiting plans, primary and secondary end points and data analysis plans. The validation study should evaluate physician communication of results and patient understanding of information communicated by the physician.
- Prepare a tutorial session for presentation at NCI and/or via webinars describing and illustrating the technology, its intended use and results from the validation study.
- In the first year of the contract, provide the project and contract officers with a letter(s) of commercial interest.
- Provide the project and contract officers with a letter(s) of commercial commitment.

Deliverables and activities include:

- Validated tool, technology or product that has been successfully used in active research or community settings by physicians or health care providers.
- Metrics demonstrating that physicians/health care providers understand information provided, and patients understand materials communicated by physicians.
- Finalized user guide and operations manual for use of tool within an active research study. This will include technical specifications, process guides/flow charts for how and by whom the tool will be used.
- Finalized trouble shooting guide as well as frequently asked questions.
- Analysis and discussions from exit interviews of study participants, physicians and counselors to understand and improve utility and usability of tool in a practical setting.
- A plan to develop the tool commercially and disseminate it to the wider research and practice communities.

NIH/NCI 439 – ADVANCED SAMPLE PROCESSING PLATFORMS FOR DOWNSTREAM SINGLE-CELL MULTI-OMIC ANALYSIS

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

Direct Phase II proposal **will be** accepted

Number of anticipated awards: 3 - 5

Budget (total costs, per award):

Phase I: up to $400,000 for up to 12 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

Single cell multimodal omics (scMulti-omics) technologies by integrating different readouts, such as DNA, RNA and protein expression, can provide greater value than the sum of the parts making these technologies powerful to characterize the cell in-depth. Isolation of unique cell populations, and simultaneous and selective extraction of different macromolecules can enable further experimental analyses to answer critical questions in basic science and clinical research and empower observational and therapeutic studies. For example, in cancer, scMulti-omic technologies will enable us to identify rare cell types and their characteristics with unprecedented accuracy, to better understand the mechanisms related

to tumorigenesis, metastasis, tumor heterogeneity, tumor immune response and immune evasion, and to improve the accuracy of tumor diagnosis, treatment, and prognosis. By 2025, the global scMulti-omics market is anticipated to be $5.32 billion, mainly driven by the increasing need for noninvasive or minimally invasive diagnosis and personalized medicine.

Recent advances have significantly improved multi-omic analysis; however, the sample processing technologies for tumors, in particular solid tumors for multi-omic analysis are lagging behind. The existing technologies are associated with low throughput, high cost, and sub-optimal processing affecting data quality, which hamper their widespread use in biology and ultimately in medicine. There is a need for robust sample processing technologies that are compatible with downstream analysis and can be easily integrated in the preanalytical workflow. In this contract topic, we will focus on improving the preanalytical workflow consisting of several steps to make the biomolecules ready for multi-omic analysis: cell isolation and enrichment for the population of interest followed by cell lysis to release biological materials and then processing of the materials, such as gDNA, mRNA, or expressed proteins, tailored for the downstream target analysis, since biomolecules from single cells are usually extremely low in quantity. Improving the preanalytical workflow may be done at different steps in the workflow such as processing of tissues to maintain integrity of biomolecules, isolation and enrichment of a cell population including unique/rare cell population, biomolecular isolation and enrichment, conversion of the molecular target species into a readable format, while ensuring reagent compatibility in the workflow for downstream analysis and also including quality control (QC) methods to assess capture, isolation and enrichment, QC tools that integrate cellular phenotypic information with the omics information to distinguish cell-to-cell variability from technical noise, and also tools that assess cell viability early on in the workflow to prevent processing of inadequate samples through costly multi-omic analysis.

Project Goals

The offerors are encouraged to integrate the preanalytical workflow from tumor cell dissociation/isolation, enrichment, tracking, cell lysis, to biomolecular isolation on a single platform to enable single cell multimodal-omic analysis. This approach should provide smoother transitions between functional components thereby leading to shorter analysis time and thus higher throughput. In addition, by omitting human intervention, workflow with higher degree of automation should ultimately translate into greater experimental reproducibility. Novel micropillar-based microfluidic platforms that are capable of providing high efficiency separation, isolation and enrichment of single cells and molecules instead of relying on a single-compartment design (*e.g.* droplet microfluidics, microwell technologies, valved and chambered microchannels, tube-based kits, etc.) for cell and biomolecular processing may be explored. Micropillar arrays within microfluidic channels may serve to physically size-separate genomic DNA from proteins and RNA during cell lysis in a manner compatible with the downstream target analysis.

Overall, at the end of the contract an offeror is expected to provide a robust sample processing platform that easily integrates with scMulti-omic analysis and allow better understanding of heterogeneity in solid tumors and the microenvironment, and also that enable analysis of rare and low-abundant cells such as circulating tumor cells and antigen presenting cells, to potentially open the door to new biomarker and therapeutic targets discoveries in cancer.

The activities that fall within the scope of this solicitation include development of technologies to improve single-cell multi-omic preanalytical microfluidic platforms that integrate steps of the preanalytical workflow such as sample processing, single-cell separation or isolation and enrichment, technologies for solid tumor dissociation/isolation, enrichment and tracking of cancer cells and/or biomolecules for scMulti-omics. Technology proposals focused on developing new or improved molecular analysis will be considered non-responsive to this contract topic.

Phase I Activities and Deliverables

Phase I activities should demonstrate the feasibility of a technology to improve single-cell multi-omic preanalytical platforms.

- Develop an early/proof-of-principle prototype, single-cell multi-omic preanalytical device/platform or technology for at least one improved step of the scMulti-omic preanalytical workflow
- If the technology developed is a novel technology for at least one step of the scMulti-omic preanalytical workflow, describe its capability for integration with other steps in the scMulti-omic workflow into a device/platform
- Establish assays and/or metrics, especially functional comparability and quality attributes, and benchmark the approach against current methods used in single-cell analysis preanalytical workflows using at least two tumor types.
- Define the target for analysis and demonstrate compatibility with the downstream analytical step (at least two downstream readouts for example DNA and RNA sequencing technologies)
- Present assay performance and validation results and demonstrate the workflow of the technology during a

potential NCI SBIR site visit.

Phase II Activities and Deliverables

Phase II activities should support establishing commercial prototype of the technology, including but not limited by the following activities:

- Demonstrate system performance and functionality by adopting commercially relevant quantitative milestones:
  - Offerors should specify quantitative technical and commercially-relevant milestones that can be used to evaluate the success of the tool or technology being developed.
  - Offerors should also provide appropriate justification relevant to both the development and commercialization of these technologies.
  - Quantitative milestones may be relative metrics (*e.g.* comparison to benchmarks, alternative assays or minimization of the pitfalls of the experimental measurements described in phase I) or absolute metrics (*e.g.* minimum level of detection in a clinically meaningful indication).
- Show potential/feasibility to scale up the technology at a throughput compatible with widespread adoption by the research and clinical community.
- Develop a working, commercial prototype device/platform for the single-cell preanalytical workflow and perform pre-market evaluation at multiple sites.
- Report throughput capacity and cost of the device/platform

NIH/NCI 440 - CANCER PREVENTION AND DIAGNOSIS TECHNOLOGIES FOR LOW-RESOURCE SETTINGS

Fast-Track Proposal **will be** accepted

Direct-to-Phase II proposal **will be** accepted

Number of Anticipated Awards: 4-6 (3 for HPV diagnostics)

Budget (total costs, per award):

Phase I: up $400,000 for 12 months

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

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

Summary

Cancer is a leading cause of premature death in low-resource settings globally, where gaps in access to cancer prevention, screening, early detection, and diagnosis present significant challenges.

For example, cervical cancer is the fourth most common cancer in women. When pre-cancer or early-stage cancer is diagnosed, it is one of the most preventable or treatable forms of cancer, respectively. As a result of complex and expensive cytology-based programs in high-income countries, cervical cancer has become a cancer that defines health disparity populations and one that is still a major cause of morbidity and mortality in low-resource settings globally, where building out a cytology-based screening program may not be realizable. Realization of that goal given the current commercially available human papillomavirus (HPV) tests is unlikely without newer, lower-cost tests coming to market.

The purpose of this solicitation is to provide funding opportunities for small business concerns (SBCs) to develop cost effective and affordable technologies for cancer prevention, early detection and/or diagnosis that target low-resource settings, both internationally and within the US. It will allow applications to any specific cancer type, however four cancer types (tissues) are of particularly interest because they are highly amenable to prevention, early detection, and diagnosis in low-resource settings. The four cancer types of interest are: cancers of the cervix, colon/rectum, esophagus, and oral cavity. These four cancer types are given a high priority because the introduction of affordable and cost-effective technologies for cancer prevention early detection and diagnosis is likely to have an especially strong impact to reduce the burden of these cancers in low-resource settings.

For cervical cancer, one of the goals for this initiative is to support the development of new alternatives to standard lab-based HPV testing to the market that are both in a form factor as well as price point that will enable primary screening paradigms based on self-collected cervicovaginal specimens to be established globally. Specifically, at- or near-patient nucleic acid amplification approaches are needed that enable rapid detection and genotyping for HPV.

Project Goals

The goal of this solicitation is to encourages applications from SBCs to develop or adapt, apply, and validate existing or

emerging technologies into low-resource setting-appropriate technologies for cancer prevention early detection and/or diagnosis. Investigators must explicitly consider potential for adoption and scale-up in the local context as design criteria for technologies proposed in applications responding to this solicitation.

Projects proposed for this contract topic will require multidisciplinary efforts to succeed, and, therefore, all applicant teams must include expertise in oncology, engineering, global health, and healthcare delivery in low-resource settings. Products addressing cancers of the cervix, colon/rectum, esophagus, and oral cavity are highly encouraged for this solicitation. However, applications may address any single cancer type.

For cervical cancer, this solicitation is particularly focused on the development of rapid HPV diagnostics at the point-of-need suitable for taking to scale (e.g., a portable loop-mediated isothermal amplification (LAMP) based assays).

Scientific/Technical Scope

Applications submitted to this solicitation must propose to develop or adapt technologies into user-friendly, affordable products for prevention, early detection, and diagnosis of cancers in a low-resource setting.

The proposed project must focus on a specific cancer type (histology) and must show preliminary evidence to deliver medical utility for improved cancer outcomes. Products addressing cancers of the cervix, colon/rectum, esophagus, and oral cavity are particularly encouraged for this solicitation. However, applications may address any single cancer type.

The proposals must include quantitative milestones and a way to document the clinical utility of the propose product within the specific low-resource healthcare system of interest. The proposed product must comply with the regulations and international standards/guidelines applicable to investigational medical products in the low-resource setting where the product will be used (examples are World Health Organization guidelines and local regulations in LMICs, and Good Laboratory Practice, Good Manufacturing Practice, FDA Investigational New Drug, and Investigational Device Exemption for US settings). All applicants should demonstrate familiarity with applicable regulatory requirements, while Phase II applications require in the commercialization plan to include a detailed regulatory strategy matched to the low-resource setting of the study.

Beyond the scope of this solicitation, it is anticipated (and encouraged) that the outcomes of successful SBIR projects will help attract strategic partners or investors to support the ultimate commercialization of the technology as a publicly available product or service.

Projects funded by this solicitation may include patient enrollment in foreign countries. Per SBIR policy, when there are special circumstances justifying the conduct of the proposed research outside the US within time and budget constraints (e.g. a high disease incidence that makes clinical validation more feasible and timely), agencies may approve performance of a portion of the SBIR R&D work outside of the US. In this case, applicants are required to include a statement in their applications on why these resources are not available in the US.

Technology areas of interest for cancer prevention, early detection and diagnosis include, but are not limited to, the following:

- Delivery technologies to improve reliability, effectiveness, and/or safety of vaccines at the point of use (e.g., needle-free delivery methods, intradermal delivery, or oral delivery)
- Diagnostic microarrays
- High-throughput cancer screening, cytology, or imaging-based screening
- *In vitro* diagnostic assays such as point-of-care (POC) analytical tools for exfoliated epithelial specimens (e.g., cervical Pap specimens), blood, saliva, or urine (e.g. lab-on-a-chip biosensors that allow remote performance of chemical and/or biological assays outside of a laboratory environment)
- Machine learning algorithms to identify precancer and cancer in optical images captured with simple devices (e.g., smart phones)
- Portable imaging devices for cancer diagnosis (e.g., optical imaging, diffuse optical tomography, endoscopy, or ultrasound)
- "pop-up" labs for cancer screening and diagnosis
- Smartphone-based technologies for cancer prevention, detection and/or diagnosis
- Software tools for cancer prevention, such as tools for screening, vaccine dissemination, or tools to improve vaccine supply chains
- Tele-oncology (e.g., tele-diagnosis, tele-screening, tele-cytology, or tele-colonoscopy)
- Tests to predict the potential effectiveness of chemotherapy
- Tools for information and communications technologies to enhance cancer data collection, sharing, or analysis

Technologies that are generally not appropriate for this solicitation include the following:

- Companion diagnostics for high-cost drugs that are not affordable in low-resource settings

- Devices that involve highly invasive interventions
- Devices that require extensive user training before they can be used (e.g., FDA definitions moderate and high complexity devices)
- Experimental diagnosis modalities that are not approved in the US
- Technologies not affordable or cannot be maintained in lower-resource settings (e.g., World Bank definitions of low-income and lower middle-income countries)

Expected Activities and Deliverables

Quantitative milestones are required for both Phase I and Phase II projects, regardless of whether they are combined in a Fast-Track application.

It should be noted that low-resource settings have limited healthcare budgets and often struggle to prioritize healthcare needs. Because of the variation in healthcare systems among LMICs and US regions with underserved populations, applicants will need to consult with local partners and organizations (beginning before they submit their application) to develop plans for product design and testing that are suitable to the low-resource setting, including strategies for regulatory approval and reimbursement (if applicable) for the proposed product.

Examples of suitable consulting organizations are local hospitals, medical schools, charities, community groups, non-governmental organizations, and local governmental offices with expertise in the setting. A portion of contract fund can go to these organizations, standard SBIR outsourcing requirements apply.

Phase I Activities and Deliverables

- Develop a working prototype based on adaptation of existing technology, or development of new technology
- Demonstrate the feasibility of the technological innovation for use in a low-resource setting (real or modeled), using a small number of biological samples or animals, where appropriate
- For software/IT tool development, applicants are required to conduct a pilot usability study with at least 25 users
- Deliver to NCI the SOPs of the system for cancer prevention, and/or diagnosis.
- Develop a regulatory strategy/plan and timeline for seeking approval from the appropriate regulatory agency to market the product
- Provide a brief business plan, which is likely to require partnering with healthcare staff local to the low-resource setting of interest

Specific activities and deliverables for applications focused on HPV diagnostics:

- Using end-user design principles, develop the prototype diagnostic device with the following characteristics:
  - Ease of use: the device must be suitable for use by local caregivers with minimal training in its operation and maintenance
  - Operable in locations with limited clinical infrastructure (i.e., design for use outside of laboratory settings)
  - Designed for use at the community level and in non-traditional healthcare settings.
  - Intended for use with self-collected cervicovaginal specimens obtained with one of the current commercially available kits
- Demonstrate a working relationship with the site(s) where the clinical validation study will take place.
- Conduct studies to establish analytical performance (analytical sensitivity, specificity) and other performance characteristics (e.g., limit of detection, consistency, reproducibility) with self-collected samples.
- Conduct studies to evaluate and test user acceptability and feasibility in both average-risk and high-risk (e.g., women living with HIV) populations.
- Conduct initial cross-validation with at least one of the current FDA-approved HPV testing assays to determine the clinical performance measures.

Phase II Activities and Deliverables

- Continue the consultation with local healthcare delivery experts in the low-resource setting of study
- Adapt the prototype device developed in Phase I to the targeted low-resource setting
- Validate the device in the low-resource setting(s) with a statistically significant number of animal and/or human samples, live animals, or human subjects (if animal work or human subjects are involved) for the proposed product. Animal studies are optional and may not be needed for many products supported by this solicitation. Animal studies need only be proposed for products where intermediate testing in animals is thought to be necessary for regulatory approval, or necessary before an IRB will approve a follow-on human study
- Validate the product with a large-scale validation/usability study with at least 100 users if a software/IT tool is developed
- To the extent possible, benchmark the product against existing commercial products used to address the same healthcare need in developed countries and include a description of competitive landscape in the

commercialization plan
- Engage with local state regulatory agency to refine the regulatory strategy
- In the first year of the contract, provide the Program and Contract officers with a letter(s) of commercial interest.
- In the second year of the contract, provide the Program and Contract officers with a letter(s) of commercial commitment, where appropriate
- By the end of Phase II, engage with the appropriate regulatory agency (e.g., US Food and Drug Administration, World Health Organization) to seek and/or obtain marketing approval for the product that was developed.

Specific activities and deliverables for applications focused on HPV diagnostics:

- Develop a well-defined diagnostic device under good laboratory practices (GLP) and/or good manufacturing practices (GMP)
- Perform manufacturing scale-up and production for multi-site and multi-test evaluations, including sites both in the U.S. and at a site in a resource-limited setting
- Demonstrate the clinical sensitivity and specificity of the device for self-sampling by performing multi-site and multi-test evaluations
- Develop a training plan for healthcare delivery users, to help assure progression toward clinical utility and benefit from the validated technology.
- Report on the sustainability/durability of the device/assay

NIH/NCI 441: AT-HOME SCREENING FOR HEPATITIS C VIRUS

Fast-Track proposals **will be** accepted.

Direct-to-Phase II proposals **will be** accepted

Number of anticipated awards: 3-5

Budget (total costs, per award):

Phase I: up to $400,000 for up to 12 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

Hepatitis C virus (HCV) causes both acute and chronic hepatitis, liver cirrhosis, and is a major cause of liver cancer. An estimated 71 million people worldwide have chronic HCV infection and approximately 400,000 people die annually from HCV-related cirrhosis and liver cancer. In the US, approximately 2.4 million people are currently living with HCV and the last decade has seen a 5-fold increase in new HCV infections primarily due to increases in intravenous injections of opioids. The greatest increases in new HCV infections has been in people aged 20-39 years. Highly effective and increasingly affordable direct-acting antiviral (DAA) therapies are now available. Currently, HCV can be diagnosed with a blood test and is curable. The CDC estimated that 50,300 acute hepatitis C cases occurred in 2018 but only 3,621 were reported to them due to under-ascertainment and under-reporting.

In 2020, the US Preventive Services Task Force (USPSTF) recommended HCV screening for people aged 18-79 years, which expands on the previous USPSTF recommendation of HCV screening born between 1945 and 1965. The current screening modality includes screening for anti-HCV antibody serology testing followed by reverse transcriptase-polymerase chain reaction (RT-PCR) testing for HCV RNA and is accurate for identifying patients with chronic HCV infection.

Given the large size of the target population for HCV screening, including populations who cannot or will not undergo clinic-based screening and marginalized high-risk populations, new strategies are needed to increase access and democratize HCV screening. A non-invasive, accurate screening test for HCV exposure or infection would allow initial screening to occur in non-clinical settings including at-home testing. A rapid test for anti-HCV antibodies is FDA approved but not for home use. A recent meta-analysis reported that oral specimens used with current anti-HCV antibody serology tests, including a rapid test, are almost as sensitive for anti-HCV antibodies as using blood. None of these tests have been optimized for use of oral specimens and only one is a rapid test. The development of a rapid and accurate at-home test for HCV antibodies for HCV exposure or HCV antigens or RNA for active HCV infection will provide a readily acceptable and accessible modality that can eventually reduce the burden of liver disease and HCC cancer morbidity and mortality.

Project Goals

The purpose of this solicitation is to develop and validate a rapid, sample-to-answer, point-of-care test for HCV exposure or

active infection that has the following required specifications: 1) can be used as a self-test in non-clinical settings including at home; 2) testing requires only the use of non-invasive specimens that can be safely collected at home such as (but not limited to) blood via finger prick, oral samples (e.g., saliva or buccal cells collections), or urine; and 3) achieves the same analytic performance as predicate tests that use blood for the detection of anti-HCV antibodies as a measure of exposure or HCV RNA or proteins as a measure of active infection.

Activities not responsive to announcement:

HCV diagnostics that do not meet the specifications in the Project Goals will be considered non-responsive. For example, tests that cannot be used at the point-of-care or as a self-test in the home setting will be considered non-responsive.

Phase I Activities and Deliverables:

Offers must propose to conduct activities that lead to development of a working prototype device ready for clinical evaluation, including but not limited to:

- Develop a working diagnostic assay and/or prototype point-of-care diagnostic device that can identify people exposed to or have an infection by HCV using oral salivary specimens, urine, or sample of blood that can be collected using a lancet (i.e., specimens that can self-collected).
- Demonstrate that the prototype diagnostic assay can be operated as a self-test by the target population.
- Determine the sensitivity, specificity, and other performance characteristics (e.g. limit of detection, cross reactivity with other infectious agents, reproducibility, feasibility for newly infected, chronically infected, and resolved infected clinical samples, test stability) of the diagnostic test for HCV.
- Conduct initial testing using samples from animal models and/or preferably on patient isolates to demonstrate feasibility.
- Offerors may need to establish a collaboration or partnership with a medical facility or research group in the US that can provide relevant positive control and patient samples; offerors must provide a letter of support from the partnering organization(s) in the proposal.

Phase II Activities and Deliverables:

- Develop a well-defined test platform under good laboratory practices (GLP) and/or good manufacturing practices (GMP).
- Perform scale-up and production for multi-site evaluations (with at least one independent CLIA-certified laboratory) using clinical isolates.
- Demonstrate suitability and operability of the test for use in non-clinical laboratory settings including self-test (with self-collection of the specimen) at home by target population.
- Establish a product development strategy for FDA regulatory approval (as appropriate).

NIH/NCI 442 – QUANTITATIVE BIOMARKERS AS MEDICAL DEVICE DEVELOPMENT TOOLS FOR CANCER

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

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

Number of anticipated awards: 2-3

Budget (total costs, per award):

Phase I: up to $400,000 for up to 12 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

For existing and novel cancer therapies, there is an unmet need for quantitative biomarkers for selecting patients for targeted therapeutic products as well as for evaluating and predicting therapeutic outcomes faster and with greater precision. These biomarker reference tools are also needed to address challenges associated with heterogeneous or difficult to biopsy tumors. Such biomarkers tests may be considered for qualification by the FDA Medical Device Development Tools (MDDT) Program.

FDA's mission is to protect and promote public health by helping to speed innovations that make medical products safer and effective for the public. The FDA MDDT Program is a mechanism for FDA to qualify tools that companies can use in the development and evaluation of medical devices subject to regulatory decision-making by the Center of Devices and

Radiological Health (CDRH). MDDTs can have a variety of uses/roles in a device clinical study such as patient selection, study population enrichment, monitoring treatment response, predicting or identifying safety problems related to treatment with a medical device, or identifying patients who are or are not candidates for certain forms of therapy. Learn more about the FDA's MDDT Program here.

FDA's MDDT Program collaboration with the NCI SBIR Development Center can help incentivize the small business community to develop these innovative tools in oncology-related regulatory decision-making and disseminate them by selling to industry or academia who are developing new device technologies, or users such as device developers that would benefit from using the MDDT in their regulatory submission. Given these similar areas of interest, FDA CDRH and NCI SBIR have developed this joint contract topic to stimulate and support innovation across our overlapping communities. Potential examples that could be MDDTs include new/high resolution multimodal imaging as biomarkers for detection of various melanomas or difficult to biopsy tumors, or laboratory-based biomarker tests to be used to help regulatory evaluation of diagnostic and therapeutic medical products.

Project Goals

The goal of this contract topic is to stimulate the participation of small businesses in the FDA's MDDT Program to develop quantitative biomarker tests. An MDDT is a method, material, or measurement used to assess the effectiveness, safety, or performance of a medical device. MDDTs can accelerate the device development process by providing developers with measurements and tools qualified by FDA that do not need to be re-evaluated within the context of use which helps streamline/speed device development and FDA regulatory decision-making.

Offerors are expected to have identified biomarkers and tools with the potential to serve in the evaluation of newly developed similar reference tests for patient selection or device safety/effectiveness evaluation by CDRH. Biomarker-based assays that may serve as reference tools and qualify as an MDDT include tests or instruments used to detect or measure a biomarker. Categories of biomarkers that could be used in clinical or nonclinical trials evaluating devices include: susceptibility/risk biomarker, diagnostic biomarker, monitoring biomarker, prognostic biomarker, predictive biomarker, pharmacodynamic/response biomarker, and safety biomarker. CDRH also intends to consider characteristics derived from medical imaging to be biomarker tests.

Activities that fall within the scope of this solicitation include development and optimization of a biomarker-based assay that meets the criteria defined by the FDA MDDT Program. Examples of technologies considered responsive to this solicitation include quantitative biomarker tests for checkpoint inhibitors to enhance cancer patient selection, quantitative imaging methods for assessing therapeutic outcomes, or an algorithm combining various biomarkers to make a comprehensive assessment in therapeutic or safety outcomes in cancer patients.

Phase I Activities and Deliverables:

- Develop a working biomarker-based assay that meets the criteria defined by the FDA MDDT program.
- Prepare an MDDT proposal using the MDDT Qualification Plan Submission Template which includes specific requirements and activities with respect to the proposed MDDT. For additional details review 'Qualification of Medical Device Development Tools - Guidance for Industry, Tool Developers, and Food and Drug Administration Staff.'
- Demonstrate the suitability of the assay for use in a regulatory setting.
- Submit a complete Qualification Plan to the FDA's MDDT Program. It should include description of the MDDT, context of use, and a detailed plan to collect evidence based on the context of use for qualification of the tool. Use the MDDT Qualification Plan Submission Template for this submission.
- Specify the quantitative technical and commercially relevant milestones that will be used to evaluate the success of the biomarker-based assay.
- Develop a regulatory strategy/plan and timeline to file a regulatory application for an MDDT.

Phase II Activities and Deliverables:

- Build the biomarker-based assay according to the specifications developed in Phase I.
- Optimize and demonstrate regulatory/clinical utility and value by testing sufficient numbers of patients from multiple sites to unequivocally prove statistical significance with regards to patient selection.
- Prepare a Full MDDT Qualification Package Submission Template which includes specific requirements and activities with respect to the proposed MDDT.
- Demonstrate the safety and efficacy of the biomarker-based assay in relevant animal models if required by FDA.
- Engage with FDA to refine and execute an appropriate regulatory strategy. If warranted, provide sufficient data to submit a regulatory application to obtain approval for clinical application.

- Submit a Full Qualification Package to the FDA's MDDT Program including the data collected according to the FDA-accepted Qualification Plan. Use the MDDT Qualification Package Submission Template for this submission.

Frequently Asked Questions

1. Who are the potential customers for an MDDT?

MDDTs can be used by other developers, researchers, small businesses, and other industry and research groups who are working to develop technologies in the same space as the MDDT technology. These tools will facilitate the regulatory decision-making process and expedite the development of new technologies, benefiting both FDA and companies with technologies under FDA review.

2. Will FDA or NCI purchase the MDDT?

Offerors must identify the eventual customers for their tool. NCI and the FDA are not potential customers for this product.

3. Are there examples of MDDTs?

Yes, the MDDT page (https://www.fda.gov/medical-devices/science-and-research-medical-devices/medical-device-development-tools-mddt) lists some examples of MDDTs. There are no examples in the biomarker or the dataset spaces, which is one reason that the FDA and NCI are interested in supporting offerors working in these areas.

4. What happens if my tool is not qualified as an MDDT?

You must submit your qualification plan to the FDA by the end of the Phase I contract. CDRH will review Full Qualification Packages submitted at the end of the Phase II contract and make a qualification decision regarding the tool's acceptance as an FDA-qualified MDDT. This risk is mitigated by a company developing their Qualification Plan in accordance with CDRH feedback prior to submitting their final Qualification Plan to FDA. If awarded, companies are highly encouraged to engage FDA early on when developing their Qualification Plan for the MDDT Program.

NIH/NCI 443 – DEVELOPMENT OF COMPUTER-AIDED DIAGNOSIS TOOLS FOR UPPER AND LOWER GASTROINTESTINAL TRACT CANCER PREVENTION

Fast-Track proposals **will be** accepted.

Direct-to-Phase II proposals **will be** accepted.

Number of anticipated awards: 2-4

Budget (total costs, per award):

Phase I: up to $400,000 for up to 12 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 use of computer-aided detection and diagnosis systems with endoscopic procedures has the potential to improve the detection of hard-to-find colonic polyps and esophageal lesions and to differentiate high-risk adenomas and dysplasia from lower risk lesions. Recent data indicate that machine learning, and artificial intelligence can help improve the detection and diagnosis of imaged precancerous lesions in the colon, liver, lung, prostate, and other organs. Because most imaging-aided diagnosis examinations are operator-dependent and thus are limited by operator experience and human error, there is a demonstrable need for systematic, unbiased quantitative approaches to improve detection and diagnostic decision-making and during preventative screening and surveillance.

Computer-aided detection and diagnosis systems for endoscopy are designed to capture all abnormalities including flat or diminutive adenomas and those hidden in poorly visualized areas of the intestine, that are commonly missed with standard endoscopic instruments. However, AI software diagnostic tools are underrepresented at present or have yet to reach their

full potential in the clinical practices. Likewise, the solicited algorithms would detect small foci of dysplasia that often go unrecognized in heterogenous Barrett's esophagus lesions. Thus, these algorithms have the potential to identify characteristics that indicate clinical relevance and cancer risk level of precisely visualized lesions, thereby helping medical professionals perform more effectively and efficiently.

Some companies are currently developing these areas of artificial intelligence and machine learning however, small business and academic institutions can provide an impetus for the development of these technologies and provide important pilot data to determine feasibility that can be further validated either in phase II or independently funded research projects (R21/R01).

Project Goals

The goal of this topic is to solicit proposals to advance the development and application of artificial intelligence-based algorithms to improve the visual human-based determination of precancerous lesions examined through visual inspection of upper and lower endoscopies. The technology should be designed for effective detection and characterization of endoscopic images to properly help decide clinically relevant next steps and to provide physicians with the diagnostic confidence that comes with AI-support.

The activities that fall within the scope of this solicitation include the development and application of algorithms for computer-aided diagnosis of Barrett's esophagus and dysplasia and colorectal polyps and adenomas. Examples of appropriate activities include the development of computer-aided algorithms that can distinguish between low-grade and high-grade dysplasia, precancerous and cancerous lesions of the upper and lower gastrointestinal tract. The offeror may develop only an upper or lower endoscopy computer aided algorithm. Adequate justification for the appropriateness of including multiple diseases or organs (upper and lower GI tract) must be provided if the same algorithm is to be used. Adenoma and dysplasia detection rates are validated quality measures for endoscopy. However, these rates vary based on several factors, endoscopy indication (surveillance vs screening and anatomical location, distal vs proximal colon). A successful computer-aided algorithm shall demonstrate statistically significant improvement of detection rates for each modality compared to standard endoscopy lesion detection rates.

Phase I Activities and Deliverables:

- Establish a multidisciplinary project team with expertise in computer-aided diagnosis, medical imaging software design, informatics, and gastroenterology or medical oncology to oversee the development of software.
- Develop tools for an artificial intelligence-based system that can analyze cell nuclei, crypt structure, and micro-vessels in endoscopic images, for the identification of esophageal or colon neoplasms (including polyps, precancers, dysplasia, and metaplasia).
- Develop an algorithm for evaluating endoscopic images for prediction of progression to more advanced disease and / or response to cancer interception intervention.
- Develop a system where the primary outcome is accurate differentiation between normal tissue, precancers, and cancers.
- Design and build a computer-aided diagnosis (CAD) tool as a prototype.
- Evaluate CAD performance via available (retrospective) image data sets.
- Refine CAD tool as needed to improve performance and sensitivity and specificity.
- Perform small scale usability testing (5-10 end users) at multiple sites.
- Finalize discussion with FDA for regulatory requirements to be completed in the SBIR Phase II.

Phase II Activities and Deliverables:

Offerors must propose activities leading to the manufacturing and regulatory approval of the computer-aided diagnosis (CAD) tool, including but not limited to:

- Validate tools developed in Phase I for an artificial intelligence-based system that can analyze neoplastic and non-neoplastic lesions including polyps, precancers, dysplasia, and metaplasia.
- Clinical validation of the algorithm/AI system for evaluating endoscopic images for prediction of the progression to more advanced disease and / or response to cancer preventive intervention.
- Include all requirements from FDA to be completed in Phase II.
- Build the final version of CAD tool and test with 5-10 end users.
- Design a prospective trial to evaluate CAD tool's ability to distinguish premalignant lesions from high-risk neoplasia at statistical significance level.
- File regulatory submission with FDA for the CAD product for the specific use.
- Develop and implement a commercialization plan for the CAD tool with customers.

NIH/NCI 444 – EVALUATION DATASETS AS MEDICAL DEVICE DEVELOPMENT TOOLS FOR TESTING CANCER TECHNOLOGIES

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

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

Number of anticipated awards: 3-5

Budget (total costs, per award):

Phase I: up to $400,000 for up to 12 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

Oncology data science and analytics is a burgeoning area of machine learning (ML) and artificial intelligence (AI) technologies that have fueled unprecedented levels of interest across the industrial and academic sectors. The past few years have witnessed many startups and large companies focusing on ML/AI technologies with the aim of reducing complexities in clinical workflow or increasing accuracy in detection, diagnosis, and treatment of cancer. To that end large, well-characterized datasets with the best available ground truth/reference standard and relevant metadata are essential for developing machine-based applications in cancer. While tremendous amounts of data are generated through clinical practice, significant gaps remain to leveraging the data for device development and evaluation, including: 1) generation/acquisition of patient outcome data; 2) truthing of images by clinicians; 3) correlation of combined imaging, comprehensive clinical, and genomic data in common repositories for developers; 4) extraction of information from unstructured electronic health records (EHR) data; and 5) availability of infrequent, but clinically relevant, variants. The goal of this topic is to promote and support an unmet need for the development of large, well-curated, and statistically robust datasets that can be used for the evaluation of cancer medical devices subjected to regulation by Center for Devices and Radiological Health (CDRH). Such datasets may be used in scientific research, to develop new devices as a measure of device performance, and have a regulatory use appropriate for the FDA Medical Device Development Tool program. A tool eligible for consideration by the MDDT Program is one that reduces the regulatory burden of industry and the FDA.

FDA's mission is to protect and promote public health by helping to speed innovations that make medical products safer and effective for the public. To qualify a dataset as an MDDT, the FDA evaluates the dataset and concurs with the available supporting evidence that the dataset produces scientifically plausible measurements and works as intended within the specified context of use. More information about the FDA's MDDT Program can be found here. FDA's MDDT program collaboration with the NCI SBIR Development Center can help incentivize the small business community to develop and qualify innovative tools for oncology-related regulatory decision-making. These tools can be sold to industry or academia developing new device technologies that would benefit from using the MDDT in their regulatory submission thus stimulating and supporting translation of innovative devices to the clinic. Given these similar areas of interest, FDA CDRH and NCI SBIR have developed this joint contract topic to stimulate and support innovation across our overlapping communities.

Project Goals

The goal of this contract topic is to stimulate the participation of small businesses in the FDA's MDDT program to develop and demonstrate the utility of qualified datasets as MDDTs to assess medical devices subject to regulation by CDRH. An MDDT can be a method, material, or measurement used to assess the effectiveness, safety, or performance of a medical device. The functionalities of such medical devices run the gamut in the cancer care continuum including prevention, detection, diagnosis, treatment planning etc. Datatypes of interest cover a broad range of data produced by those devices, and include, but are not limited to, imaging (radiology and pathology), cancer genomics, proteomics, structured data extracted from unstructured EHR, and treatment outcome data. In order to achieve the goal of developing datasets as MDDTs for a specified context of use, each dataset may have the following technical characteristics:

- Focused on a specific cancer (i.e., disease site), a specific clinical application (e.g., diagnosis, therapy), and a specific modality (e.g., radiologic imaging systems, microscopy, spectroscopy, genomics, proteomics, laboratory testing, therapeutic or surgical devices, etc.).
- Structured and well-characterized, to include the best available ground truth or reference standard and the relevant metadata and data model to help in device development and evaluation. The truthing process must be clearly described and include an appropriate number of qualified experts.
- Contain a diverse patient demography and an appropriately broad range of data acquisition systems, follow well-

described reconstruction and processing methods, include full details of the imaging systems, protocols, reconstruction methods, etc., and be presented in formats that follow the latest standards, when available.
- Anonymized with respect to the protected health information (PHI) and patient-identifying information (PII).
- Stored and tabulated as an organized collection of data and metadata electronically accessible and searchable by a computer system, and include a concise data descriptor, covering the above requirements.

Offerors are expected to follow the above requirements and conform to the two phases of the MDDT process. Please note that the MDDT process phases are separate from the SBIR phases.

Proposal Phase: The goal is to determine if the MDDT is suitable for qualification consideration through the MDDT Program by submitting a Qualification Plan that includes MDDT description, context of use, and an appropriate plan for collecting evidence to support qualification of the tool for the defined context of use. The FDA makes a decision on whether to advance the tool to the qualification phase.

Qualification Phase: The goal is to determine whether, for a specific context of use, the tool is qualified based on the evidence and justifications provided. The data collected according to the Qualification Plan is submitted as the Full Qualification Package and reviewed by FDA for qualification decision.

During the NCI Phase I contract time period, companies will engage with FDA in the proposal phase and develop their Qualification Plan for the MDDT. By the end of the Phase I contract, companies will submit their Qualification Plan to FDA, and FDA review will determine if the tool is accepted into the MDDT Program. During the NCI Phase II contract time period, companies will complete activities in the qualification phase.

Examples of technologies considered responsive to this solicitation include, cancer diagnostics (e.g., laboratory in vitro, imaging in vivo) and therapeutics (e.g., chemo, radiation, surgery, and immunotherapy).

Activities that would not be responsive under this announcement include datasets solely for the purpose of algorithm training and acquired without proper statistical considerations, or datasets that are applicable to assessing performance of only a single manufacturer's device design.

Expected Activities and Deliverables

Phase I Activities and Deliverables

- Develop a pilot dataset that demonstrates how the data will be collected and what it will look like. In addition to truth data (from the clinician, an alternate modality, or patient outcome), include important patient sub-group information (demographics, disease type and stage, therapies) and information about the source of the data (site, date, sample prep, imaging device make and model, imaging protocol, and post-acquisition image processing, like reconstruction methods).
- Develop an algorithm-assessment plan and corresponding software. Use the pilot dataset to demonstrate the algorithm-assessment plan: performance metric, uncertainty estimation, hypothesis test. This may require simulation or modeling of the dataset and a hypothetical algorithm. This should explore different levels of hypothetical algorithm performance, sources of variability from the algorithm, sources of variability from the dataset, and expected missing data.
- If truth data is from a clinician or alternate modality, characterize the related uncertainty and account for it in all analyses. Multiple clinicians or multiple replicates are needed.
- Identify precision and performance-level parameters necessary for the dataset to become a clinically relevant tool that can be used for testing and evaluation of novel medical devices. This includes a sizing analysis to determine the size of a pivotal dataset following the algorithm-assessment plan. Develop a dataset and a statistical analysis plan for algorithm assessment. The plan should estimate the expected uncertainty of the algorithm assessment results for a range of algorithm performance levels using modeling and simulation.
- Prepare an MDDT Qualification Plan Submission Template using the MDDT Qualification Plan Submission Template which includes specific requirements and activities with respect to the proposed MDDT. For additional details review 'Qualification of Medical Device Development Tools - Guidance for Industry, Tool Developers, and Food and Drug Administration Staff.'
- Demonstrate suitability of the dataset for the targeted test population and planned reference standard(s).
- Submit a complete Qualification Plan to the FDA's MDDT Program. The plan to collect evidence for qualification of the dataset should include details on the data source and planned patient population for the specified context of use. Use the MDDT Qualification Plan Submission Template for this submission.
- Specify the quantitative technical and commercially relevant milestones that will be used to evaluate the success of the dataset.

Phase II Activities and Deliverables

- Collect the pivotal dataset and prepare it for sharing: plan, establish, and demonstrate the sharing platform and methods. Fully document the data.
- Characterize the precision and performance-level parameters of the dataset. If truth data is from a clinician or alternate modality, characterize the related uncertainty and account for it in all analyses. Multiple clinicians or multiple replicates are needed.
- Compare and contrast the pivotal dataset against the simulated and modeled results related to the algorithm-assessment plan and sizing analysis from Phase I.
- Demonstrate clinical utility and value of the dataset for use in testing and assessing novel medical devices.
- Validate the dataset according to the specifications approved by the MDDT program.
- Prepare a Full MDDT Qualification Package Submission Template which includes specific requirements and activities with respect to the proposed MDDT.
- Submit a Full Qualification Package to the FDA's MDDT Program including the data collected according to the FDA-approved Qualification Plan. Use the MDDT Qualification Package Submission Template for this submission.

Frequently Asked Questions

1. Who are the potential customers for an MDDT?

   MDDTs can be used by other developers, researchers, small businesses, and other industry and research groups who are working to develop technologies in the same space as the MDDT technology. These tools will facilitate the regulatory decision-making process and expedite the development of new technologies, benefiting both FDA and companies with technologies under FDA review.

2. Will FDA or NCI purchase the MDDT?

   Offerors must identify the eventual customers for their tool. NCI and the FDA are not potential customers for this product.

3. Are there examples of MDDTs?

   Yes, the MDDT page (https://www.fda.gov/medical-devices/science-and-research-medical-devices/medical-device-development-tools-mddt) lists some examples of MDDTs. There are no examples in the biomarker or the dataset spaces, which is one reason that the FDA and NCI are interested in supporting offerors working in these areas.

4. What happens if my tool is not qualified as an MDDT?

   You must submit your qualification plan to the FDA by the end of the Phase I contract. CDRH will review Full Qualification Packages submitted at the end of the Phase II contract and make a qualification decision regarding the tool's acceptance as an FDA-qualified MDDT. This risk is mitigated by a company developing their Qualification Plan in accordance with CDRH feedback prior to submitting their final Qualification Plan to FDA. If awarded, companies are highly encouraged to engage FDA early on when developing their Qualification Plan for the MDDT Program.

NIH/NCI 445 – ADVANCED MANUFACTURING TO SPEED AVAILABILITY OF EMERGING AUTOLOGOUS CELL-BASED THERAPIES

Fast-Track proposals **will be** accepted.

Direct-to-Phase II proposals **will be** accepted.

Number of anticipated awards: 2-4

Budget (total costs, per award):

Phase I: up to $400,000 for up to 12 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

Current manufacturing processes for autologous cell-based cancer therapies are complex, slow, labor intensive, and expensive. These involve highly personalized methods requiring leukapheresis followed by ex vivo manipulation of cells before a therapy can be administered to the patient. While autologous cell-based therapies offer great promise for cancer treatment, there is growing concern that current manufacturing methods are unable to support the delivery of these treatments to the large numbers of patients eligible to receive them. In particular, the cell processing period between cell isolation and therapeutic administration, referred to as 'vein-to-vein' time, currently takes from 3-8 weeks. Using current methods, medical center laboratories that provide cell-based therapy often have the capacity to treat only 2-8 patients per month, which is insufficient to meet the high demand of clinical trials. Moreover, given that cell-based cancer therapy is still in its nascent stages, higher patient throughput is likely to accelerate the iterative bench-to-bedside-to-bench research that will be needed to improve and mature this treatment modality.

There are several areas where innovation could improve the speed of autologous cell manufacturing, therefore reducing vein to vein time and increasing the number of patients that can be treated. Innovative solutions must propose a key bottleneck in the current system. Responsive proposals could develop systems capable of processing multiple patient samples simultaneously, modify current methods or systems to become novel point of care solutions, or address known release time bottlenecks such as developing rapid QC assays for sterility and potency. Ideal solutions will decrease both the time and cost required to deliver emerging autologous cell-based therapies to a greater number of patients, including those patients with rapidly progressing disease for whom autologous therapies may not currently be feasible. Proposed systems must be capable of optimizing and maintaining the desired physiological and immunological status of the expanded cells, while overcoming issues of cell senescence and exhaustion.

Project Goals

The overall goal of this solicitation is to stimulate the development of advanced manufacturing technologies that substantially improve the speed and cost of producing autologous cell-based therapies. Technical solutions are expected to address a key bottleneck in the current manufacturing process for individual cell-based therapies. Ideal solutions will involve parallel processing, rapid release testing, or point of care technology development, although other approaches may also be considered responsive. New technologies must produce cell-based products of equal or superior quality as compared to current manufacturing methods. The development of scalable systems capable of changing the number of cell products produced simultaneously, is strongly encouraged. For example, technologies may involve a modular engineering approach in which the system can be readily adapted as the demand for autologous cell therapies changes.

To achieve the goals of the solicitation, offerors must be improving upon an existing end to end process that they have experience with, rather than developing end to end processes as part of the project. To be responsive, proposals must involve a collaboration between technology developers and clinical researchers with experience developing and treating patients with autologous cell-based cancer therapies. Projects also including an immunologist on the team will be prioritized. Phase I projects will be expected to involve feasibility testing of the proposed advanced manufacturing technology. A key activity during the Phase I project is to benchmark the novel advanced manufacturing approach against the current manufacturing method for a specific autologous cell-based product. More specifically, the research plan must include validating the proposed novel manufacturing approach against a process that has been used to produce product for clinical trials by demonstrating comparability of products with respect to specific critical quality attributes. Phase II projects will be expected to conduct full-scale processing to demonstrate a substantial increase in the speed and cost of producing autologous cell-based therapies. It is anticipated that most offerors will propose to study T-cell-based immunotherapy products, although other cell types are also encouraged (e.g., NK cells). Advanced manufacturing approaches may involve genetic engineering and optimization as appropriate for the cell-based therapy product, but the primary goal is to achieve substantial cost and throughput improvements for the overall vein-to-vein process.

Activities not responsive to announcement:

Projects proposing to use allogeneic cell-based therapies for technology validation will not be considered responsive under this solicitation. Projects improving a key part of the cell manufacturing process, but not being tested in an end to end process will be considered incomplete proposals and therefore not responsive to the topic.

Phase I Activities and Deliverables:

- Provide proof of collaboration with an immunologist(s), clinician(s), and an engineer(s) if device development activities are proposed. All collaborators must have experience developing high throughput systems and/or treating patients with autologous cell-based cancer therapies;
- Establish assays and/or metrics, especially functional comparability and quality attributes, for benchmarking the approach against current manufacturing methods;
- Establish defined specifications to enable integrated high throughput parallel manufacturing at faster speed and lower cost than current manufacturing methods;
- Develop an early prototype device or technology for integrated high throughput autologous-cell manufacturing

that include specifications designed to substantially reducing the speed, as well as any cost savings based on the new manufacturing approach;
- Demonstrate the suitability of the approach within the cell manufacturing process;
- Demonstrate pilot-scale beta-testing of the approach comparing it against appropriate benchmarking technology;
- Demonstrate the immunological functionality of the cells based on the previously identified functional comparability assays and/or metrics, and compare cell function to appropriate benchmarking technology;
- Establish cell culturing technology compatible with high throughput production and technology to monitor the cells.

Phase II Activities and Deliverables:
- Develop an at-scale prototype of the approach with detailed specifications for hardware/software that supports the manufacturing of autologous cell therapies;
- Generate scientific data demonstrating the proposed scalability (e.g. scale-out, point-of-use) of the technology and demonstrate cost and time improvements over current clinical standard;
- Demonstrate comparable quality between the current manufacturing standard and cell-products manufactured at scale with the proposed approach.

NATIONAL INSTITUTE ON AGING (NIA)

The NIA leads the federal government in conducting and supporting research on aging and the health and well-being of older people. The Institute seeks to understand the nature of aging and the aging process, and diseases and conditions associated with growing older, to extend the healthy, active years of life. As the primary Federal agency on Alzheimer's disease research, NIA has an unprecedented R&D budget to address and develop interventions and therapeutics that prevent the onset of AD/ADRD or that may lead to a cure. The NIA small business program contributes to this overall mission by providing non-dilutive funding to early-stage companies to develop novel technologies related to AD/ADRD and aging longevity.

To learn more about NIA's small business program, please visit our web page at https://www.nia.nih.gov/research/osbr.

NIA Topics

This solicitation invites proposals in the following areas:

NIH/NIA 004 - Improving CNS Gene Delivery Systems for AD/ADRD Therapy Development

Fast- Track proposals will be accepted.

Direct-to-Phase II proposals will be accepted for companies that have already demonstrated feasibility and rigorously achieved the deliverables in described for Phase

Number of anticipated awards: 2 to 5

Budget (total costs, per award): Phase I: $500,000 for 12 months; Phase II: $2,500,000 for 2 years

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

Summary:

To improve, diversify, and reinvigorate the AD/ADRD drug development pipeline, the NIA has spearheaded several innovative programs including the Accelerating Medicines Partnership-Alzheimer's Disease (AMP- AD), aimed at identifying the next generation of therapeutic targets. These target discovery programs have identified and made publicly available more than 500 novel candidate targets (to view the list of targets and supporting evidence see the open-source platform Agora) . Detailed assessment of these nascent targets using a standard biopharma target tractability evaluation has revealed that a significant number of them have low small-molecule druggability. Therefore, an expanded tool- kit of therapeutic modalities to include traditional biotherapeutics (i.e. genome editing, gene silencing, and proteins) will be required to integrate many of the next generation targets into drug discovery campaigns. This contract focuses on gene therapy, which has the advantage over protein therapy to target specific cells for gene transduction leading to production or deduction of proteins precisely where therapy is needed. For gene delivery, adeno-associated virus (AAV)-vectors are widely used gene delivery vectors for gene therapy due to features such as tissue tropism, potential of gene transfer to non-dividing cells, and long-term expression. However, vectors have several challenges including low biodistribution and brain delivery, high immunogenicity, and limited payload size. Therefore, this contract proposal focuses on gene delivery system optimization to be used for AD/ADRD gene therapy development.

Project goals:

Drug delivery systems are engineered technologies to help with the transport of therapeutic agents to a therapeutic target. This can involve movement through the circulatory system and further through cells of the blood-brain-barrier (BBB). The BBB is the biggest limiting hurdle to deliver a drug to the brain, and this is especially true in the case of gene delivery. The current mode of administration that is typically used for brain delivery for gene therapy is the highly invasive intrathecal administration, while other methods such as intravenous injection would provide less physical burden on the patients. AAV-vectors are currently known as the most advanced gene delivery vector and are used to transduce therapeutic genes to the CNS site for treatment of neurodegenerative disorders. Many AAV serotypes have been developed using capsid modification strategies, but each serotype has various limitations associated with brain delivery, cell-type targeting, immunogenicity, biodistribution, and payload size. Novel gene delivery systems can strive to overcome these challenges by providing safer and more flexible routes to gene delivery. By engineering new delivery vehicles using novel biomaterials or delivery modalities, gene therapy can have enhanced stability and bioavailability, decreased immunogenicity, increased brain delivery, and improved cell-type targeting. Novel delivery vehicles can include (but are not limited

to) nanoparticles, liposomes, micelles, and Trojan horse approaches; examples of novel delivery modalities can include ultrasound, electroporation, and implantable pumps. The short-term goals of this contract proposal are development of a gene delivery system and proof of concept in vivo testing for Phase I, and long-term goals are further development leading to IND submission to the FDA for Phase II.

Phase I Activities and Expected Deliverables:

- Details concerning special formulations or technologies (i.e., slow release, liposomes, nanoparticles, etc.).
- Perform in vitro efficacy studies in the relevant cell line(s)
- In vivo study results that include assessment of pharmacokinetics and bioavailability at the relevant site of action.
- Rigorous evidence that the agent is blood-brain-barrier penetrant.
- Immunogenicity evaluations
- Evaluation of metabolism.

Phase II Activities and Expected Deliverables:

- PK evaluations in species relevant for toxicology or human dose-prediction
- Efficacy of gene therapy in a disease-relevant model
- Testing delivery to target cells in a large animal species, as appropriate
- Preliminary safety such as safety pharmacology and/or dose-range finding toxicology
- IND-enabling toxicology, with toxicokinetics, if applicable
- Tumorigenicity evaluations
- Chemistry, Manufacturing, and Control (CMC) activities (e.g., master and working cell banks development, purification development, CMC analytical development, formulation development, scale-up manufacturing or cGMP manufacturing) for IND-enabling pharmacology/toxicology tests, as appropriate
- IND document preparation and/or pre-IND meeting
- GMP manufacturing of material for phase I clinical testing, if applicable

NIH/NIA 005 - Geroscience-based Chronic wound treatment product development

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

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

Number of anticipated awards: 1 to 2

Budget (total costs, per award): Phase I: $350,000 for 12 months; Phase II: $2,500,000 for 2 years

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

Summary:

Ulcerative wounds, including venous leg ulcers, diabetic foot ulcers and pressure ulcers, occur more commonly in older adults and their impaired healing is associated with underlying and comorbid diseases of aging, and defects of wound repair. The incidence of chronic wounds, those that are difficult to heal or do not follow a normal healing process, increases with age from the sixth to the ninth decades. Chronic wounds rarely occur in persons without multiple chronic conditions, and specific comorbid conditions exacerbate them, notably malnutrition and metabolic syndrome. Delayed wound healing increases the risk of recurrent infection and tissue necrosis.
This results in substantial morbidity, disability, hospitalization, and even mortality among older adults. Using just one clinical example, an older person with diabetes can develop a foot ulcer, it may progress and fail to heal, necessitate a foot or toe amputation, and ultimately increases the risk of death.

Until recently, approaches to chronic wound treatment have been primarily mechanical barriers and frequent dressing changes, including skin substitutes (such as acellular dermal substitutes, cellular dermal substitutes, and cellular epidermal and dermal substitutes), medical devices, and care processes such as surgery. These products are not regulated based on demonstrating

effectiveness, and comparative studies have been rare without identified superior approaches. Recent advances in the understanding of the wound-healing process have led to innovative clinical approaches to wound care including the use of stem cells, growth factors and bioactive materials to support the body's own regenerative capacity, but these approaches have not yet obtained regulatory clearance or approval by the Food and Drug Administration (FDA).

Project goals:

This initiative proposes to fund development of a new geroscience-based approach to treating chronic wounds. Novel geroscience-based approaches may target relevant mechanisms of wound healing including stem cell therapies, cell senescence, inflammation, adaptation to stress, epigenetics, metabolism, macromolecular damage and/or proteostasis. Cellular senescence was initially described by Hayflick and Morehead in 1961, and more recent work has shown that senescent cells can negatively affect their local tissue environments through multiple pathways. The inflammatory response following tissue injury has important roles in both normal and pathological healing. Inflammatory cells, cytokines and growth factors all play key regulatory roles in the complex series of events during wound healing.
Among potential inflammatory targets for wound healing therapeutics, the macrophage may be an attractive target, both in terms of reducing fibrosis and scarring, and to improve healing of chronic wounds. Vascular responses to stress may be adaptive in the wound healing process. Several epigenetic regulatory factors, such as the endogenous non-coding microRNAs, have been demonstrated to be drivers of the wound healing response. Metabolic considerations relevant to wound healing are also important and include the collagen metabolism requirements, and impairments from neuropathy and metabolic disruption in diabetes.

The goal of this solicitation is to call for the development of a geroscience-based wound healing product which may include but are not limited to: cellular products and therapies, immune modulation, microbiome-modifying therapy, human tissue, animal-derived tissue, and biosynthetic products. The product would be developed for clinical application to chronic non-healing wounds, in conjunction with current standard therapies.

Proposals should establish proof-of-concept for and/or support preclinical development of a candidate geroscience-based wound healing product, as well as standardize methods to evaluate wound healing and safety of the candidate product(s). Proposals that significantly advance a candidate product toward clinical development are highly encouraged. Offerors must outline in their proposal the preliminary data supporting selection of the geroscience-based product for wound healing, specific clinical question and unmet clinical need in the areas of chronic wound healing that their product will address. This RFA would solicit a Phase I project for a small business to advance development of their geroscience-based wound healing product. The activities could include pre-clinical development and feasibility testing in Phase I and might involve developing the design of a comparative clinical trial that might comprise a subsequent Phase II for treating older adults with chronic wounds to induce healing.

Activities not responsive to announcement:

Proposals that are limited to existing FDA approved or cleared therapies for wound healing or their equivalent (dressings, barriers, skin substitutes, etc.) would be considered non- responsive.

Phase I Activities and Expected Deliverables:

- Select one geroscience-based potential wound healing product (drug, cellular product or drug-device) and develop and test the prototype.
- Show differentiation of this product relative to other wound care products in terms cost, ease of use, efficacy, side effects, etc.
- Conduct non-clinical toxicology studies (e.g., sensitization, immunogenicity) (optional)
- Complete adequately powered animal trial with appropriate wound-healing endpoints (as appropriate for stage of development)
- Complete preparatory steps for human studies (as appropriate: e.g., finalize protocol, data and safety monitoring plan, obtain IRB approval). (if applicable)
- Perform human usability studies for the prototype with at least 10 subjects (ideally, but not required)
- Develop regulatory strategy/plan and timeline for seeking approval from FDA to conduct human trials or market the product (as appropriate).

Phase II Activities and Expected Deliverables (Phase II information is provided only for informational purposes to assist Phase I offerors with their long-term strategic planning):

- Conduct sterility and pharmaceutical testing
- Perform in vitro studies of product release over time
- Perform in vivo pharmacokinetic and biodistribution (PK /BD) studies

- Complete adequately powered human trial with appropriate wound-healing endpoints (ideally, but not required)
- Complete preparatory steps for human studies (e.g., finalize protocol, data and safety monitoring plan, obtain IRB approval).
- Develop commercialization plan that includes a go-to-market strategy and include comparable reimbursements, manufacturing, and distribution

NIH/NIA 006 - The Development of Mechanism-based Adult Stem Cell Treatments to Combat Aging Pathologies

Fast- Track proposals will be accepted.

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

Number of anticipated awards: 1 to 2

Budget (total costs, per award): Phase I: $350,000 for 12 months; Phase II: $2,000,000 for 2 years

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

Summary:

Americans are living longer than ever before. Life expectancy nearly doubled during the 20th century with a 10- fold increase in the number of Americans age 65 or older. As life expectancy increases, diseases and conditions that are associated with older age have become a major health burden. A major risk factor for the development and progression of some of the most prevalent late onset declines in function and health, such as wound healing, osteoporosis, sarcopenia, joint soft tissue deterioration and others are thought to be contributed by depletion or dysfunction of stem cells.

Stem cell rejuvenation via heterochronic parabiosis in mice has demonstrated blood stem cells and their factors from young mice contribute to improved wound repair and motor function in old mice. It has also been demonstrated by the ability to generate "youthful" induced pluripotent stem cells derived from aging tissues. In addition, the development of novel adult stem cell-based therapies is on the rise and include the use of adult stem cells or biologics that facilitate healthy repair after orthopedic surgeries and in wound repair. However, the majority of these studies have based their efficacy and mode of action using young animal models despite the need and market pressure to treat older people. Thus, a better understanding of how aging stem cells or tissue environments respond to potential treatments is needed. The goal of the SBIR contract topic is to support small businesses that are in the early to mid-developmental stages testing adult stem cell or related biologics in aging animal or aging human tissue models to develop novel adult stem cell treatments.

The impetus of this SBIR contract solicitation is to promote full use of the base of knowledge of stem cell biology for adult stem cell-related target validation and drug discovery and development for treatment and prevention of age-related afflictions. This initiative is intended to encourage and support young, upstart biotechnology companies and also more established firms to direct their efforts into new ventures in stem cell therapeutics that target the increasing aging population. Great advances have been made in the past decade in our understanding of adult stem cells in health and in aging. Many molecular processes that have gone awry during cellular aging have been identified, and new information on the difference between a young and aged stem cell continues to be added to this wealth of knowledge. It is now incumbent that this knowledge be used to mount a new direction that targets the use of this knowledge to facilitate tissue regeneration and rejuvenation of aged stem cells and to use stem cell technologies to target treatments that afflict the aging population. While the empiric approaches of stem cell therapies are on the rise, this new paradigm demands a more reasoned and knowledge-based approach. The search for molecules or agents with translational potential that will rejuvenate or subvert the deleterious effect of aging on adult stem cells or the study of biologics and the pursuit of knowledge of the molecular mechanisms that they target which facilitate the regeneration of aging tissues will be an important component of this SBIR contract solicitation. These agents could be chemical or biological, manmade or naturally occurring, but well characterized or subject to characterization as potential therapeutic agents for age-related afflictions. Areas of focus may include improved tools, methods, standards, or applied science that support a better understanding and improved evaluation of in-depth product characterization, manufacturing, potency, identity, quality, safety, in vivo function and integration, or effectiveness. The development and utilization of modern tools for target validation and drug discovery, including combinatorial libraries and high throughput screening, would be appropriate. However, the development of new assays and innovative technologies for monitoring stem cell maintenance and differentiation will not be sufficient; their development in conjunction with molecular target identification and validation, and drug discovery and development will be appropriate.

Applicable research may also include developing biologics (e.g., growth factors, cytokines) and biomaterials (e.g., extracellular matrix, scaffolds) that stimulate an older adult's stem cell self-renewal, proliferation, differentiation, and/or function or otherwise directly act upon adult stems cells to support innate host healing mechanisms, treat disease, and/or restore function. Funding could also be used for the appropriate chemistry, manufacturing, and controls development to support the production of such products for aging clinical trials using current good manufacturing practices (cGMP).

Project goals:

This contract will support research directed toward developing therapeutics with clearly established proof of mechanisms to facilitate aging tissue regeneration at the molecular, cellular, tissue organism level. The goal is to provide evidence for a stem cell-based product with defined direct and/or indirect alterations of cellular and/or molecular processes (senescence, inflammation, metabolism, DNA repair, etc.) that contributes to its therapeutic use for the aging community. Projects will include in-depth aging stem cell characterization (RNA-seq, proteomics, metabolomics, etc.) including responses in senescence and inflammation using cells, tissues, or animals. Appropriate applications will span a diverse range of technical and methodological approaches in an effort to generate adult stem-cell based therapies that can facilitate regeneration and repair for aging, mechanisms of their action, and how this knowledge may be exploited for the identification and development of novel therapeutic targets. Emphasis will be given to projects that focus on developing stem cell-based strategies and to define their molecular and/or cellular mechanisms that promote healthy stem cell aging or treatment of age-related diseases.

Research projects responsive to this FOA are expected to involve aging models which may include human and nonhuman aging cells and tissues and may include human or nonhuman adult stem cells. Research projects involving human or animal induced pluripotent stem (iPS) cells may be supported, as long as the cells used to generate the iPS cells were not of fetal or embryonic origin. Offerors must outline in their proposal the product, the molecular or cellular mechanism of action, and detailed characterization of the biologic and/or adult stem cells involved in the therapy-based approach as well as the unmet needs required to treat the aging population with stem cell-based strategies.

Inclusion: The emphasis to study the role of stem cell-based therapies in the aging population will help fulfill the commitment NIH solidified in 2020 for inclusion across the lifespan by expanding the importance and relevance of this research in an aging body.

Special Note: This initiative also supports the 21st Century Act for the Regenerative Medicine Initiative to facilitating getting these therapies into the clinic. These awards started four years ago with no further allotted support from the original allotment of $20 Million.

Activities not responsive to announcement:
The following will not be supported under this FOA and will not proceed to review:
- Research that does not utilize aging cells, tissues, or animal models
- Any research using embryonic or fetal stem cells. Such projects are non-responsive.

Phase I Activities and Expected Deliverables:
- Product testing of adult stem cells and related biologics in the aging body
- Product testing may include autologous adult stem cell transplants in animal species, exosomes, metabolites, non-translating RNAs, blood components including but not limited to exosomes and non=translating RNA
- Physiological, molecular and cell characterization of the mechanism of action for adult stem cell-based treatment for repair or regeneration of aging tissues. Included are changes in stem cell or hose tissue replication, maintenance, differentiation, senescence and inflammatory responses
- Preclinical studies that contribute to conducting clinical trials that address specific clinical indications
- Development of methods, standards and cGMP for adult stem cell-based RM products for using in aging
- Phenotypic assay development, including stem cell technology platforms for stem cell "Aging-in-a-dish" applications and the evaluation of toxicity
- Identification and validation of specific biological markers or biosignatures for aged adult stem cells including stem cell characterization and deep fingerprinting
- Demonstrate in a small-scare, proof-of-concept study with in vivo animal studies or ex vivo human cells or tissue assays the feasibility of the product as potential treatment for age-related affliction. Feasibility assays including proper controls should provide

insight into whether the product can either accelerate or enhance standardized treatment pricated or provide treatment where there are no currently effective treatment options. This study should be designed to assess the sensitivity and specificity of the molecular mechanisms involved in the repair or regeneration of aging tissue

- Deliver to NIA the Standard Operating Procedures of the system for treating the aging dysfunction
- Develop a regulatory strategy/plan and timeline for seeking approval from FDA to market the stem-cell based product

Phase II Activities and Expected Deliverables:

- Refinement or modification of tools, methods, standards, or applied science that support a better understanding and improved evaluation of in-depth product characterization, manufacturing, potency, identity, quality, safety, in vivo function and integration, or effectiveness for treating the aging population
- Emphasis will be given to projects that address critical issues needed for product development relevant for regulatory submissions
- Demonstrates readiness of regenerative medicine products with well- characterized quality attributes for advancement into clinical trials under an IND/IDE application to treat aging patients
- Addresses critical issues relevant to clinical research and regulatory submissions, including those related to improved evaluation of product quality for aging
- Helps to significantly advance the field of regenerative medicine for the aging population by addressing well-recognized challenges in clinical development to treat the aging population, including the development and evaluation of safe and effective RM products
- Perform a large-scale usability study with at least 100 *in vivo* animal studies or 500 *ex vivo* human cells or tissue assays.
- Perform a large-scale validation study in *in vivo* animal studies or *ex vivo* human cells or tissue assays. The study should be designed to show a statistically significant improvement in the performance of the treatment
- Optimally, by the end of Phase II the offeror will be able to both demonstrate commercial partnering/investment interest and submission of a regulatory application to FDA

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.

NIAID Topics

This solicitation invites proposals in the following areas:

NIH/NIAID 101 - Novel Platforms for Delivery and/or Expression of HIV Env Immunogens for HIV Vaccines

Fast-Track Proposals will be accepted.

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

Number of anticipated awards: 2-4

Budget (total costs):

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

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

Background

Efforts towards the development of an efficacious HIV vaccine have focused on improvements in the design of the HIV envelope (Env) immunogen for induction and generation of broadly neutralizing antibody (bNAb) responses and novel platforms for immunogen delivery. One major hurdle for the induction of bnAbs is that the B cell lineages for these antibodies are found at extremely low frequencies; further, the naïve B cell receptors of these lineages may only recognize an HIV envelope from the transmitted infecting virus. Therefore, considerable efforts have focused on HIV envelope design to target these rare germline B-cells receptors including minimal epitopes and modified stabilized Env trimers. Once these naïve, germline B-cell receptors have been triggered, more native-like HIV Env immunogens may be designed to drive B cell maturation and evolution towards Ab breadth.

Additionally, effective activation of rare B cell lineages will probably require an alternative delivery platform of immunogens compared to vaccination with just soluble Env immunogens. Improvements to the delivery system of these next-generation HIV Env immunogens could include multivalent antigen presentation, targeted delivery to lymph nodes, sustained antigen release, coupled co-delivery of adjuvants, etc. It is expected that the improvements to Env design coupled to improved delivery methods may increase the probability of engaging rare bNAb B cell precursors, enhance affinity maturation, and improve antibody magnitude and durability. This topic will selectively focus on the development of platforms for the delivery of HIV immunogens; immunogens may be either based on protein or nucleic acid-based design. Co-delivery of adjuvants can be included with the vaccine delivery platform.

Project Goal

The goal of this project is to develop an HIV vaccine platform for delivery of HIV Env immunogens that induce bnAbs. The platforms may include, but not be limited to: lipid- or polymer-based nanoparticles (NP) or equivalent multimeric antigen display platform and may contain immune-stimulators, such as adjuvants; the immunogen may either be recombinant protein (minimal epitopes, optimized trimers, etc.) or nucleic acids (RNA or DNA) expressing HIV Env proteins and/or Env proteins covalently linked to NP or multimerization domains. The goal will be to demonstrate that the vaccine platform/immunogen proposed will elicit a strong and durable NAb HIV Env response.

Phase I activities may include, but are not limited to:

- Engineering and fabricating nanoparticle platforms/systems and approaches (such as synthetic, self-assembling particles, conjugating technologies to attach HIV antigen to nanoparticles, lipid encapsulating technologies, etc.) for delivering existing and/or novel HIV Env immunogens (minimal epitope, native and/or native-like trimers either as a recombinant protein or expressed by nucleic acids/mRNA/self-amplifying RNAs).

- Developing and evaluating particulate systems (described above) that can facilitate co-delivery and/or co-formulation of HIV antigens (described above) with adjuvants (such as existing, licensed, biosimilar novel adjuvants/TLR agonists).
- Developing optimal parameters/conditions for incorporation of HIV Env antigen(s) into nanoparticulate formulation.
- Developing assays and test methods to analyze and characterize molecular properties of the particulate-antigen formulations through *in vitro* (biophysical, physicochemical, binding assays) and/or *in vivo* testing (small animal studies).
- Studying conditions for controlling particle size and size distribution, charge, composition, and aggregation.
- Evaluating particulated formulation technologies for fabrication and development of HIV vaccine development.
- Developing an efficient process for early-stage/pre-clinical studies, which could be adapted to scale-up studies and which can subsequently lead to the production of clinical-grade material in conformance with the Current Good Manufacturing Practice (cGMP) regulations.
- Evaluating the delivery, immunogenicity, and effectiveness of particle-based HIV vector platforms in small animal models.
- Investigating the effects of route of immunization, dose, dosage form, and dose-sparing capacity of particulate formulations on the particle distribution and kinetics of the immune response to the immunogen.

Phase II activities may include, but are not limited to:
- Developing lead vaccine formulation into an efficient, stable, and reproducible process.
- Generating a pilot lot and/or scale-up studies based on optimized conditions that can subsequently lead to the production of clinical-grade material in conformance with the cGMP regulation.
- Developing cGMP manufacturing processes for developing nanoparticle formulations.
- Translating *in vitro* studies into proof-of-concept studies in nonhuman primates, as warranted.
- Developing methods to evaluate compositional quality on critical components in nanoparticles, for example, but not limited to, quality, manufacturability, and stability/degradation of lipids and related components.
- Evaluating the performance, effectiveness, and toxicity of particulated HIV vaccine candidates compared to soluble antigen in small animal models.
- Establishing quality assurance and quality control, methodology, and development protocols for the generation of HIV antigen-adjuvanted formulations for codelivery.

NIH/NIAID 102 - Genetically Engineered Mice for Pre-clinical Evaluation of HIV Vaccine Candidates

Fast Track Proposals will be accepted.

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

Number of anticipated awards: 1-3

Budget (total costs):

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

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

Background
The development of novel HIV candidate vaccines generally requires preclinical testing in animal models before proceeding to Phase I clinical trials. Multiple efforts have focused on developing and evaluating innovative platforms and formulations of HIV envelope (Env) immunogens for the induction and generation of a durable and broadly neutralizing antibody (bNAb) response. Progress has been hampered, in part, due to the lack of an iterative, physiologically relevant, small animal model to test novel HIV vaccine candidates, concepts, and formulations that elicit bnAbs. Human immunoglobulin (IgG) gene knockin (KI) technology has been used to engineer mice with relevant pre-rearranged V(D)J exons of mature bnAbs or un-rearranged human V, D, and J segments to generate the desired bNAb lineage. There is a need for methodological improvements of existing KI models and creation of new lines using current state-of-the-art, e.g., genome editing technologies. Several limitations due to immune tolerance mechanisms in mice need to be overcome. Humanized mice may express B cell precursors of the desired bNAb germline lineage at more variable frequencies than found in humans; other germline genes may not be functionally expressed due to the inability to overcome B cell tolerance mechanisms, yet others may be lethal to the mouse line. Existing mouse lines and novel improved second-generation human immunoglobulin KI mice or those generated by crossbreeding to other transgenic mice expressing relevant immunological receptors may

expedite translation of HIV vaccine concepts. Such strains could be used to rapidly test, for instance, HIV vaccination strategies, contribution of B cell precursor frequencies to elicit a robust bNAb response, factors that modulate B cell dominance and sub-dominance, affinity maturation (AM), somatic hypermutations (SHM), and factors that drive germinal center responses. This topic will focus on evaluating proof-of-concept HIV vaccine strategies in existing KI models or in newly created next-generation KI and transgenic mice to accelerate translation of HIV vaccine candidates for testing in Phase I clinical trials.

Project Goal

The goal of this project is to utilize genetically engineered mouse models, such as human immunoglobulin KI or other transgenic mice expressing relevant human genes, to accelerate testing and development of HIV vaccine candidates. Genetically engineered mice expressing human genes, for example, V(D)J immunoglobulin genes, Fc receptors, and/or other protein receptors on diverse cell types and further modified with gene-editing technologies, such as CRISPR-Cas, should offer an iterative, robust, small animal platform for rapidly testing HIV vaccine immunogens and formulations. Such models may lead to the generation of a flexible preclinical model that more accurately reflects the human humoral immune response. Ultimately, development of a predictive *in vivo* small animal model could accelerate testing of novel HIV vaccine concepts into Phase I clinical trials.

Phase I activities may include, but are not limited to:

- Investigation of proof-of-concept HIV vaccine studies in existing KI models that express human IgG germline genes of bnAbs, e.g., unmutated common ancestors of HIV bnAbs lineage
- Modulation of the human B cell repertoire in existing KI models to elicit a bNAb response to HIV vaccine immunogens and particle-based HIV vector platforms
- Determination of mechanism(s) required to elicit a bNAb response to HIV vaccine candidates
- Determination of *in vivo* factors contributing to a weak humoral response, e.g., B cell tolerance, anergy, clonal deletion, sub-dominance
- Identification of immunogen platforms that will elicit a rapid, robust, and durable humoral response in the mouse model
- Measurement of neutralizing bnAbs of B cell lineages and other functions (e.g., non-neutralizing) of antibodies in response to HIV immunogens
- Testing antibody-antigen and adjuvant formulations that promote successful B cell responses during vaccination
- Evaluating the performance, effectiveness, and toxicity of particulate HIV vaccine candidates versus soluble antigens in KI models
- Investigating the effects of route of immunization, dose, dosage form, and dose-sparing capacity of particulate formulations on the particle distribution and kinetics of the immune response to the immunogen

Phase II activities may include, but are not limited to:

- Creation and development of next-generation pre-clinical genetically engineered mouse model(s) for the rapid evaluation of HIV vaccine candidates and testing immunogen-guided bNAb lineage HIV vaccine concepts
- Rapid creation of novel lines of human IgG KI models by crossbreeding with other transgenic mice expressing relevant human genes to enhance bnAbs to HIV immunogens
- Testing proof of concept studies, outlined as Phase I activities, in next-generation, novel KI models
- Characterization, genotyping, and detailed phenotyping of new mouse models associated with existing mouse strains and made publicly available, if applicable
- Ensure availability of the newly created mouse models to academic, government, and private sector scientists, for example through NIH-supported mouse repositories
- Creation of the cryopreserved archive for all new strains of mice, to enable storage of strains, for which there is no immediate need and serve as a backup supply of pathogen-free and genetically stable genetically engineered strains
- Establishment of a live, specific pathogen-free colony for research use and distribution for a mouse strain upon request (Animal genotype should be verified, and health and disease status should be assessed.)
- Maintenance of the breeding colonies to be conducted using standard breeding schemes appropriate to the strain, with maintenance of pedigree records
- Maintenance as a live breeding colony for several months, if needed, after which it is retired to the cryopreserved archive if no further use or interest is expressed or if no orders are received.

This SBIR will not support:

- The design and conduct of clinical trials (see http://www.grants.nih.gov/policy/clinical-trials/definition.htm for the NIH definition of a clinical trial)
- Testing non-HIV immunogens or studies unrelated to HIV vaccine development efforts
- Humanized mouse models engrafted with human cells or human fetal tissue (such as hu-PBL, hu-CD34, and BLT mice)

- Investigation of transplantation, autoimmune diseases, allergic diseases, other immune-mediated diseases, and cancer.

NIH/NIAID 103 - Development of Diagnostics to Differentiate HIV Infection from Vaccine Induced Seropositivity

Fast Track Proposals will be accepted.

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

Number of anticipated awards: 1-3

Budget (total costs):

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

Phase II: $ 2 million for up to 3 years.

Background
HIV/AIDS continues to be a major health problem throughout the world, with the greatest impact on vulnerable and underserved populations. A safe and effective HIV vaccine has been pursued for several decades. Ongoing efficacy trials with the latest HIV vaccine candidates can change this scenario and may lead the way to approval of a licensed vaccine in the near future.

Several years of clinical trials have revealed that some HIV vaccines can elicit long-lasting (>15 years) serological immune responses that can be confused with HIV infection in common diagnostic tests. This phenomenon, known as vaccine-induced sero-reactivity or sero-positivity (VISR/VISP), can severely impact several life aspects of clinical trial participants: immigration, marriage, military service, blood/organ donation and employment, among others. VISR/VISP seems to be more prevalent with vaccines that incorporate (completely or partially) the gp41 region of the HIV envelope. Although a VISP result can be differentiated, most of the time, from a true HIV infection by nucleic acid tests (NAT) (e.g. RT-PCR), these are more expensive and technically challenging tests, and not always readily available. Furthermore, deployment of NATs might not be the single solution to VISP. In fact, the use of highly active antiretroviral therapy (HAART) or pre-exposure prophylaxis (PrEP) therapies can cause false-negative NAT results due to undetectable viral load. Previous attempts to develop a serological test agnostic to responses elicited by HIV vaccine candidates failed to reach the high sensitivity and specificity demanded by the regulatory agency (>99% sensitivity and specificity). The parallel detection and/or quantification of IgM and IgG antibodies against antigens absent in HIV vaccines, such as peptides of gp41, and systemically circulating HIV antigens, such as p24, are promising approaches.

In order to prepare for the deployment of an HIV vaccine, after FDA registration and approval, companion diagnostic tests must be in place to avoid the problems associated with VISR/VISP in vaccine recipients.

Project Goal
The overarching goal of this project is to support the development of new serological and nucleic acid assays that can identify HIV infection while avoiding false-positive results due to VISP, with high sensitivity and specificity. These next-generation assays should be developed to address one or all applications/indications of HIV tests, namely: (1) laboratory-based tests; (2) point-of-care and clinical practices; and (3) self-testing.

Ideally, these assays should be scalable and adaptable for manual performance (point-of-care, medical practices and self-testing) as well as fully or partially automated for high throughput (medical laboratories). They can be developed for performance in already existing, commercially available platforms and automated equipment or for performance using new devices.

The newly developed assays should accept different biological samples, such as serum/plasma, whole blood, and saliva, although the specific application/indication might dictate the best sample collection method to reach the highest assay performance. During the development and qualification of the new assays, the proper algorithm for each application/indication should be defined.

Since test(s) will also be deployed in low-to-middle-income countries and remote areas, dependency on refrigeration and electricity must be kept to a minimum and shelf life should be maximized. Special attention must be given to how results are obtained or communicated in order to protect confidentiality and privacy. Finally, production and operating costs should be

as low as possible to make it affordable to individuals and institutions, and practical for repeated testing by the end-user.

Phase I activities may include, but are not limited to:
- Development of Target Product Profile to address applications and assay performance indicators;
- Development of assay concept/methodology and assessment of feasibility;
- Generation/procurement of critical reagents and controls;
- Pilot studies with prototype methodologies and antigens and/or nucleic-acid targets/sequences to determine feasibility;
- Development of SOPs for the assay(s);
- Primary assessment of sensitivity, specificity, low limit of detection, and linearity; and
- Small scale screening of biological samples.

Phase II activities may include, but are not limited to:
- Market assessment and cost analysis;
- Development of testing workflow for a specific product application/indication;
- Adaptation of methodologies to equipment (different degrees of automation);
- Large scale testing of biological samples and assessment of equivalence;
- Assay validation (establishment of sensitivity, specificity, low limit of detection, and linearity and precision); and
- Submission for FDA approval.

This SBIR contract topic will NOT support:
- The design and operation of clinical trials (see http://www.niaid.nih.gov/researchfunding/glossary/pages/c.aspx#clintrial for the NIH definition of a clinical trial); and
- Testing non-HIV immunogens or studies unrelated to HIV vaccine development efforts.

NIH/NIAID 104 - Adjuvant Discovery for Vaccines and for Autoimmune and Allergic Diseases

Fast-Track proposals will be accepted.

Direct-to-phase II 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 with appropriate justification by the applicant 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 the treatment of autoimmune or allergic diseases. For the purpose of this SBIR, the definition of vaccine adjuvants follows that of the U.S. Food and Drug Administration (FDA): “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 transplantation, or environmental antigens in allergic diseases.

Currently, only a few adjuvants other than aluminum salts (“Alum”) have been licensed as components of vaccines in the United States (U.S.): 4’-monophosphoryl lipid A (MPL), adsorbed to alum as an adjuvant for an HPV vaccine; MPL and QS-21 combined in a liposomal formulation for a varicella vaccine; CpG Oligodinucleotide as an adjuvant for a recombinant Hepatitis B vaccine; and the oil-in-water emulsion MF59 as part of an influenza vaccine for people age 65 years and older.

In addition, adjuvants may facilitate the development of immunotherapeutics for 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 U.S. and immune-mediated diseases are treated mostly with broadly immunosuppressive drugs or long-term single- or multi-allergen immunotherapy. In contrast to drugs, tolerogenic or immunomodulatory adjuvants may regulate immune responses to specific antigens through a variety of mechanisms,

including induction of regulatory T cells or alterations in the profile of the pathogenic lymphocyte response (e.g., Th1 to Th2 or vice versa). For tolerogenic and immune modifying adjuvants, the antigens may originate from environmental (allergy) or endogenous (autoimmunity) sources and may not need to be supplied exogenously together with the adjuvant. When pursuing this approach, the proposal must describe a compelling mechanism by which the adjuvant would modulate an antigen-specific response, and include studies demonstrating altered or suppressed responses against the allergen or autoantigen.

Recent advances in understanding of innate immune mechanisms have led to new putative targets for vaccine adjuvants and for immunotherapy. Simultaneously, progress is 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 gaps that need to be addressed by new adjuvants include improvements to existing vaccines (e.g., the acellular pertussis vaccine, influenza, etc), and development of vaccines for: emerging and re-emerging threats (e.g., Coronaviruses, Enteroviruses, MRSE); special populations that respond poorly to existing vaccines (e.g., elderly, newborns/infants, immunosuppressed patients); or treatment/prevention of immune-mediated diseases (e.g., allergic rhinitis, asthma, food allergy, autoimmunity, transplant rejection). For example, the combination of putative tolerogenic adjuvants with allergen immunotherapy should aim at accelerating tolerance induction, increasing the magnitude of tolerance and decreasing treatment duration. For transplantation, donor-derived major and minor histocompatibility molecules that are not matched between donor and recipient may be formulated with novel tolerogenic adjuvants and used to induce transplant tolerance in the recipient.

Program 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, or transplantation; their characterization; and early-stage optimization.

Phase I Activities may 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
- Conduct pilot screening assays to validate high-throughput screening (HTS) approaches for identifying adjuvant candidates
- Develop or conduct *in silico* screening approaches to pre-select adjuvant candidates for subsequent *in vitro* screens and validation

Phase II Activities may include, but are not limited to:
- HTS 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 or formulation
- Screening of adjuvant candidates for their usefulness in vulnerable populations, such as the use of cells from cord blood of infants or elderly/frail humans
- Screening of adjuvant candidates in animal models representing vulnerable human populations

This SBIR will not support:
- The development of immunostimulatory compounds or formulations as stand-alone immunotherapeutics (i.e., without a specific antigen/pathogen-specific vaccine component) unless the putative adjuvant is used to modulate or suppress the response against an allergen or autoantigen. In this case, the proposal must include assays to demonstrate the effect of the treatment with an adjuvant on specific allergens or autoantigens.
- The testing of newly identified immunomodulatory compounds or formulations in cancer models
- The further development of previously identified adjuvants
- The conduct of clinical trials (see https://grants.nih.gov/policy/clinical-trials/definition.htm for the NIH definition of a clinical trial)

NIH/NIAID 105 - Adjuvant Development for Vaccines and for Autoimmune and Allergic Diseases

Fast-Track proposals will be accepted.

Direct-to-phase II 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 with appropriate justification by the applicant for up to 3 years.

Background
The goal of this program is to support the preclinical development of novel vaccine adjuvants for use in vaccines against infectious diseases or of tolerogenic adjuvants for the treatment of immune-mediated diseases. 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 a few adjuvants other than aluminum salts ("Alum") have been licensed as components of vaccines in the United States (U.S.): 4'-monophosphoryl lipid A (MPL), adsorbed to alum as an adjuvant for an HPV vaccine; CpG Oligodinucleotide as an adjuvant for a recombinant Hepatitis B vaccine; MPL and QS-21 combined in a liposomal formulation for a varicella vaccine; and the oil-in-water emulsion MF59 as part of an influenza vaccine for people age 65 years and older. Additional efforts are needed to develop promising novel adjuvants, particularly for vulnerable populations such as the young, elderly and immune-compromised.

In addition, adjuvants may facilitate the development of immunotherapeutics for 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 U.S. and immune-mediated diseases are treated mostly with broadly immunosuppressive drugs or long-term single- or multi-allergen immunotherapy. In contrast to drugs, tolerogenic or immunomodulatory adjuvants may regulate immune responses to specific antigens through a variety of mechanisms, including induction of regulatory T cells or alterations in the profile of the pathogenic lymphocyte response (e.g., Th1 to Th2 or vice versa). For tolerogenic and immune modifying adjuvants, the antigens may originate from environmental (allergy) or endogenous (autoimmunity) sources and may not need to be supplied exogenously together with the adjuvant. When using this approach, the proposal must describe a compelling mechanism by which the adjuvant would modulate an antigen-specific response, and include studies demonstrating altered or suppressed responses against the allergen or autoantigen.

Adjuvanticity may be obtained with a single immunostimulatory (or immunoregulatory/tolerizing) compound or formulation, or with a combination adjuvant. 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 depending on the focus and nature of the vaccine antigen; 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.

Project Goal
The goal of the project must be the pre-clinical development and optimization of a single lead adjuvant candidate or a selected combination-adjuvant for prevention of human disease caused by non-HIV infectious pathogens, or for the treatment of autoimmune or allergic diseases, or induction/maintenance of organ transplant tolerance. The adjuvant products supported by this program must be studied and further developed toward human licensure with currently licensed or new investigational vaccines and may not be developed as stand-alone agents unless the adjuvant is used to modulate or suppress immune responses against an allergen. In response to this topic, offerors must include the following information in the proposal:

- A clear description of the single lead adjuvant or selected combination-adjuvant;
- Data demonstrating that the adjuvant has adjuvant activity;
    - For Phase I proposals, that data may be within any context (e.g., in combination with a different antigen than used in the proposal, etc.);
    - For Phase II proposals, preliminary data from *in vivo* studies must support the utility of the selected adjuvant with the proposed vaccine candidate;
- Evidence that the offeror has guaranteed access to the adjuvant to be used in the project (e.g., is the IP holder, or has an agreement in place with the IP holder);
- Narrative describing that the offeror has the appropriate intellectual property protections or agreements in place and/or proprietary freedom to commercially develop the adjuvant.

Phase I activities may include, but are not limited to:

- Optimization of one candidate compound for enhanced safety and efficacy. Studies may include:
    - Structural alterations of the adjuvant,
    - Formulation modifications (adjuvant alone or in combination with antigen(s)),
    - Optimization of immunization 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;
- Preliminary studies in a suitable animal model to evaluate: immunologic profile of activity; immunotoxicity and safety profile; protective or tolerizing efficacy of a lead adjuvant:antigen/vaccine combination

Phase II activities may include, but are not limited to:

- 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;
- Pharmacokinetics/absorption, distribution, metabolism and excretion studies;
- Establishment and implementation of quality assurance and quality control protocols.

Areas of Interest:

- Adjuvants to improve the efficacy of vaccines to protect against infectious disease, particularly for vaccines targeted towards vulnerable populations;
- Novel combination adjuvants;
- Tolerogenic or immune deviating adjuvants for allergen immunotherapy.

This SBIR will not support:

- Projects that are not focused on a single lead adjuvant candidate or a selected combination-adjuvant;
- The discovery or initial characterization of an adjuvant;
- Further development of an adjuvant that has been previously used with any FDA licensed vaccine, unless such an adjuvant is used as a component of a novel combination adjuvant as defined above;
- The conduct of clinical trials (see https://grants.nih.gov/policy/clinical-trials/definition.htm for the NIH definition of a clinical trial);
- The development of adjuvants within the context of vaccines to prevent or treat cancer or HIV;
- Development of platforms technologies or delivery systems that have no immunostimulatory or tolerogenic activity themselves;
- The development of the vaccine's antigen component;
- The development of immunostimulatory compounds or formulations as stand-alone immunotherapeutics (i.e., without a specific antigen/pathogen-specific vaccine component) unless the adjuvant is used to modulate or suppress the response against an allergen. In this case, the proposal must include assays to demonstrate the effect of the treatment with an adjuvant on specific allergens;
- The development of adjuvants where the offeror has not demonstrated intellectual property (IP) protection and/or proprietary freedom to commercially develop the adjuvant.

NIH/NIAID 106 - Production of Adjuvants Mimics

Fast-Track proposals will be accepted.

Direct-to-phase II proposals will be accepted.

Number of anticipated awards: 3-5

Budget (total costs):

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

Phase II: $1,000,000/year with appropriate justification by the applicant for up to 3 years.

Background
Many experimental and licensed vaccines depend on adjuvants to exert their protective effect. While several immunostimulatory compounds and formulations are available commercially for use in preclinical studies, these compounds generally cannot be advanced into clinical trials. Furthermore, head-to-head comparisons of novel experimental and existing adjuvants is hampered by limited availability of such reagents. NIAID supports the discovery and development of novel adjuvants through different mechanisms, and this Funding Opportunity Announcement (FOA) is intended to address the limited availability of adjuvants that: mimic those with a favorable clinical track record; or show high potential in late pre-clinical testing.

Program Goal
Development, validation and production of adjuvants that are based on, or similar to, compounds or formulations previously successfully used in clinical trials, for use by the broader research community, either as commercial products or through licensing agreements.

Phase I Activities must include at least the following 2 activities:
- Development of one or more adjuvants (or adjuvant combinations)/adjuvant formulations that are based on, or similar to, an adjuvant with a proven clinical track record of high adjuvanticity; and
- Preclinical testing to assure immune potency and safety. Immune potency studies shall include comparison to at least one well-established reference adjuvant that is expected to be effective in the disease model under study.

Phase II Activities include, but are not limited to:
- Establishment of an immunological profile of the lead product;
- Pharmacological and toxicological studies in appropriate animal models;
- Product validation, that includes *in vitro* and *in vivo* approaches using a relevant disease model;
- Production scale-up; and
- Development of a marketing plan.

This SBIR will not support
- Development of aluminum-based adjuvants as marketable products, unless the aluminum-component is used as a co-adjuvant or carrier;
- Discovery of novel immunostimulatory compounds;
- Commercial development of adjuvants that do not have the ability or potential to activate human immune cells;
- Development of adjuvant mimics that would violate existing patents;
- Data analyses, pattern discovery from aggregated datasets; or
- Development of AS01 biosimilars without previous consultation with NIAID.

Intellectual Property: The awardee is solely responsible for the timely acquisition of all appropriate proprietary rights, including intellectual property rights, and all materials needed for the awardee to perform the project. Before, during, and subsequent to the award, the U.S. Government is not required to obtain for the awardee any proprietary rights, including intellectual property rights, or any materials needed by the awardee to perform the project.

NIH/NIAID 107 - Reagents for Immunologic Analysis of Non-mammalian and Underrepresented Mammalian Models

Fast-Track proposals will be accepted.

Direct-to-phase II proposals will be accepted.

Number of anticipated awards: 3-6

Budget (total costs):

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

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

Background
This program addresses the limited availability of reagents (e.g., antibodies, proteins, ligands) for the identification and discrimination of immune cells and the characterization of immune responses in non-mammalian models or in specific underrepresented mammalian models. Non-mammalian and under-represented mammalian models of interest include: arthropods, amphibians, fish (e.g., jawless fish, sharks, zebrafish), nematodes, marine echinoids; and guinea pig, ferret, bat, mink, hamster, bird, cotton rat, pig (including minipigs), cat, rabbit and marmoset, respectively.

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 significantly accelerated progress made in 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-κB pathway in mosquitoes, the intermediate hosts for *Plasmodia* parasites. However, studies to better understand immune regulation within non-mammalian models have been constrained by the limited availability of antibodies and other immune-based reagents for use in scientific studies.

Certain mammalian models display many features of human immunity but are similarly underutilized due to the limitations noted above. For example, the progression of disease that follows infection of guinea pigs with *Mycobacterium tuberculosis*, the causative agent of tuberculosis (TB), displays many features of human TB. While this model has been used for more than 100 years as a research tool to understand and describe disease mechanisms, immunologic analyses are constrained by the limited availability of immunological reagents specific for the guinea pig. Another example is the ferret model, one of the best animal models of human influenza infection, where immunologic studies also have been limited by the lack of immunological reagents. In addition, minks and cats are highly susceptible to SARS-CoV-2 infection with potential for zoonotic pathogen transmission. However, there are almost no reagents available for immunological studies in these species. Lastly, although bats are the natural reservoir and vector for several major zoonotic diseases that cause severe human diseases, the lack of reagents has impeded studies of how bat adaptive or innate immune responses control these pathogens.

Project Goal
This program supports the development and validation of reliable antibodies and reagents for the identification and tracking of immune cells or the analysis of immune function/responses (e.g., cytokines, chemokines, intracellular signaling) in non-mammalian models or underrepresented mammalian models. Non-mammalian models are limited to arthropods, amphibians, fish (e.g., jawless fish, sharks, zebrafish), nematodes, and marine echinoids. Underrepresented mammalian models are limited to guinea pig, ferret, bat, mink, hamster, cotton rat, pig (including minipigs), cat, rabbit and marmoset.

Phase I Activities must include the following activities:
- Selection of targets, which may include: immune cell markers; receptors with immune function; or other molecules important for immune function;
- Development of antibodies or other reagents against these targets,
    - If polyclonal antibodies are being developed, the plan also must include the development of monoclonal antibodies;
- Characterization of antibodies or reagents developed,
    - Initial determination of affinity/avidity and specificity
    - Confirmation of binding to the intended native antigen/immunogen by flow cytometry and/or other assays.

Phase II Activities must include but are not limited to:
- Comprehensive evaluation of specificity and sensitivity, functional utility, and cross-reactivity/off-target binding of antibodies/reagents by Western blotting (denatured and native protein); immunoprecipitation; immunohistochemistry; and flow cytometry.
    - The functional studies must minimally include analysis of primary cells or target antigens from host species;
    - The off-target binding must minimally include evaluation of non-specific binding to other cells or unrelated molecules from host species;
    - The cross-reactivity must at least contain a screening of binding to related cells or molecules from other species.
- Optimization (e.g., secondary modifications/conjugations) of the antibodies/reagents for the intended application.
- Development of well-established protocols by:
    - setting up working concentrations, assay linearity, assay validation, and functional activity test;

    - determining quantitative criteria such as binding kinetics and signal versus background, and quality control acceptance criteria (e.g., purity requirement, endotoxin testing, specificity and activity(titer) threshold, molecular mass confirmation, multiple freeze-thaw stability) in assay performance and manufacturing.
- Scale-up production of the reagents, batch to batch comparison, and backup plan(s) to guard against loss of source material (e.g., hybridoma cells).
- A commercialization plan for distribution and marketing of the reagents.

This SBIR will not support:
- Identification of immune target molecules and development of antibodies/reagents against immune markers or molecules for animal models not listed in the solicitation;
- Development of antibodies/reagents for molecules or mechanisms not involved in immune responses;
- Development of novel or refined animal models

NIH/NIAID 108 - Development of Rapid POC Diagnostics for Treponema pallidum

Fast-Track proposals will be accepted.

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

Number of anticipated awards: 1-2

Budget (total costs):

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

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

Background
Cases of syphilis, caused by the pathogen *T. pallidum*, are increasing in the US and globally. In 2018, the total number of syphilis cases (all stages) in the U.S. was the highest it had been in over 25 years. From 2017 to 2018, syphilis cases increased 13.3%, and congenital syphilis cases increased by 39.7% (CDC's 2018 STD Surveillance Report). Current diagnostics for syphilis are inefficient, cumbersome to use, and outdated. Attempts to control or eradicate syphilis will require the development of straightforward, easy-to-use diagnostics that take advantage of modern molecular technology.

Project goal
The goal of this project is to develop a rapid (≤ one hour), point-of-care diagnostic capable of detecting *T. pallidum* directly from patient specimens.

Phase I activities may include:
- Development of a prototype assay that demonstrates the rapid (less than 60 minutes) detection of *T. pallidum* from clinical specimens
- Integration of platform and assay to rapidly identify *T. pallidum*
- Development of sample preparation methods consistent with the product platform

Phase II activities may include:
- Development of sample preparation methods consistent with the product platform
- Further development of the prototype product to determine performance characteristics
- Final validation testing and scale-up manufacturing of test kits

This SBIR will not support:
- The design or conduct of clinical trials; please see https://grants.nih.gov/policy/clinical-trials/definition.htm 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.

NIH/NIAID 109 - Development of monoclonal antibody-mediated interventions to combat malaria

Fast-Track proposals will be accepted.

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

Number of anticipated awards: 1-3

Budget (total costs):

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

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

Background
According to the World Malaria Report 2020, progress towards malaria control and elimination appears to be slowing in recent years. Although a moderately efficacious vaccine (RTS,S/AS01 [MosquiRix®] has been made available for pilot implementation in selected African countries, novel immunization approaches to combat malaria are still urgently needed. It has been demonstrated previously that polyclonal sera from malaria-exposed individuals could be used to confer protection against malaria in recipients. Research in animal models has also shown that passive transfer of monoclonal antibodies (mAbs) can protect against malaria infection. Recently, passive immunization using mAbs either as immunotherapy or pre-exposure prophylaxis has been explored for other infectious diseases, such as SARS-CoV-2, HIV or RSV, and has demonstrated promising feasibility both preclinically and clinically. If passive immunization with mAbs or mAb-based interventions against malaria similarly demonstrates promising clinical feasibility, it could be incorporated into public health program strategies, such as for seasonal malaria prophylaxis, prophylaxis for pregnant women or for migrant workers entering malarious areas, or outbreak control, thus enhancing global malaria control and elimination efforts. The availability of well-characterized and appropriately designed mAbs will not only support development of mAb-based immune prophylaxis or immunotherapy strategies but could also provide credentialing of vaccine antigen(s) and necessary tools for rational immunogen design for active immunization approaches.

Project Goals
The overall goal of this solicitation is to develop mAb or mAb-based candidates for malaria prevention or treatment. The scope of the research can range from product candidate discovery or optimization to preclinical process development leading to IND filing. Applicants may propose to establish initial proof-of-concept data in animals, conduct preclinical process development or production of mAb(s) or mAb-based candidates to combat *Plasmodium falciparum* or *P. vivax* malaria by targeting one or more life cycle stages (i.e., pre-erythrocytic, asexual blood, or sexual stages). Proposals to address innovative potential uses for novel indications (e.g., prevention of malaria relapse, overcoming or prevention of emergence or spread of antimalarial drug resistance, etc.) are also encouraged.

Phase I activities may include but are not limited to:
- Identification, construction, optimization/refinement, and/or evaluation (e.g., biophysical, epitope mapping, etc.) of novel mAbs and mAb-based product candidates (e.g., mAb-conjugates), and technology platforms (e.g., viral vector-encoded mAb);
- Establishment of preliminary process development to demonstrate technical feasibility;
- Demonstration of potential efficacy and/or safety of the proposed candidates either by *in vitro* functional assays or in animal models;

Phase II activities may include but are not limited to:
- Preclinical process development leading to IND filing; activities may include formulation studies, process scale up, stability studies, analytical assay development, cGMP production, or GLP safety assessment;
- Further preclinical assessment in animal models, including non-human primates;
- Stability testing to support product stability program for later stages of product development.

This SBIR will not support:
- The design and conduct of clinical trials (see https://grants.nih.gov/policy/clinical-trials/definition.htm for the NIH definition of a clinical trial).

NIH/NIAID 110 - Point of Care (POC) Diagnostics for Antimicrobial Resistant (AMR) Enteric Bacterial and Parasitic Pathogens

Fast-Track proposals will be accepted.

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

Number of anticipated awards: 3-4

Budget (total costs):

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

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

Background
Diarrheal diseases are the 5th leading cause of mortality in children less than 5 years of age (Lancet Infect Dis 2018; 18: 1211–28) and antimicrobial resistance in the causative agents is increasingly problematic (CDC report: Antibiotic Threats in the United States 2019). Recent technological advances may facilitate the development of simple, rapid and inexpensive point-of-care diagnostics for the detection of enteric bacterial and parasitic pathogens in children under five years of age with moderate to severe diarrheal disease. Rapid identification of the pathogen(s) and associated antimicrobial resistance profile(s) are needed to determine treatment options, especially for infants under 12 months of age for whom persistent diarrheal disease is particularly risky.

Project Goal
The goal is to develop a rapid (≤ one hour) point-of-care diagnostic capable of detecting infectious enteric pathogens (≥ two) and associated antimicrobial resistance profile(s) directly from patient specimens *(e.g.,* stool samples). The end product must identify antimicrobial resistance profiles; detection of both bacterial and parasitic pathogens in the same device is strongly encouraged where feasible. Diagnostic devices and associated methodologies, *e.g.*, microfluidic PCR, should be designed for use in clinical or field settings, such as physician's offices or in the field during outbreaks of diarrheal disease that impact the population across all ages. Diagnostics that focus on multiple enteric bacterial pathogens with known drug resistance, as well as parasitic pathogens, such as *Giardia* and *Cryptosporidium*, would be considered responsive.

Phase 1 activities may include, but are not limited to:

- Define the targets for pathogen identification
- Identify the antimicrobial resistance markers
- Demonstrate assay feasibility for rapid detection of enteric pathogens and their antimicrobial resistance profiles
- Develop sample preparation methods consistent with the product platform
- Conduct validation testing of true clinical specimens

Phase 2 activities may include, but are not limited to:

- Integrate platform and assay for rapid detection of enteric pathogens and antibiotic resistance profiles
- Conduct final analytical validation testing and scale-up manufacturing of test kits
- Complete development of the final prototype product up to, but not including, verification

This SBIR will not support:
- The design or conduct of clinical trials; please see https://grants.nih.gov/policy/clinical-trials/definition.htm for the NIH definition of a clinical trial.

NIH/NIAID 111 - Data Science Tools for Infectious and Immune-mediated Disease Research

Fast Track proposals will be accepted.

Direct to Phase II proposals will not be accepted.

Number of anticipated awards: 1-3

Budget (total costs):

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

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

Background
Data intense infectious and immune-mediated research projects are generating unprecedented amounts of complex and diverse basic research and clinical data sets. Increasing the use and re-use of these data by basic and clinical scientists studying infectious, immune and allergic diseases will drive discovery and accelerate the development of diagnostic, preventative and therapeutic interventions. Yet, managing, preserving, sharing, finding, accessing, integrating, visualizing, and analyzing these data sets from multiple sources and platforms remains challenging.

Innovation in optimal search and discovery of biomedical data is still lacking. Moreover, non-interoperable data impedes the ability to answer sophisticated biological questions across diverse data types without significant harmonization. Although there is considerable effort in developing standards and data curation programs to address these challenges, they are mostly manual, expensive, and not scalable. Visualization tools that integrate new and emerging 3D technologies to visualize and communicate research data are also needed.

This broad topic includes investments in data resources and repositories, development of computational tools, their use, and tools to enhance timely data sharing and adherence to FAIR Data Principles (Findable, Accessible, Interoperable, and Reusable). Tools that can enhance privacy in an environment that maximizes sharing are also sought. This includes novel approaches to share de-identified individual patient level data while maintaining the complexity of the original data. If developed, they have the potential to confirm reproducibility, promote transparency of clinical studies, increase confidence in therapeutic interventions, and inform and accelerate new clinical research and trials.

Project Goal

The goal is to support the new development of innovative, robust informatics/data science tools, or enhancement or adaptation of existing tools for use in infectious, immune, and allergic diseases. These tools should be appropriate for, but not limited to, data from natural history studies, biomarkers, in vitro assays, correlates of vaccine protection, animal models and non-human primates. The tools can aim to improve data management, or the FAIR-ness of data, or can focus on data visualization, integration, or analysis.

Potential projects relevant but not limited to this topic include the development, enhancement, modification, or adaptation of existing informatics and data science tools for

- Increase the findability of data by utilizing information that includes, but is not limited to data, metadata, associated literature, and text;
- Improve indexing by popular search engines and recommend or discover relevant data sets beyond the original search;
- Visualize and integrate analysis of “big”, multi-scale, complex data from multiple sources and their dissemination;
- Perform automated curation and quality control;
- increase data interoperability and query-ability across multiple resources by application and adoption of community standards and ontologies that may include software pipelines or platforms to automate annotation, markup, or curate datasets not compatible with community standards, formats, or controlled vocabularies;
- Harmonize clinical data via customized data harmonization pipelines which among other features could combine data sets or un-merge combined data sets;
- Standardize the de-identification, and other privacy-preserving approaches, of individual patient level data and allow the timely sharing of human clinical research data including tools that can assess and minimize the risk of re-identification.

Phase I Activities:
- Establish a project team composed of experts in software development and as appropriate to the project include but not limited to expertise in statistics, infectious and immune mediated diseases, or clinical research.
- Provide an overall development plan with milestones and deliverables for the proposed tool.
- Provide justification and unique value proposition for the development, adaptation or enhancement of this specific tool in light of the currently available tools.
- Describe the potential user communities and provide relevant use cases.

- Develop an (early) prototype for the tool, perform alpha testing, and address issues from testing and solicit feedback from the appropriate user community.

Phase II Activities:
- Enhance and optimize the prototype developed in phase I.
- Improve robustness, scalability, and usability of the tool.
- Conduct beta tests for the software tool with the appropriate user communities and use cases, demonstrate the usability of the tool by the infectious, immune or allergic community.
- Gather feedback from the beta testing by the research community.
- Add functionalities and capabilities based on feedback and deploy a production version.
- Develop documentation, user guides, SOPs and training materials.

The SBIR will not support:

- Projects proposing significant data generation and analysis for validation and testing of the tool.
- Projects developing wet-laboratory, experimental methods, research or technologies.
- Projects that are not focused on developing tools directly applicable to infectious, immune or allergic basic and clinical research.

NIH/NIAID 112 - Digital Tools Against Misinformation about Infectious Disease Treatments and Vaccines

Fast Track proposals will be accepted.

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

Number of anticipated awards: 1-2

Budget (total costs):

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

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

Background:
It has been estimated that as many as 40% of the US population choose not get certain established and newly approved vaccines (e.g., HPV, flu) and recently, there has been hesitancy about receiving the SARS-CoV-2 vaccines. In many cases, the underlying reasons for this decision can be traced back to widespread dissemination of misinformation about the vaccine itself or about the process used to test and obtain regulatory approval for these vaccines. Similarly, despite the overwhelming scientific body of evidence supporting the safety of other vaccines, like measles, mumps and rubella (MMR), there is a not-insignificant proportion of the population that continues to be skeptical and cite misinformation about vaccine adverse events, which have been discredited.

Research has shown that much of this misinformation is disseminated through digital platforms and social media, where this type of misinformation can spread widely – like a virus. During the COVID-19 pandemic, many other falsehoods about the spread (or lack of spread) of the virus, the severity of the disease, and whether interventions were effective or not were widely disseminated among social and popular media. Therefore, it is critically important to develop digital tools to rapidly identify misinformation and minimize the effects of this unintended or malicious information to ensure effectiveness of public health measures and eliminate vaccine hesitancy and increase effectiveness of vaccinations, including but not limited to vaccination programs.

Project Goal:
The goal of this solicitation is to develop digital tools to identify and combat malicious digital bots that spread misinformation about infectious disease treatments and vaccines. The proposed digital tools could be specific to a single digital platform or social media outlet. The tools could either identify or combat misinformation, or it could be a holistic solution that both identifies and combats misinformation. The solicitation will support efforts to implement and test proposed solutions.

Phase 1 activities may include, but are not limited to:

- Development of digital tools and/or methods to identify and/or combat malicious digital spread of misinformation and bots related to diagnosis, prevention and treatment of infectious diseases directly from digital platforms or social media.
- Provide justification and unique value proposition for the development, adaptation or enhancement of this specific software tool and pipeline.
- Describe the potential user(s) communities and provide two relevant use cases.
- Development and/or improvement of sensitivity, specificity and other performance characteristics (e.g., time to identify, limit of detection, feasibility for implementation) of the digital tool or solution.
- Development of methods to ensure the usability of the tool or solution in various scenarios, including but not limited to implementing routine vaccine recommendations, new and re-emerging outbreaks, epidemics, pandemics, rapidly spreading vs. sporadic or endemic infections
- Develop an (early) prototype for the tool, perform alpha testing, and address issues from testing and evaluate with appropriate user community to solicit user feedback.

Phase 2 activities may include, but are not limited to:

- Further optimization of the methods and protocols and validation of reproducibility.
- Final validation testing and scale-up for deployment on a specific platform.
- Demonstration that methods developed in Phase I are applicable to a broader range of platforms
- Enhancement and optimization of the prototype developed in phase I
- Improve robustness, scalability, and usability of the tool
- Conduct beta tests with the appropriate user communities and use cases, demonstrating the usability of the tool by the infectious, immune or allergic community
- Gather feedback from the beta testing by the research community
- Add functionalities and capabilities based on feedback and deploy a production version
- Develop user documentation, user guides, SOPs and training materials.

This SBIR will not support:

- Clinical trials (see http://www.niaid.nih.gov/researchfunding/glossary/pages/c.aspx#clintrial for the NIH definition of a clinical trial).
- Projects proposing significant data generation and analysis for validation and testing of informatics tool.

CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

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.

Using science and innovation to prevent, detect, and respond, CDC's Strategic Framework consists of five core capabilities that enable the agency's three strategic priorities as follows:
5 Core Capabilities:

- World-Class data and analytics
- State-of-the-art laboratory capacity
- Elite public health expertise
- Responding to Outbreaks at their source
- Global Capacity and domestic preparedness

3 Strategic Priorities:

- Securing Global Health and America's Preparedness
- Eliminating Disease
- Ending Epidemics

Our Strategic Framework and Priorities are a bold promise to the nation (and the world). With this strategic framework, CDC commits to save American lives by securing global health and America's preparedness, eliminating disease, and ending epidemics. As the nation's leading science-based, data-driven service organization for more than 70 years, we've put science into action to help children stay healthy so they can grow and learn; to help families, businesses, and communities fight disease and stay strong; and to protect the public's health.

CDC's strategy to save American lives cascades from an ambitious aspiration to granular action plans and detailed measures of success. CDC's foundational scientific work remains vital to the overall mission of this agency, and the contributions of the diverse scientific and programmatic workforce are critical to continued success.

NATIONAL CENTER FOR BIRTH DEFECTS AND DEVELOPMENTAL DISABILITIES (NCBDDD)

The mission of CDC's National Center on Birth Defects and Developmental Disabilities (NCBDDD) is to promote the health of babies, children and adults and to enhance the potential for full, productive living. To achieve its mission, the Center works to identify the causes of birth defects and developmental disabilities, helps children to develop and reach their full potential, and promotes health and well-being among people of all ages with disabilities, including blood disorders. NCBDDD seeks to accomplish these goals through research, partnerships, and prevention and education programs. Additionally, NCBDDD encourages submission of research application with innovative research technologies designed to reduce health disparities and promote health equity.

Please visit their web site at: http://www.cdc.gov/ncbddd/index.html

CDC/NCBDDD 020 - Open-Source and User-Friendly Record Linkage/De-duplication Tool

Phase I SBIR proposals **will** be accepted. Fast-Track proposals will **not** be accepted. Phase I clinical trials will **not** be accepted.

Number of anticipated awards: 1
Budget (total costs): Phase I: up to **$243,500** for up to 6 months; Phase II of up to $1,000,000 and a Phase II duration of up to 2 years

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

Background
Record linkage (or de-duplication) is an essential component of many CDC-supported projects and programs. If an individual is reported as a case by more than one data source, or reported at multiple times, it is vital to link records so that an individual will not be counted as multiple incident cases. There are powerful algorithms that can automatically detect matches in many situations. However, these software tools are often proprietary or require programming/coding skills that may not be available in every state or jurisdiction. A free and easy-to-use solution would strengthen public health expertise, as the same tools could be used across programs, and users who cannot write code could use the same underlying packages and algorithms as more technically inclined users.

Motivating example: CDC's Autism and Developmental Disabilities Monitoring (ADDM) Network currently supports autism surveillance in different states. States receive information from various medical and educational providers, and states must link records to ensure each child is counted once and that all critical data elements are linked to the child's record. The ADDM surveillance program uses "The Link King", a SAS-based record linkage program, for data linkages. There are several beneficial attributes of this tool: it uses high-performing algorithms, is free (but requires a paid SAS subscription), and it has a graphical user interface that allows easy use by non-coders. However, it is no longer actively supported or developed (the team received permission to host an archival copy at www.the-link-king.party). Future updates to SAS, Microsoft Windows, or any dependency could jeopardize the functioning of the tool, and therefore the surveillance program.

Project Goals
Short term project goals –

- Understand basic needs and use cases for record linkage in public health applications
- Develop an R package that provides an R Shiny front-end to a high-performance record linkage package (such as fastLink, RecordLinkage, or csvdedupe)
    - Functionality should include the ability to facilitate linkage parameters (select variables used for linkages), identify data sets to be used, manually verify and review results, and export the resulting matched and non-matched data.
    - Create documentation to instruct users on its use (such as a "getting started" vignette)
    - Create a public GitHub repository for the code, as well as for tracking issues and feature requests from end-users

Phase I Activities and Expected Deliverables
During the Phase I period, the activities can include, but are not limited to:

The following deliverables should be produced by the end of the project period:
- R Package providing interface to record linkage/de-duplication program(s)
- Includes documentation (built into package, and vignette)
- Package and materials hosted on CRAN
- Source code maintained on a public GitHub repository
- Demonstration to CDC/public health community
- Summary of potential enhancements and community feedback/requests

Impact
This project could have both long- and short-term impact on CDC surveillance programs and other projects. Most immediately, it will provide a sustainable solution for the ADDM Network, as the current record linkage software is effectively "abandonware" and requires SAS licenses.

Other "free options" (summarized here and here) often lack easy-to-use interfaces, are not updated, or are only available in programming languages that would add complexity to (or be incompatible with) a public health program. Commercial tools could be expensive (as shown here) or require uploading sensitive data to a cloud-based service, which might violate public health data privacy requirements. Proprietary software could also be custom-tailored to each surveillance system and include this functionality. For example, the ADDM Network discontinued a $500,000 annual contract to build and maintain a proprietary data system that included rudimentary record linkage functionality. Other customizable products have linkage/de-duplication functionality, such as Conduent's Maven software, but can be expensive and encourage fragmentation between different systems by virtue of requiring software licenses/contracts.

More broadly, this tool could fill similar gaps in functionality in other CDC and public health programs without having to resort to custom-developed software. There are already thousands of R users at CDC, and they would be able to easily integrate this tool into other systems that could benefit, such as during Epi Aids, when simple tools are needed immediately. When we designed our current data system, we spoke with other surveillance programs and often heard that record linkage / de-duplication processes were lacking in performance (such as when a basic matching algorithm is integrated into custom software) or were deemed responsibilities that were "left up to the states" to complete without explicit support from CDC.

If selected, this project would have a high likelihood of success, as the core record linkage algorithms are already available – this project would make them easier to use by non-programmers and better integrate them into typical public health / surveillance workflows.

Commercialization Potential

Many open source software projects have successful commercial models through selling professional services, including enhanced support, customized features, consultation, training, or analytic capacity. This record linkage tool could become part of a suite of widely-used data management and analytic tools that are commonly deployed in the public health community. The developer would be well-positioned to offer premium support and technical services to programs that use the tools or need custom solutions built upon an open-source platform.

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 has identified the following Social Determinants of Health (SDoH) as priorities: built environment, clinical-community linkages, social connectedness, tobacco control policy, and food and nutrition security. Additionally, the Center encourages submission of research applications with innovative technologies designed to reduce health disparities and promote health equity.

Please visit their web site at: http://www.cdc.gov/chronicdisease/index.htm

CDC/NCCDPHP 044 - Algorithmic Database Food Product Tool to Align Food Service with Guidelines

Phase I SBIR proposals **will** be accepted. Fast-Track proposals will **not** be accepted. Phase I clinical trials will **not** be accepted.

Number of anticipated awards: 1
Budget (total costs): Phase I: up to **$243,500** for up to 6 months; Phase II of up to $1,000,000 and a Phase II duration of up to 2 years

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

Background
Improving nutrition and reducing obesity are key objectives for Healthy People 2030. In addition, reducing consumption of calories from added sugars by persons aged 2 years and over is a leading 2030 health indicator for the nation. As part of the effort to encourage availability of healthier food and beverage options, numerous business industry standards and practice guidelines have been developed. For example, the US federal government has developed food service guidelines that include nutrition standards based on Dietary Guidelines for Americans. Food service guidelines, such as the Food Service Guidelines for Federal Facilities, are used widely by institutional purchasers including government facilities, worksites, hospitals, universities, and schools. Notably, these guidelines provide desired food standards but do not list specific food products meeting the guidelines.

The difficulty in identifying qualifying packaged products is a major obstacle in using food service guidelines, particularly when guideline specifications may differ slightly from one jurisdiction to another. For example, New York City's and Los Angeles County's food service operations, which serve 25 million people combined, have reported difficulty meeting their own food service guidelines because their primary suppliers do not have the resources (i.e., time, staff) to determine which of their products meet guidelines. The problem faced by these large purchasers led to creation of an excel list tool, but the current format and its databases are not automatized and require users to hand search product lists to determine which foods meet guidelines. We are aware of static PDF versions such as on the Costco website and the Business to Business section for ordering on Amazon. However, non-automated paper type methods quickly become outdated as products and their ingredients change frequently and excel sheets need input from the product by a person.

An algorithmic processing tool that creates a database of foods and beverages meeting nutrition standards within food service guidelines can increase the ease of operationalizing food service guidelines by food service operators, retail, or the charitable food system (food banks/pantries). Identifying foods that meet food service guidelines is crucial for food service operators to fulfill contractual requirement to institutional clients. Easy identification of foods that meet guidelines is also helpful for retailers who want to market specific products to personal or demographic interests.

Project Goals
The goal of this project is to create a mobile and desktop computer software tool that enables food service, retail, and charitable food sectors to identify food and beverage products that align with various food service guidelines.

Phase I Activities and Expected Deliverables
During the Phase I period, the activities can include, but are not limited to:

The deliverable is an easy-to-use web-based application that is able to import food databases, determine which foods meet guidelines by comparing the individual food records with particular food service guidelines and export the results as a list. The tool must be easy to use by food service operators, retailers, charitable food systems, manufacturers, and distributors.

Expected key activities include:

Phase 1 (6 months)

- Create computer program with algorithms that identify foods and beverages meeting food service guidelines. The program must be able to process large food databases, incorporate nutritional and other information into algorithms and provide output of foods that meet guidelines.
    - Provide ability to import individual or groups of food items from food databases or other sources and determine if they meet guidelines.
    - Program must be able to process and translate input from primary computer database software (i.e., MS Access, MS Excel) and food management software (i.e., Computrition Hospitality Suite, Foodservice Suite, etc.).
    - Include algorithms representing the major public food service guidelines, including but not limited to: Food Service Guidelines for Federal Facilities, Smart Snacks guidelines, NYC's Food Standards, LA County's food procurement initiative, Philadelphia's Comprehensive Nutrition Standards, and Department of Defense's food service guidelines. Use programing infrastructure that enables the addition of further sets of guidelines that may be of interest by the private or public sectors.
    - Ability to analyze products against several different sets of guidelines or standards simultaneously.
    - Output must create a list of products that meet guidelines that is usable in ordering and meal planning software.
    - Algorithm results need to include foods that fail to meet guidelines and the reasons they fail.
    - Ability to assess product costs to determine most affordable products meeting guidelines.
- User Interface (UI) features need to include:
    - Easy to use UI for the target audience.
    - Operator-end and supplier-end interfaces.
    - Enable user to input available list of products from a company database and generate a formatted list of foods that comply with customer's food service guidelines.
    - Secure user account.
    - Account and login system.
    - Functionally easy to use.
    - Overall aesthetic experience.
    - User training.
- Conduct concept and feasibility testing to identify any issues with user experience, algorithm guidelines processing, or outputs.
    - Collect data and modify application based on operability, acceptability, efficiency, and sustainability.
    - Test on most potential users, including manufacturers/producers, distributors, wholesale clubs, and food service operators. NOTE that testing can only be done on 9 or less persons.
    - The proof-of-concept can be tested and refined with a selected industry partner (manufacture, distributor, etc) and a single set of guidelines, such as the Food Service Guidelines for Federal Facilities.
- Business Plan

- The offeror needs to provide an assessment of the tool's commercial potential, including methods to remain solvent by both making profit and expanding reach, while supporting a public health mission.

Impact

Operationalizing nutrition guidelines in institutional settings has the potential to improve dietary intake by aligning available dietary options with dietary requirements. This tool will assist institutional food operators to align their offerings more efficiently with food and nutrition guidelines by providing lists of products that meet guidelines. It will also assist retail and charitable food operations to procure and provide food items that align with guidelines and, in turn, are healthier. We envision that program recipients funded by CDC such as State Physical Activity and Nutrition (SPAN), Racial and Ethnic Approaches to Community Health (REACH), and High Obesity Program (HOP) would be able to use such a tool via their partners to support organizational purchasing efforts.

This tool will enable manufactures and distributors to provide more easily to their customers (e.g., food service operators) products that meet specific jurisdictional guidelines or standards included in food service contracts. The tool will also enable food service operators to quickly identify and select products that align with guidelines or that appeal to specific health-conscious market segments. In areas with difficulty accessing healthier foods (e.g. rural areas and inner cities), this tool can incentivize broader distribution and easier access of those foods, thereby enabling greater prominence of heathier foods and beverages in the supply chain. Furthermore, food banks might use this tool to purchase food for donation that meets dietary guidelines.

Commercialization Potential

Currently, public health departments and other organizations responsible for procurement of food service contracts must use scarce resources to develop one-time lists of products that meet guidelines or spend time adding nutrition facts label information into excel macros. Current tools are static PDFs or excel sheets. This creates an attributable time and cost burden and does not provide a consistent tool for the user. Placing the ability to determine foods that meet guidelines within the hands of suppliers, eliminates the burden of developing these lists. It also helps suppliers use a new type of tool to enhance their business model and advances competition in the marketplace.

NATIONAL CENTER FOR EMERGING ZOONOTIC AND INFECTIOUS DISEASES (NCEZID)

The National Center for Emerging and Zoonotic Infectious Diseases (NCEZID) 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 environment can be attained. Research to address reducing health disparities and increasing health equity is strongly encouraged.

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

NCEZID Topic

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

CDC/NCEZID 028 - Develop Rapid, Portable, Point-of-Care C. auris Diagnostic

Phase I SBIR proposals **will** be accepted.
Fast-Track proposals will **not** be accepted.
Phase I clinical trials will **not** be accepted.

Number of anticipated awards: 1
Budget (total costs): Phase I: up to **$243,500** for up to 6 months; Phase II of up to $1,000,000 and a Phase II duration of up to 2 years

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

Background
Candida auris is an emerging multidrug resistant fungal pathogen that has spread rapidly through networked healthcare facilities in the United States since it was first identified in 2016. C. auris heavily colonizes patients' skin and extensively contaminates the healthcare environment, making this pathogen highly transmissible and hard to control. The admission of just a single colonized patient can lead to sustained outbreaks in facilities caring for highly vulnerable populations. Colonization is an established risk factor for subsequent C. auris infections, which have high associated morbidity and mortality, and are difficult to treat. Rapid identification of C. auris is therefore essential for the timely implementation of infection control measures.

Currently, C. auris colonization screening is primarily performed by specialized regional public health laboratories when validated as lab-developed tests (LDT). The dependency on highly specialized laboratories limits the total capacity for C. auris colonization screening, and is not ideal for admission screening, which is best implemented at the point of care. Because C. auris impacts many healthcare facilities that do not have laboratories, efficient admission screening is not feasible with existing technologies. A simple, fast, and portable test that could be performed at the point of care in resource limited settings, without requiring specialized laboratory equipment, would greatly improve testing capacity and broader C. auris response efforts. The purpose of this work is to support development of such a test. Project Goals

The goal is to develop a simple, fast and highly portable test that could be performed at the point of care, even in resource-limited settings, without a laboratory. Dipsticks and Lateral Flow Assays are examples of how such a test could be achieved. The test should detect an analyte directly indicative of C. auris rather than an associated antibody or other immune response indicator of exposure. The test should generate results that can be interpreted without the requirement of sophisticated equipment, such as a visually observable color change, or appearance of a positive indicator, as commonly seen in CLIA-waved test platforms. Each individual test should include an internal positive control sensitive to inhibitors. External positive and negative controls should also be provided, which could be accomplished through inclusion in a kit of multiple tests, or as otherwise appropriate, to sufficiently control for the associated production lot. Phase I Activities and Expected Deliverables

Phase 1 deliverables should include a functional prototype and preliminary data indicating potential for further development. Expected Phase I deliverables include:

1. A physical prototype suitable for further testing.
2. Preliminary assessment of the prototype's ability to detect C. auris. This assessment should utilize fresh cultures of C. auris AR 0381, when normalized to concentrations of ~105 CFU/mL in AMIES buffer. This isolate is freely available through the CDC-FDA AR bank. Data from biological replicates, performed on different days, should be provided.

3. Preliminary assessment of the prototype's specificity. This assessment should utilize cultures of Saccharomyces cerevisiae AR 0399, when normalized to concentrations of ~105 CFU/mL in AMIES buffer. This isolate is freely available through the CDC-FDA AR bank. Data from biological replicates, performed on different days, should be provided.
4. A report summarizing progress including both raw and summary data.

Impact
A simple, fast, and highly portable test that can be performed at the point of care, even in resource-limited settings, will improve public health efforts to control C. auris. The requested test will help expand capacity by enabling healthcare facilities to determine their patient's colonization status upon admission without sending samples to a specialized laboratory. This will help facilities act quickly when positive cases are identified, and therefore provide a greater opportunity to control C. auris before an outbreak occurs.

Commercialization Potential
If successful through all phases, this technology would result in a diagnostic test that could be commercialized and marketed directly to healthcare facilities. Demand would be driven by increasing awareness and growing financial incentives for facilities to reduce healthcare-associated infections. This test would provide a valuable tool to this end by helping healthcare facilities prevent C. auris-related transmission and infections.

CDC/NCEZID 029 - Product to Inactivate and Stabilize Wastewater Samples for Shipping and Transport

Phase I SBIR proposals **will** be accepted.
Fast-Track proposals will **not** be accepted.
Phase I clinical trials will **not** be accepted.

Number of anticipated awards: 1-2
Budget (total costs): Phase I: up to **$243,500** for up to 6 months; Phase II of up to $1,000,000 and a Phase II duration of up to 2 years

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

Background
Wastewater surveillance provides a powerful independent approach to complement existing surveillance systems. Wastewater surveillance is currently being used to support the COVID-19 response. SARS-CoV-2 RNA is shed in the feces of individuals with both symptomatic and asymptomatic infections and SARS-CoV-2 RNA in wastewater has been demonstrated to be a leading indicator of reported cases and hospitalizations. There is no evidence to date that anyone has become sick with COVID-19 because of exposure to wastewater, but wastewater is a hazardous material and molecular analyses of samples that could potentially contain multiple human pathogens are severely restricted. This results in significant barriers for laboratories onboarding testing and there is a need for a product or procedure to provide molecular preservation (stabilization) and pathogen inactivation from post-sampling of wastewater to help overcome these barriers. Project Goals

The goal of the proposed research is to develop a product to inactivate and stabilize wastewater samples for shipping and transport. This product must be amenable to on-site use by stakeholders, such as State Agencies for wastewater monitoring, etc., and could be physical or chemical inactivation. The product can be an all-encompassing portable sampler that inactivates and provides molecular preservation of pathogens in wastewater or be used sequentially with existing samplers without adding additional biosafety risks to the collection procedure. The product will provide a qualitative indicator that the inactivation process has occurred, and the inactivation of the wastewater sample must not interfere with downstream molecular testing. Phase I Activities and Expected Deliverables

The expected deliverables are:

1. Develop or adapt a method to inactivate and molecularly preserve SARS-CoV-2, or the proxy virus controls, bovine coronavirus (BCoV), murine coronavirus (MCoV, e.g., murine hepatitis virus), bacteriophage Phi6, or human coronavirus OC43, in wastewater samples; the method must be able to provide an indicator that the inactivation process has occurred.
2. Quantify molecular detection before and after the molecular preservation and inactivation procedure for SARS-CoV-2, or the proxy virus controls bovine coronavirus (BCoV), murine coronavirus (MCoV, e.g., murine hepatitis virus), bacteriophage Phi6, or human coronavirus OC43, in wastewater samples. Method development with surrogate viruses will be considered but final evaluation with SARS-CoV-2 must be included.

3. Conduct matrix evaluation to understand the assay performance using different wastewater types (e.g., raw wastewater, sludge).

Impact

The product of this proposed research will allow laboratories to test and monitor their wastewater supplies for SARS-CoV-2 and other emerging pathogens without the need for dedicated containment laboratories, which is currently not possible. Once safe processing is available, laboratory capacity can scale up and expand to other pathogens that pose a public health threat and thereby inform control processes and ultimately reduce the burden of infections.

Commercialization Potential

This research will lead to the development of new products that inactivate infectious material in wastewater samples and provide molecular preservation to benefit stakeholders at every point in the wastewater surveillance process from collection to testing. Potential products include inactivation and stabilization systems, inactivation indicator kits, storage and transport products, and wastewater sampling devices that provide an all-in-one "sample collection-to-inactivated and stabilized infectious material" transport sample container. These products could be used by water managers, universities, businesses, correctional facilities, and healthcare facilities, as well as federal, state, and local public and environmental health agencies. The market for products for wastewater surveillance sample collection and testing has grown exponentially during the COVID-19 pandemic and is likely to continue to grow as public health departments establish longer-term wastewater-based disease surveillance programs for SARS-CoV-2 and other disease targets.

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 areas:

CDC/NCHHSTP 052 - Electronic Health Record Algorithm to Identify Persons with HIV Not in Care

Phase I SBIR proposals **will** be accepted.
Fast-Track proposals will **not** be accepted.
Phase I clinical trials will **not** be accepted.

Number of anticipated awards: 1
Budget (total costs): Phase I: up to **$243,500** for up to 6 months; Phase II of up to $1,000,000 and a Phase II duration of up to 2 years

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

Background
Electronic health record (EHR) technologies are increasingly promoted as innovative platforms to streamline preventive health programs and improve compliance with clinical guidelines. EHR alerts have been created to streamline hepatitis C virus (HCV) and HIV screening processes in primary care settings and to develop predictive models that identify patients at a high risk of HIV acquisition who may benefit from pre-exposure prophylaxis (PrEP). To our knowledge, there is a lack of such functionality to identify patients with HIV who are not in care; only at one medical center in New York has such a "homegrown" electronic medical record algorithm been developed to identify persons lost to HIV care. This SBIR project seeks to utilize EHR data that are typically available in EHR systems to develop a "core" algorithm that can be used in multiple healthcare systems to identify patients newly and previously diagnosed with HIV and categorize their linkage to care, antiretroviral (ART) prescriptions, retention in care, and viral suppression status. Interoperability of different EHR systems regarding this functionality will also be explored to improve generalizability and functionality throughout the country.

Persons living with HIV may not be engaged in HIV care but may continue to access the health care system in other settings, such as other primary care or specialty clinics, emergency rooms, urgent care, and inpatient admissions. Such access can provide opportunities to re-engage them to HIV care. The data derived from the algorithm could be displayed on an EHR dashboard which would be accessible in any clinical setting affiliated with a healthcare system. Healthcare providers could utilize the information displayed to immediately identify a patient as not-in-care, and initiate care coordination and re-engagement efforts. Alternatively, a health care system could query its EHR data at regular intervals, to identify patients who may have fallen out of care.

Project Goals
This SBIR project seeks to develop a novel EHR-based algorithm to create a dashboard that identifies all patients with HIV and display their current linkage to care, antiretroviral therapy and viral load status. Specific groups highlighted by the algorithm may include patients with a new HIV diagnosis, patients that never linked to HIV care, patients that have disengaged from care (last visit with an HIV provider >6 months prior) and patients with an unsuppressed viral load (VL) on last measurement. Additional

information, such as age appropriate cancer screening, immunizations (e.g., COVID-19, pneumonia) could also be displayed.

Phase I Activities and Expected Deliverables
Create an algorithm that uses different data parameters to identify persons with HIV, and their current linkage to care, ART prescription and viral suppression status. Examples of data parameters that can be used include ICD 10 codes, laboratory results, appointment data, pharmacy refill data or similar data sources. Information from the algorithm would be displayed on a new dashboard (utilizing visualization software) within the EHR. The dashboard could use a color system (e.g., red, yellow, green) to easily identify if a patient has diagnosed HIV (new versus known infection), linkage to care status (last visit with HIV clinic provider), on ART (last ART refill date), and/or viral suppression status (last HIV RNA VL result).

The goal of Phase I is to determine the feasibility of designing an algorithm based on EHR information that will correctly and accurately identify persons with HIV who may not be engaged in HIV care or have not achieved viral suppression. The expected deliverable will be the algorithm to identify persons with HIV who are not engaged in care or are not virally suppressed using data available in EHR systems and create a dashboard to flag this information. Interoperability of different EHR systems regarding this functionality may also be explored.

ImpactPersons with HIV who are retained in care and are virally suppressed are 94% less likely to transmit HIV than persons with undiagnosed HIV. Accordingly, re-engaging people who are not in care confers important individual-level health and population-level prevention benefits, with retention in care and viral suppression as critical components of the HIV care continuum.

The national goal of Ending the HIV Epidemic (EHE) is to reduce the number of incident HIV transmissions in the U.S. by at least 90% by 2030. The Treat Pillar of the EHE initiative seeks to treat HIV rapidly and effectively to reach sustained viral suppression. We hypothesize that development of this EHR-based algorithm could be an innovative and effective model to identify out-of-care persons with HIV, including priority groups and hardly reached populations, with the goal of re-engaging them in HIV care.

Commercialization Potential
There are an estimated 250,000 individuals in the U.S. who are aware of their HIV infection, but not receiving HIV care and treatment. The U.S. government spends $20 billion in annual direct health expenditures for HIV prevention and care.

The Ending the HIV Epidemic (EHE) plan will focus on areas where HIV transmission occurs most frequently, providing 57 geographic focus areas (Phase 1 jurisdictions) with an infusion of resources, expertise, and technology. This innovative algorithm should be of interest to EHE Phase 1 jurisdictions, large healthcare systems, hospitals, clinics, and urgent care systems. This algorithm could help identify and re-engage persons with HIV who are not in care, not receiving antiretroviral treatment and/or not virally suppressed. CDC estimates the overall viral suppression rate in the United States is 53 percent. This SBIR project would be a novel and innovative intervention sought after by multiple healthcare systems and models as a necessary component to help jurisdictions achieve the important EHE goals to increase viral suppression to 90 percent nationally by 2030.

In addition, technology developed through this project could be applied to other chronic health conditions (such as diabetes, hypertension, or others), for which lifelong or long-term treatment and engagement in care are necessary, potentially leading to a much wider commercialization potential.

CDC/NCHHSTP 053 - Simultaneous Detection of Molecular and Serological Markers via Next-Generation Sequencing

Phase I SBIR proposals **will** be accepted.
Fast-Track proposals will **not** be accepted.
Phase I clinical trials will **not** be accepted.

Number of anticipated awards: 1
Budget (total costs): Phase I: up to **$243,500** for up to 6 months; Phase II of up to $1,000,000 and a Phase II duration of up to 2 years

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

Background
Simultaneous detection of serological markers including different antibody classes (IgM and IgG) and antigens in a multiplex fashion, as well as the characterization of molecular fingerprints of infectious agents is important for accurate diagnosis of several diseases. Proper identification of all necessary serological and molecular markers is of particular interest for outbreak investigations

and molecular surveillance. Thus, the development of platforms capable to simultaneously capture the required molecular and serological information is needed. Advanced characterization of a plethora of infectious agents relies on next generation sequencing (NGS) approaches, primarily using deep amplicon sequencing and Illumina sequencing technology. Cellular indexing of transcriptomes and epitopes by sequencing (CITE-Seq) allows next generation RNA sequencing as well as qualitative and quantitative analysis of proteins using capturing antibodies. CITE-Seq can be easily modified from single cell- to a bead-based approach for the specific detection of serological markers while simultaneously performing the conventional NGS protocols for genetic characterization. In combination, such methodologies could significantly improve the diagnosis for several diseases and syndromes including viral hepatitis.

Project Goals

Develop a multiplex NGS Illumina method for the simultaneous detection of viral hepatitis molecular and serological markers.

Phase I Activities and Expected Deliverables

1. Create a standard operating procedure for antibody and antigen labeling.
2. Complete test runs on a MiSeq system to sequence viral hepatitis RNA and detect viral hepatitis serological markers.
3. Create a standard operating procedure for the complete molecular and serological laboratory detection of viral hepatitis.

Impact

Implementation of a NGS multiplex assay for the simultaneous detection of molecular and serological markers should significantly improve outbreak investigations, molecular surveillance and genetic relatedness studies for viral hepatitis and other infectious diseases.

Commercialization Potential

State laboratories are likely to benefit from implementing a multiplex approach for outbreak investigation and molecular surveillance of infectious agents able to capture both molecular and serological markers.
Commercial labs will also likely benefit from implementing methodologies capable to characterize all serological and molecular markers for given infectious agents in a multiplex fashion.

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. Research to address reducing health disparities and increasing health equity is strongly encouraged.

Please visit their web site at: http://www.cdc.gov/ncird/

CDC/NCIRD 035 - Nanoparticle-based Multi-Antigen Influenza Vaccine that Induces both Antibody and Cell-Mediated Immune Responses

Phase I SBIR proposals **will** be accepted.
Fast-Track proposals will **not** be accepted.
Phase I clinical trials will **not** be accepted.

Number of anticipated awards: 1
Budget (total costs): Phase I: up to **$243,500** for up to 6 months; Phase II of up to $1,000,000 and a Phase II duration of up to 2 years

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

Background
Influenza is the cause of considerable morbidity and mortality globally resulting in an estimated 290,000-650,000 fatalities annually and is a pathogen of significant public health importance. Vaccination remains the most effective measure against influenza infection. In addition to annual epidemics, pandemics are also a major concern as demonstrated by three major influenza pandemics in the 20th century in 1918, 1957 and 1968, and the first influenza pandemic of the 21st century in 2009 that spread worldwide in a short period, causing significant morbidity and mortality. In addition, circulation and infection of humans with novel avian influenza viruses from subtypes H5N1, H7N7, H7N1, H7N3, H7N9, and H9N2 has occurred. Vaccination remains the most effective measure against influenza infection. However, currently available vaccines include egg- or cell-derived inactivated split or live attenuated vaccines or insect cell-derived recombinant hemagglutinin (HA) protein. Apart from antibody responses to the globular head region of HA, antibody responses to the HA stalk, neuraminidase (NA), M2e and cell-mediated immune (CMI) responses to conserved internal proteins such as nucleoprotein (NP) have been shown to play a major role in viral clearance. Currently available vaccines are standardized based on HA content, although inactivated detergent-split vaccines do contain variable amounts of other viral proteins and the antibody responses to them varies. Furthermore, inactivated vaccines are not efficient in inducing/recalling CMI responses. Hence, a vaccine that induces antibody responses to all known antibody targets of influenza virus and, when delivered as nanoparticles, induces CMI responses to major conserved internal proteins, is needed to provide both the depth and breadth required.

Project Goals
The primary objective is to develop a recombinant protein and/or peptide-based influenza vaccine that can induce both humoral and cell-mediated immune responses, with sufficient breadth and depth to major antibody and CMI target proteins, when delivered with appropriate nanoparticles.

The nanoparticle technology and recombinant protein/peptide synthesis process should be scalable with batch-to-batch consistency.

Phase I Activities and Expected Deliverables
1. Develop a recombinant protein and/or peptide-based vaccine that contains HA, NA, M1, stalks of HA and the conserved protein, NP, from H1N1, H3N2 and B (Yamagata and Victoria lineages) viruses.

2. Demonstrate induction of antibody responses to HA, NA, M2e, stalks of HA and CMI responses to NP induced by the candidate vaccine as compared to those induced by a licensed, inactivated vaccine in appropriate animal models, mice and/or ferrets.

3. Compare immune responses induced by candidate vaccine by intranasal vs intramuscular routes in animal models, mice and/or ferrets.

Impact

Currently available influenza vaccines induce strain-specific antibody responses against the vaccine strains included in the vaccine. Furthermore, they are poor inducers of CMI responses. If there is a mismatch between the circulating strain/s and vaccine strains, the vaccine efficacy will be suboptimum. Hence, a vaccine that induces a broader antibody and CMI responses to confer protection against disease, reduces morbidity, viral loads and symptoms will have a major impact on public health.

Commercialization Potential

Currently, there are no licensed recombinant protein/peptide influenza vaccines that contain, apart from HA, defined amounts of NA, M1 and NP to induce both humoral and cell-mediated immune responses. Hence, a vaccine that induces antibody responses to HA, NA, M2e, and stalk, and CMI responses to conserved internal protein NP, would increase the needed breadth and depth of vaccination and would have tremendous commercialization potential as this will provide broader protection from disease, even when the circulating strains of viruses are different from those contained in the vaccine.

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)

APPENDIX H.1 — INSTRUCTIONS, HUMAN SUBJECTS AND CLINICAL TRIALS INFORMATION FORM

PDF (https://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixH.1.pdf)

Note: Revised Instructions are being developed and will be provided via solicitation amendment.

APPENDIX H.2 — HUMAN SUBJECTS AND CLINICAL TRIALS INFORMATION FORM

Fillable PDF (https://oamp.od.nih.gov/sites/default/files/DGS/contracting-forms/PHSHumanSubjectsAndClinicalTrialsInfo_2_0-V2.0.pdf)

***Due to large file size, Appendix H.2 - Human Subjects and Clinical Trials Information Form, and Appendix H.3. – Study Record, can only be opened in Internet Explorer. However, you may download them from any browser, then view them once you have saved them onto your computer. ***

APPENDIX H.3. — STUDY RECORD, ATTACHMENT TO HUMAN SUBJECTS AND CLINICAL TRIALS INFORMATION FORM

Fillable PDF (https://oamp.od.nih.gov/sites/default/files/DGS/contracting-forms/HumanSubjectStudy_2_0-V2.0.pdf)

***Due to large file size, Appendix H.2 - Human Subjects and Clinical Trials Information Form, and Appendix H.3. – Study Record, can only be opened in Internet Explorer. However, you may download them from any browser, then view them once you have saved them onto your computer. ***

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

APPENDIX I.1 — 52.204-24 Representation Regarding Certain Telecommunications and Video Surveillance Services or Equipment.

REPRESENTATION REGARDING CERTAIN TELECOMMUNICATIONS AND VIDEO SURVEILLANCE SERVICES OR EQUIPMENT (OCT 2020)

The Offeror shall not complete the representation at paragraph (d)(1) of this provision if the Offeror has represented that it "does not provide covered telecommunications equipment or services as a part of its offered products or services to the Government in the performance of any contract, subcontract, or other contractual instrument" in paragraph (c)(1) in the provision at 52.204-26, Covered Telecommunications Equipment or Services—Representation, or in paragraph (v)(2)(i) of the provision at 52.212-3, Offeror Representations and Certifications-Commercial Items. The Offeror shall not complete the representation in paragraph (d)(2) of this provision if the Offeror has represented that it "does not use covered telecommunications equipment or services, or any equipment, system, or service that uses covered telecommunications equipment or services" in paragraph (c)(2) of the provision at 52.204-26, or in paragraph (v)(2)(ii) of the provision at 52.212-3.

(a) *Definitions.* As used in this provision—

Backhaul, covered telecommunications equipment or services, critical technology, interconnection arrangements, reasonable inquiry, roaming, and substantial or essential component have the meanings provided in the clause 52.204-25, Prohibition on Contracting for Certain Telecommunications and Video Surveillance Services or Equipment.

(b) *Prohibition*.

(1) Section 889(a)(1)(A) of the John S. McCain National Defense Authorization Act for Fiscal Year 2019 (Pub. L. 115-232) prohibits the head of an executive agency on or after August 13, 2019, from procuring or obtaining, or extending or renewing a contract to procure or obtain, any equipment, system, or service that uses covered telecommunications equipment or services as a substantial or essential component of any system, or as critical technology as part of any system. Nothing in the prohibition shall be construed to—

(i) Prohibit the head of an executive agency from procuring with an entity to provide a service that connects to the facilities of a third-party, such as backhaul, roaming, or interconnection arrangements; or

(ii) Cover telecommunications equipment that cannot route or redirect user data traffic or cannot permit visibility into any user data or packets that such equipment transmits or otherwise handles.

(2) Section 889(a)(1)(B) of the John S. McCain National Defense Authorization Act for Fiscal Year 2019 (Pub. L. 115-232) prohibits the head of an executive agency on or after August 13, 2020, from entering into a contract or extending or renewing a contract with an entity that uses any equipment, system, or service that uses covered telecommunications equipment or services as a substantial or essential component of any system, or as critical technology as part of any system. This prohibition applies to the use of covered telecommunications equipment or services, regardless of whether that use is in performance of work under a Federal contract. Nothing in the prohibition shall be construed to—

(i) Prohibit the head of an executive agency from procuring with an entity to provide a service that connects to the facilities of a third-party, such as backhaul, roaming, or interconnection arrangements; or

(ii) Cover telecommunications equipment that cannot route or redirect user data traffic or cannot permit visibility into any user data or packets that such equipment transmits or otherwise handles.

(c) *Procedures.* The Offeror shall review the list of excluded parties in the System for Award Management (SAM) (https://www.sam.gov) for entities excluded from receiving federal awards for "covered telecommunications equipment or services".

(d) *Representation.* The Offeror represents that—

(1) It □ will, □ will not provide covered telecommunications equipment or services to the Government in the performance of any contract, subcontract or other contractual instrument resulting from this solicitation. The Offeror shall provide the additional disclosure information required at paragraph (e)(1) of this section if the Offeror responds "will" in paragraph (d)(1) of this section; and

(2) After conducting a reasonable inquiry, for purposes of this representation, the Offeror represents that—

It □ does, □ does not use covered telecommunications equipment or services, or use any equipment, system, or service that uses covered telecommunications equipment or services. The Offeror shall provide the additional disclosure information required at paragraph (e)(2) of this section if the Offeror responds "does" in paragraph (d)(2) of this section.

(e) *Disclosures.*

(1) Disclosure for the representation in paragraph (d)(1) of this provision. If the Offeror has responded "will" in the representation in paragraph (d)(1) of this provision, the Offeror shall provide the following information as part of the offer:

(i) For covered equipment—

(A) The entity that produced the covered telecommunications equipment (include entity name, unique entity identifier, CAGE code, and whether the entity was the original equipment manufacturer (OEM) or a distributor, if known);

(B) A description of all covered telecommunications equipment offered (include brand; model number, such as OEM number, manufacturer part number, or wholesaler number; and item description, as applicable); and

(C) Explanation of the proposed use of covered telecommunications equipment and any factors relevant to determining if such use would be permissible under the prohibition in paragraph (b)(1) of this provision.

(ii) For covered services—

(A) If the service is related to item maintenance: A description of all covered telecommunications services offered (include on the item being maintained: Brand; model number, such as OEM number, manufacturer part number, or wholesaler number; and item description, as applicable); or

(B) If not associated with maintenance, the Product Service Code (PSC) of the service being provided; and explanation of the proposed use of covered telecommunications services and any factors relevant to determining if such use would be permissible under the prohibition in paragraph (b)(1) of this provision.

(2) Disclosure for the representation in paragraph (d)(2) of this provision. If the Offeror has responded "does" in the representation in paragraph (d)(2) of this provision, the Offeror shall provide the following information as part of the offer:

(i) For covered equipment—

(A) The entity that produced the covered telecommunications equipment (include entity name, unique entity identifier, CAGE code, and whether the entity was the OEM or a distributor, if known);

(B) A description of all covered telecommunications equipment offered (include brand; model number, such as OEM number, manufacturer part number, or wholesaler number; and item description, as applicable); and

(C) Explanation of the proposed use of covered telecommunications equipment and any factors relevant to determining if such use would be permissible under the prohibition in paragraph (b)(2) of this provision.

(ii) For covered services—

(A) If the service is related to item maintenance: A description of all covered telecommunications services offered (include on the item being maintained: Brand; model number, such as OEM number, manufacturer part number, or wholesaler number; and item description, as applicable); or

(B) If not associated with maintenance, the PSC of the service being provided; and explanation of the proposed use of covered telecommunications services and any factors relevant to determining if such use would be permissible under the prohibition in paragraph (b)(2) of this provision.

(End of provision)

APPENDIX I.2 — 52.204-25 Prohibition on Contracting for Certain Telecommunications and Video Surveillance Services or Equipment.

PROHIBITION ON CONTRACTING FOR CERTAIN TELECOMMUNICATIONS AND VIDEO SURVEILLANCE SERVICES OR EQUIPMENT (AUG 2020)

(a) Definitions. As used in this clause—

Backhaul means intermediate links between the core network, or backbone network, and the small subnetworks at the edge of the network (e.g., connecting cell phones/towers to the core telephone network). Backhaul can be wireless (e.g., microwave) or wired (e.g., fiber optic, coaxial cable, Ethernet).

Covered foreign country means The People's Republic of China.

Covered telecommunications equipment or services means-

(1) Telecommunications equipment produced by Huawei Technologies Company or ZTE Corporation (or any subsidiary or affiliate of such entities);

(2) For the purpose of public safety, security of Government facilities, physical security surveillance of critical infrastructure, and other national security purposes, video surveillance and telecommunications equipment produced by Hytera Communications Corporation, Hangzhou Hikvision Digital Technology Company, or Dahua Technology Company (or any subsidiary or affiliate of such entities);

(3) Telecommunications or video surveillance services provided by such entities or using such equipment; or

(4) Telecommunications or video surveillance equipment or services produced or provided by an entity that the Secretary of Defense, in consultation with the Director of National Intelligence or the Director of the Federal Bureau of Investigation, reasonably believes to be an entity owned or controlled by, or otherwise connected to, the government of a covered foreign country.

Critical technology means-

(1) Defense articles or defense services included on the United States Munitions List set forth in the International Traffic in Arms Regulations under subchapter M of chapter I of title 22, Code of Federal Regulations;

(2) Items included on the Commerce Control List set forth in Supplement No. 1 to part 774 of the Export Administration Regulations under subchapter C of chapter VII of title 15, Code of Federal Regulations, and controlled—

(i) Pursuant to multilateral regimes, including for reasons relating to national security, chemical and biological weapons proliferation, nuclear nonproliferation, or missile technology; or

(ii) For reasons relating to regional stability or surreptitious listening;

(3) Specially designed and prepared nuclear equipment, parts and components, materials, software, and technology covered by part 810 of title 10, Code of Federal Regulations (relating to assistance to foreign atomic energy activities);

(4) Nuclear facilities, equipment, and material covered by part 110 of title 10, Code of Federal Regulations (relating to export and import of nuclear equipment and material);

(5) Select agents and toxins covered by part 331 of title 7, Code of Federal Regulations, part 121 of title 9 of such Code, or part 73 of title 42 of such Code; or

(6) Emerging and foundational technologies controlled pursuant to section 1758 of the Export Control Reform Act of 2018 (50 U.S.C. 4817).

Interconnection arrangements means arrangements governing the physical connection of two or more networks to allow the use of another's network to hand off traffic where it is ultimately delivered (e.g., connection of a customer of telephone provider A to a customer of telephone company B) or sharing data and other information resources.

Reasonable inquiry means an inquiry designed to uncover any information in the entity's possession about the identity of the producer or provider of covered telecommunications equipment or services used by the entity that excludes the need to include an internal or third-party audit.

Roaming means cellular communications services (e.g., voice, video, data) received from a visited network when unable to connect to the facilities of the home network either because signal coverage is too weak or because traffic is too high.

Substantial or essential component means any component necessary for the proper function or performance of a piece of equipment, system, or service.

(b) Prohibition.

(1) Section 889(a)(1)(A) of the John S. McCain National Defense Authorization Act for Fiscal Year 2019 (Pub. L. 115-232) prohibits the head of an executive agency on or after August 13, 2019, from procuring or obtaining, or extending or renewing a contract to procure or obtain, any equipment, system, or service that uses covered telecommunications equipment or services as a substantial or essential component of any system, or as critical technology as part of any system. The Contractor is prohibited from providing to the Government any equipment, system, or service that uses covered telecommunications equipment or services as a substantial or essential component of any system, or as critical technology as part of any system, unless an exception at paragraph (c) of this clause applies or the covered telecommunication equipment or services are covered by a waiver described in FAR 4.2104.

(2) Section 889(a)(1)(B) of the John S. McCain National Defense Authorization Act for Fiscal Year 2019 (Pub. L. 115-232) prohibits the head of an executive agency on or after August 13, 2020, from entering into a contract, or extending or renewing a contract, with an entity that uses any equipment, system, or service that uses covered telecommunications equipment or services as a substantial or essential component of any system, or as critical technology as part of any system, unless an exception at paragraph (c) of this clause applies or the covered telecommunication equipment or services are covered by a waiver described in FAR 4.2104. This prohibition applies to the use of covered telecommunications equipment or services, regardless of whether that use is in performance of work under a Federal contract.

(c) Exceptions. This clause does not prohibit contractors from providing—

(1) A service that connects to the facilities of a third-party, such as backhaul, roaming, or interconnection arrangements; or

(2) Telecommunications equipment that cannot route or redirect user data traffic or permit visibility into any user data or packets that such equipment transmits or otherwise handles.

(d) Reporting requirement.

(1) In the event the Contractor identifies covered telecommunications equipment or services used as a substantial or essential component of any system, or as critical technology as part of any system, during contract performance, or the Contractor is notified of such by a subcontractor at any tier or by any other source, the Contractor shall report the information in paragraph (d)(2) of this clause to the Contracting Officer, unless elsewhere in this contract are established procedures for reporting the information; in the case of the Department of Defense, the Contractor shall report to the website at https://dibnet.dod.mil. For indefinite delivery contracts, the Contractor shall report to the Contracting Officer for the indefinite delivery contract and the Contracting Officer(s) for any affected order or, in the case of the Department of Defense, identify both the indefinite delivery contract and any affected orders in the report provided at https://dibnet.dod.mil.

(2) The Contractor shall report the following information pursuant to paragraph (d)(1) of this clause:

(i) Within one business day from the date of such identification or notification: the contract number; the order number(s), if applicable; supplier name; supplier unique entity identifier (if known); supplier Commercial and Government Entity (CAGE) code (if known); brand; model number (original equipment manufacturer number, manufacturer part number, or wholesaler number); item description; and any readily available information about mitigation actions undertaken or recommended.

(ii) Within 10 business days of submitting the information in paragraph (d)(2)(i) of this clause: any further available information about mitigation actions undertaken or recommended. In addition, the Contractor shall describe the efforts it undertook to prevent use or submission of covered telecommunications equipment or services, and any additional efforts that will be incorporated to prevent future use or submission of covered telecommunications equipment or services.

(e) Subcontracts. The Contractor shall insert the substance of this clause, including this paragraph (e), in all subcontracts and other contractual instruments, including subcontracts for the acquisition of commercial items.

(End of clause)

APPENDIX I.3 — 52.204-26 Covered Telecommunications Equipment or Services-Representation

COVERED TELECOMMUNICATIONS EQUIPMENT OR SERVICES-REPRESENTATION (OCT 2020)

(a) *Definitions.* As used in this provision, "covered telecommunications equipment or services" and "reasonable inquiry" have the meaning provided in the clause 52.204-25, Prohibition on Contracting for Certain Telecommunications and Video Surveillance Services or Equipment.

(b) *Procedures.* The Offeror shall review the list of excluded parties in the System for Award Management (SAM) (https://www.sam.gov) for entities excluded from receiving federal awards for "covered telecommunications equipment or services".

(c) (1) *Representation.* The Offeror represents that it □ does, □ does not provide covered telecommunications equipment or services as a part of its offered products or services to the Government in the performance of any contract, subcontract, or other contractual instrument.

(2) After conducting a reasonable inquiry for purposes of this representation, the offeror represents that it □ does, □ does not use covered telecommunications equipment or services, or any equipment, system, or service that uses covered telecommunications equipment or services.

(End of provision)