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 2024-1

Closing Date: November 14, 2023 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 November 14, 2023, 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%20SBIR_STTR_POLICY_DIRECTIVE_May2023.pdf to read the SBIR/STTR Policy Directive issued by the Small Business Administration for further information.

Attention is directed to the inclusion of a new proposal requirement: Appendix J – Disclosure of Foreign Relationships. Please reference SECTION 13 – APPENDICES within this solicitation, read the document in full, and include a completed disclosure form within your business proposal.

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1 INTRODUCTION

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

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 024	Yes	No	No	Small Manufacturing Systems to Produce Research Grade Pharmaceutical Intermediates
NIH/NCI 455	Yes	Yes	No	Point-of-Care Detection of Prostate Specific Antigen
NIH/NCI 456	No	Yes	Yes	Rapid and Affordable Point-of-Care HPV Diagnostics for Cervical Cancer Control
NIH/NCI 457	Yes	Yes	No	Technologies for Detecting Tumor-Derived Cell Clusters
NIH/NCI 458	Yes	No	No	Microbiome-Based Tests for Cancer Research, Diagnosis, Prognosis and/or Patient Management
NIH/NCI 459	Yes	Yes	No	Automated Software for Point-of-Care Testing to Identify Cancer-Associated Malnutrition
NIH/NCI 460	Yes	No	No	Evaluation Datasets as Medical Device Development Tools for Testing Cancer Technologies
NIH/NCI 461	Yes	Yes	Yes	Ultra-Fast Dose Rate (FLASH) Radiation Detectors and Safety Systems for Cancer Treatment
NIH/NCI 462	Yes	Yes	Yes	Organ-on-Chip for Preclinical and Translational Radiobiological Studies
NIH/NCI 463	Yes	Yes	Yes	Translation of Novel Cancer-specific Imaging Agents and Techniques to Mediate Successful Image-guided Cancer Interventions
NIH/NCI 464	Yes	Yes	Yes	Cloud-Based Multimodal Data Analysis Software for the Cancer Research Data Commons
NIH/NCI 465	Yes	Yes	Yes	Cancer Prevention and Treatment Clinical Trials Tools for Recruitment and Retention of Diverse Populations
NIH/NIA 010	Yes	Yes	Yes	Technology to facilitate characterization of the exosome in under –resourced populations for AD/ADRD Studies

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 124	Yes	Yes	No	Development of Next-Generation Devices and Materials-Based Platforms for the Administration of HIV-1 Broadly Neutralizing Antibodies
NIH/NIAID 125	Yes	Yes	No	Development of Long-Acting Treatments for HCV Cure
NIH/NIAID 126	Yes	Yes	No	Rapid Diagnostic Assays for Self-Monitoring of Acute or Rebound HIV-1 Infection
NIH/NIAID 127	Yes	Yes	No	Multiplexed Patient Administered Diagnostics for Hepatitis B, Hepatitis C, and HIV
NIH/NIAID 128	Yes	Yes	Yes	Adjuvant Development for Vaccines for Infectious and Immune-Mediated Diseases
NIH/NIAID 129	Yes	Yes	Yes	Reagents for Immunologic Analysis of Non-mammalian and Underrepresented Mammalian Models
NIH/NIAID 130	Yes	Yes	Yes	Adjuvant Discovery and Down-Selection for Vaccines against Infectious and Immune-Mediated Diseases
NIH/NIAID 131	Yes	Yes	No	Development of Bacteriophage for Treatment of Mycobacterial Infections
NIH/NIAID 132	Yes	Yes	No	Novel Diagnostic Biomarker Discovery and Validation for Malaria and Select Neglected Tropical Diseases (NTDs)
NIH/NIAID 133	Yes	Yes	No	Development of a Serological Test for Herpes Simplex Types 1 and 2 Infections
NIH/NIAID 134	Yes	Yes	Yes	Alternatives to Benzathine Penicillin for Treatment of Syphilis
NIH/NIAID 135	Yes	Yes	Yes	Software or Web Services to Automate Metadata Enrichment and Standardization for Data on Infectious and Immune – Mediated Diseases
NIH/NIAID 136	Yes	Yes	Yes	Software or Web Services to Re-Represent Existing Scientific Data and Knowledge into a Knowledge Graph Format
NIH/NHLBI 115	Yes	Yes	Yes	Clinical Instrument for Para-Hydrogen (pH2) Based Signal Amplification by Reversible Exchange (SABRE) for Hyperpolarizing 13C-Pyruvate and Other Probes for MRI Imaging
NIH/NIMH 001	Yes	No	No	Point-of-Care HIV Viral Load and Drug Adherence Assays
NIH/NIMH 002	Yes	No	No	Development of novel In-vitro and In-vivo Models to support NeuroHIV Research

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
CDC/NCEZID 031	Yes	No	No	Development of SHERLOCK Assay for Detection of High Threat Orthopoxviruses
CDC/NCHHSTP 055	Yes	No	No	Software Solutions: Bridging the Gap between Public Health and Pharmacies
CDC/NCHHSTP 056	Yes	No	No	EHR Algorithm to Identify Persons with HIV Not in Care
CDC/NCHHSTP 057	Yes	No	No	Device for point-of-care nucleic acid purification and detection of HCV
CDC/NCIRD 036	Yes	No	No	Improved Diagnostic Assays for Measles, Mumps, Rubella, and Varicella
CDC/NCIRD 037	Yes	No	No	Rapid Diagnostic Tests for Measles, Mumps, Rubella, and Varicella

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 May 3, 2023. 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, NIAID, NHLBI, and NIMH), as well as **CDC/NCEZID**.

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

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

The I-Corps™ at NIH program is selective, with each NIH/CDC cohort consisting of up to 24 companies, split amongst current grant and contract SBIR Phase I award recipients throughout the NIH and CDC. For a firm fixed price option amount not to exceed $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)
- Technical Lead/Expert (TL)
  (or, the PD/PI of the predicate award is strongly preferred however, 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 25 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, however, currently virtual due to the COVID-19 pandemic), 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://seed.nih.gov/I-Corps-at-NIH 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 costs. 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 25 hours per week for 8 weeks for the 3 team member roles discussed above – as well as travel costs (when appropriate) 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 2025 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 2025 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. Depending on the logistical and programmatic considerations, the cohorts may be completely virtual.

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 November 2024 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 (NIH ONLY): Some NIH Institutes/Centers (ICs) offer Phase II SBIR/STTR awardees the opportunity to apply for Phase IIB Competing Renewal grant awards. Phase II contract awardees are eligible to apply for Phase IIB grants offered by those participating NIH ICs. The Phase II contract must be completed prior to award of a Phase IIB grant, although the Phase II contract need not be completed prior to application. Phase IIB Competing Renewal grant awards are available for those projects that require extraordinary time and effort, 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 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 (NIH ONLY): 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)

National Heart Lung and Blood Institute (NHLBI)

National Institute of Mental Health (NIMH)

Centers for Disease Control and Prevention (CDC) Components:

National Center for Emerging Zoonotic and Infectious Diseases (NCEZID)

National Center for HIV, 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.

Computer Software. Computer programs, source code, source code listings, object code listings, design details, algorithms, processes, flow charts, formulae, and related material that would enable the software to be reproduced, recreated, or recompiled. Computer Software does not include Computer Databases or Computer Software Documentation.

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.

Data. All recorded information, regardless of the form or method of recording or the media on which it may be recorded. The term does not include information incidental to contract or grant administration, such as financial, administrative, cost or pricing or management information.

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.

Form, Fit, and Function Data. Data relating to items, components, or processes that are sufficient to enable physical and functional interchangeability, and data identifying source, size, configuration, mating and attachment characteristics, functional characteristics, and performance requirements. For Computer Software it means data identifying source, functional characteristics, and performance requirements, but specifically excludes the source code, algorithms, processes, formulas, and flow charts of the software.

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.

Government Purpose. Any activity in which the United States Government is a party, including cooperative agreements with international or multi-national defense organizations or sales or transfers by the United States Government to foreign governments or international organizations. Government Purposes include competitive procurement, but do not include the rights to use, modify, reproduce, release, perform, display, or disclose Technical Data or Computer Software for commercial purposes or authorize others to do so.

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, that includes the development of new technology, the refinement of existing technology, or the development of new applications for existing technology.

Intellectual Property. The separate and distinct types of intangible property that are referred to collectively as “Intellectual Property,” including but not limited to: patents, trademarks, copyrights, trade secrets, and mask works

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.

Operations, Maintenance, Installation, or Training Purposes (OMIT) Data. Data that is necessary for operation, maintenance, installation, or training purposes (but not including detailed manufacturing or process data).

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 product, material, object, system, or process, or a model thereof, that is in development, regardless of whether it is in tangible, electronic, graphic or other form, at any stage of development prior to its intended ultimate commercial production and sale. The term "Prototype" includes Computer Programs embedded in hardware or devices.

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

SBIR/STTR Computer Software Rights. The Federal Government's rights during the SBIR/STTR Protection Period in specific types of SBIR/STTR Data that are Computer Software.

A. The Federal Government may use, modify, reproduce, release, perform, display, or disclose SBIR/STTR Data that are Computer Software within the Government. The Federal Government may exercise SBIR/STTR Computer Software Rights within the Government for:
    1. Use in Federal Government computers;
    2. Modification, adaptation, or combination with other Computer Software, provided that the Data incorporated into any derivative software are subject to the rights in § 3(ee) of the SBIR/STTR Policy Directive and that the derivative software is marked as containing SBIR/STTR Data;
    3. Archive or backup; or
    4. Distribution of a computer program to another Federal agency, without further permission of the Awardee, if the Awardee is notified of the distribution and the identity of the recipient prior to the distribution, and a copy of the SBIR/STTR Computer Software Rights included in the Funding Agreement is provided to the recipient.
B. The Federal Government shall not release, disclose, or permit access to SBIR/STTR Data that is Computer Software for commercial, manufacturing, or procurement purposes without the written permission of the Awardee. The Federal Government shall not release, disclose, or permit access to SBIR/STTR Data outside the Government without the written permission of the Awardee unless:
    1. The non-Governmental entity has entered into a non-disclosure agreement with the Government that complies with the terms for such agreements outlined in § 8 of the SBIR/STTR Policy Directive; and
    2. The release or disclosure is—
        i. To a Federal Government support service contractor or their subcontractor for purposes of supporting Government internal use or activities, including evaluation, diagnosis and correction of deficiencies, and adaptation, combination, or integration with other Computer Software provided that SBIR/STTR Data incorporated into any derivative software are subject to the rights in § 3(ee) of the SBIR/STTR Policy Directive; or
        ii. Necessary to support certain narrowly-tailored essential Government activities for which law or regulation permits access of a non-Government entity to a contractors' data developed exclusively at private expense, non-SBIR/STTR Data, such as for emergency repair and overhaul.

SBIR/STTR Data. All Data developed or generated in the performance of an SBIR or STTR award, including Technical Data and Computer Software developed or generated in the performance of an SBIR or STTR award. The term does not include information incidental to contract or grant administration, such as financial, administrative, cost or pricing or management information.

SBIR/STTR Data Rights. The Government's license rights in properly marked SBIR/STTR Data during the SBIR/STTR Protection Period as follows: SBIR/STTR Technical Data Rights in SBIR/STTR Data that are Technical Data or any other type of Data other than Computer Software and SBIR/STTR Computer Software Rights in SBIR/STTR Data that is Computer Software. Upon expiration of the protection period for SBIR/STTR Data, 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. The Government receives Unlimited Rights in all Form, Fit, and Function Data, OMIT Data, and unmarked SBIR/STTR Data.

SBIR/STTR Protection Period. The period of time during which the Government is obligated to protect SBIR/STTR Data against unauthorized use and disclosure in accordance with SBIR/STTR Data Rights. The SBIR/STTR Protection Period begins at award of an SBIR/STTR Funding Agreement and ends not less than twenty years from that date. (See § 8(b)(4) of this Policy Directive).

SBIR/STTR Technical Data Rights. The Federal Government's rights during the SBIR/STTR Protection Period in SBIR/STTR Data that are Technical Data or any other type of Data other than Computer Software. 15 (1) The Government may, use, modify, reproduce, perform, display, release, or disclose SBIR/STTR Data that are Technical Data within the Federal Government; however, the Federal Government shall not use, release, or disclose the data for procurement, manufacture or commercial purposes; or release or disclose the SBIR/STTR Data outside the Government except as permitted by paragraph (2) below or by written permission of the Awardee. (2) SBIR/STTR Data that are Technical Data may be released outside the Federal Government without any additional written permission of the Awardee only if the non-Governmental entity or foreign government has entered into a non-disclosure agreement with the Federal Government that complies with the terms for such agreements outlined in § 8 of this Policy Directive and the release is: (i) Necessary to support certain narrowly-tailored essential Government activities for which law or regulation permits access of a non-Government entity to a contractors' data developed exclusively at private expense, non-SBIR/STTR Data, such as for emergency repair and overhaul; (ii) To a Government support services contractor in the performance of a Government support services contract for internal Government use or activities, including evaluation, diagnosis or modification provided that SBIR/STTR Technical Data incorporated into any derivative Data are subject to the rights in paragraph (ii), and the release is not for commercial purposes or manufacture; (iii) To a foreign government for purposes of information and evaluation if required to serve the interests of the U.S. Government; or (iv) To non-Government entities or individuals for purposes of evaluation.

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.

Technical Data. Recorded information, regardless of the form or method of the recording, of a scientific or technical nature (including Computer Software Documentation and Computer Databases). The term does not include Computer Software or financial, administrative, cost or pricing, or management information, or other data incidental to contract or grant administration. The term includes recorded Data of a scientific or technical nature that is included in Computer Databases.

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.

Unlimited Rights. The Government's rights to access, use, modify, prepare derivative works, reproduce, release, perform, display, disclose, or distribute Data in whole or in part, in any manner and for any purpose whatsoever, and to have or authorize others to do so.

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 and the SBIR and STTR Extension Act of 2022. the following performance benchmarks have been established for companies participating in SBIR programs.

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 21 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 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 this performance benchmark.

For SBIR and STTR Phase I applicants that have received more than 50 Phase I awards over the past 5 fiscal years (excluding the most recently-completed fiscal year): Companies that do not meet or exceed the benchmark minimum Transition Rate of 0.5 will not be eligible to receive more than 20 total Phase I and Phase II awards for a period of one year from the date on which such determination is made.

On June 1 of each year, SBA will identify the companies that fail to meet minimum performance requirements. SBA calculates individual company Phase I to Phase II Transition Rates using SBIR and STTR award information across all federal agencies. SBA will notify companies and the relevant officials at the participating agencies.

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 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 this performance benchmark.

For companies that have received more than 50 Phase II awards from all agencies over the past 10-fiscal years (excluding the two most recently completed Fiscal Year): Companies that meet this criterion must show an average of at least $250,000 of aggregated sales and investment per Phase II award over the past 10-fiscal year period. Applicants that fail this benchmark will not be eligible to receive more than 20 total Phase I and Phase II awards for a period of one year from the date on which such determination is made. This requirement does not apply to companies that have received 50 or fewer Phase II awards over the 10-fiscalyear period, excluding the two most recently-completed fiscal years.

For companies that have received more than 100 Phase II awards from all agencies over the past 10-fiscal years (excluding the two most recently completed Fiscal Year): Companies that meet this criterion must show an average of at least $450,000 of aggregated sales and investment per Phase II award over the past 10-fiscal year period. Applicants that fail this benchmark will not be eligible to receive more than 20 total Phase I and Phase II awards for a period of one year from the date on which such determination is made. This requirement does not apply to companies that have received 100 or fewer Phase II awards over the 10-fiscalyear period, excluding the two most recently-completed fiscal years.

On June 1 of each year, SBA will identify the companies that fail to meet minimum performance requirements. SBA will notify companies and the relevant officials at the participating agencies.

4.4 Multiple Principal Investigators (NIH Only)

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 have an active registration 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.

Note: On April 4, 2022, the unique entity identifier used across the federal government changed from the DUNS Number to the Unique Entity ID, a 12-character alphanumeric ID assigned to an entity by SAM.gov. Entity registration, searching, and data entry in SAM.gov now require use of the new Unique Entity ID.

Existing registered entities can find their Unique Entity ID by following the steps here. New entities can get their Unique Entity ID at SAM.gov and, if required, complete an entity registration.

Proposals do not need to include proof of SAM registration – however, proposals should note the company's Unique Entity ID, 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:

- If you are a previous SBIR/STTR awardee from any agency, go to www.sbir.gov and login to your SBIR.GOV user account. Click on DASHBOARD and select 'Download SBC Registration (Proof of Registration/Certification)' from MY DOCUMENT BOX.
- If you are a first-time applicant, navigate to the SBA Company Registry and use the registration tool to complete your company's registration.
- 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.

Each Phase I and II Applicant is required to provide information on www.SBIR.gov (see Appendix II as posted on www.SBIR.gov). Each SBC applying for a Phase II award is required to update its Commercialization information on www.SBIR.gov for all of its prior Phase II awards (see Appendix II as posted on www.SBIR.gov)

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.

Disclosures of Foreign Affiliations or Relationships to Foreign Countries

All offerors must complete and submit the Required Disclosure of Foreign Affiliation of Relationships to Foreign Countries form as part of your Business Proposals which is attached and incorporated as Solicitation APPENDICES J.

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 (TABA)

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 TABA 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. Any SBIR/STTR Data delivered by the Awardee, and in which the Awardee intends to limit the Federal Government's rights to SBIR/STTR Data Rights, must be delivered with restrictive markings. The Federal Government assumes no liability for the access, use, modification, reproduction, release, performance, display, disclosure, or distribution of SBIR/STTR Data without markings. The Awardee or its subcontractors or suppliers shall conspicuously and legibly mark all such SBIR/STTR Data with the appropriate legend.

(1) The authorized legend shall be placed on each page of the SBIR/STTR Data. If only portions of a page are subject to the asserted restrictions, the SBIR/STTR Awardee shall identify the restricted portions (e.g., by circling or underscoring with a note or other appropriate identifier). With respect to SBIR/STTR Data embodied in 194 Computer Software, the legend shall be placed on:

a. the printed material or media containing the Computer Software; or
b. the transmittal document or storage container. The legend shall read as follows:

"SBIR/STTR DATA RIGHTS Funding Agreement No. _____ Award Date _____ SBIR/STTR Protection Period _____ SBIR/STTR Awardee ____ SBIR/STTR Awardee Address _____ This is SBIR/STTR Data (or is Computer Software or a Prototype that embodies or includes SBIR/STTR Data) to which the SBIR/STTR Awardee has SBIR/STTR Data Rights and to which the Federal Government has received SBIR/STTR Technical Data Rights (or SBIR/STTR Computer Software Rights) during the SBIR/STTR Protection Period and rights of use for Government Purposes after the SBIR/STTR Protection Period, as those terms are defined in the SBIR/STTR Funding Agreement. Awards issued by the U.S. Department of Energy are subject to Unlimited Rights after the SBIR/STTR Protection Period, as that term is defined in the SBIR/STTR Funding Agreement. Any reproduction of SBIR/STTR Data or portions of such data marked with this legend must also reproduce the markings."
(End of Legend)

(2) Data submitted without correct or appropriate markings may be corrected within 6 months from the date the data is delivered.

Relation to patents. Nothing regarding SBIR/STTR Data Rights in this clause shall imply a license to or imply a requirement to license to the Federal Government any patent to a Subject Invention (as defined under the Bayh-Dole Act implemented at 37 CFR 401) made under an SBIR/STTR award.

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: https://olaw.nih.gov/policies-laws/phs-policy.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 ofCompliance.

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 ofclause)

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 August 25, 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:
https://grants.nih.gov/policy/inclusion/women-and-minorities/guidelines.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 Inclusion of Individuals Across the Lifespan as Participants in Research Involving Human Subjects

Section 2038 of the 21st Century Cures Act, enacted December 13, 2016, enacts new provisions requiring NIH to address the consideration of age as an inclusion variable in research involving human subjects, to identify criteria for justification for any age-related exclusions in NIH research, and to provide data on the age of participants in clinical research studies. The **NIH Policy and Guidelines on the Inclusion of Individuals Across the Lifespan as Participants in Research Involving Human Subjects** applies to all NIH conducted or supported research involving human subjects, including research that is otherwise "exempt" in accordance with Sections 101(b) and 401(b) of 45 CFR 46 - Federal Policy for the Protection of Human Subjects. The NIH Policy and Guidelines on the Inclusion of Individuals Across the Lifespan as Participants in Research Involving Human Subjects applies to all NIH conducted or supported research involving human subjects, including research that is otherwise "exempt" in accordance with Sections 101(b) and 401(b) of 45 CFR 46 - Federal Policy for the Protection of Human Subjects.

Effective on all solicitations issued on or after January 25, 2019, individuals of all ages, including children (i.e. individuals under the age of 18) and older adults, must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific or ethical reasons not to include them. The inclusion of individuals across the lifespan as subjects in research must be in compliance with all applicable subparts of 45 CFR 46 as well as with other pertinent federal laws and regulations.

The Contractor must address the age-appropriate inclusion or exclusion of individuals in the proposed research project. The Contractor must provide a description of plans for including individuals across the lifespan, including a rationale for selecting the specific age range justified in the context of the scientific question proposed. If individuals will be excluded from the research based on age, the contractor must provide acceptable justification for the exclusion.

The Contractor must submit cumulative data as prescribed in the Age Enrollment Report template on participant age at enrollment in monthly progress reports. Investigators planning to conduct research involving human subjects should design their studies in such a way that de-identified individual level participant data on sex/gender, race, ethnicity, and age at enrollment may be provided in progress reports.

5.8 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.

5.9 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.

5.10 Posting Clinical Trial Informed Consent Forms to Clinicaltrials.Gov

The Revised Common Rule sections 46.102(b) and 46.116(h) requires Contractors to post one IRB-approved version of an Informed Consent Form that has been used to enroll participants on a public federal website designated for posting such Consent Forms. Contractors shall post the Informed Consent Form to the National Institutes of Health's (NIH's) clinical trials registry and results database ClinicalTrials.gov . Note: ClinicalTrials.gov only accepts Informed Consent Forms written in English; non-English language forms must be submitted to Regulations.gov . The Informed Consent Form must be posted after recruitment closes, and no later than 60 days after the final study visit. The Contracting Officer (CO) and/or Contracting Officer Representative (COR) may permit or require redactions as appropriate.

5.11 Certificate of Confidentiality

Section 2012 of the 21st Century Cures Act, enacted December 13, 2016, enacts new provisions governing the authority of the Secretary of Health and Human Services (Secretary) to protect the privacy of individuals who are the subjects of research, including significant amendments to the previous statutory authority for such protections, under subsection 301(d) of the Public Health Service Act.

Effective October 1, 2017, all research that was commenced or ongoing on or after December 13, 2016 and is within the scope of the NIH Policy for Issuing Certificate of Confidentiality (CoC) NOT-OD-17-109, the Contractor shall protect the privacy of individuals who are subjects of such research in accordance with subsection 301(d) of the Public Health Service Act as a term and condition of the contract. The certificate will not be issued as a separate document.

NIH considers research in which identifiable, sensitive information is collected or used, to include:

- Human subjects research as defined in the Federal Policy for the Protection of Human Subjects (45 CFR 46), including exempt research (except for human subjects' research that is determined to be exempt from all or some of the requirements of 45 CFR 46) if the information obtained is recorded in such a manner that human subjects cannot be identified or the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
- Research involving the collection or use of biospecimens that are identifiable to an individual or for which there is at least a very small risk that some combination of the biospecimen, a request for the biospecimen, and other available data sources could be used to deduce the identity of an individual;
- Research that involves the generation of individual level, human genomic data from biospecimens, or the use of such data, regardless of whether the data is recorded in such a manner that human subjects can be identified or the identity of the human subjects can readily be ascertained as defined in the Federal Policy for the Protection of Human Subjects (45 CFR 46); or
- Any other research that involves information about an individual for which there is at least a very small risk, as determined by current scientific practices or statistical methods, that some combination of the information, a request for the information, and other available data sources could be used to deduce the identity of an individual, as defined in subsection 301(d) of the Public Health Service Act.

The Contractor shall not:

- Disclose or provide, in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding, the name of such individual or any such information, document, or biospecimen that contains identifiable, sensitive information about the individual and that was created or compiled for purposes of the research, unless such disclosure or use is made with the consent of the individual to whom the information, document, or biospecimen pertains; or
- Disclose or provide to any other person not connected with the research the name of such an individual or any information, document, or biospecimen that contains identifiable, sensitive information about such an individual and that was created or compiled for purposes of the research. The Contractor is permitted to disclose only in below circumstances. The Contractor shall notify the CO minimum ten (10) calendar days prior to disclosure.
- Required by Federal, State, or local laws (e.g., as required by the Federal Food, Drug, and Cosmetic Act, or state laws requiring the reporting of communicable diseases to State and local health departments), excluding instances of disclosure in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding;
- Necessary for the medical treatment of the individual to whom the information, document, or biospecimen pertains and made with the consent of such individual;
- Made with the consent of the individual to whom the information, document, or biospecimen pertains; or
- Made for the purposes of other scientific research that is in compliance with applicable Federal regulations governing the protection of human subjects in research.

In accordance with 45 CFR Part 75.303(a), the Contractor shall maintain effective internal controls (e.g., policies and procedures) that provide reasonable assurance that the award is managed in compliance with Federal Statutes and regulations.

The recipient of CoCs shall ensure that any company/institution/individual not funded by NIH who receives a copy of identifiable, sensitive information protected by a Certificate is subject to the requirements of subsection 301(d) of the Public Health Service Act. The Contractor shall ensure that Subcontractors who receive funds to carry out part of the Federal award are subject to subsection 301(d) of the Public Health Service Act and the NIH Policy for Issuing CoC.

5.12 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.

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. 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. 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.

5.13 Human Materials (Assurance of OHRP Compliance)

The acquisition and supply of all human specimen material (including fetal material) used under this contract shall be obtained by the Contractor in full compliance with applicable State and Local laws and the provisions of the Uniform Anatomical Gift Act in the United States, and no undue inducements, monetary or otherwise, will be offered to any person to influence their donation of human material.

The Contractor shall provide written documentation that all human materials obtained as a result of research involving human subjects conducted under this contract, by collaborating sites, or by subcontractors identified under this contract, were obtained with prior approval by the Office for Human Research Protections (OHRP) of an Assurance to comply with the requirements of 45 CFR 46 to protect human research subjects. This restriction applies to all collaborating sites without OHRP-approved Assurances, whether domestic or foreign, and compliance must be ensured by the Contractor.

Provision by the Contractor to the Contracting Officer of a properly completed "Protection of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption", Form OMB No. 0990-0263(formerly Optional Form 310), certifying IRB review and approval of the protocol from which the human materials were obtained constitutes the written documentation required. The human subject certification can be met by submission of a self-designated form, provided that it contains the information required by the "Protection of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption", Form OMB No. 0990-0263(formerly Optional Form 310).

5.14 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 /.

5.15 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.

5.16 NIH Policy on Enhancing Public Access to Archived Publications Resulting from NIH-Funded Research

NIH-funded investigators shall submit to the NIH National Library of Medicine's (NLM) PubMed Central (PMC) an electronic version of the author's final manuscript, upon acceptance for publication, resulting from research supported in whole or in part with direct costs from NIH. NIH defines the author's final manuscript as the final version accepted for journal publication, and includes all modifications from the publishing peer review process. The PMC archive will preserve permanently these manuscripts for use by the public, health care providers, educators, scientists, and NIH. The Policy directs electronic submissions to the NIH/NLM/PMC: https://www.ncbi.nlm.nih.gov/pmc/.
Additional information is available at **https://grants.nih.gov/grants/guide/notice-files/NOT-OD-21-013.html and https://publicaccess.nih.gov/.**

5.17 Technical Data Rights

Allocation of SBIR/STTR Data Rights.

(1) An SBC retains ownership of all SBIR/STTR Data it develops or generates in the performance of an SBIR/STTR award. The SBC retains all rights in SBIR/STTR Data that are not granted to the Federal Government in accordance with the SBIR/STTR Policy Directive. These rights of the SBC do not expire.
(2) During the SBIR/STTR Protection Period, the Federal Government receives SBIR/STTR Technical Data Rights in appropriately marked SBIR/STTR Data that is Technical Data or any other type of Data other than Computer Software; and SBIR/STTR Computer Software Rights in appropriately marked SBIR/STTR Data that is Computer Software.
(3) After the protection period, the Federal Government may use, and authorize others to use on its behalf, for Government Purposes, SBIR/STTR Data that was protected during the SBIR/STTR Protection Period. Awards issued by the U.S. Department of Energy are subject to Unlimited Rights after the expiration of the SBIR/STTR Protection Period.
(4) The Federal Government receives Unlimited Rights in Form Fit, and Function Data, OMIT Data, and all unmarked SBIR/STTR Data

5.18 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. NIH and CDC require 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

Office of Science
Office of the Director
Centers for Disease Control and Prevention (CDC)
1600 Clifton Road, NE MS H21-8
Atlanta, Georgia 30329
Phone: 404-718-1386
E-mail: SBIR@cdc.gov

5.19 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 2023, Executive Schedule, Level II of the Federal Executive Pay Scale is $212,100.

5.20 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, sexual orientation, gender identity, 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 Products and Commercial Services**. Contracts resulting from this solicitation will include FAR clause 52.244-6 (Jan 2022), 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://sharing.nih.gov/
  - Data Management and Sharing Plan http://grants.nih.gov/grants/policy/data_sharing
  - Model Organism Sharing Plan https://sharing.nih.gov/other-sharing-policies/model-organism-sharing-policy
  - 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

* An Offeror's plan for the management and sharing of final research data (Data Management and Sharing Plan), plans for sharing model organisms, and submission of genome-wide association study (GWAS) data to the NIH designated GWAS data repository shall be assessed by Government Program Staff in the funding ICO for appropriateness, adequacy, and reasonableness.

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
- Security risk as assessed by the HHS Due Diligence Program.

Denial of Awards

Offerors are encouraged to consider whether their entity's relationships with foreign countries of concern will pose a security risk. Prior to issuing an award, NIH, CDC and FDA will determine whether the SBC submitting the proposal:

- has an owner or covered individual that is party to a malign foreign talent recruitment program;
- has a business entity, parent company, or subsidiary located in the People's Republic of China or another foreign country of concern; or
- has an owner or covered individual that has a foreign affiliation with a research institution located in the People's Republic of China or another foreign country of concern.

A finding of foreign involvement with countries of concern will not necessarily disqualify an offeror. NIH and CDC will provide SBC offerors the opportunity to address any identified security risks prior to award. Final award determinations will be based on whether the applicant's involvement falls within any of the following risk criteria, per the SBIR and STTR Extension Act of 2022:

- interfere with the capacity for activities supported by NIH, CDC, or FDA to be carried out;
- create duplication with activities supported by NIH, CDC, or FDA;
- present concerns about conflicts of interest;
- were not appropriately disclosed to NIH, CDC, or FDA;
- violate Federal law or terms and conditions of NIH, CDC, or FDA; or
- pose a risk to national security.

NIH or CDC will not issue an award under the SBIR program if the covered relationship with a foreign country of concern identified in this guidance is determined to fall under any of the criteria provided above, and the risk cannot be resolved.

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 29, 2023**. 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 September 27, 2023 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_qA_CUEqTRdikOdxAVhM-zQ. Following registration, a confirmation e-mail will be sent containing information about joining the webinar.

Presentation material from this webinar shall be posted on 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. Proposals shall not include links to internet website addresses (URLs) or otherwise direct readers to alternate sources of information, other than citations.

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, 6 and 7, 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
- Draft Statement of Work (Appendix E)

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 4.12 for Directions)

Item 6: Summary of Related Activities (Appendix F)

Item 7: Disclosure of Foreign Relationships form (Appendix J)

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 4.12 for Directions)

Item 6: Summary of Related Activities (Appendix F)

Item 7: Disclosure of Foreign Relationships form (Appendix J)

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.

    NIH encourages, to the maximum extent practicable, the sharing of final research data to serve public health for the common good and this contract is expected to generate research data that must be shared with the public and other researchers. NIH's Data Management and Sharing policies may be found at the following websites:

- NOT-OD-14-124 - NIH Genomic Data Sharing Policy;
- NOT-OD-21-013 - Final NIH Policy for Data Management and Sharing;

- NOT-OD-21-014 - Supplemental Information to the NIH Policy for Data Management and Sharing: Elements of an NIH Data Management and Sharing Plan;
- NOT-OD-21-015 - Supplemental Information to the NIH Policy for Data Management and Sharing: Allowable Costs for Data Management and Sharing; and
- NOT-OD-21-016 - Supplemental Information to the NIH Policy for Data Management and Sharing: Selecting a Repository for Data Resulting from NIH-Supported Research.

NIH recognizes that data sharing may be complicated or limited, in some cases, by institutional policies, local IRB rules, as well as local, state and Federal laws and regulations, including but not limited to the Privacy Act of 1974 (2020 Edition), the Privacy Rule (see HHS-published documentation on the Privacy RFP Handbook updated 5/2023 230 Rule at https://www.hhs.gov/ocr/index.html), the Health Insurance Portability & Accountability Act of 1996 (HIPAA), and the Health IT for Economic & Clinical Health (HITECH) Act, which was enacted as part of the American Recovery & Reinvestment Act of 2009 (ARRA).

As per NIH Notice NOD-OD-21-013, "Final NIH Policy for Data Management and Sharing," respect for participant autonomy and maintenance of participant privacy and confidentiality can be consistent with data sharing. The rights and privacy of people who participate in NIH-funded research shall be protected at all times and Contractors shall anonymize and aggregate (or otherwise fully protect from release) any personally identifiable information (PII), HIPAA-protected personal health information (PHI), and/or HITECH-protected electronic health information which they receive, use, and/or reference; thus, data intended for broader use should be free of any and all personal identifiers that would permit linkages to individual research participants and/or variables that could lead to any disclosure of the identity of individual subjects, direct or deductive, for which the Government shall have no liability whatsoever.

a) **Management and Sharing of Research Data Plan:** NIH encourages, to the maximum extent practicable, the sharing of final research data to expedite the translation of research results into knowledge, products, services, and/or procedures to improve the human health condition. This contract is anticipated to generate such research data. Therefore, the Offeror shall submit a plan in its technical proposal for data management and sharing or state why such data sharing is not possible. If data sharing is limited, the Offeror shall explain the rationale and nature of such limitations in its Data Management and Sharing Plan. NIH's Data Management and Sharing Policy may be found at the following Web site: NOT-OD-21-013 - Final NIH Policy for Data Management and Sharing; NIH Sharing Policies and Related Guidance on NIH-Funded Research Resources are found at: https://grants.nih.gov/policy/sharing.htm.

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.

(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 from 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.

   NIH encourages, to the maximum extent practicable, the sharing of final research data to serve public health for the common good and this contract is expected to generate research data that must be shared with the public and other

researchers. NIH's Data Management and Sharing policies may be found at the following websites:

a) NOT-OD-14-124 - NIH Genomic Data Sharing Policy;
b) NOT-OD-21-013 - Final NIH Policy for Data Management and Sharing;
c) NOT-OD-21-014 - Supplemental Information to the NIH Policy for Data Management and Sharing: Elements of an NIH Data Management and Sharing Plan;
d) NOT-OD-21-015 - Supplemental Information to the NIH Policy for Data Management and Sharing: Allowable Costs for Data Management and Sharing; and
e) NOT-OD-21-016 - Supplemental Information to the NIH Policy for Data Management and Sharing: Selecting a Repository for Data Resulting from NIH-Supported Research.

NIH recognizes that data sharing may be complicated or limited, in some cases, by institutional policies, local IRB rules, as well as local, state and Federal laws and regulations, including but not limited to the Privacy Act of 1974 (2020 Edition), the Privacy Rule (see HHS-published documentation on the Privacy RFP Handbook updated 5/2023 230 Rule at https://www.hhs.gov/ocr/index.html), the Health Insurance Portability & Accountability Act of 1996 (HIPAA), and the Health IT for Economic & Clinical Health (HITECH) Act, which was enacted as part of the American Recovery & Reinvestment Act of 2009 (ARRA).

As per NIH Notice NOD-OD-21-013, "Final NIH Policy for Data Management and Sharing," respect for participant autonomy and maintenance of participant privacy and confidentiality can be consistent with data sharing. The rights and privacy of people who participate in NIH-funded research shall be protected at all times and Contractors shall anonymize and aggregate (or otherwise fully protect from release) any personally identifiable information (PII), HIPAA-protected personal health information (PHI), and/or HITECH-protected electronic health information which they receive, use, and/or reference; thus, data intended for broader use should be free of any and all personal identifiers that would permit linkages to individual research participants and/or variables that could lead to any disclosure of the identity of individual subjects, direct or deductive, for which the Government shall have no liability whatsoever.

f) **Management and Sharing of Research Data Plan:** NIH encourages, to the maximum extent practicable, the sharing of final research data to expedite the translation of research results into knowledge, products, services, and/or procedures to improve the human health condition. This contract is anticipated to generate such research data. Therefore, the Offeror shall submit a plan in its technical proposal for data management and sharing or state why such data sharing is not possible. If data sharing is limited, the Offeror shall explain the rationale and nature of such limitations in its Data Management and Sharing Plan. NIH's Data Management and Sharing Policy may be found at the following Web site: NOT-OD-21-013 - Final NIH Policy for Data Management and Sharing; NIH Sharing Policies and Related Guidance on NIH-Funded Research Resources are found at: https://grants.nih.gov/policy/sharing.htm.

g) **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.

h) **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 (Item 2)

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

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

Information Required for ALL Clinical Research Proposals

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

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

The proposal must include the following information:

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

For purposes of this policy, a child is defined as an individual under the age of 18 years.

All Offerors proposing research involving human subjects should read the "Inclusion of Children in Clinical Research: Change in NIH Definition " which was published in the NIH guide notice on October 13, 2015 and 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. For example, some states consider a person aged 18 to be an adult and therefore one who can provide consent without parental permission.

8.12.6 Research Involving Prisoners as Subjects

A. HHS Regulations at 45 CFR Part 46, Subpart C provide additional protections pertaining to biomedical and behavioral research involving prisoners or those individuals who, during the period of the contract become prisoners, as subjects. These regulations also set forth the duties of the Institutional Review Board (IRB) where prisoners are involved in the research. HHS funded research involving prisoners as subjects may not proceed until the Office for Human Research Protections (OHRP) issues approval, in writing, as required by 45 CFR 46.306(a)(2). In addition, OHRP Guidance on the Involvement of Prisoners in Research may be found at: http://www.hhs.gov/ohrp/policy/prisoner.html.

B. HHS Waiver for Epidemiological Research Involving Prisoners as Subjects

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

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

1. The sole purposes are:
    a. to describe the prevalence or incidence of a disease by identifying all cases, or
    b. to study potential risk factor associations for a disease, and
2. The Institution responsible for the conduct of the research certifies to the OHRP that the Institutional Review Board (IRB) approved the research and fulfilled its duties under 45 CFR 46.305(a)(2 7) and determined and documented that:
    a. the research presents no more than minimal risk, and
    b. no more than inconvenience to the prisoner subjects, and
    c. prisoners are not a particular focus of the research.

For more information about this Waiver see http://www.gpo.gov/fdsys/pkg/FR-2003-06-20/html/03-15580.htm.

8.12.7 Public Health Surveillance Exclusion

An Offeror may request an exclusion from applicability of the "revised Common Rule" (*Code of Federal Regulations (CFR) Title 45, Public Welfare, Department of Health and Human Services, Part 46, Protection of Human Subjects, Revised 19 January 2017, Effective 19 July 2018, with a General Compliance Date of 21 January 2019 (45 CFR part 46)), and not its predecessor, the Pre-2018 Common Rule (Common Rule). The revised Common Rule is also known or referred to as the "2018 Requirements" or the "2018 Rule."*) if it believes that NIH-funded or -conducted activities associated with this solicitation should be considered "public health surveillance

activities deemed not to be research" for the purposes of the revised Common Rule. All requests for the public health surveillance exclusion from the revised Common Rule for NIH-funded research-whether conducted or supported-must receive NIH approval, as per the process outlined below, to be considered a public health surveillance activity deemed not to be research under the revised Common Rule's Sections §46.102(k), Public health authority, and §46.102(l)(2), Public health surveillance activities. NIH expects that NIH-supported or -conducted research will be determined to be a public health surveillance activity only in extremely rare cases. **Please note that NIH will not consider any NIH-defined clinical trials for a public health surveillance exclusion request. In addition, NIH will not consider studies that contain any activity that does not meet the requirements for an exclusion for a public health surveillance determination, including any intent to store specimens and/or data for future use.**

Requesting a Determination that NIH-Funded or -Conducted Activities be Considered Public Health Surveillance:

Offerors shall provide a compelling justification as to why NIH-funded or -conducted activities should be considered public health surveillance activities deemed not to be research for the purposes of the revised Common Rule. All activities for which approval of the exclusion will be sought must be disclosed and described.

The justification shall include information that demonstrates **all three (3)** of the following:

a) The proposed activity is strictly limited to only that necessary for NIH to identify, monitor, assess, or investigate:

i. Potential public health signals; or
ii. Onsets of disease outbreaks; or
iii. Conditions of public health importance (including trends, signals, risk factors, or patterns in diseases).

AND

b) The activities include those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters).

AND

c) The activities will directly inform NIH public health decision-making or action.

Note: An Offeror shall submit its compelling justification for exclusion with its technical proposal as a separate attachment, so that the justification can be detached from and evaluated apart from the Offeror's technical proposal. The Government reserves the right to not consider any public health surveillance exclusion requests if the justification is not provided at the time of original proposal submission.

Offerors shall complete and submit the PHS Human Subjects and Clinical Trials Information Form, following instructions in the solicitation, as applicable. Offerors should not assume that approval of an exclusion will be granted when completing the PHS Human Subjects and Clinical Trials Information Form.

Note that the proposed budget in the proposal must reflect all necessary/required costs for the full and proper conduct of research involving human subjects, in complete compliance with all applicable laws, protocols, rules, and/or regulations at all levels, without approval of any exclusion. Offerors should not assume that approval of an exclusion will be granted when considering the costs to include in any proposed budget and therefore, must respond and price accordingly.

Notice of Approval or Disapproval of Request for Exclusion

Exclusion requests will be considered separate from the NIH peer review of technical proposals. Offerors will be issued written notification of approval or denial by the NIH Contracting Officer of any request(s) for exclusion prior to award. Any decision by NIH on an Offeror's request for a Public Health Surveillance Exclusion shall be final.

The award budget may then be adjusted accordingly if approval of an exclusion is granted by NIH.

8.12.8 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.

8.12.9 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

8.12.10 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.

8.12.11 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/

8.12.12 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 3).

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 4.18.

- 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)	2-3	Scientific and Technical Merit Review: January-February 2024 Anticipated Award Date: August-September 2024
National Institutes of Health (NIH) National Cancer Institute (NCI)	31-50	Scientific and Technical Merit Review: March-May 2024 Anticipated Award Date: August-September 2024
National Institutes of Health (NIH) National Institute on Aging (NIA)	1-2	Scientific and Technical Merit Review: January-February 2024 Anticipated Award Date: August-September 2024
National Institutes of Health (NIH) National Institute of Allergy and Infectious Diseases (NIAID)	23-42	Scientific and Technical Merit Review: March 2024 Anticipated Award Date: August 2024
National Institutes of Health (NIH) National Heart Lung and Blood Institute (NHLBI)	1-5	Scientific and Technical Merit Review: February-April 2024 Anticipated Award Date: July-September 2024
National Institutes of Health (NIH) National Institute of Mental Health (NIMH)	2-6	Scientific and Technical Merit Review: March 2024 Anticipated Award Date: August 2024
Center for Disease Control and Prevention (CDC) National Center for HIV, Viral Hepatitis, STD, and TB Prevention (NCHHSTP)	4	Scientific and Technical Merit Review: March 2024 Anticipated Award Date: August 2024
Center for Disease Control and Prevention (CDC) National Center for Immunization and Respiratory Diseases (NCIRD)	2	Scientific and Technical Merit Review: March 2024 Anticipated Award Date: August 2024

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

General Questions about the NIH SBIR Program
Email: seedinfo@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)

KJ Shaikh
Contracting Officer
NIDA Office of Acquisition
Phone: (301) 435-1777
Email: kj.shaikh@nih.gov

Valerie Whipple
Contracting Officer
NIDA Office of Acquisition
Phone: (301) 827-5218
Email: valerie.whipple@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
NIDA Office of Acquisition
Phone: (301) 435-7479
E-mail: karen.mahon@nih.gov

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES (NIAID)

Jonathan Bryan
Contracting Officer
Office of Acquisitions, DEA, NIAID
Phone: (240) 669-5180
Email: jonathan.bryan@nih.gov

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE (NHLBI)

Lynn M. Furtaw
Operations Support Team Lead
Office of Acquisitions, OM, NHLBI
Phone: (301) 827-7713
E-mail: lynn.furtaw@nih.gov

NATIONAL INSTITUTE OF MENTAL HEALTH (NIMH)

Christine Frate
Contracting Officer
NIDA Office of Acquisition
Phone: (301) 443-3846
Email: Christine.Frate@nih.gov

CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

NATIONAL CENTER FOR EMERGING ZOONOTIC AND INFECTIOUS DISEASES (NCEZID)

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

Marie Claxton
Contract Specialist
Centers for Disease Control and Prevention (CDC)
Office of Financial Resources
Phone: (770) 498-3158
E-mail: UTJ4@cdc.gov

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

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

NATIONAL CENTER FOR IMMUNIZATION AND RESPIRATORY DISEASES (NCIRD)

Mark Draluck
Contract Specialist
Centers for Disease Control and Prevention (CDC)
Office of Financial Resources
Phone: (770) 488-0938
E-mail: SYQ1@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 024- Small Manufacturing Systems to Produce Research Grade Pharmaceutical Intermediates

(Fast-Track and Direct to Phase 2 proposals will not be accepted. Phase II information is provided only for informational purposes to assist Phase I offerors with their long-term strategic planning.)

Number of anticipated awards: 2 to 3

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;
Preclinical drug development is a time and cost-intensive process that involves synthesizing analogs as part of a medicinal chemistry drug discovery campaign. Typically, chemists in small and mid-sized laboratories are tasked with preparing multiple targets at the same time, relying on cumbersome batch synthesis methods in order to find key intermediates that can rapidly undergo the final transformations prior to biological testing. To reduce the steps to obtain the intermediate that will support structure-activity relationship (SAR) studies by medicinal chemists, the key pharmacophore or key structural component must be known where one can perform strategic chemical modification. The translational burden required in the process of synthesizing iterative rounds of analogs for biological screening activities can be alleviated by keeping to a minimum, the amount of work involved in tuning the synthesis of each new target. Often this can be achieved by identifying the shortest synthetic route, requiring the least number of isolation methods, while maintaining desired purity and yields for lead compounds. The key to accelerating molecules into the clinic is the ability to use automation to make the lead compound, and the early involvement of process chemists with medicinal chemists to identify the correct late-stage intermediate to produce the final drug target. Major advancements in the area of computer-aided drug discovery/design methods have proven to play a critical role in the development of therapeutically important small molecules in recent decades. Critical finished products such as pharmaceutical drugs rely on intermediate materials utilized to produce the bulk drug substance. Often vulnerable to supply chain disruptions, the availability of these important intermediates as starting materials, dictate production capabilities of critical pharmaceutical drug products in both local and national scenes, which in turn directly impact healthcare outcomes.

This initiative seeks proposals from the small business community to support the development of compact tools and devices capable of manufacturing key chemical intermediates at the benchtop, for just-in-time delivery of such materials in quantities that optimally

impact the throughput of research operations. Using new or existing chemistries, in tandem with innovative solutions through engineering approaches, the purpose of this device is to speed up the preclinical drug development stage, by providing on-demand access to key intermediates that can be rapidly diversified to analogs or used to scale-up material for animal studies. Robust laboratory instruments that are amenable to automation and real-time data acquisition/monitoring will assist medicinal chemists in synthesizing critical intermediates. Like the development of peptide synthesizers in the mid-80's, the paradigm shift envisioned in this project is an innovative platform capable of supporting a broad range of chemical transformations as opposed to a single transformation type (e.g. peptide synthesis), in a reliable manner suitable to automation.

We seek to leverage trends in automation in synthetic chemistry to shift the way that common intermediates in medicinal chemistry are currently acquired in the laboratory. The innovative platform must incorporate creative solutions to address current limitations in reagent delivery systems, reagent formulations, and data interpretation through a versatile, reconfigurable system that utilizes step changes in the workflow based on the type of chemistries involved. This project also supports innovation for the acceleration of molecules into the drug development pipeline using these newly developed tools, in lieu of traditional synthetic chemistry efforts. This may potentially have implications in domestic supply chain availability of pharmaceutical intermediates, especially for those that are largely produced overseas. By shortening the design-synthesize-test cycle in drug discovery, this project aims to increase access to preclinical candidates and allow for more rapid exploration of chemical space surrounding a disease target.

Project Goals:
To develop an integrated technology platform through a compact device capable of manufacturing key pharmaceutical intermediates on-demand. Specifically, this project seeks to:

- Develop a compact device for synthetic chemists that allow for on-demand manufacturing of pharmaceutical intermediates that can be utilized in medicinal chemistry campaigns to rapidly prepare diverse analogs for biological testing.
- Utilize current automation technology in synthetic chemistry in the development of a device capable of performing a broad range of chemical methodologies in the preparation of key synthetic intermediates on demand, which may be further amenable to reconfiguration, standardization, and rapid scale-up.
- Develop a platform for chemical synthesis that is adaptable to real-time data acquisition, monitoring, and interpretation.
- Provide additional support to develop pharmaceutical intermediates for laboratory use and non-GMP preclinical candidates for animal testing.

Phase I Activities and Expected Deliverables (up to 1 year)
"Compact" as defined here, fits inside or does not exceed dimensions of a standard size vertical fume hood (maximum internal dimension: 39" width x 24" depth x 47" height), and must be transportable using a laboratory cart. Strict adherence to compact dimensions is not required in Phase I of the contract. However, it is a requirement that must be met for Phase II.

Demonstration of Feasibility and Prototyping

- Develop a compact (as defined above) prototype instrument that meets and demonstrates all of the following criteria indicated below:

Hardware Capabilities

- Produce at least two (2) research grade pharmaceutical intermediates, that have been identified as key materials to produce important bulk pharmaceutical drug products, on the 1-25g scale.
    a. Synthesis of each intermediate should include a minimum of three (3) chemical reactions that involve three (3) different types of reaction processes performed in sequence, leading to a crude product.
    b. A chemical reaction performed on this device should include the addition of up to (5) reaction components not including the solvent used in the reaction. Examples of physical processes this device will perform include: heating and cooling; handling of gaseous reagents and/or byproducts at elevated pressures (to include applying an inert atmosphere); addition of corrosive and hygroscopic reagents; applying radiant energy to induce thermal, photochemical, or electrochemical changes; and changing the reaction solvent as necessary to complete the desired reaction sequences.
    c. Offerors may provide the intended synthetic route and associated intermediates list for demonstration, with strong justification for fit-for-purpose. Emphasis should be on synthetic simplicity, flexibility to produce many other intermediate targets from a common set of reactions, and on-board process monitoring. Proposed synthetic routes and targets must be approved by NCATS. Alternatively, offerors may select from a list of intermediate targets and associated synthetic routes provided by NCATS.
- Demonstrate the ability to safely handle and mix strongly acidic, basic, and air/water reactive reagents (i.e., trifluoroacetic acid, n-butyllithium, etc.) within the scope of a chemical reaction.

Hardware Configuration

- Have provisions for basic purification (liquid or solid phase extraction, filtration, and collection of solids) and evaporation of

reaction mixtures, or capability to integrate with separate systems to allow for these functionalities.
- Demonstrate modularity and reconfigurability of system (manual or automated), including all cleaning performed by a non-expert, in less than six (<6) hours.
- Integrate onboard process analytics for chemical reactions to be monitored and interpreted in real-time by at least three (3) of the of the following analytical characterization methods: LC, MS, NMR, UV/VIS, IR, Raman.

Documentation
- Participate in regular monthly meetings with NCATS contracts and scientific team to report on scientific progress and discuss research approaches to ensure alignment with project goals.
- Provide cost estimates for the manufacture of a device meeting the specifications listed above. Cost estimates will be evaluated separately from the technical review of proposals.
- Present Phase I findings, report on operation including operating procedures, and demonstrate the prototype instrument to the NCATS contracts and scientific team via webinar.
- Provide NCATS with all technical details for construction, including list of parts and system design(s); and materials resulting from Phase I Activities and Deliverables.
- Provide a market analysis of the commercial application of the proposed technology, including analysis for demonstrated targets, and broader projected accessible targets mapped to end-state application.

Phase II Activities and Expected Deliverables (up to 2 years)

If Phase I objectives are met, feasibility is demonstrated, and sufficient evidence of commercial viability is provided, the Offeror can apply for Phase II. Phase II activities and deliverables will include the following:

Demonstration of Hardware Capabilities
- Test a working compact prototype instrument meeting Phase I specifications.
- Provide the list of at least three (3) pharmaceutical intermediate targets, intended to be produced in a purity of >95%.
    a. Synthesis of each intermediate should include a minimum of three (3) chemical reactions that involve three (3) different types of reaction processes, performed in sequence, toward the preparation of a pharmaceutical intermediate, with no user input apart from set-up. Synthesis routes and associated intermediate targets must be approved by NCATS.
- Demonstrate modularity and reconfigurability of system, with ability to switch between targets in less than six (<6) hours, including cleaning performed by a non-expert. Develop detailed procedures to quantify the instrument's throughput, and provide evidence based on process analytical data, material carryover of less than <1% between production runs.

Software and Onboard In-line Analytics
- Provide software for comparison of multiple datasets to allow for robust statistical analysis and further analytical data processing of metrics collected during the experiment.
- Integrate onboard process analytics for chemical reactions to be monitored and interpreted in real-time by at least three (3) of the of the following analytical methods: LC, MS, NMR, UV/VIS, IR, Raman.
- Optimize reaction conditions in an automated way using the capabilities provided by the onboard in-line analytics.
- Allow for separate custom interfaces to be built to control and extract analytical information from the instrument *via* an Application Program Interface (API)
- Demonstrate export of real-time analytical data (collected during the experiment) into standard laboratory data (e.g. JSON, XML, CSV) and/or image and video formats that allow for machine-readable data analytics and computer vision algorithms.
- Allow for the handling of errors during run-time in a safety-compliant way without user input.

Documentation and Final Deliverables
- Participate in regular monthly meetings with NCATS contracts and scientific team to report on scientific progress and discuss research approaches to ensure alignment with project goals.
- Provide a framework for effective documentation and records keeping, aligned to current Good Manufacturing Practice (GMP) in the development of methods and protocols, and as basis for managing product quality.
- Develop a manufacturing plan for the instrument, market analysis of demonstrated and other relevant targets, and projections of platform flexibility across various accessible key synthetic reactions and associated pharmaceutical intermediate targets.
- Present Phase II findings, report on operation including operating procedures, and demonstrate the prototype instrument to the NCATS contracts and scientific team via webinar.
- Provide the program and contract officers with a letter(s) of commercial interest in the first year of the contract.
- Provide the program and contract officers with a letter(s) of commercial commitment in the second year of the contract.
- Provide NCATS with all technical details for construction, including list of parts and system design(s) such as CAD files and part specifications; and materials resulting from Phase II Activities and Deliverables.
- Fulfill a requirement for a site visit by an NCATS-appointed subject matter expert (SME) to perform inspection or test the platform on the premises of the Contractor or subcontractor engaged in contract performance before the conclusion of the project. Inspections and tests will be performed in a manner that will not unduly delay the work. If inspections or tests are made at other than the Contractor or subcontractor's premises, NCATS will bear the expense of the evaluation.

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 potential follow-on 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.

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. The specific requirements for the current Phase IIB Bridge Award can be reviewed in the full RFA announcement: https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-23-034.html. 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 455 – Point-of-Care Detection of Prostate Specific Antigen

Fast-Track proposals will 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

Among men, prostate cancer is the second leading cause of cancer mortality in the US and fifth worldwide. The largest, randomized clinical trial of prostate-specific antigen (PSA) screening (ERSPC) reported a 20% reduction in prostate cancer mortality at 16 years among screened men compared to an unscreened control group and a 30% reduction in the cumulative risk of metastases after a median follow-up of 12 years. In 1994, the FDA approved PSA testing to aid in the detection of prostate cancer. In the first 20 years following this approval, prostate cancer mortality decreased by 50%. However, after the 2012 United States Preventive Services Task Force (USPSTF) recommended against prostate cancer screening, the prostate cancer mortality curve flattened, and the incidence of metastatic disease increased. In 2018, the USPSTF recommended that men aged 55-69 years engage in shared decision-making with healthcare providers to consider the benefits and harms of PSA screening in the context of family history, race, comorbid medical conditions, values, and preferences. The National Comprehensive Cancer Network, American Urology Association, and the American Cancer Society recommend that men discuss the pros and cons of PSA screening with their healthcare provider, starting at age 40 to 55 years.

The prostate cancer mortality rate is high among African American men, who face disproportionately greater barriers to health care services, including cancer screening, compared to the general population. Decision analysis models suggest that PSA-based screening may provide greater benefit to African American men. Therefore, greater adoption of PSA screening in African American and other high-risk men has the potential to reduce the burden of cancer treatment by increasing the detection of disease amenable to curative therapy (when indicated) or surveillance (when appropriate). The development of an accurate, inexpensive home test for PSA is both an unmet need and an NCI priority in the context of President Biden's Moonshot goal of reducing cancer mortality by half within 25 years. While the availability of home or point-of-care testing cannot overcome structural impediments to screening, the knowledge that one has an elevated PSA would remove a substantial barrier to screening by helping men prioritize this issue.

This topic is aligned with the Cancer Moonshot Blue Ribbon Panel recommendation to expand the use of proven cancer prevention and early detection strategies (G).

Project Goals

The goal of this concept is to demonstrate analytic performance of a home PSA test at an appropriate price point (less than $20.00). The technology should be designed for ease of use at home, analogous to home COVID-19 testing, using a finger stick to obtain a blood sample. The risk-benefit ratio of PSA testing can be improved by raising the threshold for a positive test to a PSA > 10 ng/ml. This would reduce both the number of false positive tests and, more importantly, the detection of clinically insignificant cancers, the treatment of which represents pure harm. In addition, a qualitative test with a read-out of "less than 10 ng/ml or greater than 10 ng/ml" would greatly simplify the counseling process for men with positive tests in that fewer men will be called "positive." In addition, there is general agreement that men with a confirmed PSA > 10 ng/ml and a life expectancy of 10 years should be referred for biopsy absent an obvious cause of transient PSA elevation, such as acute prostatitis.

Phase I Activities and Deliverables:

Offerors 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, point-of-care, diagnostic prototype, self-collection blood test using user-centric design principles.
- Demonstrate that the diagnostic assay can be operated as a self-test by men $\geq$ 40-years old (target population).
- Conduct studies to evaluate and test user acceptability and feasibility.
- Conduct initial clinical testing with at least one of the current FDA-approved PSA assays to demonstrate accuracy of PSA measurement compared to a gold standard test.
- 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:

Offerors must propose activities leading to the manufacturing and regulatory approval of the device, including but not limited to:

- Develop a well-defined self-sampling device 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 the operability of the test for use in non-clinical laboratory settings including at-home self-testing (with self-collection of the specimen) by the target population.
- Establish a strategy for FDA regulatory approval and insurance and/or CMS reimbursement.
- Develop educational materials for interpretation of the test results and when to seek medical guidance.

NIH/NCI 456– Rapid and Affordable Point-of-Care HPV Diagnostics for Cervical Cancer Control

Fast-Track proposals will be accepted.

Direct-to-Phase II proposals will be accepted.

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

Cervical cancer is the fourth most common cancer in women. When pre-cancer or cancer is diagnosed early, cervical cancer is one of the most preventable or treatable forms of cancer. Cervical cancer has become a cancer that defines global health disparity populations based on inequities in the feasibility of delivering effective, but complex and costly screening programs based on cytology and colposcopic diagnosis in low-resource settings.

Because of this, the World Health Organization (WHO) Cervical Cancer Elimination strategy calls for screening the majority of women with a high-performance HPV test twice in their lifetime. Realization of that goal using current commercial HPV tests is unlikely. To realize cervical cancer screening elimination goals in low-resource settings, it is essential that new tests can be performed and analyzed outside of traditional healthcare settings and are at a price point that is affordable to enable scalability. Fortunately, emerging test chemistries, including those based on isothermal amplification of HPV DNA, have shown significant promise for the design of highly accurate HPV diagnostics at a lower cost than existing tests. Recent developments in microfluidics, microfabrication, and hand-held computers further improve the prospects for adaptation of accurate, low-cost point-of-care versions of existing lab-based assays.

The overarching goal of the work to be supported by this initiative is to bring new alternatives for HPV testing to the market that are, both in a form factor as well as price point, will enable self-testing programs to be established globally at point-of-care or near point-of-care. This topic is aligned with the Cancer Moonshot Blue Ribbon Panel recommendation to expand the use of proven cancer prevention and early detection strategies (G).

Project Goals

Projects in response to this FOA should first develop a functioning prototype for a portable HPV diagnostic designed for near-patient use. Projects should establish initial clinical performance for the device using clinician-collected samples before moving to a larger prospective validation of the device using self-collected specimens. Applicants can propose modifying an existing device such that it can be used for HPV diagnostics at the point-of-need; simplify or add new features to a device to enable the device to operate outside a laboratory; and/or apply existing or emerging technologies that have not been

previously used for HPV diagnostics. Supported work includes both the development of the device as well as approaches for simplifying sample preparation and reducing knowledge and training needs for its use.

Adaptation/test menu expansion of platforms developed for COVID-19 diagnostics, especially low-cost, portable Nucleic Acid Amplification Test (NAAT) tests, is encouraged as part of this solicitation.

After implementation, the proposed technologies/devices are expected to provide clear clinical utility at the point-of-need. To that end, supported activities should include end-user design and usability studies centered around minimally-trained health workers at the community level. The technology must comply with the applicable regulations and international standards/guidelines such as Good Laboratory Practice (GLP), Good Manufacturing Practice (GMP), WHO guidelines, FDA Investigational New Drug (IND), FDA Investigational Device Exemption (IDE), and local regulations at project sites outside the US.

Investigators must explicitly consider affordability and cost-effectiveness design criteria for technologies proposed in applications responding to this FOA. Considerations of cost and affordability must include any consumable products required to effectively perform the test. Technologies should be sustainable and affordable to local providers (either low enough in cost to easily replace, easily replaceable parts/ease of repair, or durability).

Note: This FOA focuses on the development of novel HPV diagnostic platforms and does not support the development of associated devices for self-collection and/or transport/storage of cervicovaginal specimens.

Phase I Activities and Deliverables:

- Offerors must provide a letter of support from the partnering organization(s) in the proposal.
- 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 either provider or self-collected cervicovaginal specimens obtained with one of the current commercially available kits. Note: Showing that the test works only with provider collected specimen is not sufficient for this deliverable.
- Demonstrate a working relationship with the site(s) where the clinical validation study will take place.
- Conduct studies to establish analytical performance (e.g., 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.

NOTE: Phase I activities likely require a collaboration or partnership with a research group or medical facility that can provide relevant patient access; As such, the offeror should provide a letter of support from the partnering organization(s) in the proposal to that end.

Phase II Activities and Deliverables:

- Develop educational materials for interpretation of the test results and when to seek medical guidance.
- Develop a well-defined diagnostic device under GLP and/or GMP.
- Perform manufacturing scale-up and production for multi-site and multi-test evaluations, including sites both in the US and at a site in a resource-limited setting.
- Demonstrate the clinical sensitivity and specificity of the device for provider-collected and self-collected specimens 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.

- Establish a strategy for FDA regulatory approval and insurance and/or CMS reimbursement.

NIH/NCI 457 – Technologies for Detecting Tumor-Derived Cell Clusters

Fast-Track proposals will 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

Technologies that can assess metastatic risk early and facilitate prompt interventions can significantly improve cancer outcomes because most cancer deaths are due to metastasis. Currently, very few markers are available for predicting metastatic risk. Disseminated tumor cells that enter circulation are pivotal in the metastatic cascade, and circulating tumor cells (CTCs) are being used as putative markers for monitoring tumor dynamics and treatment response. However, accumulating evidence suggests that tumor-derived cell clusters (TDCCs) may be a more important factor in metastasis and associated poor progression-free survival and overall survival. Clustering is an adaptive mechanism that enhances CTC survival and migration in the harsh conditions of the bloodstream, confers stemness, immune evasiveness, and increases their metastatic potential.

TDCCs are reported to consist of either homotypic clusters composed of only cancer cells; or heterotypic clusters made of stromal cells or immune cells including fibroblasts (CAFs), macrophage-like cells (CAMLs), endothelial cells (TECs), tumor-macrophage hybrid cells (TMHCs), and neutrophils, along with tumor cells. Compared to single CTCs, TDCCs have been shown to have distinct molecular features, exhibit a higher proliferation rate, and 20 to 230-fold more metastatic potential than individual CTCs. Overall, these data suggest that composition and heterogeneity of TDCCs may be more informative for assessing metastatic risk or for predicting and following treatment response than assays based on single CTCs.

The biology of formation, dissemination, and metastatic mechanisms associated with TDCCs are poorly understood because currently, very few technologies exist to study TDCCs. Studies that detect TDCCs or elucidate their biology merely adapt existing CTC-based technologies that are grossly inadequate for heterotypic clusters. There is an unmet need for technologies that combine cluster enrichment, enumeration, and downstream molecular analysis to better understand biology and the role of different cells in metastasis.

Project Goals

The goal of this concept is to encourage offerors to develop *in vitro* technologies that can enumerate and identify cell types in TDCCs with or without enrichment. Offerors may employ a combination of biophysical and biochemical approaches for this purpose. Offerors may also opt to develop non-invasive or minimally invasive *in vivo* modalities for frequent monitoring of TDCCs. When isolating and enriching, integrity of the TDCCs must be ensured for downstream analysis including enumeration of clusters and the cells of different cell types in the clusters, molecular profiling, and/or drug-sensitivity testing. In Phase I, offerors must demonstrate reproducibility, accuracy, and significance of enumeration and identification of different cell types in the TDCCs. They may use experimental animal models for this purpose. In Phase II, the utility of the cluster enumeration and identification in assessing metastatic risk should be explored using retrospective (if TDCCs are stable during storage) or prospective clinical samples from primary and metastatic cancer cases. Offerors should demonstrate the utility of their platform by using a sufficient number of samples from at least two cancer types, and samples from multiple race/ethnic groups should be included to ensure the technology is broadly applicable. For both experimental animal and clinical studies in Phase I and II, offerors are encouraged to characterize the TDCCs and investigate correlations between TDCC parameters and response to relevant cancer therapies.

Activities not responsive to this announcement:

Developing technologies for CTCs or individual cells of tumor origin; and development of computational tools that decipher heterogeneity without the accompanying biophysical or biochemical technology

Phase I Activities and Deliverables:

- Assemble a multidisciplinary team of investigators with appropriate expertise in cell and/or clusters isolation, enrichment, enumeration, molecular and cellular analysis, functional analysis, drug/immunotherapy sensitivity testing, assay/method/device design and engineering, oncology, and other areas of expertise as appropriate for the proposed project.
- Define quantitative milestones to be met at each step of the technology's development.

In vivo TDCCs monitoring technologies:
- Develop minimally invasive (e.g., sensors embedded in a catheter; continuous, real-time, antibiofouling, and calibration-free devices) or non-invasive sensor-based devices for continuously monitoring TDCCs.
- Demonstrate reproducibility and accuracy of the *in vivo* monitoring.

In vitro technologies (device/assay/method/technology) for TDCCs:
- Develop sample preparation protocols, including appropriate blood drawing (phlebotomy or finger prick) and handling of blood.
- Develop TDCCs isolation, enrichment and enumeration technologies, and protocols while ensuring the clusters integrity.
- Assess reproducibility and accuracy of the workflow and demonstrate the TDCCs purity.

In vitro imaging methods:
- Develop *in vitro* imaging methods for TDCCs analysis, and demonstrate specificity and sensitivity, reproducibility, and accuracy.

Common for all the above modalities:
- Establish working prototypes.
- Demonstrate usability of the *in vivo* or *in vitro* technology in an experimental animal model (bear in mind the morphological and molecular markers selected for technology development should be applicable to human monitoring).
- Establish collaborations with investigators who can provide access to cancer cases and controls.
- Establish robust quality control and quality assurance protocols.
- Submit SOPs to NCI SBIR.

Phase II Activities and Deliverables:

- Demonstrate the technology using cancer cases and controls. Investigators: i) should justify the sample number and the statistical power, and ii) MUST validate the technology using cases and controls from multiple race/ethnic groups to make the technology broadly applicable.
- Assess usabilities (such as technology acceptability, ease of use), and clinical utility of the technologies in profiling clusters and predicting metastatic risk.
- Characterize the clusters by multiomics, immunohistochemistry, and/or functional analysis.
- Assess the clusters metastatic potential in experimental animal models.
- Demonstrate the TDCCs preparation in drug/immunotherapy sensitivity testing (may use blood samples from animal models or patients for this purpose).
- Develop commercial prototypes.
- Develop the plan for regulatory agency approval for clinically relevant technologies.
- Develop the plan for commercialization of the technologies.
- Submit final SOPs to NCI SBIR.

NIH/NCI 458 – Microbiome-Based Tests for Cancer Research, Diagnosis, Prognosis and/or Patient Management

Fast-Track proposals will NOT be accepted.

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

Number of anticipated awards: 4-6

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

This proposal is for the development of microbiome-based technologies for cancer research, diagnosis, and patient management (e.g., prognosis, treatment assignment, and efficacy monitoring). Although early and accurate diagnosis is key to successful treatment, effective methods for early detection do not exist for many cancers. Indeed, the available diagnostic tests are characterized by either high false positive rates due to low specificity resulting in unnecessary surgeries for diagnostic confirmation (e.g., CT scan for lung cancers) and/or high false negative rates due to low sensitivity (e.g., CA125 and trans-vaginal ultrasound for ovarian cancers). For example, the sole FDA-approved biomarker for pancreatic cancer, serum CA19-9, is mostly used for disease monitoring rather than screening due to inherent limits in specificity as its levels can be elevated in several other concomitant conditions. Other types of diagnostics using liquid biopsies can detect cell-free-circulating DNA (ctDNA) derived from tumors in late-stage cancers (stages III and IV), as traditional ctDNA-based analyses lack the sensitivity required to detect small tumors/early lesions. Furthermore, accurate technologies are also needed for cancer prognosis, treatment assignment, and efficacy monitoring. In addition to addressing the specificity/sensitivity issues of the currently available approaches, microbiome-based technologies would ideally be capable of using liquid biopsies that are safer, more cost-effective, and faster to obtain than solid biopsies for a wider adoption in clinics. Recently, the microbiome was added to the list of cancer hallmarks and multiple clinical and preclinical studies have revealed an association of specific microbiome signatures with individual cancers and with response to therapy (chemotherapy, immunotherapy, and radiotherapy). In addition, recent advances integrating the analysis of large datasets from next-generation DNA sequencing, and new methods of computational modeling using AI and machine learning, have shown the feasibility of using microbial biomarkers for early cancer detection, and personalized medicine. Thus, the development of microbial signatures from cancer patient samples, ideally from liquid biopsies, to be used alone or in combination with other biomarkers, offers an exciting opportunity to develop new and innovative tools for better cancer diagnosis, prognosis, and patient management. These technologies using microbial signatures as biomarkers for cancer detection and patient management will also enable researchers to better understand the fundamental underlying biology and molecular dynamics of microbe-tumor interactions as the causes and roles of microbial changes associated with cancer are not well understood.

Project Goals

The short-term goal for this topic is to develop new and innovative tests (kits or services) for early cancer detection/diagnosis, prognosis and/or treatment assignment and monitoring to be used in research. The mid- and long-term goals are, respectively, to provide to the clinical community microbiome-based CLIA tests (laboratory-developed or research use only tests) and FDA-approved diagnostic or companion diagnostic tests. Activities that fall within the scope of this solicitation include the development of tests (kits or services) for early cancer diagnosis, prognosis, treatment assignment and/or monitoring, and/or cancer research that identify and use microbial signatures (presence, absence, and/or abundance of certain microbes) of different types (DNA and/or RNA, proteins, metabolites), alone or in combination with host molecular markers. The microbial signature can be bacterial alone or include other microbes (e.g., fungi and viruses). These technologies should show some improvements (e.g., safer technologies using noninvasive biopsies, more cost-effective, better accuracy, more user-friendly) compared to the current existing methods. They may include, but not be limited to, electromechanical sensors, hybridization or PCR technology other than sequencing to be faster and more affordable for a wider adoption in different clinical settings.

Phase I Activities and Deliverables:

Phase I activities should generate scientific data confirming the clinical potential of the proposed technology. The phase I

research plan must contain specific, quantifiable, and testable feasibility milestones.

Expected activities and deliverables include:

- Provide data of the verification and optimization study of the proposed technology using clinical samples collected from the population of interest including:
  - The assay performance characteristics (e.g., sensitivity, specificity and reproducibility); and
  - The strategy and data to:
    - Minimize the contribution of contaminants to microbial signatures by, for example, establishing protocols for sample collection, storage and molecular extraction, and/or bioinformatic decontamination analysis methods.
    - And/or correct for preanalytical variables such as different collection and storage methods.
- Analytically validate the technology in a CLIA-certified laboratory (i.e., analytical sensitivity, specificity, LOD, repeatability) and describe the technical limitations of the technology.
- Provide the technology workflow and the SOPs.
- Establish QC and QA measures to ensure and maintain the quality of the results generated (accuracy and reproducibility).
- Report the throughput of the technology and the cost per sample.
- Establish a clinical validation plan/strategy:
  - Estimate the number of clinical samples (patients and controls) required for the clinical validation.
  - Establish a collaboration with a clinical cancer research site and/or a strategic business partner (e.g., a commercial CLIA-certified laboratory or a pharmaceutical company) to obtain sufficient clinical samples and a gold standard method/reference for technology validation.
  - Draft the study objectives and hypothesis.
  - In addition to the protocols, SOPs, and QC and QA measures established in phase I, describe the data collection strategy (retrospective or prospective study) and patient eligibility criteria.
  - Obtain all the regulatory approvals needed for the performance of the study using human samples.
- Present Phase I results and future development plan to NCI staff.

Phase II Activities and Deliverables:

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

- Conduct the clinical validation study in CLIA-certified laboratory(ies) for one potential use of the technology using the plan established in Phase I and report:
  - On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry).
  - Where and when potentially eligible participants were identified (setting, location, and dates).
  - Test undergoing validation, in sufficient detail to allow replication as well as the definition of and rationale for test positivity cut-offs or result categories of the test.
  - Rationale for choosing the reference standard (if alternatives exist).
  - Reference standard, in sufficient detail to allow replication as well as definition of and rationale for test positivity cut-offs or result categories of the reference standard.
- Provide the results (or at least some preliminary data) of the clinical validation study to potentially:
  - Demonstrate similar or superior assay performance (sensitivity, specificity, repeatability) compared to a reference standard.
  - Describe the clinical limitations of the test, if any, observed in the clinical validation study (e.g., disease, age, medication, time after meal ingestion, lifestyle habits [cigarette consumption, drug, alcohol, etc.]).
- Benchmark the technology to the current existing methods in terms of clinical feasibility, cost, throughput, and safety.
- Establish a product development strategy to obtain FDA regulatory approval for diagnostic test and/or a partnership/alliance with a strategic business partner (e.g., diagnostic or device company or a commercial clinical lab).
- Present Phase II findings to NCI program staff.

NIH/NCI 459 – Automated Software for Point-of-cCare Testing to Identify Cancer-Associated Malnutrition

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

The NIH Office of Disease Prevention recently held a Pathways to Prevention workshop, which explored the evidence for nutritional interventions and cancer health outcomes. A report of the workshop by an independent panel recommended baseline screening for nutrition risk following cancer diagnosis and repeated through treatment. This recommendation is supported by evidence linking cancer-associated malnutrition to poorer outcomes, including decreased treatment completion, greater healthcare utilization, and overall worse survival. The poor outcomes are driven substantially by the depletion of skeletal muscle, such as in sarcopenia, and by the emerging abnormal body composition phenotype of low muscle mass and high adipose tissue or sarcopenic obesity. Nutritional screening is the first step in the identification and treatment of patients with or at risk for malnutrition, especially those patients with cancer types that have the highest prevalence of malnutrition including upper gastrointestinal, head and neck, hematological, gynecological, colorectal, and lung cancers. Several quick and simple-to-administer questionnaire-based screening tools validated in the oncology setting capture changes in appetite and unintentional weight loss; they are often short, easy to administer, and can be incorporated into the electronic health record (EHR). However, they fail to capture abnormal body composition, which is fundamental for the identification of hidden abnormalities, such as sarcopenia and myosteatosis. State-of-the-art approaches based on diagnostic imaging are available to quantify the depletion of skeletal muscle and abnormal body composition changes that occur in patients with cancer. For example, CT scans, which are accessible in most cancer populations for routine diagnosis and follow-up of treatment response, can be ‘re-purposed’ for assessing muscle and adipose tissue and is considered gold standard methodology. Biomedical image segmentation and automated segmentation of skeletal muscle and adipose tissue from CT scans provides a time-efficient, clinic-friendly, and accurate assessment of muscle and adipose tissues.

Developing an automated nutrition screener that combines the questionnaire-based tools with diagnostic imaging would greatly improve the identification of cancer patients with or at risk for malnutrition and will aid in the optimal timing for nutritional intervention.

Project Goals

The overall goal of the contract solicitation is to facilitate the commercial development of novel automated point-of-care nutrition screeners that combine first-line questionnaires with automated segmentation from diagnostic imaging, such as from repurposed CT images, to detect malnutrition risk early and repeatedly during cancer care and in cancer populations with higher prevalence of malnutrition. In the short term, patients who might be overlooked as malnourished may be able to receive nutrition therapy and avoid the physiological and metabolic alterations that contribute to worse outcomes, including patients in the early stages of cachexia or pre-cachexia, who may be responsive to treatment. In the long-term, nutritional treatment will be an integral component of cancer care and the poor outcomes associated with malnutrition will be less burdensome to those suffering from cancer.

The technical scope of this initiative encompasses the design and manufacturing of an automated screening tool for clinical use. The novel screening tool may utilize new or existing nutrition screeners, such as the Malnutrition Screening Tool, NUTRISCORE, or others, combined with existing or newly developed automated segmentation from diagnostic imaging, such as CT, DXA, MRI, ultrasound, or other body composition methodology. The tool should be quick, easy to use, and be incorporated into the EHR. Any member of the healthcare team, such as a medical technician should be able to incorporate the screener into their patient check-in.

Activities not responsive to announcement:

Tools that are lengthy, time consuming, or cumbersome to the patient or caregiver; tools that involve the use of non-standard-of-care blood sampling or other invasive examinations.

Phase I Activities and Deliverables:

- Establish a project team, including proven expertise in nutrition and body composition, screening tool development, radiology, user centered design, software and hardware expertise, including in EHR, and other areas of expertise as appropriate for the project.
- Applying user-centric design principles, develop a cost-effective, non-invasive, and accessible device prototype capable of nutritional screening.
- Provide the design of the pilot technology.
- Characterize the tool, measure the functionality, and test the quality control parameters.
- Test the feasibility and acceptability of the technology within an EHR testing environment and with at least 25 patients and oncology practitioners.
- Develop plans for transitioning the tool for clinical application; identify at least two clinical settings where the technology may be used and integrated for pilot user testing.
- Engage stakeholders and determine clinical consensus if differing recommendations or insufficient data occur.
- Include the ability to continuously incorporate new information on nutrition and body composition as it is released by the appropriate organizations.
- Propose a validation plan consistent with the combined imagining device and questionnaire-based tool; imaging technology may require validation against whole body CT skeletal muscle volume; newly developed questionnaire-based screeners may require validation against tools already validated in their respective setting, such as the Subjective Global Assessment or the Patient Generated Subjective Global Assessment.
- Provide the technical specifications, including privacy and security protections, as well as an operations/user guide.
- Outline the metrics that can be used to assess the successful application of the technology.

Phase II Activities and Deliverables:

- Develop metrics and provide a report demonstrating successful use of the technology, including comprehension of the information by oncology providers.
- Conduct a validation study, as appropriate, and provide a report of the feasibility/acceptability and successful use of the integrated screening technology in a well justified sample of oncology patients.
- Demonstrate reliability, robustness, and usability in clinical delivery settings.
- Describe the challenges encountered during the technology development and measures taken to mitigate the challenges.
- Develop a plan to implement the technology in EHR systems.
- Develop a dissemination plan for the technology and a training course on the intended use of the technology.
- Develop a plan for commercialization of the integrated screening technology.
- Provide letter(s) of commercial interest and commitment to the project and contract officers in the first year of the Phase II contract.
- Provide a report with a finalized user guide and operations manual for use of technology within a range of oncology providers; these documents will include technical specifications, process guides/flow charts for how and by who the technology will be used, and privacy and security protections.

NIH/NCI 460 – 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 artificial intelligence (AI) and machine learning (ML) technologies that have fueled interest across the industrial and academic sectors. During the past few years, several startups and large companies have focused on AI/ML technologies with the aim of reducing complexities in clinical workflow or increasing accuracy in detection, diagnosis, and treatment of cancer. While tremendous amounts of data are generated through clinical practice, significant gaps remain to leverage the data for device development and evaluation, including: 1) generation/acquisition of patient outcome data; 2) truthing of images by clinicians; 3) correlation of multi-modal imaging, comprehensive clinical, and genomic data in common repositories; 4) extraction of information from unstructured electronic health records (EHR) data; and 5) availability of clinically infrequent variants. This topic supports 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 subject to regulation by Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA). Datasets that may be used to develop new devices as a measure of device effectiveness or performance, and support regulatory decision-making may be eligible for CDRH's Medical Device Development Tools (MDDT) program. A tool eligible for consideration by the MDDT Program is one that reduces the regulatory burden of industry and the FDA.

CDRH's mission is to protect and promote public health by assuring that patients and providers have timely and continued access to safe, effective, and high-quality medical devices. To qualify a dataset as an MDDT, CDRH 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. CDRH'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 product development and evidence generation for a 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 support innovation across our overlapping communities.

Project Goals

The goal of this contract topic is to stimulate the participation of small businesses in CDRH's MDDT program to develop datasets that can be used to assess medical devices in oncology settings. An MDDT can be a method, material, or measurement used to assess the safety, effectiveness, or performance of a medical device. MDDTs can accelerate the device development process by providing developers with qualified tools that do not need to be re-evaluated within each regulatory submission, thus streamlining device development and FDA regulatory decision-making.

Several examples of datasets considered responsive under this solicitation include, but are not limited to:

- Imaging (radiology and pathology) with ground truth for algorithm validation of tumor/nuclei segmentation, prediction, classification, etc.
- Cancer genomics and proteomics for evaluation of analytic tools for genome variation, integrative analysis of gene expression, protein expression, survival analysis, etc.
- Structured data extracted from unstructured EHR.
- Treatment outcome data (prospective or retrospective) for evaluation of clinical utility tools and methods.

The following technical characteristics should be considered:

- Focused on a specific cancer, clinical application (e.g., diagnosis, therapy), and modality (e.g., radiologic imaging systems, microscopy, spectroscopy, genomics, proteomics, laboratory testing, therapeutic or surgical devices, etc.).
- Structured and well-characterized data, to include the best available ground truth or reference standard and the relevant metadata and data model to help with device development and evaluation.
- Inclusion of a diverse patient population and multicenter data (prospective or retrospective).
- Anonymized with respect to protected health information and patient-identifying information.

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 an MDDT Proposal that includes MDDT description, context of use, and an appropriate Qualification 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 MDDT Proposal is submitted as the Full Qualification Package and reviewed by FDA for qualification decision.

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

Examples of technologies considered responsive to this solicitation include, datasets intended for evaluation of cancer diagnostics (e.g., laboratory *in vitro* or imaging *in vivo*) and therapeutics (e.g., chemo, radiation, surgery, or immunotherapy). Offerors are expected to include in their project scope a demonstration that the dataset can be used for medical device evaluation. For example, FDA qualified a modeling software MDDT that can be used for medical device evaluation.

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.

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. Inclusion of a diverse patient population and multicenter data (prospective or retrospective) is ideal.
- 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 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 suitability of the dataset for the targeted test population and planned reference standard(s).
- Submit a complete MDDT Proposal to CDRH'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.
- 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 with end users: 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 and feedback in the MDDT Proposal decision letter.
- Prepare an MDDT Qualification Package based on the feedback in the MDDT Proposal decision letter.
- Submit a Full Qualification Package to CDRH's MDDT Program including the data collected according to the FDA-approved Qualification Plan from the MDDT Proposal.

NIH/NCI 461 – Ultra-Fast Dose Rate (FLASH) Radiation Detectors and Safety Systems for Cancer Treatment

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 has fewer side effects than regular radiation therapy at the same delivered dose. 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. To safely utilize FLASH treatment technique in the clinic, radiation detectors need to be developed that can reliably function at dose rate from 2-10 Gy/minute to 40-120 Gy/second. Additionally, the time structure and the fluence shape of the pulse must be verified to meet FLASH specifications. FLASH radiation delivery's biological effect may be a function of a unique fine delivery structure that requires ultrafast dose measurement capacity to confirm that the proper, optimal time structure is being used (pulses versus continuous beam delivery).

Project Goals

The goal of this concept is to solicit proposals to advance the development and/or application of devices, that enable FLASH radiation therapy to be properly evaluated and ultimately translated into the clinic. Ultra-fast radiation dose detector and safety-related beam delivery components are the focus of this topic solicitation. By promoting 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.

Examples of the products are:

(1) 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.

(2) Systems to record dose delivery rapidly and precisely enough to measure any over- or under-dose, and stop dose delivery if needed, quickly enough to prevent radiation dose misadministration.

Activities not responsive to announcement:

Tools that do not measure FLASH dose rate reproducibly; tools that cannot measure the time structure of flash radiation therapy; design approaches that do not account for scalability, interoperability, or the need to be tested for daily validation in a non-destructive fashion; approaches that do not 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 systems, systems that cannot stop the beam fast enough to prevent more than 5% dose over/under the goal (prescribed) dose.

Submissions that include necessary safety-system deliverables in the context of FLASH radiotherapy clinical trials will be seen as maximally responsive.

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 Page 75 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 implementing 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 462 – Organ-on-Chip for Preclinical and Translational Radiobiological Studies

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

2D monolayer cultures fail to recapitulate the totality of the tumor microenvironments. More complex cancer *in vitro* models have been developed, but they still lack organ-level structures, fluid flows, and mechanobiological cues that cells experience *in vivo*. Therefore, physiologically and clinically relevant reproducible models that mimic tissue and tumor microenvironments are urgently needed to improve preclinical radiobiological research. Such model systems could impact several areas, such as the ability to predict efficacy and toxicities of drug-radiation combinations, to determine the relative biological effectiveness of proton therapy, etc. These models are also applicable in other areas of cancer research. Generally, they will reduce the cost of research by improving the preclinical research quality and potentially reducing animal use in research. Microfluidics (materials and techniques) have potential applications in radiobiology, and commonly used silicone-based compounds, such as polydimethylsiloxane (PDMS), have already been tested and found resistant to radiation-induced brittleness and aging and have demonstrated required stability and water equivalency. Lab-on-chip (LOC) microfluidic and "tissue mimetic" technologies have evolved into advanced Organ-on-Chips (OoC). OoC systems containing perfused hollow microchannels populated with living cells have the ability of multiplexed drug testing and may be applied to many radiobiological studies. OoC technologies are already at a higher technological level of maturity. Further development and validation of OoC guided by its intended context of use for translational radiobiological studies are necessary. This SBIR contract mechanism accelerates further development and integration of advanced OoCs into cancer treatment development and translational pipelines in radiobiology and drug radiation combination studies.

Project Goals

This contract topic's goal is to further develop and validate OoCs devices for research and preclinical applications for studies with radiation and drug radiation combinations. Successful completion of the deliverables and the data obtained from experiments performed under controlled conditions using OoCs from this contract solicitation will ultimately improve the predictability of clinical outcomes in preclinical radiobiological assays that currently suffer from reproducibility and

outcome predictability issues. OoC devices developed with this contract solicitation may also have potential cross-utilities in other areas of cancer research.

Some examples of potential OoC commercial applications for preclinical research include but are not limited to an evaluation of the effects of therapeutic radiation, radiation-effect modulators, and drug-radiation combinations; monitoring of tumor response, progression, and recurrence after treatment; quantitative measurement of immune infiltrates into tumors after treatment; smart dosimetry technologies traceable to the national standard to improve the quantitation of radiotherapy dose at the biological level (e.g., determining relative biological effects); measurement of defined gradients of oxygen tensions across the OoC to study hypoxia-mediated responses; any other relevant preclinical radiobiology and/or drug radiation combination studies.

Phase I Activities and Deliverables:

- Design, review, improvise, integrate, and/or fabricate advanced OoC devices for the specific intended use that is compatible with any one or more of the following areas of study:
    a) Evaluation of the effects of radiation, radiation-effect modulators, and/or drug radiation combinations.
    b) Monitoring of tumor response and progression after treatment.
    c) Quantifying immune infiltrate dynamics into tumor microenvironments and normal tissues after treatment.
    d) Smart dosimetry technologies traceable to the national standard to improve quantitation of radiation dose at the biological level (e.g., determining relative biological effects).
    e) Study the impact of defined gradients of oxygen tensions across the OoC to study hypoxic-mediated responses.
    f) Any other relevant preclinical radiobiology and/or drug radiation combination studies.
    g) Provide defined metrics for measurement of success.
- Demonstrate maintenance of sterility, temperature, nutritional, physiological, oxygen status, and other conditions in the OoC for the intended use.
- Stability of the materials and compatibility of advanced OoC used against one or more radiation sources, routinely used in laboratories designed for irradiating cell cultures, small animals, or external beam radiotherapy sources used in the clinic.
- Demonstrate tissue functional equivalency necessary for radiobiological studies.

The Phase I contract technical proposal should include the following information:

- The intended setting (context of use), its preclinical utility, technology development, and validation plan.
- An assessment of the technology maturity level of the system or component subsystems of the planned advanced OoC at present and upon completion of the proposal.
- Design concept, material selection, and fabrication procedures, approach for sterilization, selection of biological elements and supporting cell types, life-supporting materials, and methods, such as culture medium, incubation, perfusion circuits, etc., and monitoring of tissue microenvironment in OoC, including but not limited to microbial contamination, adhesion status, etc.
- Detailed plans for:
    a) Designing and fabrication of advanced OoC devices by integrating the 3D scaffolds with microfluidics for co-culturing of at least two or more relevant cell types and/or excised tumor samples from orthotopic xenograft animal models, as needed for intended use.
    b) Demonstrate stability and shelf-life of the OoC system and system components.
    c) Irradiation with dosimetry traceable to the national standard and demonstration of compatibilities with radiation and drug radiation combination experiments.
    d) Online (integrated), offline, and/or *in situ* endpoint analysis (e.g., clonogenic survival, analysis of circulating immune and/or tumor cells from the sampled medium from the OoC, microscopy, cell proliferation, and death, gene expression analysis, imaging, etc.).
    e) Demonstrating technical validity with scientific rigor and reproducibility.
    f) Demonstrating analytical validity with scientific rigor and reproducibility.

g) The developmental pathway for regulatory approval and commercialization. An early discussion with FDA is encouraged if necessary and applicable. In such meetings with the FDA, the offeror is expected to invite NCI's experts in preclinical radiobiology and translation.

Phase II Activities and Deliverables:

Offerors must propose activities leading to the manufacturing and regulatory approval of the device, including but not limited to:

- Successfully demonstrate the ability to grow co-cultures of at least two or more cell types or excised biospecimen from one or more animal orthotopic xenograft tumor models in OoCs that are routinely treated with radiation or drug radiation combinations.
- Perform online (integrated), offline, and/or *in situ* endpoint analysis (e.g., analysis of circulating cells such as immune and circulating tumor cells from the sampled aliquots from the OoC, microscopy, cell proliferation, and death, gene expression analysis, imaging, etc.).
- Demonstrate technical validity with scientific rigor and reproducibility.
- Demonstrate analytical validity with scientific rigor and reproducibility.
- Demonstrating the superiority of the technology over 2D cell culture models to predict outcomes in suitable orthotopic xenograft animal models by comparison for the selected endpoints under controlled conditions.
- Demonstrate preclinical utility in radiobiology and drug radiation combination studies and enhancement of relevance to clinical studies by comparison of OoC technologies with outcomes in animal models as relevant and needed for the intended use.
- Demonstrate the ability to study one or more radiobiologically relevant issues as below with scientific rigor and reproducibility:
    a) Evaluation of the effects of radiation, radiation-effect modulators, and drug radiation combinations.
    b) Monitoring of tumor response and progression after treatment.
    c) Quantifying immune infiltrate dynamics into tumors and normal tissues after treatment.
    d) Smart dosimetry technologies traceable to the national standard to improve quantitation of radiation dose at the biological level (e.g., determining relative biological effects).
    e) Any other relevant preclinical radiobiology and/or drug radiation combination studies.

Phase II contract proposals should include a description of:

- Logical path to commercialization.
- Description of the advanced OoC device and the assay.
- Proposed schedule for meetings with the FDA regulators regarding approval if needed.

NIH/NCI 463 – Translation of Novel Cancer-Specific Imaging Agents and Techniques to Mediate Successful Image-guided Cancer Interventions

Fast-Track proposals will be accepted.

Direct-to-Phase II proposals will be accepted.

Number of Anticipated Awards: 3-5

Budget (total cost, 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

The purpose of this technology-agnostic contract solicitation is to bring highly sensitive cancer-specific imaging agents and technologies capable of detecting very small volume (1 mm^3) tumors in humans to clinical utility. Current imaging technologies/techniques are in use for non-invasive cancer detection, but clinical methods are limited to detecting masses several millimeters to centimeters in size. To image small primary or metastatic tumor sites composed of 1 – 10 million cells, imaging sensitivity must be improved. This can be achieved without significant hardware advances by improving the contrast between diseased and healthy tissue captured in the image. Thus, there is a clinical need for techniques that improve image contrast between tumors and surrounding normal tissue. There are several methods that rely on the use of specialized agents that are activated when coupled to a tumor target. Such activatable agents dramatically increase the contrast between small tumor cell masses and surrounding tissue. Efforts to develop activated imaging agents and techniques have been ongoing for over a decade, and successful demonstration in cancer-bearing animals has been achieved. These developmental successes now need to be translated for clinical use.

This SBIR solicitation thus supports translation of novel activatable agents and/or techniques for sensitive cancer detection in human subjects. Clinical translation and validation should be the primary goals of the proposed research. The bulk of the proposed research must focus on translating improvements in imaging sensitivity to a clinical environment with the goal of demonstrating that tumor cell aggregates on the order of 1 mm^3 in volume can be detected in cancer patients. Research toward development and establishing biological safety of the agent or technique in preparation for clinical validation will be accepted under this solicitation in Phase I. Thus, this solicitation supports translation of developing technologies for small tumor detection in human subjects. It is not intended to support continued major development and testing of techniques or novel agents. Any technique or strategy that dramatically enhances contrast between very small cancer and normal tissue is acceptable for consideration, which can include software techniques (such as AI/ML) that have already been validated in cancer-bearing animal models prior to submission of the application.

Project Goals

Projects in response to this solicitation will bring a new enabling imaging technique capable of sensitive tumor detection to clinical utility. The goal is to build upon existing development successes with activatable diagnostic probes and to translate these methods into clinical utility and to demonstrate that exceedingly small tumor cell clusters (1 mm^3 in volume) can be detected in human subjects by imaging methods. Studies will focus on first-in-human protocols that demonstrate small tumor volume imaging feasibility. Confirmation of detected tumor size sensitivity should be made through biopsy or other methods.

Support under this contract solicitation will be focused on translation of novel cancer-specific imaging agents and techniques that mediate successful image-guided cancer interventions (e.g., surgical, pharmacological, immunotherapeutic, etc.) with teams that have previously demonstrated success in developing activated agents / or techniques that target a specific cancer problem in an animal model.

In addition to demonstrating development success, investigator teams must demonstrate collaboration across the "bench-to-bedside" gap by including clinical specialists and imaging scientists on the team from the start of the proposed work. Clinical translation and validation must be the primary goals of the proposed research. The bulk of the research must focus on determining the improvements to imaging sensitivity in a clinical environment. Probe refinements and determination of its biological safety will be accepted in Phase I in preparation for clinical validation in Phase II.

Phase I Activities and Deliverables:

- Identify the targeted cancer patient population and explicitly define how the identified cancer patient population would benefit clinically from the proposed imaging probe or technique.
- Refine a GMP grade selected probe to yield maximal biological safety and validate very small volume tumor detection of primary and metastatic cancers in selected animal models.
- Convene the project team with expertise in imaging science, cancer surgery, and pathology.
- With the selected cancer population, submit an institutional IRB request for approval to recruit at least 15 cancer patients for a dose escalation safety study, and in parallel, submit an institutional IRB for approval to recruit at least 30 cancer patients to validate the probe's capabilities (at the highest safe dose) to identify additional cancers that were not detected by standard detection methods.

- Develop plans for a pre-regulatory submission dialogue with the FDA, to be completed before submission of an SBIR Phase II proposal, so that FDA requirements can be included in the SBIR Phase II research plan.

Phase II Activities and Deliverables:

- With the selected cancer population, initiate dose escalation safety study on 15 cancer patients who are scheduled to undergo cancer surgery with the selected GMP grade molecular probe.
- At the completion of the dose escalation safety study, initiate validation study on at least 30 cancer patients (from the selected cancer population) to test the probe's capabilities (at the highest safe dose) to identify additional cancers that were not detected by standard detection methods,
- File regulatory submission with FDA by the end of year 2, following the 510(k) path (as required by FDA for the specific product use and claims sought by the contractor).
- Secure at least one or two letters of commercial interest from potential customer(s) to buy the product near the end of completion of contract Phase II.
- Present SBIR Phase II findings and demonstrate the system via a webinar at a time convenient to the offeror and NCI program staff.

NIH/NCI 464 – Cloud-Based Multimodal Data Analysis Software for the Cancer Research Data Commons

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

The cancer research field has become intensely focused on the generation of high-throughput datasets to better understand cancer and, ultimately, to inform the development of better treatment and prevention tools. NIH and NCI have supported numerous programs, including The Cancer Genome Atlas (TCGA), The Cancer Imaging Archive (TCIA), Therapeutically Applicable Research to Generate Effective Treatment (TARGET), Clinical Proteomic Tumor Atlas Consortium (CPTAC), and Human Tumor Atlas Network (HTAN) to generate a wealth of multi-modal data to be leveraged by the cancer research community. However, we are still limited in our ability to draw insights and meaningful interpretations from these datasets, which include multi-omics, imaging, and clinical data, by challenges in integration across disparate datasets. To address these challenges, NCI has created the Cancer Research Data Commons (CRDC) as part of the National Cancer Data Ecosystem recommended by the Cancer Moonshot^{SM} Blue Ribbon Panel. The CRDC brings together data with cloud computing infrastructure to provide secure access to various data types across scientific domains which allows users to analyze, share, and store results by leveraging the storage and elastic compute of the cloud.

This contract topic will support commercial sector participation to develop novel and impactful commercial analytic tools for the cancer research community that integrate CRDC multimodal data. The SBIR contract funding mechanism will offer the opportunity for small businesses to contribute solutions to address unmet challenges of big data analysis that are not currently provided by existing tools in the CRDC through the development of tools and resources that integrate into the rapidly evolving CRDC. Through this contract topic, NCI seeks to enable engagement of the CRDC community by offering enhanced data analysis capabilities, visualization tools, and data access and sharing platforms to enhance users' ability to make data-driven discoveries.

Project Goals

The goal of this contract topic is to provide support for the development and implementation of innovative solutions for continued advancement and evolution of cloud-based multimodal informatics tools to integrate with the CRDC for broader user community engagement. Unmet challenges that should be addressed through this solicitation include but are not limited to: 1) integration of existing tools widely utilized by the cancer research community with the CRDC through adoption of the Data Commons Framework (DCF) and extension of these tools to support unique data analysis opportunities of this platform; 2) development of novel tools that incorporate multimodal (e.g., omics, imaging, spatial omics) datasets; and 3) collaboration with academic developers of popular tools to integrate them with the CRDC and support commercialization. Development and adaptation of tools that support innovative, integrative data analysis (particularly software using machine learning algorithms) across the CRDC are of particular interest. The activities that fall within the scope of this contract topic include delivery of design specifications for the development/extension of informatics tools and demonstration of successful integration of early-phase prototypes with the CRDC. Examples of effective integration with CRDC through DCF include executing the offeror's pre-existing or new informatics tools on multi-omics and imaging datasets stored in CRDC (such as CPTAC) and performing co-analysis with user-provided data. Successful offerors are expected to develop and implement a business process for broad adoption of their tools and resources by actively engaging with the user communities and conducting outreach and training activities as well as providing appropriate system documentation. The business process should also include business plans for marketing and long-term sustainability, such as sustained hosting of tools, training, and associated resources.

Activities not responsive to announcement:

Proposals for the development of big data analysis tools without consideration for integration with the CRDC will not be responsive to this solicitation.

Phase I Activities and Deliverables:

Phase I projects are expected to clearly demonstrate at minimum a 'proof of concept' feasibility of adaption of the offeror's informatics tool(s) or development of new tool(s) to the CRDC through the Data Commons Framework. The proposal should also identify potential barriers for commercial translation and plans to overcome those barriers. Phase I work should include software system specifications of cloud-based platforms for Phase II deployment of the proposed tools and resources.

Key activities and deliverables include:

- Project team- establish a project team composed of experts in software development, cloud infrastructure, big data informatics (e.g., proteogenomics, imaging, spatial omics), project management, team communication, and user-centered design.
- Design specification for the development/extension of cloud-based informatics tools to operate in the Cancer Research Data Commons.
- Develop an early-phase prototype.
- Demonstrate the feasibility of CRDC integration through DCF. Example of feasibility qualification include, but are not limited to, user authentication using Fence to access datasets stored in at least one CRDC repository such as Imaging Data Commons (IDC), Genomic Data Commons (GDC), and Proteomic Data Commons (PDC), which exist now and providing authorization to datasets the user has access to.
- Conduct pilot usability testing with at least 25 participating users.
- Provide a report on the results of the first round of usability testing and the approach to modify the platform based on this user feedback.
- Present Phase I findings and demonstrate the functional prototype system to an NCI evaluation panel via webinar.

Phase II Activities and Deliverables:

Phase II projects will be expected to implement requirements identified in all Phase I deliverables and launch a prototype that demonstrates successful integration with CRDC and, as appropriate, other data commons. The system design process should encourage interactions between users and developers for evaluation and further advancement of the tools and resources.

Key activities and deliverables include:

- Enhance, beta test, and finalize prototype development.
- Provide detailed plans for implementation of technical assistance and delivery of tool(s) within CRDC.
- Demonstrate the tool's integration with CRDC through DCF by successfully accessing and analyzing data from one or more CRDC nodes. Examples include, but are not limited to:
  - Demonstration of integration of user-provided data with a controlled-access data, such as TCGA, to perform comparative analyses.
  - Access and analysis of data from multiple CRDC nodes.
- Conduct usability testing with the participation of at least 100 users.
- Provide a report that synthesizes feedback from all relevant categories of end-users, including biomedical researchers and computational scientists, and summarizes the modifications made to the platform after each round of usability testing.
- Develop systems documentation and user guides.
- Develop and implement a business process for broader adoption of tools and resources by actively engaging with the user communities.
- Develop business process that includes plans for marketing and long-term sustainability, such as sustained hosting of tools and user training.
- Conduct outreach and training activities.
- Present Phase II findings and demonstrate the system via a webinar at a time convenient to the offeror and NCI program staff.
- In the first year of the contract, provide the program and contract officers with a letter(s) of commercial interest.
- In the second year of the contract, provide the program and contract officers with a letter(s) of commercial commitment.

NIH/NCI 465 – Cancer Prevention and Treatment Clinical Trials Tools for Recruitment and Retention of Diverse Populations

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

Slow and incomplete accrual of diverse participants to cancer prevention and treatment clinical trials continues to hamper the rate of drug development and medical progress. A study in 2014 reported that 1 in 4 cancer clinical trials were terminated early with 1 in 10 being terminated for poor accrual. A recent study found worsening underrepresentation of patients from racial and ethnic minority groups in Phase 1 cancer clinical trials between 2000 and 2018. There are no easy solutions to solving accrual challenges. Retention of subjects enrolled in trials can also be a challenge, especially in long-term or demanding trials. Recruitment, retention, and adherence obstacles are magnified in cancer prevention trials due to eligible participants being at varying levels of cancer risk, generally asymptomatic and active, lacking the motivation of a patient with a cancer diagnosis, and finding non-standard-of-care procedures more objectionable. Many NCI networks provide program and protocol-specific recruitment manuals, tools, and educational resources. However, more innovative, generalizable tools that increase accrual of diverse participant populations and are based on empirical evidence are mostly lacking. This solicitation has the potential to enhance clinical trials recruitment, retention, and adherence through the development of tools that could be used across the cancer continuum. The goal of these tools is to enhance communication

between study staff and participants, build long-term trusted relationships, improve the study participation experience, and reduce the burden of clinical trials to both staff and participants.

This topic is aligned with the Cancer Moonshot Blue Ribbon Panel recommendation to establish a network for direct patient engagement (A).

Project Goals

The goal of this concept is to solicit proposals to advance the development of tools to improve clinical trial recruitment. The tool may be participant-facing, clinic-facing, or both. If clinic-facing, the tool should help identify recruitment barrier(s) and present targeted options for effective recruitment strategies to overcome these barrier(s), help improve staff communication and relationship-building skills, integrate with electronic medical records, and allow for tracking of screening efforts. If the tool is participant-facing, it should be designed to engage potential participants, help them better understand details of a given trial, and be adaptable for different trials. Some of the best practices for recruitment and retention that are relevant to tool development include: (1) Consider the patient point of view and identify and address reasons why eligible patients decline trial participation. (2) Simplify informed consent documents and enhance personal communication during the informed consent process, including clarifying possible financial liability the patient may incur by participating in the trial. (3) Educate patients and the community, including community providers, about clinical trials using culturally appropriate material. (4) Use smart devices, social media, patient registries, and electronic databases to identify potential participants, notify providers, and boost recruitment and retention. (5) Provide access to peer mentors (other patients who have participated in a clinical trial) and patient navigators for those patients identified as in need of additional support. (6) Increase awareness and provide easy access to information on all ongoing clinical trials.

The tools should incorporate these best practices and may:

- Develop and test culturally sensitive participant educational tools/interventions that support varied communication preferences reducing bias (e.g., written, visual, etc.).
- Develop and test provider-based tools to facilitate identification of and discussion with potential participants.
- Facilitate understanding costs associated with clinical trials participation.
- Integrate with smart devices, social media, patient registries, and electronic medical records.
- Enhance the consenting process.
- Enhance study adherence through interactive participant and/or study-team engagement.
- For retention, provide a two-way platform for participant communication to study team and support conveying team information to the study participants.

Phase I Activities and Deliverables:

Phase I is to develop proof-of-concept or prototype tools, technologies, or products for monitoring and enhancing cancer prevention, treatment, and control clinical trials recruitment and retention.

- Develop and characterize a prototype tool/technology and demonstrate that the tool addresses specific recruitment and/or retention concern(s).
- Specify and justify quantitative milestones that can be used to evaluate the success of the tool or technology being developed.
- Provide a proof-of-concept SOP for the tool or technology.
- Consider human subjects protection compliance.
- Demonstrate feasibility and usability with a pilot user testing. Provide a report on the results of the first round of usability testing and the approach to modify the platform based on this user feedback. Offerors shall provide a technical evaluation and quality assurance plan with specific detail required for use.
- Demonstration that the tool, technology, or product can be adapted to multiple clinical trials at a price point that is compatible with market success and widespread adoption by the clinical research community.
- Present Phase I findings and demonstrate the functional prototype system to an NCI evaluation panel via webinar.

Phase II Activities and Deliverables:

The goal of Phase II is an optimized commercial resource, product, or tool for cancer prevention, treatment, and control clinical trials recruitment and retention.

- Enhance, test, and finalize the tool with refinement of SOPs to allow for user friendly implementation of the tool, technology, or product by the target market including human subjects' protection compliance.
- Provide a report that synthesizes feedback from all relevant categories of end-users (such as physicians, oncologists, nurses, patients, and patient navigators) and summarizes the modifications made to the platform after each round of usability testing.
- Validate scaled up tool, technology, or product. Specifically, demonstrate the utility, of the tool, technology, or product across clinical trials.
- Develop systems documentation and user guides to facilitate commercialization, including citation and details of how systems align with current regulations and best practices in user-centered design, interoperability, and protection of privacy and confidentiality of information.
- Present Phase II findings and demonstrate the system via a webinar at a time convenient to the offeror and NCI program staff.

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 010 – Technology to facilitate characterization of the exposome in under-resourced populations for AD/ADRD Studies

Number of anticipated awards: 1 to 2

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

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 as described for Phase I.
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:

Characterizing the exposome requires collection of both environmental and biological samples. However, under resourced populations, who often carry the highest burden of age-related diseases, are often precluded from participating in epidemiologic studies due to difficulties in collecting these environmental and/or biological samples. By lowering the barriers to these data collection efforts, NIA will be better able to study the etiology of complex diseases such as Alzheimer's and related dementias in more representative populations.

The development of technologies that will enable remote or self-sampling will enable greater participation of under resourced populations in research. However, there are several unmet needs for remote sampling tools that enable self- or caregiver-collected specimens that will allow longitudinal population-based studies to link environmental exposures to molecular changes associated with adverse aging and development of Alzheimer's and related dementias over a period of time. Short term changes (weeks/months) are useful for following disease progression, while longer term changes (years/decades) are useful for developing predictive biomarkers and understanding the etiology of disease.

Furthermore, there is a need for portable air sampling devices that capture both physical and bioaerosols in liquid media to maintain their viability, as well as a need for need for technologies that are user friendly and enable sample capture at the point of exposure (e.g., homes, workplaces, public spaces) with the samples shipped back to a central lab facility for high content biological and chemical analysis.

The ability to combine remote/point-of-exposure collection devices with technology that samples human specimens will provide a powerful lens into a person's exposure and their physiological response to those exposures. For large population-based cohort studies, environmental and physiological samples can be collected prospectively and analyzed at a later point once it is known which study participants will experience outcomes later in life (e.g., onset of dementia, etc.).

Project goals:

The purpose of this project will be to facilitate the development and adoption of technologies that enable the remote or self-collection of measures to characterize the exposome in under-resourced populations. Short term goals include identifying and developing technologies that can characterize the exposome using remote and/or self-sampling collection techniques. Long-term goals include facilitating the adoption of technologies that can characterize the exposome by validating measures and reducing costs to increase uptake in underserved and under-resourced populations.

Important technologies of interest will demonstrate or establish a credible capability of perform the following traits:

- Ability to follow subjects over varied timescales (e.g., weeks/months or years/decades) to capture markers throughout the progression of a disease
- Measure characteristics of the environment accurately and cost-effectively
- User-centric design that encourages long-term retention in longitudinal studies
- Complete solutions that enable biospecimen sampling and stabilization at the point of collection
- The potential to perform multi-analyte analysis
- High content and -omic readouts
- Technologies that are scalable and manufacturable

Phase I Activities and Expected Deliverables (as applicable):

- Identify special formulations or technologies details (i.e., address gaps in current technology, Measure characteristics of the environment accurately and cost-effectively, etc.)
- Demonstrate significant improvement over current capabilities (Feasibility demonstration)
- Demonstrate performance in sample preservation and analysis using traditional methods.
- While the long-term goal will be for collection methods to be as good as the gold standard, ultimately, in Phase 2, the goal would be for this technique (in Phase 1) would be to demonstrate improvement in sample preservation and analysis compared to current techniques and technologies.
- Demonstrate usability performance in terms of participant self-collection across a wide range of participants
- Demonstrate ability to follow subjects over varied timescales

Phase II Activities and Expected Deliverables (as applicable):

- Adopt a user-centric design that encourages long-term retention in longitudinal studies (Establishment of quality control systems, design controls, and regulatory approvals (if necessary) to facilitate a user-centric design)
- Transition from prototype to scaled distribution (Expansion of the Phase 1 products to broader geographies, diversification of participants, etc.)
- Achieve performance targets (in terms of sample collection and preservation) at larger scales compared to gold-standard
- Scaled manufacturing to drive down costs per unit to achieve wider adoption in epidemiologic studies

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 124 - Development of Next-Generation Devices and Materials-Based Platforms for the Administration of HIV-1 Broadly Neutralizing Antibodies

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

Passive immunization by antibody administration has been used to prevent and/or treat several infectious diseases, including RSV, hepatitis A and B, rabies, and COVID-19. The Antibody Mediated Prevention (AMP) trials established proof-of-concept that delivery of a broadly neutralizing antibody (bNAb), VRC01, can protect against acquisition of bNAb-sensitive HIV-1 strains. VRC01 has an excellent safety profile, does not depend on daily adherence for efficacy, and lacks the side effects that can deter pre-exposure prophylaxis (PrEP) use. NIAID and its partners are building on the success of the AMP trials by engineering next-generation bNAb candidates to enhance potency, increase tissue levels, extend half-life, and contend with the ever-evolving global diversity of HIV-1. Effective antibody-based HIV prevention will require a more potent combination of bNAbs with greater neutralization breadth than VRC01 and must target multiple sites of vulnerability on the HIV Envelope (Env) glycoprotein. Developing bNAb cocktails presents additional challenges: complex pharmacokinetics, larger injection volumes, multi-product formulations, and complicated manufacturing.

Currently, HIV-1 bNAb administration requires frequent injections. In the AMP trials, recipient acceptability of intravenous (IV) administration was high. However, high cost and logistical burdens slowed the early uptake of monoclonal antibodies for prevention and treatment of SARS-CoV-2, suggesting that IV administration can be challenging outside the context of a clinical trial. Subcutaneous (SC) administration has low recipient acceptability due to local reactogenicity. Improvements in bNAb delivery would benefit the field as NIAID and its partners develop the next generation of bNAbs for HIV-1 prevention or other indications. Examples of devices and materials include, but are not limited to, dermal patches, controlled-release hydrogels, nanoparticle carriers, vaginal rings, implantable devices, and nucleic acid delivery. New or improved delivery devices and materials have the potential to increase end-user acceptability, increase adherence, reduce administration-associated cost and time, and improve efficacy by maintaining sustained antibody titers.

Project Goal

The goal of this project is to support small businesses in the development of devices and/or materials for administration of HIV-1 bNAb(s) and bNAb derivatives (e.g., bispecific antibodies), resulting in increased protection from infection. Devices or materials should demonstrate enhanced 1) sustained release, 2) bioavailability, and/or 3) protective durability of the bNAb(s) relative to standard intravenous or subcutaneous administration methods. Offerors will be responsible for obtaining the bNAb(s) and other materials for their formulation efforts and for resolving any intellectual property issues that might arise regarding the use of these products. Proposals may include testing of a single HIV bNAb or combination of bNAbs.

To apply for this topic, offerors should:

- Identify candidate HIV-1 bNAb(s) for use with the proposed technology and justify their selection

- Describe how the proposed device(s) and/or material(s) are intended to enhance 1) sustained release, 2) bioavailability, and/or 3) protective durability of the bNAb(s) relative to standard administration methods (bolus intravenous or subcutaneous injection)
- Define criteria for benchmarking the proposed device(s) and/or material(s) against existing conventional administration methods (bolus intravenous or subcutaneous injection)

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

- Generation or procurement of necessary reagents, materials, and supplies
- Development of relevant SOPs
- Design and construction of prototype bNAb(s) administration device and/or material
- Optimization of selected bNAb(s) formulation for use with candidate device(s) or material(s) for release kinetics, routes of administration, doses, dosing schedules, and/or delivery to specific cell types and tissues
- Development of assays to assess product quality, antibody release, antibody integrity, formulation purity, biocompatibility, biodegradability, and stability
- Development of assays to measure bNAb biodistribution, including methods of sampling and sample processing
- Pilot *in vivo* studies in animal models to determine bioavailability, pharmacokinetic/pharmacodynamic profiles, and/or durability

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

- Proof-of-concept of performance and/or efficacy testing in relevant animal models, including non-human primates, and/or evaluation of performance compared to bNAb administered using standard methods
- Establishment of quality control, methodology, and development protocols for the generation of optimal bNAb formulations for device(s), material(s), and/or mode of delivery
- Development of an efficient material production process for early-stage/pre-clinical studies, with the potential to scale-up, and for production of clinical-grade material in conformance with the current Good Manufacturing Practice (cGMP) regulations
- Preparation of a regulatory package, including IND-enabling studies and pre-IND discussions with the FDA

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)
- Testing antibodies with targets other than HIV-1
- Antibody engineering (e.g., Fc modification, glycan modification) absent device or material development

NIH/NIAID 125 – Development of Long-Acting Treatments for HCV Cure

Phase I and Fast Track proposals will be accepted
Direct-to-Phase II proposals will not be accepted
Number of anticipated awards: 2-3

Budget (total costs):
Phase I: $ 300,000 for up to 2 years
Phase II: $ 1 million for up to 3 years.

Background

Globally, an estimated 58 million people have chronic hepatitis C virus (HCV) infection, with about 1.5 million new cases occurring per year. Among people living with human immunodeficiency virus (HIV), morbidity and mortality are increasingly driven by coinfections. For such individuals, the odds of acquiring HCV are six times higher than for their HIV-negative counterparts. In the United States, an estimated 15 to 30% of persons living with HIV have HCV coinfection, but these rates vary significantly based on the individual's risk factor for acquiring HIV.

WHO-recommended direct-acting antiviral (DAA) drug combination therapy can cure up to 95% of persons with hepatitis C infection, and treatment duration is usually 8-12 weeks (in the absence of cirrhosis). However, access to HCV diagnosis and treatment, although improving worldwide, remains limited, especially in low-income and lower-middle-income countries. Compliance is also of concern in treatment success, particularly in people co-infected with HIV-HCV who are required to adhere to co-administration of multiple drugs. These challenges may potentially be overcome by the use of long-acting (LA) treatments for HCV to allow intermittent dosing intervals, and, ideally, a one-dose alternative to cure the HCV infection.

It is anticipated that LA treatments will be more expensive than standard drug regimens due to increased costs in manufacture, storage, and delivery. However, such LA products, now being highly acceptable by patients and providers, offer notable advantages as (1) they would allow a much-simplified test and treat strategies, (2) reduce the health care infrastructure needs for HCV medicines thereby enabling treatments to be deployed even in very remote settings, and (3) significantly mitigate concern about drug resistance development due to non-compliance. Thus, in the long term, the LA drug products could potentially help to eradicate Hepatitis C.

Project Goal

The overarching goal of this project is to develop a novel LA drug product as a one-dose cure for HCV. Targeted drug product should have a favorable safety profile and provide sustained virological response to enable a therapeutic effect at a drug dosing interval of at least 2 months. Intended research activities under this contract will potentially lead to the filing of an Investigational New Drug (IND) application with the US Food and Drug Administration (FDA).

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

- Development of a Target Product Profile to include critical parameters of a new long-acting drug product for HCV
- Formulation development activities
- Assessment of efficacy, toxicity, and drug release kinetics *in vitro*
- Lead optimization studies
- Pharmacokinetic studies in a suitable animal model
- Initial efficacy testing *in vivo*

At the end of Phase I, the contractor should demonstrate the feasibility of the proposed drug product for HCV treatment with a dosing interval of at least 1 month as an initial step.

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

- Additional optimization studies to select a lead candidate with refined biological properties and a drug release profile of at least 2 months
- Efficacy studies in a standardized, reproducible, validated animal model
- Advanced formulation and process development activities
- Pilot lot production
- IND-directed toxicology and pharmacology studies in suitable animal models

At the end of Phase II, the contractor should (1) demonstrate the effectiveness of the LA drug product in treating HCV infection in animals by providing high sustained virological response and potentially a 2-month cure after single

administration, (2) determine safe and efficacious dosing range, and (3) demonstrate scale-up feasibility of the platform.

This SBIR contract topic will not support:

- Design or conduct of a clinical trial
- Development of drug product with less than 1 month (phase I) or 2 months (phase II) interval dosing.

NIH/NIAID 126 - Rapid Diagnostic Assays for Self-Monitoring of Acute or Rebound HIV-1 Infection

Phase I and Fast Track proposals will be accepted
Direct-to-Phase II proposals will not be accepted
Number of anticipated awards: 4-5

Budget (total costs):
Phase I: $ 300,000 for up to 2 years
Phase II: $ 1 million for up to 3 years

Background

An estimated 1.1 million people in the US are living with HIV, and one in seven are unaware of their infection. As a result, they are not accessing the care and treatment they need to stay healthy and reduce the likelihood of transmitting the virus to their partners. A US Government initiative, Ending the HIV Epidemic (https://www.hiv.gov/federal-response/ending-the-hiv-epidemic/overview), and the National HIV/AIDS Strategy (https://www.hiv.gov/federal-response/national-hiv-aids-strategy/national-hiv-aids-strategy-2022-2025#) seeks to reduce the number of new HIV infections in the United States by 90 percent by 2030. Part of this goal includes widespread HIV testing to reduce undiagnosed HIV infection and connect people to HIV medical care as soon as possible, which will improve the health of people living with HIV and prevent transmission. The small business innovation program is uniquely suited to reduce HIV incidence in the US because funds can only be spent domestically and not abroad.

Project Goals

The goal of this solicitation is to develop low-cost, rapid diagnostic assays needed to enable untrained individuals to test for HIV-1 infection during the earliest stages of initial infection or during loss of viral suppression in chronic treated infection – times when antibody responses are not an accurate surrogate for viral load. Assays should be designed for self-testing at home (or in other locations), so that individuals collect their own samples, perform the test, and read the results without the need to send a sample to a laboratory. The assay should be easy to be carried out and designed for use by individuals who are at risk of HIV infection, including those taking pre-exposure prophylaxis (PrEP), who wish to detect HIV infection as early as possible, as well as people living with HIV (PLWH) who wish to detect viral spikes or rebound either while on antiretroviral therapy or during treatment interruption.

- Device-free, disposable units are preferred; small reusable devices to be used with individual test strips or cartridges also would be acceptable. Although not required, the technology may include the capacity to connect results to healthcare providers.
- The assay should be a semiquantitative antigen or molecular test that detects HIV from finger-stick blood or other biospecimens with a minimum sensitivity of <2,000 RNA copies per mL or protein equivalent for antigen detection.
- The assay should detect HIV-1 strains circulating in the United States; detection may be extended to other HIV-1 subtypes.
- The assay should have a qualitative sensitivity of at least 98% and a specificity of at least 98%.
- The assay should have a short diagnostic time from sample to final result (ideally 30 minutes or less, and no longer than 1 hour).

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

- Develop prototype assays considering specificity, sensitivity, dynamic range, interference, robustness, reproducibility, accuracy (precision), and analysis of assay performance;
- Demonstrate that the assays can detect the analyte in the intended sample matrix, such as finger-stick blood;
- Preliminary studies to determine the assay feasibility;
- Define process controls; and
- Establish potential for commercialization.

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

- Continued development and validation of prototype;
- Further determination of the sensitivity, specificity, and other performance characteristics (e.g., time to result, limit of detection, test stability) of the assay;
- Final validation testing and prototype manufacturing;
- Product development strategy for regulatory approval and demonstration of clinical application; and
- Finalization of the commercialization plan.

This SBIR contract topic will not support:

- The conduct of clinical trials

NIH/NIAID 127 - Multiplexed Patient Administered Diagnostics for Hepatitis B, Hepatitis C, and HIV

Phase I or Fast Track proposals will be accepted.
Direct-to-Phase II proposals will not be accepted.
Number of anticipated awards: 2-3

Budget (total costs):
Phase I: $ 300,000 for up to 1 year
Phase II: $ 2 million for up to 3 years

Background

Viral infections due to hepatitis B virus (HBV) and hepatitis C virus (HCV) are major global public health burdens, and account for more than 3.0 million new cases and over 1.1 million deaths each year (WHO 2020). Despite the existence of a safe and effective vaccine for HBV, and effective antiviral medications for HCV cure, diagnosis and linkage to care are poor in both developing and high-income countries. Consequently, 80-90% of all people living with HBV and HCV remain undiagnosed and untreated each year, leading to increased morbidity and death due to cirrhosis and hepatocellular carcinoma (HCC). In the United States alone, it is estimated that only 15% of all people living with HBV are aware of their status, and of these, only 4.5% are treated. These global gaps highlight the critical need for novel, innovative, and improved strategies to target hard-to-reach populations and facilitate earlier detection, diagnosis, and linkage to care and treatment for people living with HBV and HCV. Experiences and lessons learned from implementation of HIV self-testing strategies, and the COVID-19 pandemic, have demonstrated the importance of self-testing as an approach to increase access to and uptake of testing among key populations, including many first-time testers.

HIV and viral hepatitis infections share common modes of transmission and social and structural barriers to accessing care and services among key populations, including men who have sex with men (MSM), injection drug users (IDUs), and commercial sex workers. Of the estimated 38 million people living with HIV (PLWH), 2.7 and 2.3 million people are estimated to be coinfected with HBV and HCV, with a global prevalence of 7.4 and 6.2 percent, respectively (WHO 2020). Coinfection with HIV significantly impacts the pathogenesis of HBV and HCV and is associated with reduced spontaneous clearance of HCV and HBsAg, higher rates of chronicity and occult HBV, higher HCV viral loads, rapid disease

progression, and increased risk of morbidity and mortality due to cirrhosis and HCC. Integrated strategies for screening and diagnosis of HIV and viral hepatitis infections are therefore critical to an effective global health response.

Technological innovations, including the development of multiplexed patient administered (e.g., self-collection, self-testing) tests, have the potential to overcome barriers to healthcare access and stigma, increase access to testing, facilitate early diagnosis and treatment initiation, reduce transmission, and improve linkage to care and health outcomes for currently undiagnosed and hard-to-reach populations who have either never been tested or have limited access to clinical care.

Project Goal

The overarching goal of this solicitation is to support the development, evaluation, and implementation of reliable, quality-assured, and cost-effective, multiplexed patient administered diagnostic testing strategies for HBV, HCV, and HIV. The device should enable qualitative or semi-quantitative detection of HIV, HBV, or HCV (RNA, DNA, protein, or other biomarker) in a dual (HIV/HBV or HIV/HCV) or multiplexed (HIV/HBV/HCV) format, suitable for home (self-collection or self-testing) and community-based use and treatment referral. Projects should establish initial clinical performance for the device using patient samples or clinical isolates prior to large-scale prospective validation of the device using self-collected patient specimens.

Applicants may propose to develop a novel device; modify an existing rapid diagnostic test (RDT) or point-of-care device, simplified with additional features to enable self-collection and self-testing outside of a clinic or laboratory; and/or adapt emerging self-testing technologies. The device should be developed in compliance with applicable regulations and international standards, including Good Laboratory Practice (GLP), Good Manufacturing Practice (GMP), World Health Organization (WHO), FDA Investigational Device Exemption (IDE), and/or local regulations at project sites within and outside the US. Collaborations with research groups that can provide access to relevant patient samples and populations are strongly encouraged. If applicable, the Offeror should provide a letter of support from the partnering organization(s) in the proposal.

Phase I activities may include, but are not limited to, any of the following:

- Development of assay concept/methodology or prototype device, taking into consideration the following characteristics:
    - Ease-of-use: simplified processes for sample collection (e.g., fingerpick), preparation, use, and result interpretation
    - Robust and rapid: results available in under 60 minutes (1 hour)
    - Cost-effective and affordable
- Studies to establish analytical performance (analytical sensitivity, specificity) and other performance characteristics (e.g., limit of detection, consistency, reproducibility) with self-collected samples.
- Studies to evaluate user acceptability and feasibility in both average and high-risk (e.g., MSM, IDUs) populations.
- Cross-validation with at least one FDA-approved test to determine the clinical performance measures.
- Development of a rapid and low-cost readout.
- Development, integration, and validation of internal process controls.

Phase II activities may include, but are not limited to, any of the following:

- Continued development and validation of the assay/prototype device.
- Development of a quality control program to ensure lot-to-lot consistency.
- Perform manufacturing scale-up and production for multi-site and multi-test evaluations, including sites both in the U.S. and in resource-limited endemic settings.
- Demonstrate the clinical sensitivity and specificity of the device for self-collected specimens through multi-site and multi-test evaluations.

- Conduct market assessment and cost-effectiveness analysis.
- Development of testing workflow for a specific product application/indication.
- Development of product development plan/strategy for regulatory approval.

This SBIR contract topic will not support:

- Clinical trials (see https://grants.nih.gov/grants/glossary.htm#ClinicalTrial for the NIH definition of a clinical trial).

NIH/NIAID 128 - Adjuvant Development for Vaccines for Infectious and Immune-Mediated 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
Mission: IID and BIOD
COR: Kentner Singleton

Background

The goal of this program is to support the pre-clinical development of vaccine adjuvants for use in vaccines to prevent or treat human disease caused by infectious pathogens or immune-mediated diseases (e.g., allergic diseases, autoimmune diseases).

Vaccine adjuvants are agents that stimulate and direct the immune system, which are used to enhance or modulate immune responses to a target antigen. The quality, magnitude, tissue distribution, isotype and subclass, and duration of antibody responses elicited by a vaccine can be influenced by the choice of adjuvant. Adjuvants also can drive antigen specific CD8 T cell responses, which are important for eliciting protection against some target pathogens. Adjuvants are used to specifically improve vaccine efficacy in at-risk populations such as neonates, young children, pregnant women, the immunocompromised, and the elderly as these populations have unique immune system characteristics and needs. Adjuvants can broaden vaccine accessibility worldwide by reducing the effective antigen dose or booster requirements, thereby extending the number of doses available or simplifying immunization schedules. Within the context of immune-mediated diseases (e.g., allergy, autoimmunity), adjuvants could drive immune deviation (e.g., Th2 to Th1 immune response) or induce immune unresponsiveness/tolerance in an antigen-specific manner (e.g., Treg induction). In the field of allergic diseases, adjuvants could help reduce the dose, frequency, and duration of allergen administration in the context of allergen immunotherapy and reduce adverse allergic reactions thus leading to higher acceptance and effectiveness.

New, improved, and widely accessible adjuvants are needed to support vaccine development. Because different pathogens or immune-mediated diseases require different immune responses for protection or treatment, each vaccine will require an appropriate adjuvant. Some adjuvants have increased or decreased vaccine efficacy in different populations; for example, a vaccine for use in the elderly may require a different adjuvant than one for a pediatric population. Different routes of administration (intranasal vs. intramuscular) or antigens can have different formulation needs, which some adjuvants are able to accommodate, while others cannot. Finally, intellectual property (IP) can restrict use of an established vaccine adjuvant, where having additional options, including functional mimics of late-stage adjuvants or adjuvants in licensed vaccines, would offer more flexibility to vaccine developers, for the net benefit of the public.

Topic Goal

Proposals must describe a milestone-driven program to support the pre-clinical development and optimization of a single lead adjuvant for use in vaccines to prevent or treat human disease caused by infectious pathogens or to treat immune-mediated diseases (e.g., allergic diseases, autoimmune diseases). The lead adjuvant may be a single entity (e.g., a single TLR agonist) or a combination adjuvant (e.g., a TLR agonist combined with a saponin based adjuvant). Adjuvants may be

chemical, biological, or genetic adjuvants (i.e., adjuvants encoded by RNA or DNA templates). Adjuvants may be novel or may functionally replicate adjuvants used in licensed vaccines.

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)
    - 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 IP protections or agreements in place and/or proprietary freedom to commercially develop the adjuvant.
- A Gantt chart that includes the proposed tasks and milestones

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
    - 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
- Comparative adjuvanticity studies between a late-stage adjuvant/adjuvant used in a licensed vaccine and a mimic of the adjuvant

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
- Adjuvants that functionally replicate those used in licensed vaccines (i.e., adjuvant mimics)

- Novel adjuvants or adjuvant mimics that improve the pandemic preparedness efforts of the US Government, including adjuvant that allow for significant antigen dose sparing, adjuvant with high stability to facilitate stockpiling, adjuvant based on components from sustainable sources, adjuvants for RNA-based vaccines
- Tolerogenic or immune deviating adjuvants for use in the prevention or treatment of immune mediated diseases
- Novel combination adjuvants

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
- 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 IP protection and/or proprietary freedom to commercially develop the adjuvant

NIH/NIAID 129 - 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: 3-5
Mission: IID or BioD or both: both
COR: Joy Liu

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, immune receptor ligands) for the identification and discrimination of immune cells and the characterization of immune responses in non-mammalian models and/or in specific underrepresented mammalian models. Non-mammalian models of interest include amphibians, arthropods, fish (e.g., jawless fish, sharks, zebrafish), marine echinoids, and nematodes; and under-represented mammalian models of interest include bats, cats, cotton rats, dogs, ferrets, guinea pigs, hamsters, marmosets, minks, pigs (including minipigs), rabbits, and sheep.

Many non-mammalian models are easily tractable model systems to study basic, conserved immune defense pathways and mechanisms. For example, the characterization of the *Drosophila* Toll signaling pathway facilitated the discovery of mammalian Toll-Like Receptors (TLR), which significantly accelerated progress 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-kB 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. Certain mammalian species display specific features of human immunity that make them highly valuable models but are similarly underutilized due to the limitations noted above. For example, sheep are useful for understanding the role of the immune system in pregnancy and in xenotransplantation studies. However, the lack of high-quality immunologic reagents for sheep immune markers continues to slow advances in these areas. Minks are highly susceptible to SARS-CoV-2 infection with the potential for zoonotic pathogen transmission. However, there are almost no reagents available for immunological studies in this species. Similarly, bats are the natural reservoir and vectors for several major zoonotic diseases that cause severe human diseases, but the lack of reagents has impeded studies of how bats' adaptive or innate immune responses control these pathogens without the manifestation of disease.

Advances have been made recently in the development of reagents for a number of these under-represented mammalian and non-mammalian models, and relevant immune reagents may already be commercially available. Therefore, offerors are urged to focus on potential targets for which no antibodies are available, or for which commercially available reagents do not perform well in specific assays, produce inadequately strong signals, or have undesirable off-target effects. Proposals that focus on targets for which sub-optimal reagents already exist must include the corresponding commercially available reagent(s) as a comparator.

Project Goal

Development and validation of reliable antibodies and/or other reagents for the identification and tracking of primary immune cells (e.g., cell surface markers and receptors) 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 **amphibians, arthropods, fish (e.g., jawless fish, sharks, zebrafish), marine echinoids and nematodes**. **Underrepresented mammalian models *are limited*** to **bats, cats, cotton rats, dogs, ferrets, guinea pigs, hamsters, marmosets, minks, pigs (including minipigs), rabbits,** and **sheep**.

Phase I Activities <u>must</u> include the following activities:

- Selection of immunologically relevant targets, which may include immune cell markers; receptors with immune function; or other molecules important for immune function such as cytokines, chemokines, and cytotoxic factors.
    - Please include the following information when selecting targets:
        - Results from a market analysis of commercially available reagents for the target (including cross-reactive reagents)
        - A justification for proposing to work on a specific target (need by the research community)
        - A description of how a commercially available reagent(s) for the selected target will be included in the proposed evaluation, and validation of the reagent(s) to be generated (<u>where applicable</u>)
- Development of antibodies or other reagents against select targets on immune cells of the species listed above under "background".
    - If polyclonal antibodies are being generated, the plan also must include the development of monoclonal antibodies
    - Mammalian system to express/produce the target antigen proteins will be prioritized over the use of bacterial expression systems
    - When using peptides as immunogens to generate antibodies, the method by which the peptide sequences are selected must be described
    - When using a non-traditional adjuvant/carrier or a novel delivery system for immunization, a justification describing the significant advantages the platform provides must be provided
- Characterization of antibodies or reagents developed:
    - Determination of the affinity of any antibodies or other affinity reagents using biosensors (such as surface plasmon resonance, biolayer interferometry) or similar methods. Simple ELISA assays are inadequate for determining affinity.
    - Determination of the specificity of antibodies or other reagents using knock-in (transfected) and/or knock-

out cell lines

- Confirmation of binding of antibodies/reagents to the intended native antigens/immunogens by flow cytometry and other assays using at least two different assays with appropriate controls
- Competition assay to show that recombinant antigens (e.g., immunogen used for making the mabs) can block the binding of the produced antibodies/reagents to their native antigen
- If more than one antibody is generated for the same target, at least two different antibody clones must be used in the same assay to confirm antigen specificity.

Phase II Activities must include:

- Comprehensive evaluation of specificity, functional utility, and cross-reactivity (off-target binding) of antibodies/reagents, which must include the evaluation of non-specific binding to cells or unrelated molecules and utility of antibodies/reagents, using three independent assays: flow cytometry and any of the two following - Western blotting (denatured and -optionally- native protein), immunoprecipitation, immunofluorescent staining, immunohistochemistry, or ELISA,
- Screening for cross-reactivity with related molecules on at least three other non-mammalian species or mammalian immune cells
- Optimization (e.g., secondary modifications/conjugations) of the antibodies/reagents for use in two to three different assays and platforms
- Scale-up production and stability studies of the antibodies/reagents
- 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 reagents for molecules or mechanisms not involved in immune responses
- Development of novel or refined animal models

NIH/NIAID 130 - Adjuvant Discovery and Down-Selection for Vaccines against Infectious and Immune-Mediated Diseases

Fast-Track proposals will be accepted
Direct-to-phase II proposals will be accepted
Number of anticipated awards: 1-3
Mission: BioD
COR: Wolfgang Leitner

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 1) the screening for new vaccine adjuvant candidates against infectious diseases or for tolerogenic adjuvants for the treatment of autoimmune or allergic diseases, or 2) the down-selection of adjuvants to support the subsequent development of novel adjuvanted vaccines. 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 in the United States (U.S.) as components of vaccines against infectious diseases. 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 and no adjuvanted vaccines have been licensed yet in the U.S. In contrast to drugs that are primarily used for treatment, 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.

Advances in understanding of innate immune mechanisms continue to lead 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.

In addition to the need for novel adjuvants, there is a need to identify the most suitable adjuvant for a novel vaccine candidate. Adjuvants are frequently selected purely based on availability, rather than as a result of systematic side-by-side comparisons of candidates to determine which adjuvant-antigen combination induces the most desirable response. This solicitation supports studies to down-select a lead adjuvant-antigen combination to generate the data for a subsequent vaccine development effort.

Program Goal

The objectives of this program are to a) 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; or b) the down-selection of adjuvants for subsequent vaccine development in side-by-side comparisons. To gauge the potency of newly discovered adjuvant candidates, at least one widely available adjuvant must be included as a reference in *in vivo* studies.

Phase I Activities include, but are not limited to:

- Optimize and scale-up screening assays to identify new potential vaccine- or tolerogenic adjuvant candidates
- Create targeted libraries of putative ligands of innate immune receptors
- 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
- Establish and obtain a panel of adjuvants to be tested with an antigen, optimize parameters such as formulation and dose for each adjuvant-antigen combination, conduct initial immunogenicity studies. Projects focused on the down-selection of a lead adjuvant for a novel adjuvant-antigen combination are expected to compare a panel of adjuvants that had previously been shown to have adjuvant activity. These adjuvants may be obtained from a third party, and the offeror must provide evidence that they would be able to pursue a product development effort with the lead from the side-by-side comparison. The offeror must also specify the criteria that will be used to select a lead candidate from a side-by-side comparison of established adjuvants.

Phase II Activities 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 novel 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 novel adjuvant candidates in animal models representing vulnerable human populations
- Conduct efficacy studies of vaccines containing the same antigen, but different adjuvants to identify the most promising candidate for further product development.

This SBIR will <u>not</u> 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 an adjuvant-antigen combination
- 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 131 - Development of Bacteriophage for Treatment of Mycobacterial Infections

Fast-Track proposals will be accepted.
Direct-to-Phase II proposals will NOT be accepted.
Number of anticipated awards: 2-3

Budget (total costs): Phase I: $300,000 for up to one year; Phase II: $1,500,000 for up to 3 years

Background

There is an urgent need for new therapeutics products for treating pulmonary diseases caused by mycobacteria. These include tuberculosis (TB), caused by *Mycobacterium tuberculosis*, and pulmonary infections caused by non-tuberculous mycobacterium (NTM) species such as *Mycobacterium abscessus* or *Mycobacterium avium*. In recent years, there has been an increase in the number of registered clinical studies focused on the therapeutic use of bacteriophage (i.e. "phage") and there have been several published clinical studies using laboratory phage reagents compassionately and with sometimes beneficial individual results. However, currently there are no mycobacteria-directed, therapeutic phage products in commercial development. Additional research and development are needed to advance new phage therapies to clinical trial testing.

Project Goal

The goal of this solicitation is to provide support for preclinical research and development of therapeutic phage products that target mycobacteria. Within this scope, special emphasis is placed on preclinical development of:

- Phage for treatment of pulmonary mycobacterial infections such as TB or clinically relevant NTM infections; and
- Phage in combination with antibiotics for treatment of pulmonary mycobacterial infections, including antibiotic-resistant mycobacterial infections.

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

- Phage screening, including selection or engineering of phage to have enhanced properties appropriate for a therapeutic product.
- Profiling phage susceptibilities of different mycobacteria variants as well as assessing the mechanisms of phage resistance in mycobacteria.
- Consideration of therapeutic phage efficacy *in vivo*, including how to use phage in combination treatments involving other phage as well as antibiotic drugs.
- Assessing treatment optimization based on the number (amount) and diversity of phage for treatment including different platforms, assays, technologies, and approaches to rapidly design and select phage therapy.
- Determining phage infection mechanisms of action and how this relates to susceptibility to phage across mycobacterial strains as well as to host immunologic response.
- Determining how to utilize phage safely, including assessing pharmacokinetic and other properties of phage that are needed for an optimal therapeutic product profile and exploration of different routes of administration appropriate for a disease indication.

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

Continuation of any of the above Phase I activities, including a focus towards later stage preclinical development, such as but not limited to:

- Expanded preclinical characterization of pharmacologic and pharmacokinetic properties of phage to determine suitability for therapeutic use, such as determining the frequency of resistance, clearance half-life, distribution, and penetration of phage to sites of infection, including organs, lesions, infected host cells or bacterial biofilms.
- Further assessing the correlation of treatment outcomes in preclinical models with the dose and diversity of phage utilized.
- Advanced preclinical exploration of different routes of administration in preclinical models appropriate for a disease indication and driven by considerations of patient safety and efficacy.
- Additional assessment of safety in preclinical models, including characterizing immune responses to chronic or repeated phage dosing and potential for adverse events from rapid lysis of high bacterial loads in a host.

This SBIR will not support:

- Development of bacteriophage targeting bacteria other than pulmonary-related mycobacteria.
- The design and conduct of clinical trials (see NIH definition of a clinical trial).

NIH/NIAID 132 – Novel Diagnostic Biomarker Discovery and Validation for Malaria and Select Neglected Tropical Diseases (NTDs)

Fast-Track proposals will be accepted.

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

Number of anticipated awards: 2-3

Budget (total costs): Phase I: $300,000 for up to one year; Phase II: $1,500,000 for up to 3 years.

Background

Diagnostics in current use for malaria and specific NTDs (visceral leishmaniasis, lymphatic filariasis, onchocerciasis, schistosomiasis) do not meet the sensitivity and/or specificity thresholds required to achieve elimination goals. As diseases

approach elimination, decreased prevalence and intensity of infection require highly sensitive and specific diagnostics to ensure that all true cases are detected and treated, to avoid false negatives, and to manage the larger volume of samples that must be tested to confirm interruption of transmission.

NTDs that are targeted by mass drug administration (MDA), such as lymphatic filariasis, onchocerciasis and schistosomiasis, require the use of diagnostics that are increasingly sensitive and specific when progressing from monitoring, to MDA-stopping, to post-elimination surveillance. For *P. falciparum* malaria, rapid diagnostic tests (RDTs) in current use lack sensitivity to detect the asymptomatic reservoir, which contributes to onward transmission. Additionally, some *P. falciparum* isolates have deleted the targets (histidine-rich protein genes *pfhrp2/3*) of the most sensitive RDTs, therefore escaping detection all together. Assays to detect non-*falciparum* malaria species also lack needed sensitivity. Disease elimination goals are further threatened by an insufficient pipeline of novel, validated diagnostic biomarkers.

Project Goal

The purpose of this solicitation is to support combined genomic, proteomic, metabolomic, and bioinformatic approaches to identify and characterize novel malaria and/or NTD diagnostic biomarkers (either parasite or host response biomolecules) in human biofluids. This solicitation further supports candidate biomarker verification and validation, and incorporation into a diagnostic assay suitable for use in resource-constrained settings, in order to address one or more specific disease elimination needs. Diseases targeted by this concept include: malaria, visceral leishmaniasis, lymphatic filariasis, onchocerciasis, and schistosomiasis.

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

- Unbiased candidate biomarker discovery employing multi-omic approaches
- Assessment of sensitivity; confirmation of sufficient abundance and expression of candidate biomarkers
- Verification to assess candidate biomarker specificity
- Development of prototype assays
- Analytical validation of credentialed candidates: measure precision, specificity, sensitivity, recovery and stability

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

- Demonstration that prototype performance is superior to assays in current use using clinical samples from diverse cohorts
- Advanced development of the final prototype platform
- Scale-up manufacturing of test components and final validation studies
- Product development strategy for regulatory approval and demonstration of clinical application
- Process development for manufacturing the diagnostic assay, including Quality Assurance/Quality Control

This SBIR will not support:

- The design and conduct of clinical trials (see NIH definition of a clinical trial)
- Assay development using known and previously validated biomarkers

NIH/NIAID 133 - Development of a Serological Test for Herpes Simplex Types 1 and 2 Infections

(Direct to Phase II proposals will **not** be accepted)
(Fast-Track proposals will be accepted)
Number of anticipated awards: 1-2

Budget (total costs): Phase I: $300,000 for up to 1 year; Phase II: $1,500,000 for up to 3 years

Background

Over 60 million people in the U.S. have genital herpes which is caused by infection with herpes simplex virus type 1 or 2 (HSV-1, HSV-2). The WHO's 2021 global progress report indicates that more than 500 million people are infected with HSV globally. Currently, genital herpes can be diagnosed based on clinical manifestations of the disease combined with very accurate nucleic acid tests to detect the virus in lesions or on mucosal surfaces. However, many patients with genital herpes are asymptomatic and do not shed virus and therefore a serological test is used to confirm HSV infection. Most available serologic tests, based on the enzyme-linked immunosorbent assay, are efficient but have very high false positive rates with positive predictive values (PPV) of about 50% or lower. Serologic tests for HSV infection using the Western blot have been shown to have high PPV and can readily distinguish HSV-1 and HSV-2. However, the Western blot is not suitable for wide-scale use in clinical settings.

Project Goal

The goal of this project is to develop a serological test for genital herpes that has high specificity, sensitivity and PPV. The test should distinguish between HSV-1 and HSV-2 infection and use technology such that the test could be distributed for broad use.

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

- Development of a prototype product that demonstrates detection of antibodies to HSV-1 and HSV-2 serum antibodies
- Integration of an assay into a diagnostic platform technology
- Development of sample preparation methods consistent with the product platform

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

- 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 134 - Alternatives to Benzathine Penicillin for Treatment of Syphilis

Fast-Track proposals will be accepted
Direct-to-Phase II proposals will be accepted
Number of anticipated awards: 2-3

Budget (total costs): Phase I: $300,000 for up to one year; Phase II: $1,500,000 for up to 3 years

Background

Injectable benzathine penicillin (BPG) is currently the only CDC-recommended first line therapy for treatment of infection with *Treponema pallidum* (syphilis) in all populations, including pregnant persons and infants. There are several barriers that limit use of BPG:

- BPG is not available orally.
- Only a limited number of facilities in a single country currently manufacture the raw active pharmaceutical ingredient which means the supply chain can easily be disrupted and shortages of BPG are common in the US and globally.

- BPG may sometimes not be administered at lower-level facilities or by non-physician medical staff out of fear of anaphylactic reactions that might require referral to a tertiary care center.

Alternative therapies to BPG that address some of these barriers are urgently needed, as acquired and congenital syphilis rates are increasing rapidly. WHO estimates over six million persons per year are infected with syphilis, and many more are treated presumptively for syphilis. Clinicians and health systems are eager for BPG alternatives. Recent advances in the ability to culture *T. pallidum* mean that identification of alternatives to BPG is now more feasible than has been possible in the past.

Project Goal

The goal of this solicitation is to support preclinical development of lead candidates for syphilis indications or repurposing of drugs to be more suitable for syphilis treatment.

Phase I activities may include but are not limited to:

- Preclinical development or reformulation of existing antibiotics
- *In vitro* minimal inhibitory concentration (MIC) determination for *T. pallidum*
- Efficacy of candidates in animal models of infection
- Qualitive studies incorporated into product development to assess end user preferences
- Establishment of target product profiles

Phase II activities may include but are not limited to:

- Evaluation of PK/PD of promising candidates in animal models
- PK/PD modelling to extrapolate human equivalent exposure in mothers and their fetuses
- PK/PD modelling of drug-drug interactions with anti-retroviral therapies
- Continued development and validation of candidate drugs
- Definition of dosing regimen for different populations and stages of disease
- Scale-up and production for multi-site evaluations using clinical samples
- Product development strategy for regulatory approval and demonstration of clinical application

This SBIR will not support

- Early compound screening of a chemical library
- Conduct of clinical trials (see http://www.niaid.nih.gov/researchfunding/glossary/pages/c.aspx#clintrial for the NIH definition of a clinical trial).

NIH/NIAID 135 – Software or Web Services to Automate Metadata Enrichment and Standardization for Data on Infectious and Immune – Mediated Diseases

Fast Track Proposals will be accepted.
Direct-to-Phase II will be accepted.
Number of anticipated awards: 1-3

Budget (total costs):
Phase I: $ 300,000 for up to 1 year.
Phase II: $ 1.5 million for up to 3 years.

Background

The ability of innovative data science approaches to accelerate research on infectious and immune-mediated diseases highly depends on the availability of high-quality, machine-actionable data compliant with the FAIR (Findable, Accessible, Interoperable, and Reusable) guiding principles. A central tenet of the FAIR principles is rich, standardized, and interoperable metadata in machine-actionable format. FAIR compliant metadata can accelerate discovery of new knowledge through automated, machine-assisted methods, such as automated reasoning, machine-learning, and artificial intelligence.

Different types of metadata are used by the community, including descriptive, structural, administrative, reference, and other metadata. The term metadata is also used by some to denote patient phenotypic information related to clinical specimens. In some cases, the distinction between metadata and data can be unclear as both data and metadata represent knowledge and information about entities and relationships. This contract topic focuses on descriptive and administrative metadata that enable the discovery of data for secondary use, including information about the creators, data provenance, access and use permissions, data content and methods used to collect the data, etc.

Creating FAIR-compliant metadata is time-consuming and requires specialized skills. As a result, metadata is often incomplete, of limited quality, and rarely machine actionable. There is an urgent need for (semi-)automated approaches and technologies that help researchers and data curators with creating new and augmenting existing metadata. Automated approaches should create, and augment metadata based on widely used and well documented ontologies and standard vocabularies, to enable computer algorithms to interpret the metadata. More efficient approaches for creating and augmenting metadata will also help researchers to comply with the growing demand for FAIR data sharing as recommended by new data sharing policies by publishers and funding agencies, such as the new NIH Data Management and Sharing Policy.

Goal

The goal of this solicitation is to develop software or web services that will make it easier for researchers and data curators to create high-quality, rich metadata, by automating (part of) the process for creating and enriching metadata. Rich metadata contains information that helps researchers and computer algorithms decide if, and how, they can use the data. To that end, this topic is focused on descriptive and administrative metadata that describe, for example, the content and provenance of the data, methods for accessing the data, and permissions that may need to be obtained before the data can be accessed. Rich metadata should not only include common administrative information, such as the author or creator of the data, but also scientific information, such as a description of the data content and the scientific methods used to create the data. The metadata created by the software or web services developed as part of this contract topic should meet the requirements stated by the FAIR guiding principles, should use ontologies and standard vocabularies to represent information, and should comply with metadata schema's used by major biomedical data repositories, so that researchers and data curators can submit the metadata resulting from the software or web service to the relevant repositories.

This solicitation is focused on making it easier for researchers to create or augment metadata for data relevant for infectious- and immune-mediated diseases. Areas of interest in this domain are, but are not limited to: clinical and immunological data, structural biology and immune epitope data, and data related to the efficacy and safety of diagnostics, therapeutics, and vaccines against infectious- and immune-mediated diseases.

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

- Development of software or web services to automate metadata enrichment and standardization;
- Development of computational methods and algorithms, such as AI-based Natural Language Processing (NLP) methods, to automate metadata enrichment and standardization;
- Modification of existing software or web services for automatic metadata enrichment to meet specific needs for infectious- and immune-mediated disease research;
- Expansion of software or web services for metadata enrichment or standardization to include FAIR-compliance testing and augmentation;
- Hardening and improving user-friendliness of software or web services for automatic metadata enrichment through user-based testing;

- Improving inter-operability of software or web services for automating metadata enrichment and standardization with data submission workflows used by data repositories.

At the end of Phase I, the contractor should demonstrate software or web services that automates (part of) the process for creating, enriching and/or standardizing metadata compliant with a significant number of the FAIR principles. The contractor needs to demonstrate that the software or web service results in new or augmented metadata of higher quality or completeness compared to commonly available metadata. The contractor needs to demonstrate compliance of the metadata resulting from the software or web service with one or more ontologies or standard vocabularies used by one or more major data repositories relevant for infectious- and immune-mediated diseases. The software or web service needs to be developed based on user stories from the infectious- and immune-mediated disease research community and must have been tested by members of the community.

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

- Expansion of the capabilities of software or web services to automate metadata enrichment and standardization, e.g., improved automation, larger range of data types or FAIR elements addressed;
- Hardening and improving the user-friendliness of the software or web service for a broad user community;
- Improving documentation, demonstrations, tutorials, and adoption of the software by a broad user community;
- Expand the scope of the software or web service with additional types of data, ontologies, or metadata schemas;
- Expand the number of steps in the metadata creation process that the software or web service can automate;
- Expand the number of FAIR principles that metadata produced by the software or web service will be compliant with.

NIH/NIAID 136 – Software or Web Services to Re-Represent Existing Scientific Data and Knowledge into a Knowledge Graph Format

Fast Track Proposals will be accepted.
Direct-to-Phase II will be accepted.
Number of anticipated awards: 1-3

Budget (total costs):
Phase I: $ 300,000 for up to 1 year.
Phase II: $ 1.5 million for up to 3 years.

Background

Scientific research produces more data and knowledge than ever before and it is becoming increasingly challenging for researchers to digest and analyze the data to derive new knowledge and insights. Increasingly, researchers will depend on computer algorithms to assist them with data analysis and with the discovery of new information and knowledge. For example, during the COVID-19 pandemic, the discrepancy between the speed of data generation and the ability to digest and analyze the data was acutely illustrated with almost 25 thousand new papers published in the first half of 2020[1]. The public health response against emerging pandemic threats and the treatment and control of existing infectious- and immune-mediated diseases requires the continuous analysis of newly emerging data, information, and knowledge; a task that is increasingly complicated by the large volume of data that is being generated.

Knowledge graphs (KG's) have emerged as a prominent technology for data representation and integration and are widely used in the industry. KG's represent information about entities and relationships between entities in a semantically rich way that enables efficient data retrieval and analysis by computational algorithms, such as automated reasoners and AI, and have shown great promise for data management and knowledge discovery. A familiar use case for KG's in the scientific domain is for the analysis of collaborations between authors based on published papers, for the exploration of pathways in

[1] Teixeira da Silva JA, Tsigaris P, Erfanmanesh M. Publishing volumes in major databases related to Covid-19. Scientometrics 2021;126:831-842. DOI: 10.1007/s11192-020-03675-3

molecular biology, and for drug repurposing. A major bottleneck for leveraging KG's for biomedical research and discovery is the difficulty to represent data and knowledge into a KG-compatible format. Many biomedical data are stored in formats that are not compatible with KG's, such as spreadsheets and databases, and cannot be used by automated reasoners and other computer-assisted knowledge discovery methods, unless these data are represented in a KG format. Given the complexity of accurately representing semantic information on scientific data and related methods, automated methods and software will be essential to scale up the amount of data on infectious- and immune-mediated diseases available in KG's for accelerating scientific discovery.

Goal:

The goal of this solicitation is to develop software or web services that make it easier for researchers, data curators, and others to extract, transform, and load (ETL) existing scientific data, information, and knowledge from their current format into a KG-compatible format. The process of representing existing data into a KG may need to include human-based curation for the foreseeable future, but the software or web service should automate the process to the degree possible to scale up KG applications for research on infectious- and immune-mediated diseases. Technically competent users with valuable biomedical data or information in commonly used formats should be able to use the software or web service to represent their data or information into a KG-format. The software does not need to connect to any particular existing KG but should be able to produce data in a format that can be easily integrated in any KG that uses a data model and standards adopted by a broad community. The software or web service should enable ETL of data that the user has access to. The software does not need to change the data use permissions, such as making data public that was previously not public. The result of the software or web service should be data in a format that is compatible with a KG and that the user can contribute to appropriate KG's as allowed by their data use permissions. The software or web service should be usable by a broad range of technically capable users in the biomedical research community, to enable community-based contributions of valuable data to domain-specific KG's for infectious- and immune-mediated diseases.

This solicitation is focused on making it easier to represent data relevant for infectious- and immune-mediated diseases into KG's. Areas of interest in this domain are, but are not limited to: clinical and immunological data, structural biology and immune epitope data, data related to the efficacy and safety of diagnostics, therapeutics, and vaccines against infectious- and immune-mediated diseases, and data about pathogens of pandemic potential.

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

- Development of software or web services that can extract facts and findings from published research and represent these in a KG format;
- Development of software or web services that can re-represent commonly produced scientific data types and formats into a KG format;
- Development of software or web services that can add deep semantic information about relationships between entities from scientific data, into a KG format;
- Improvement of documentation for existing software or web services that represent existing scientific data into KG format, to make the software or web service more accessible to biomedical researchers and data curators;
- Adoption or expansion of existing software or web services to enable extraction, transformation, and loading of information on infectious- and immune-mediated diseases into a KG format

At the end of Phase I, the contractor needs to demonstrate that the software or web service can represent existing scientific data into a widely used KG format, compatible with examples of existing KG's and related analytical methods. The software or web service should be usable by a specified user group within the biomedical science community and must have been tested by target users from this group.

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

- Expansion of the software or web service to represent a broader range of data types into KG format;
- Expansion of the software or web service to represent more complex semantic relations into KG format;
- Expansion of the software or web service to map entities or relationships to a broader set of ontologies;
- Hardening of the software or web service to enable use by a broader community of researchers and data curators;

- Improvement of documentation, testing, tutorials, and adoption of the software or web service by a broad user community;
- Integration of the software or web service into existing research work environments to enable adoption by a broad user community

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE (NHLBI)

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

For more information on the NHLBI SBIR/STTR programs, visit our website at: https://sbir.nih.gov/nhlbi

Limited Amount of Award

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

NHLBI Topics

This solicitation invites proposals in the following areas:

NIH/NHLBI 115 Clinical Instrument for Para-Hydrogen (pH2) Based Signal Amplification by Reversible Exchange (SABRE) for Hyperpolarizing 13C-Pyruvate and Other Probes for MRI Imaging

Budget and number of awards:

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

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

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

Budget (total costs per award): Phase I: **$350,000** for **12** months; Phase II: **$3,000,000** 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

Hyperpolarized carbon 13 (13C) MRI is a rapid, noninvasive, and pathway-specific investigation of dynamic metabolic and physiologic processes. This emerging molecular imaging enables real-time in vivo investigations of metabolism in a variety of diseases, including cancer (13C-ketogutarate, 13C-pyruvate), cardiovascular disease (15N-metronidazole), lung fibrosis (15N-isoniazide), inflammation (13C-NAcetyl cysteine), and diseases of the liver and kidney. Current hyperpolarized imaging with dissolution DNP and superconducting MRI scanners is very powerful, but experiments are burdensome, slow, and expensive. The SABRE (Signal Amplification by Reversible Exchange) approach allows transfer of the 100% pure singlet spin order of parahydrogen (para-H2) into a target molecule with impressive levels of polarization, short signal build-up times, low cost, and scalability making SABRE promising modalities for studying metabolism in vivo using MR techniques. This method requires the design, implementation and fabrication of a dedicated clinical instrument.

Project Goals

The goal of this **contract** solicitation is to develop and test a 510(k)-approved Class II medical device to deliver hyperpolarized MRI probes for animal imaging (Phase I) and clinical imaging (Phase II).

Phase I Activities and Expected Deliverables

A Phase I award would be used to develop an instrument to provide hyperpolarized probes for MRI animal imaging based on SABRE using parahydrogen and fluorous catalyst removed by filtration through a column. The expected milestones and deliverables are as follows:

1. Device incorporating a ferromagnetic free reaction chamber with temperature control to 0°C, magnetic field control and degaussing units. Adaptation to reaction chamber >100 ml and temperature control for 0°C need to be done. The purification unit needs to include filtration system and sprayer/concentrator which require to be designed and implemented. This milestone will be

verified by 13C NMR of hyperpolarized 13C pyruvate using fluorous-Iridium catalyst .

2. Regulation and disposal of parahydrogen from reaction vessel. Disposal may be achieved with ionic liquids (https://doi.org/10.1021/ef060481t), or other technology available from the fuel cell industry. This milestone will be verified by conducting milestone 1 with no detectable release of hydrogen from the reaction vessel (employs hydrogen sensor).
3. Rapid controlled fluid delivery to move liquid from the reaction chamber through a fluorous column into a "sprayer/concentrator". The fluorous column will allow the removal of the Iridium-based SABRE catalyst from the hyperpolarized solution. The fluid flow should also allow for redissolution concentrated probe in clinically acceptable buffer for rapid injection. The whole process should be completed in less than 40 seconds. This milestone will be validated by successful 13C NMR of hyperpolarized 13C pyruvate in deuterated methanol with no remaining catalyst present.
4. Rapid concentration of the filtrate containing the hyperpolarized pyruvate. It is anticipated that this would be done via a vacuum spray dryer with temperature control (https://www.labrotovap.com/portfolio-item/laboratory-vacuum-spray-dryer-atomizer/0. Alternatively, the concentration could be completed with controlled temperature centrifuge under vacuum. (https://doi.org/10.1016/j.ejps.2018.10.026; https://doi.org/10.1016/j.lwt.2011.03.021). Development of the sprayer concentrator to rapidly remove <100 ml of methanol (less than 45 seconds). This milestone will be validated by demonstration of concentration in the time specified.
5. Integration of all systems to provide hyperpolarized 13C pyruvate in a buffer system for animal injection. This milestone will be verified by 13C NMR of 13C-pyruvate in aqueous buffer.

Phase II Activities and Expected Deliverables

The Phase II award will be used to develop a Class II medical device for clinical delivery of hyperpolarized probes via parahydrogen-based SABRE with documentation for 510(k) approval. The expected milestones and deliverables are as follows:

1. Increased scalability and robustness of phase I instrument for clinical needs. This system will incorporate a sterile source of the Iridium catalyst, a fluorous column, 13C-pyruvate, methanol, and a clinical buffered system.
2. Analytical quality control system for monitoring the purity and hyperpolarization of 13C-pyruvate, absence of catalyst and residual solvent. Additional monitoring of potential hydrogen gas leaks and temperature control will be necessary at this stage.
3. Software to monitor and document all systems and confirm the production of final hyperpolarized 13C-pyruvate.
4. The completion of all documentation for a 510(k) submission.

NATIONAL INSTITUTE OF MENTAL HEALTH (NIMH)

The National Institute of Mental Health (NIMH) aims to transform the understanding and treatment of mental illnesses through rigorous scientific research. NIMH aims to reduce the burden of mental illness by supporting and conducting research on the causes, prevention, diagnosis, and treatment of mental disorders. The Institute strives to foster innovation and scientific discovery in the field of mental health, promote the integration of research findings into clinical practice, and work towards the development of personalized, effective interventions for individuals with mental illnesses. The NIMH Division of Aids Research (DAR) supports research to reduce the incidence of HIV/AIDS and to alleviate the burden of people living with HIV.

Limited Amount of Award

For budgetary, administrative, or programmatic reasons, the NIMH may not fund a proposal more than the budget listed for each topic.

NIMH Topics

This solicitation invites proposals in the following areas:

NIH/NIMH 001 - Point-of-Care HIV Viral Load and Drug Adherence Assays

(Fast-Track and Direct to Phase 2 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: $2,000,000 for up to 2 years.

Background
According to the Centers for Disease Control and Prevention (CDC), HIV remains a significant public health challenge both in the United States and globally. In the United States, an estimated 1.2 million people are currently living with HIV and globally over 38 million people are affected by HIV. Antiretroviral therapy (ART) has transformed the management of HIV infection, significantly improving patient outcomes and altering the trajectory of people living with HIV. ART involves the use of combinations of antiretroviral drugs that target different stages of the HIV life cycle, suppressing viral replication and restoring immune function. The goal of ART is to achieve and maintain viral suppression, defined as a decrease in HIV RNA levels to undetectable levels in the blood. Viral suppression not only benefits the individual by preserving immune function and reducing the risk of opportunistic infections but also has public health implications by reducing the risk of HIV transmission. However, the effectiveness of ART is highly dependent on consistent medication adherence and monitoring of viral load. One of the needs for people with HIV to maintain sustained viral suppression and reduce HIV incidence in the US are point-of-care assays that can measure viral load and adherence to ART.

Project Goals
The long-term goals are to develop novel, low-cost, real-time point-of-care (POC) assays for:

1. HIV Viral Load Monitoring
- The assays should be designed as a home test or for use in local clinics or pharmacies to detect HIV from finger-stick blood or other biospecimens at the earliest possible time after initial infection or after loss of viral suppression. For assays to be used at home, the design should be user-driven. The technology can include the capacity to connect results to healthcare providers, but it is not required.

- The assays should be designed for use by people living with HIV (PWH) on/off antiretroviral therapy or on PrEP (pre-exposure prophylaxis) to detect viral spikes during ART therapy, viral rebound during analytical treatment interruption, HIV breakthrough infection during PrEP, and/or to rule out HIV infection in the presence of an HIV vaccine-induced immune sero-reactivity.

- Assays should be capable of detecting infection in at least one of the following groups: acutely infected people who may have no antibody response and low viral loads; Pre-Exposure Prophylaxis (PrEP) users who may have a very low viral load and a delayed antibody response; vaccine-induced sero-reactive people who will have antibody present even during acute infection; and/or ART-treated people after the loss of viral suppression.

- The method should be semiquantitative and should detect HIV RNA or other biomarkers, such as p24, immune markers, etc., with a qualitative sensitivity of at least 98% and specificity of at least 98%.
- The assays should
  - have a minimum sensitivity of <500 RNA copies per mL of HIV-1 or equivalent if a biomarker is used.
  - at a minimum be able to detect HIV strains circulating in the US but detection can be extended to other HIV-1 subtypes.
  - have a short diagnostic time to the result (optimally 20 minutes or less but no longer than 1 hour).
  - be culture-independent, easy to use, and cost-effective.
- Proposals can include the development of a small handheld unit to be used with individual test strips or cartridges, but device-free, disposable units are preferred. Test units may require refrigeration, but stability at room temperature is preferable.
- All necessary materials should be supplied with the test and no additional materials should be required.
- The amount of handling required by the operator should be suitable for home testing by untrained individuals.

2. Pharmacological Adherence Monitoring
- Rapid point-of-care methods that measure long-term (> 7 days) adherence to antiretrovirals.
- Need to be able to measure drug levels in various biological matrices, e.g., urine, hair, dried blood spots, etc.
- Need to be able to monitor
  - PrEP adherence
  - ART adherence to trigger adherence interventions
  - Drug levels of long-acting ART or PrEP formulations
  - Monitor blood donations for PrEP or ART drug levels (as a risk indicator of HIV exposure or infection)

The ultimate goal of the above efforts is to ensure monitoring of sustained viral suppression with adequate quantifiable measures of adherence to combination ART as well as to monitor the effectiveness of novel long-acting ART or PrEP formulations.

Phase I activities may include, but are not limited to:
- Develop prototype assays considering specificity, sensitivity, dynamic range, interference, robustness, reproducibility, accuracy (precision), and analysis of assay performance;
- Demonstrate that the assays can detect the analyte in various matrices, such as blood, dried blood spots, urine, saliva, and hair (for drugs) dependent on the application;
- Preliminary studies to determine the assay feasibility;
- Define process controls; and
- Establish potential for commercialization.

Phase II activities may include, but are not limited to:
- Further development of the prototype point-of-care diagnostic products;
- Further determination of the sensitivity, specificity, and other performance characteristics (e.g., time to result, limit of detection, test stability) of the assay;
- Final validation testing and scale-up manufacturing of test kits;
- Development of a quality control program to enable longitudinal measurements in compliance with Good Clinical Laboratory Practice; and
- Finalization of the commercialization plan.

This SBIR contract topic will <u>not</u> support:
- The conduct of clinical trials

NIH/NIMH 002 – Development of novel In-vitro and In-vivo Models to support NeuroHIV Research

(Fast-Track and Direct to Phase 2 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: $2,000,000 for up to 2 years.

Background
Central Nervous System complications associated with HIV continues to persist in people with HIV (PWH) despite effective

Antiretroviral therapy (ART). Although excellent virologic control in the periphery and brain has been achieved, CNS disease (NeuroHIV) including neurologic, neurocognitive, and mental health problems are observed. Considerable gaps exist in our understanding of pathogenesis of CNS disease associated with HIV. Basic research in the NeuroHIV field has primarily focused on modeling neuronal damage in the context of active viral replication or the impact of HIV proteins such as Tat/gp120, with endpoints such as encephalitis and neuronal death. However, the CNS disease outcomes observed in the pre-ART era, such as atrophy and encephalitis, are not apparent in the current era. Other mechanisms, such as neuroimmune dysfunction, legacy effects of long-term ART medications and chronic inflammation, in the context of co-morbidities, may play a role in the observed HIV-associated CNS disease outcomes. Other potential unexplored mechanisms and pathways may drive the development of CNS disease, such as subtle neuro-metabolic changes, alterations in neuronal circuitry, or altered signal transmission. There is a need for novel model systems that will help better understand the Immune-Central Nervous System (CNS) interactions in the context of HIV.

Project Goals
The long-term goals are to develop novel models for NeuroHIV research including:

- Organoid models incorporating human immune cells amenable to HIV infection and neuronal cells with measurable neuro-modulatory outcomes;
- Humanized small animal models with systemic and CNS immune cells amenable to HIV infection that can be used to understand mechanisms such as neuroimmune dysfunction in the context of long-term infection with HIV and to comprehend the role of the CNS viral reservoirs;
- Develop Blood brain barrier systems using organoid based framework with human immune cells, neuronal cells and vascular components to help comprehend the pathways leading to adverse CNS outcomes in the context of HIV and ART;
- Develop in-vitro and in-vivo models to test the impact of HIV associated immune dysfunction on synaptic transmission and plasticity.

Phase I activities may include, but are not limited to:
- Conceptualize and develop exemplar in-vitro and in-vivo models considering, sensitivity, robustness, reproducibility, accuracy (precision) of quantifiable outcomes;
- Preliminary studies to determine the model feasibility with HIV infection and ART; and
- Establish potential for commercialization.

Phase II activities may include, but are not limited to:
- Further development of the prototype models to incorporate additional refinements;
- Further determination of the sensitivity, specificity, and other performance characteristics (e.g., neuromodulatory outcomes) of the model;
- Final validation testing and feasibility of scaling up of in-vitro and in-vivo model systems;
- Finalization of the commercialization plan.

This SBIR contract topic will <u>not</u> support:
- Clinical studies and/or conduct of clinical trials

CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

CDC is the nation's leading science-based, data-driven, service organization that protects the public's health. 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 works 24/7 to protect America from health, safety and security threats, both foreign and in the U.S. Whether diseases start at home or abroad, are chronic or acute, curable or preventable, human error or deliberate attack, CDC fights disease and supports communities and citizens to do the same.

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

The 2022-2027 CDC Strategic Plan advances science and health equity and affirms the agency's commitment to one unified vision — equitably protecting health, safety, and security. The plan continues to leverage 5 core capabilities of the agency reflecting our commitment to: equity and diversity, world-class data and analytics, state-of-the-art laboratories, rapid response to outbreaks at their source, and strong global capacity and domestic preparedness. Our work is underscored by the agency's Pledge to the American People and dedication to use timely data and science to drive and communicate customer-centered, high-impact public health action.

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 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 031 - Development of SHERLOCK Assay for Detection of High Threat Orthopoxviruses

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 **$1,927,828** 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
Point of care diagnostic assays in outbreak or response settings are crucial for rapid detection of infection and determining appropriate next steps (isolation, contact tracing, treatment, etc.). Additionally, it's critical to develop new diagnostics to meet evolving public health needs as testing availability can be impacted by competition for limited reagents/consumables during an outbreak. The development of a unique field-deployable diagnostic assay using non-overlapping reagents will address both preparedness concerns to improve response in the event of a Variola virus (VARV- the causative agent of smallpox) bioterror event, as well as monkeypox virus (MPXV) which continues to be an expanding global health threat. The SHERLOCK (specific high-sensitivity enzymatic reporter unlocking) test will need to incorporate

multi-pathogen panels and be adjusted to various levels of specificity based on oligonucleotide sequences. These technologies have been documented to work with a variety of pathogens. Approaches for assay design could be two targets, one specific for MPXV and another for non-MPXV pathogens.

Project Goals
As described within this paper (Detection of SARS-CoV-2 with SHERLOCK One-Pot Testing | NEJM): CRISPR (clustered regularly interspaced short palindromic repeats)–based diagnostic tests collectively provide a nascent platform for the detection of viral and bacterial pathogens. Methods such as SHERLOCK (specific high-sensitivity enzymatic reporter unlocking), which typically use a two-step process (target amplification followed by CRISPR-mediated nucleic acid detection), have been used to detect SARS-CoV-2. These approaches, however, are more complex than those used in point-of-care testing because they depend on an RNA extraction step and multiple liquid-handling steps that increase the risk of cross-contamination of samples. Within this paper (Detection of SARS-CoV-2 with SHERLOCK One-Pot Testing | NEJM authors describe a simple test for detection of SARS-CoV-2. The sensitivity of this test is similar to that of reverse-transcription–quantitative polymerase-chain-reaction (RT-qPCR) assays. STOP (SHERLOCK testing in one pot) is a streamlined assay that combines simplified extraction of viral RNA with isothermal amplification and CRISPR-mediated detection. This test can be performed at a single temperature in less than an hour and with minimal equipment. The goal of this SBIR proposal is for the development of a similar STOP assay to detect high threat orthopoxviruses.

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

Phase one will focus on assay development (i.e., primer design, pathogen panels, reagent selection/concentration, readout options), and pilot testing of pathogens of interest. To meet goals in phase I (6-month timeline), company may select only an orthopoxvirus generic target to start. If successful in phase one, follow-up testing will focus on examining the acceptable range of shelf life and storage conditions for reagents, assay optimization and validation, and adding additional orthopoxvirus targets (i.e., sample workflows, readout options, identifying limits of detection, specificity, sensitivity, and repeatability).

Impact
Typical diagnostic screening is conducted using expensive and intricate machinery, requiring highly trained laboratorians. The SHERLOCK/STOP novel methodologies will have reduced machinery requirements and be able to provide point of care results, with potential to be modified to detect a variety of pathogens, simultaneously improving preparedness for a smallpox bioterror event, and can be used in field settings for orthopoxvirus detection, thereby increasing general public health preparedness to improve pathogen identification and detection.

Commercialization Potential
Following the start of the COVID pandemic, there have been numerous companies engaged in SHERLOCK assay development. In the wake of the mpox outbreak, there should be tremendous commercialization potential for both MPXV and other orthopoxviruses.

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

The National Center is committed to our vision of a future free of HIV, viral hepatitis, STDs, and TB. NCHHSTP is responsible for public health surveillance, prevention research, and programs to prevent and control HIV, other STDs, viral hepatitis, and TB.CDC's National Center for HIV, Viral Hepatitis, STD, and TB Prevention's (NCHHSTP) Strategic Plan articulates a vision, guiding principle, and overarching goals and strategies 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/

NCHHSTP topics

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

CDC/NCHHSTP 055-Software Solutions: Bridging the Gap between Public Health and Pharmacies

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: 2

Budget (total costs): Phase I: up to **$243,500** for up to 6 months; Phase II of up to **$1,972,828** 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
An estimated 13 billion pharmacy visits occur per year, which is more than 10 times the annual number of patient contacts with all other primary care providers combined. Public health partnerships with pharmacies can provide new access points for sexually transmitted infections (STIs) and HIV services. More than ever, we saw this need during the COVID-19 pandemic when many public health clinics had to reduce hours or suspend services. In recent years, pharmacy practices have embraced more patient-centered care approaches and trained providers to deliver counseling, point-of-care (POC) or rapid tests, administer injectables, vaccines/immunizations, and offer clinical referrals for a variety of health conditions. Opportunities exist for public health departments to strengthen partnerships with these accessible and trusted health professionals.

Pharmacists are taking on a more significant role in delivering sexual health services in conjunction with health departments. For example, local health departments have been funded to partner with local pharmacies to offer expanded STD/HIV services (including PrEP) in their communities. Both entities have expressed a need to have software capabilities that would allow health departments and partnering pharmacies (and potentially patients) to all see testing and treatment info for a particular individual as close to real time as possible. However, there is no interoperable electronic system that enables the pharmacy and health department to securely transmit data and innovation is needed to ensure collaborative care communication, case and disease management, and reporting (among other things) between health departments and pharmacy practices.

As part of the Pharmacist eCare Plan Initiative, approximately 20 pharmacy management with embedded clinical documentation systems exist. These software solutions are innovative tools that enable collaborative care communication, case and disease management, treatment, and can support workflows, billing, automation, and compliance. Similar software with real-time detection capabilities has been developed to help monitor prescription drugs for to detect opioid substance misuse and detect outbreaks. Software solutions exist, but enhancements are needed to ensure successful collaboration between the two entities.

The software would need to allow for a pharmacist or any provider to be able to document treatment and close the loop. The following are some potential scenarios where this type of collaborative communication would be beneficial:

- Pharmacist should be able to send STI test results to the health department (pharmacist ordered under a collaborative practice agreement (CPA) or standing order) – this would be a scenario where rapid STI POC tests were available at the pharmacy.
- Pharmacist and health department are both able to see patient test results from self-collection kit (where the health department is working with 3rd party lab vendor)

Pharmacist providing oral or injectable treatment can document that treatment was administered. This could be extended to include expedited partner therapy [EPT] patients, too

Project Goals
The immediate goal of this project is to facilitate the development of a Pharmacist eCare software add-on to enable enhanced information sharing between health departments and partner pharmacies by assessing needs, functionality, and demand. A functionality between pharmacy dispensing software and health department surveillance would allow pharmacies to utilize the reporting already being conducted at health departments. Longer term (Phase II), as informed by the needs assessment and usability testing, the software add-on would be evaluated and made applicable for other infectious and chronic diseases and public health biomedical tools (e.g., flu, immunizations, etc.).

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

- Conduct a software needs assessment among dyads of pharmacies and health departments partnering on STI/HIV testing and treatment, including PrEP.

1. Identify software needs that enhance reporting and information sharing for:
   i. patient assessment, including counseling,
   ii. testing (e.g., test performed, where administered),
   iii. test result, and
   iv. action(s) taken (e.g., type of treatment, PrEP, doxycline administered as postexposure prophylaxis, partner notification, referral).
2. Assess compatibility of data elements/interoperability with standardized state and federal surveillance systems.
3. Identify back-end capabilities and assess needs for data generation and monitoring. Explore need for patients to have access to certain levels of their health care data.
4. Identify potential implications for disease surveillance, billing, and reimbursement. Identify training needs for optimal workflow integration.
5. Assess and recommend potential price-points for these additional features, maintenance, and customization fees to assess level of interest/demand for commercialization.

- Use needs assessment to inform the development of the software add-on's feature and capabilities.
- Conduct beta-testing with a prototype software between a sample of the health department and pharmacy dyads to assess usability of the add-on and needed improvements. Refine software for use among a broader set of entities.
- Develop a proof-of concept software add-on for partnering health departments and pharmacies to use in their everyday operations that enhances information share and reporting for STI/HIV testing, treatment, and care.
- Analyze needs assessment findings and prepare recommendations, and next steps for further development of the prototype.

Impact

The goal of this project is to develop a software solution to further expand the STI safety net via partnerships between local health departments and pharmacies delivering preventive care and treatment. Potential impact includes the ability to increase local-level collaboration, and improve reporting, community-based surveillance, and community health. Early diagnoses and treatment of STIs can interrupt future transmission and improve patient health outcomes, thus decreasing morbidity. Increased access, faster turnaround of testing and treatment would be highly impactful for patients, their partners, and the community.

Moreover, software capabilities like this that track tests performed by the pharmacy, positive test results to meet health department reporting requirements, and treatment administered can serve as an example to expand to other POC or self-testing that could be performed in a pharmacy or under a collaborative practice agreement. This could eventually expand opportunities for pharmacist billing and reimbursement if each patient care encounter is documented (e.g., test administered, treatment administered). This project's potential for impact extends well beyond the context of the infectious diseases of focus and could have positive implications for the entire field of public health where pharmacy practices are more directly involved in health promotion, patient care, and outcomes.

Commercialization Potential

Whereas there are only ~3,400 local health departments nationwide, there are approximately ~70,000 community pharmacies in the United States, of which retail chain and independent pharmacies account for 40% and 35%, respectively; and roughly 311,000 pharmacists practicing in the community setting (while the remainder were comprised of mass retailer (12%), food store, (10%), clinic-based (3%) or government. More than 90% of the US population lives within 5 miles of a community pharmacy and those in more urban areas live < 2 miles from one. An estimated 13 billion pharmacy visits occur per year, which is more than 10 times the annual number of patient contacts with all other primary care providers combined.

As more rapid diagnostics and treatment options come to market, pharmacists will continue to play an integral role in public health. Scope of practice laws have the potential to legally expand their role as providers too. As the demand for pharmacy-based services increases, so will the demand for data sharing and care management capabilities, especially when the next public health emergency arrives.

CDC/NCHHSTP 056-EHR 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 **$1,972,828** 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). There is a lack of such functionality to identify patients with HIV not in care-to our knowledge; few medical centers have any "homegrown" electronic medical record algorithms in place 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 with regards to 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 a 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
During the Phase I period, the activities can include, but are not limited to:

In collaboration with CDC HIV subject matter experts, 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 PWH 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 with regards to this functionality may also be explored.

Impact
Persons with HIV (PWH) 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 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. We believe that this innovative algorithm would 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 among people diagnosed with HIV in the United States is 65 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 95 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 057-Device for point-of-care nucleic acid purification and detection of HCV

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 **$1,972,828** 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
Hepatitis C virus (HCV) infection is a major global health problem and chronic HCV infection is a leading cause of cirrhosis and liver cancer. HCV infects an estimated 2.4 million people in the U.S. and 58 million people, globally. Effective and well-tolerated direct acting antiviral (DAA) drugs are available for the treatment of HCV infections and the World Health Organization (WHO) has established elimination goals of 90% reductions in the number of new HCV cases and 65% reductions in deaths associated with HCV infection by the year 2030. Achievement of these goals will require expanding access to HCV testing as only 20% of current infections have been globally diagnosed. Current HCV infections are diagnosed by the detection of either circulating HCV RNA or HCV core antigen in a person's blood. HCV diagnostic testing methods often have high costs, slow turnaround times, and need to be performed in a laboratory, which lead to access problems and the potential to lose patients to health care provider follow up after a positive diagnosis. Ideally, HCV diagnosis would occur at the point of care while the patient waits, allowing for immediate linkage to care and treatment in people with HCV infections. Currently there are no point-of-care tests for the detection of HCV RNA available in the US. The development of a simple and inexpensive device that can perform nucleic acid extraction and detection workflows with minimal user intervention would allow for the diagnosis of HCV infection at the point of care, and greatly expand access to HCV diagnostic testing.

Project Goals
A sensitive point-of-care compatible workflow for the rapid detection of HCV RNA from whole blood has been developed at CDC (U.S. Provisional Patent Application No. 63,489,519). This workflow involves the chemical lysis of blood-derived HCV, the capture of HCV RNA by paramagnetic beads, reverse transcription loop-mediated isothermal amplification of nucleic acids (RT-LAMP), and the detection of amplified nucleic acid products by either fluorescence or lateral flow technology. The goal of this solicitation is to develop a simple device that can be used to perform this workflow or a similar workflow with minimal user intervention. The device should be compatible with point-of-care testing, inexpensive to mass-produce, and have potential for use in a variety of patient settings. Minimally, the device will be able to perform extraction and purification of HCV RNA from whole blood samples with minimal user intervention within 15 minutes. Additional feature that will be attractive in a device will be the ability to perform HCV RNA amplification (RT-LAMP, RT-PCR, etc.), to detect nucleic acid amplification products (real-time fluorescence measurements, end-point fluorescence measurements, lateral flow, etc.), and to process multiple samples simultaneously. The finalized device design based on the existing workflow should be able to detect of HCV RNA from whole blood samples at a level of 1000 IU/mL or below within 60 minutes and with minimal user intervention.

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

1. Propose design concepts for device capable of HCV RNA extraction and purification from whole blood samples with integration of nucleic acid amplification and detection of nucleic acid amplification products. The processes to be accommodated on such device are already described in a CDC-developed workflow. The design should allow HCV RNA detection in a point-of-care format, not to exceed 1 hour sample to result time. This project design phase is not to exceed 2 months.
2. By the end of the design concept phase (end of month two of the grant), the grantee would be anticipated to have at least one design prototype selected in consultation with CDC SMEs.

3. After the design selection, we anticipate that a functioning prototype will be built to be used for testing the performance and reproducibility of the HCV RNA assay workflow. We expect the delivery of a device capable of accommodating the rapid extraction and purification of HCV RNA from whole blood for use in subsequent nucleic acid amplification reactions. Additional attributes of the device could be integration of nucleic acid amplification and the detection of nucleic acid amplification products by an appropriate method. The building of the device would be expected to be accomplished by the end to the fourth month of the grant.
4. Evaluate the performance of the prototype device with HCV RNA positive and negative samples. The actual testing of the product could be done at the developer worksite with CDC supporting the developer with appropriate negative and positive control materials. Alternatively, in case that the developer does not have appropriate facilities for work with BSL2 infectious material, they could provide the prototype device to the CDC location for performance testing.
5. Estimate production costs and scalability.

Impact
The current standard testing algorithm for the diagnosis of current HCV infections starts with testing for anti-HCV antibodies followed by reflex testing anti-HCV positive samples for HCV RNA. This two-tiered approach is used to reduce expensive HCV RNA testing of samples from patients who are unlikely to be infected. However, this approach does miss HCV infected people with acute or recent infections who have yet to seroconvert for anti-HCV antibodies. This approach is incompatible with receiving a diagnosis during a single health care visit.

The desired device could impact HCV diagnostics by making HCV RNA testing immediately accessible, affordable, and able to be performed at the point of care. This will streamline linkage of HCV-infected people to care and promote awareness of HCV infections and the ways to prevent its spread. The availability of such a device is expected to dramatically improve the volume of HCV testing. Diagnosis and linkage to treatment could be accomplished in a single visit with a recommended treatment with DAAs having a curative rate of >95% at 12 weeks, this would in turn greatly facilitate the WHO's goals of viral hepatitis elimination.

Commercialization Potential
There is a considerable interest in inexpensive point-of-care tests for HCV detection to assist in meeting WHO viral hepatitis elimination goals. A device that achieves the project goals will have a high potential for successful commercialization. No point-of-care tests for HCV diagnosis are approved for clinical use or available in the U.S. A device that can perform extraction and purification of HCV RNA from blood and potentially integrate the detection of HCV would meet a critical need. Thus, a need exists for simple, low-cost, rapid, and sensitive methods for the detection of HCV RNA for the diagnosis of current HCV infections.

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.

NCIRD website: http://www.cdc.gov/ncird/

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

CDC/NCIRD 036-Improved Diagnostic Assays for Measles, Mumps, Rubella, and Varicella

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 **$1,972,828** 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
Acute infections of measles, mumps, rubella, and varicella continue to place an undue burden on public health systems despite the availability of vaccines for all four pathogens. Over 100,000 deaths are still attributed to measles infection globally each year, and rubella

infection continues to cause over 100,000 children to be born with congenital rubella syndrome annually – mostly in developing countries. Sporadic mumps and varicella outbreaks – ranging from tens to thousands of cases – continue to occur in the United States. Strong surveillance systems are necessary for detecting sporadic cases of disease, preventing disease outbreaks, and maintaining disease elimination status. An essential component of surveillance is laboratory testing to rapidly confirm the presence of a specific pathogen and to help guide the public health response.

Project Goals
The goal of this research includes but is not limited to activities that support the development, optimization, and evaluation of the following tools: 1) serologic tests with improved diagnostic sensitivity and specificity; 2) multiplexed molecular assays for concomitant pathogen detection; and 3) tools for quality control of diagnostic assays.

Phase I Activities and Expected Deliverables
During the Phase I period, the activities can include, but are not limited to:
Phase 1 deliverable would include a prototype test kit to detect any of the viral pathogens listed in the "Background" section above. The protype test kit should be able to be performed in a standard reference laboratory with standard equipment. Multiplex molecular assays capable of detecting multiple pathogens, especially measles and rubella, are also desirable. Assay sensitivity and specificity should exceed 90% for a test panel of residual specimens.

Impact
This research will lead to the development of practical testing solutions for the diagnosis of vaccine-preventable diseases and prevention of disease outbreaks that have a significant impact on the economy, healthcare system capacity, and overall wellbeing of society. The goal of the research supported through this mechanism is expected to improve diagnostic testing capacity for measles, mumps, rubella, and varicella on a global scale, allowing for more rapid and accurate diagnosis of cases which will lead to a more rapid mobilization of resources to limit disease transmission.

Commercialization Potential
The innovative technologies and solutions developed through this program will make it possible to improve domestic and global public health laboratory response in a variety of settings, thereby placing no foreseeable limits on the commercialization potential.

CDC/NCIRD 037-Rapid Diagnostic Tests for Measles, Mumps, Rubella, and Varicella

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 **$1,972,828** 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
Acute infections of measles and rubella continue to place an undue burden on public health systems, especially in countries with nascent vaccine programs or logistical challenges for achieving high levels of vaccination coverage or disease surveillance. Over 100,000 deaths are still attributed to measles infection globally each year, and rubella infection continues to cause over 100,000 children to be born with congenital rubella syndrome annually. Sporadic importations of measles and rubella continue to occur in the United States, with measles importations occasionally seeding large-scale outbreaks among susceptible communities. Strong surveillance systems are necessary for detecting sporadic cases of disease, preventing disease outbreaks, and maintaining disease elimination status. An essential component of surveillance is rapid confirmation of a specific pathogen to help guide the public health response.

Project Goals
The goal of this research includes but is not limited to activities that support the development, optimization, and evaluation of the following tools: 1) rapid diagnostic tests (RDTs) for the detection of pathogen-specific antibodies (IgM/IgG); 2) RDTs for the detection of pathogen-specific markers of infection (such as viral antigens or nucleic acids); and 3) tools for quality control of RDTs.

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

Phase 1 deliverables would include a prototype RDT to detect IgM and/or IgG to measles or rubella, or a prototype RDT to detect nucleic acid or viral antigens for measles or rubella. Prototype RDTs should be require minimal laboratory equipment to be used in a local clinic of field setting. Prototypes should have at least 80% sensitivity and specific after testing small panel of archived specimens.

Impact

This research will lead to the development of practical testing solutions for the diagnosis of vaccine-preventable diseases and prevention of disease outbreaks that have a significant impact on the economy, healthcare system capacity, and overall wellbeing of society. RDTs offer the advantage of rapid test results without the need for specialized laboratory equipment and can readily be used by non-specialized field workers. The goal of the research supported through this mechanism is expected to improve diagnostic testing capacity for measles and rubella on a global scale, allowing for more rapid and accurate diagnosis of cases which will lead to a more rapid mobilization of resources to limit disease transmission.

Commercialization Potential

The innovative technologies and solutions developed through this program will make it possible to improve domestic and global public health laboratory response in a variety of settings, thereby placing no foreseeable limits on the commercialization potential.

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 I AND 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. ***

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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)

APPENDIX J - Disclosure of Foreign Relationships

All offerors must disclose all funded and unfunded relationships with foreign countries, using the Required Disclosures of Foreign Affiliations or Relationships to Foreign Countries form (referred to as the "Disclosure Form" hereafter), for all owners and covered individuals. A "covered individual" is defined as all senior key personnel identified by the SBC in the application (i.e., individuals who contribute to the scientific development or execution of a project in a substantive, measurable way).

Disclosure of Foreign Relationships Reporting Requirements
Contractors are responsible for monitoring their relationships with foreign countries of concern post-award, for any changes that may impact previous disclosures. SBCs receiving an award under the SBIR program are required to submit an updated Disclosure Form to report any of the following changes to NIH or CDC throughout the duration of the award:

- any change to a disclosure on the Disclosure Form;
- any material misstatement that poses a risk to national security; and
- any change of ownership, change to entity structure, or other substantial change in circumstances of the SBC that NIH or CDC determine poses a risk to national security.

Updated Disclosure Forms are required within 30 days of any change in ownership, entity structure, covered individual, or other substantive changes in circumstance, as described above.

If the contractor reports a covered foreign relationship that meets any of the risk criteria prohibiting funding described in this solicitation, NIH and CDC may withhold funding until the covered relationship has been dissolved. The contractor will be required to submit documentation verifying the relationship has been terminated. If the risk cannot be resolved, NIH and CDC may deem it necessary to terminate the award for material failure to comply with the federal statutes, regulations, or terms and conditions of the federal award. Contractors are encouraged to monitor their covered foreign relationships post-award and avoid entering into relationships, both funded and unfunded, that may pose a security risk and jeopardize their ability to retain their award.

Agency Recovery Authority and Repayment of Funds
An SBC will be required to repay all amounts received from NIH, CDC, and FDA under the award if either of the following determinations are made upon assessment of a change to their disclosure:

- the SBC makes a material misstatement that NIH, CDC, and FDA determine poses a risk to national security; or
- there is a change in ownership, change in entity structure, or other substantial change in circumstances of the SBC that NIH, CDC, and FDA determine poses a risk to national security.

Required Form in MS Word:
(https://grants.nih.gov/grants/funding/SBIR-STTR%20Disclosures%20of%20Foreign%20Affiliations-%20Final%206-13-2023.docx.)

Additional information and instruction to complete the form:
(https://grants.nih.gov/grants/forms/all-forms-and-formats/required-disclosures-foreign-affiliations-or-relationships)