**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 2023-1

## Closing Date: November 4, 2022 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 4, 2022, 5:00 PM Eastern Daylight

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

IMPORTANT: All proposals must be submitted using the electronic contract proposal submission (eCPS) website.
**Paper proposals will not be accepted.**

Please go to https://www.sbir.gov/sites/default/files/SBA_SBIR_STTR_POLICY_DIRECTIVE_OCT_2020_v2.pdf to read the SBIR/STTR Policy Directive issued by the Small Business Administration for further information.

# Table of Contents

## 1 INTRODUCTION

The National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) invite small business concerns (SBCs) to submit research proposals under this Small Business Innovation Research (SBIR) Contract Solicitation. Firms with the capability to conduct research and development (R&D) in any of the health-related topic areas described in Section 12.0, and to commercialize the results of that R&D, are encouraged to participate.

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

**This solicitation contains opportunities to submit a proposal under a variety of different Topics, which are summarized below. Some Topics allow for only a Phase I proposal to be submitted at this time. Some Topics allow for only a Phase II proposal to be submitted, through the 'Direct to Phase II' process. Some Topics allow for 'Fast Track' proposals, which include both a Phase I proposal and a Phase II proposal. For more information on the SBIR program, including the Fast Track and Direct to Phase II processes, refer to Section 2.**

| TOPIC NUMBER | PHASE I ALLOWED? | FAST TRACK ALLOWED? (A Phase I proposal and a Phase II proposal submitted simultaneously) | DIRECT TO PHASE II ALLOWED? (Includes only a Phase II Proposal) | TOPIC TITLE |
|---|---|---|---|---|
| NIH/NCATS 023 | Yes | No | No | Development of Automated Cell Culture Flask Cleaning Instrument |
| NIH/NCI 446 | Yes | Yes | Yes | Development of Senotherapeutic Agents for Cancer Treatment |
| NIH/NCI 447 | Yes | Yes | No | Non-invasive Device Technology Research & Development for Chemotherapy-Induced Peripheral Neuropathy Management |
| NIH/NCI 448 | Yes | Yes | Yes | Wearable Devices for Dosimetry of Radiopharmaceutical Therapy |
| NIH/NCI 449 | Yes | Yes | Yes | Wearable Technologies to Facilitate Remote Monitoring of Cancer Patients Following Treatment |
| NIH/NCI 450 | Yes | Yes | No | Technology Platforms for Circulating Tumor-Macrophage Hybrid Cells |
| NIH/NCI 451 | Yes | Yes | Yes | Rapid and Affordable Point-of-Care HPV Diagnostics for Cervical Cancer Control |
| NIH/NCI 452 | Yes | Yes | Yes | Translation of Novel Cancer-Specific Imaging Agents and Techniques to Mediate Successful Image-Guided Cancer Interventions |
| NIH/NCI 453 | Yes | Yes | Yes | Digital Tools to Integrate Cancer Prevention Within Primary Care |
| NIH/NCI 454 | Yes | No | No | Software to Evaluate Artificial Intelligence/Machine Learning Medical Devices in Oncology Settings |
| NIH/NIA 007 | Yes | Yes | Yes | High Throughput CHIP (clonal hematopoeisis of indeterminate potential) Assay as a Powerful Tool to Study CHIP Related Age Associated Diseases |

| 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/NIA 008 | Yes | Yes | Yes | Improving Microphysiological Systems for AD/ADRD Therapy Development |
| NIH/NIA 009 | Yes | Yes | Yes | AI/ML Tool for Visualizing Behavioral and Social Science Research |
| NIH/NIAID 113 | No | Yes | No | Development of a Simian Immunodeficiency Virus (SIV) and Simian Human Immunodeficiency Virus (SHIV) Database |
| NIH/NIAID 114 | Yes | Yes | No | Point-of-Care HIV Viral Load, Drug Resistance, and Adherence Assays |
| NIH/NIAID 115 | Yes | Yes | No | Development of Diagnostics to Differentiate HIV Infection from Vaccine Induced Seropositivity |
| NIH/NIAID 116 | Yes | Yes | Yes | Adjuvant Discovery for Vaccines for Infectious and Immune-Mediated Diseases |
| NIH/NIAID 117 | Yes | Yes | Yes | Adjuvant Development for Vaccines for Infectious and Immune-Mediated Diseases |
| NIH/NIAID 118 | Yes | Yes | Yes | Reagents for Immunologic Analysis of Non-mammalian and Underrepresented Mammalian Models |
| NIH/NIAID 119 | Yes | Yes | No | Adaptation of CRISPR-based in vitro diagnostics for rapid detection of select eukaryotic pathogens |
| NIH/NIAID 120 | Yes | Yes | No | Modular Sample Preparation for In-Field Viral Discovery |
| NIH/NIAID 121 | Yes | Yes | No | Artificial Intelligence to Improve Clinical Microscopy for Diagnosis of Infectious Diseases |
| NIH/NIAID 122 | Yes | Yes | Yes | Advanced and Immersive Visualization Tools for Infectious and Immune-mediated Disease Research |
| NIH/NIAID 123 | Yes | Yes | Yes | Data Science Tools for Infectious and Immune-mediated Disease Research |
| NIH/NHLBI 113 | 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/NHLBI 114 | Yes | Yes | Yes | Device to Permit Continuous Self-Monitoring of Blood Oxygen Saturation During Activities of Daily Living for Individuals at Risk for Desaturation During Physical Exertion |
| NIH/NIDA 167 | Yes | Yes | Yes | Cause of Death Elucidated (CODE) in Drug Overdose: research and development of new postmortem toxicology screening devices that are portable, rapid, accurate, affordable, and accessible |

| 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 030 | Yes | No | No | Developing an Over-the-Counter Diagnostic Test for Valley Fever |
| CDC/NCHHSTP 054 | Yes | No | No | School Illness-Related Absenteeism and Learning Modality Surveillance |

All firms that are awarded Phase I contracts originating from this solicitation will be eligible to participate in Phases II and III. Awarding Components (see Section 2.7) will notify Phase I awardees of the Phase II proposal submission requirements. Submission of Phase II proposals will be in accordance with dates provided by individual Awarding Component instructions. The details on the due date, content, and submission requirements of the Phase II proposal will be provided by the Awarding Component either in the Phase I award or by subsequent notification.

The HHS is not obligated to make any awards under Phase I, Phase II or provide additional non-SBIR funding. All awards are subject to the availability of funds. HHS is not responsible for any monies expended by the offeror before award of any contract.

## 2 PROGRAM DESCRIPTION

### 2.1 Objectives

The objectives of the SBIR program include stimulating technological innovation in the private sector, strengthening the role of small business in meeting Federal research or research and development (R/R&D) needs, increasing private sector commercialization of innovations developed through Federal SBIR R&D, increasing small business participation in Federal R&D, and fostering and encouraging participation by socially and economically disadvantaged small business concerns and women-owned small business concerns in the SBIR program.

The basic design of the NIH/CDC SBIR program is in accordance with the Small Business Administration (SBA) SBIR Program Policy Directive dated October 1, 2020. This SBIR contract solicitation strives to encourage scientific and technical innovation in areas specifically identified by the NIH/CDC awarding components. The guidelines presented in this solicitation reflect the flexibility provided in the Policy Directive to encourage proposals based on scientific and technical approaches most likely to yield results important to the NIH/CDC and to the private sector.

The NIH is interested in developing products and services via the SBIR program that improve the health of the American people. In its commitment to also support Executive Order 13329, encouraging innovation in manufacturing-related research and development, NIH seeks, through the SBIR program, biomedical research related to advanced processing, manufacturing processes, equipment and systems, or manufacturing workforce skills and protection. This solicitation includes some topic areas that are considered relevant to manufacturing-related R&D. Additional information will be posted on the NIH Small Business Research Funding Opportunities Web site and in the NIH Guide for Grants and Contracts as it becomes available. Small businesses may be interested in reading a U.S. Department of Commerce 2004 report, "Manufacturing in America: A Comprehensive Strategy to Address the Challenges to U.S. Manufacturers."

### 2.2 Phased Program

The SBIR program consists of separate phases.

***Phase I: Feasibility***

The objective of Phase I is to determine the scientific or technical feasibility and commercial merit of the proposed research or R&D efforts and the quality of performance of the small business concern, prior to providing further Federal support in Phase II.

***Phase II: Full R/R&D Effort***

The objective of Phase II is to continue the research or R&D efforts initiated in Phase I. Funding shall be based on the results of Phase I and the scientific and technical merit and commercial potential of the Phase II proposal. *Phase I contractors will be informed of the opportunity to apply for Phase II, if a Phase II proposal was not submitted concurrently with the initial Phase I proposal under the Fast Track procedure. Only one Phase II award may result from a single Phase I SBIR contract.*

***Phase III: Commercialization stage without SBIR funds***

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

The competition for SBIR Phase I and Phase II awards satisfies the competition requirements of the Competition in Contracting Act. Therefore, for an agency that wishes to fund an SBIR project beyond the Phase II, it is sufficient to state for purposes of a Justification and Approval pursuant to FAR 6.302-5 that the project is derived from, extends, or logically concludes efforts performed under prior SBIR funding agreements and is authorized under 10 U.S.C. 2304(b)(2) or 41 U.S.C. 253(b)(2).

### 2.3 Fast Track Proposals (NIH Only)

If a Topic notes that Fast Track proposals will be accepted, a Phase I proposal and a Phase II proposal may be submitted

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

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

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

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

### 2.4 Direct to Phase II Proposals (NIH Only)

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

### 2.5 I-Corps™ at NIH

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

- **All NIH awarding components** (NCATS, NCI, NIA, NIAID, NHLBI, and NIDA), 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://sbir.cancer.gov/programseducation/icorps for further information on this program. Example timelines for the selection process and for course components may be viewed here, although specific dates are subject to change: https://sbir.cancer.gov/programseducation/icorps/cohortcurriculum.

*Application Process*

The first step in the I-Corps™ at NIH application process is submitting an additional, separate "Appendix C – Contract Pricing Proposal," in your Business Proposal. Specify "I-Corps" in the "Title of Proposal" field. This separate budget must not exceed $55,000 in total 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 2023 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 2023 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 evolving Covid-19 pandemic situation, 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 early January 2023 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 PHS 2022 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 on Drug Abuse (NIDA)

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)

## 3 DEFINITIONS

### 3.1 General Definitions

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

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

**Applicant.** The organizational entity that qualifies as an SBC at all pertinent times and that submits a contract proposal or a grant application for a funding agreement under the SBIR Program.

**Affiliate.** This term has the same meaning as set forth in 13 CFR part 121—Small Business Size Regulations, section 121.103. How does SBA determine affiliation? (Available at http://www.ecfr.gov/cgi-bin/text-idx?SID=b02d16dbfcddf646e5c0728d5e632a61&mc=true&node=se13.1.121_1103&rgn=div8). Further information about SBA's affiliation rules and a guide on affiliation is available at www.SBIR.gov and www.SBA.gov/size.

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

**Awardee.** The organizational entity receiving an SBIR Phase I award, SBIR Phase II award, or follow-on non-SBIR Federal funding agreement.

**Commercialization.** The process of developing products, processes, technologies, or services and the production and delivery (whether by the originating party or others) of the products, processes, technologies, or services for sale to or use by the Federal government or commercial markets.

**Consultant.** An individual who provides professional advice or services for a fee, but normally not as an employee of the engaging party. In unusual situations, an individual may be both a consultant and an employee of the same party, receiving compensation for some services as a consultant and for other work as a salaried employee. To prevent apparent or actual conflicts of interest, awardees and consultants must establish written guidelines indicating the conditions of payment of consulting fees. Consultants may also include firms that provide paid professional advice or services.

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

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

**Covered Small Business Concern.** A small business concern that:

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

(2) Is majority-owned by multiple venture capital operating companies, hedge funds, or private equity firms on the date of the SBIR award.

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

**Essentially Equivalent Work.** Work that is substantially the same research, which is proposed for funding in more than one contract proposal or grant application submitted to the same Federal agency or submitted to two or more different Federal agencies for review and funding consideration; or work where a specific research objective and the research design for accomplishing the objective are the same or closely related to another proposal or award, regardless of the funding source.

**Feasibility.** The practical extent to which a project can be performed successfully.

**Federal Agency.** An executive agency as defined in 5 U.S.C. § 105, and a military department as defined in 5 U.S.C. 102 (Department of the Army, Department of the Navy, Department of the Air Force), except that it does not include any agency within the Intelligence Community as defined in Executive Order 12333, section 3.4(f), or its successor orders.

**Federal Laboratory.** As defined in 15 U.S.C. § 3703, means any laboratory, any federally funded research and development center, or any center established under 15 U.S.C. §§ 3705 & 3707 that is owned, leased, or otherwise used by a Federal agency and funded by the Federal Government, whether operated by the Government or by a contractor.

**Fraud, Waste, and Abuse.**

**Fraud** includes any false representation about a material fact or any intentional deception designed to deprive the United States unlawfully of something of value or to secure from the United States a benefit, privilege, allowance, or consideration to which an individual or business is not entitled.

**Waste** includes extravagant, careless or needless expenditure of Government funds, or the consumption of Government property, that results from deficient practices, systems, controls, or decisions.

**Abuse** includes any intentional or improper use of Government resources, such as misuse of rank, position, or authority or resources.

**Funding Agreement.** Any contract, grant, or cooperative agreement entered into between any Federal agency and any SBC for the performance of experimental, developmental, or research work, including products or services, funded in whole or in part by the Federal Government.

**Funding Agreement Officer.** A contracting officer, a grants officer, or a cooperative agreement officer.

**Grant.** A financial assistance mechanism providing money, property, or both to an eligible entity to carry out an approved project or activity. A grant is used whenever the Federal agency anticipates no substantial programmatic involvement with the awardee during performance.

**HUBZone Small Business Concern.** A small business concern that appears on the List of Qualified HUBZone (Historically Underutilized Business Zone) Small Business Concerns maintained by the Small Business Administration (13 CFR 126.103).

**Innovation.** Something new or improved, having marketable potential, including: (1) development of new technologies, (2) refinement of existing technologies, or (3) development of new applications for existing technologies. Innovation encompasses the full commercialization pathway.

**Intellectual Property.** The separate and distinct types of intangible property that are referred to collectively as “intellectual property,” including but not limited to: (1) Patents; (2) trademarks; (3) copyrights; (4) trade secrets; (5) SBIR technical data (as defined in this section); (6) ideas; (7) designs; (8) know-how; (9) business; (10) technical and research methods; (11) other types of intangible business assets; and (12) all types of intangible assets, either proposed or generated by an SBC as a result of its participation in the SBIR Program.

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

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

**Principal Investigator/Project Manager.** The one individual designated by the applicant to provide the scientific and technical direction to a project supported by the funding agreement.

**Program Solicitation.** A formal solicitation for proposals issued by a Federal agency that notifies the small business community of its R/R&D needs and interests in broad and selected areas, as appropriate to the agency, and requests proposals from SBCs in response to these needs and interests.

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

**Prototype.** A model of something to be further developed, which includes designs, protocols, questionnaires, software, and devices.

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

**SBIR Technical Data.** All data generated during the performance of an SBIR award.

**SBIR Technical Data Rights.** The rights an SBIR awardee obtains in data generated during the performance of any SBIR Phase I, Phase II, or follow-on award that an awardee delivers to the Government during or upon completion of a Federally-funded project, and to which the Government receives a license.

**Service-Disabled Veteran-Owned Small Business Concern.** A small business concern note less than 51 percent of which is owned by one or more service-disabled veterans or, in the case of any publicly owned business, not less than 51 percent of the stock of which is owned by one or more service-disabled veterans; and, the management and daily business operations of which are controlled by one or more service-disabled veterans or, in the case of a service-disabled veteran with permanent and severe disability, the spouse or permanent caregiver of such a veteran. Service-disabled veteran means a veteran, as defined in 38 U.S.C. 101(2), with a disability that is service-connected, as defined in 38 U.S.C. 101(16).

**Small Business Concern (SBC).** A concern that meets the requirements set forth in 13 CFR 121.702:

To be eligible for award of funding agreements in the SBA's Small Business Innovation Research (SBIR) program, a business concern must meet the requirements of paragraphs (a) and (b) below:

*(a) Ownership and control.*

(1) An SBIR awardee must:

(i) Be a concern which is more than 50% directly owned and controlled by one or more individuals (who are citizens or permanent resident aliens of the United States), other small business concerns (each of which is more than 50% directly owned and controlled by individuals who are citizens or permanent resident aliens of the United States), or any combination of these; OR

(ii) Be a concern which is more than 50% owned by multiple venture capital operating companies, hedge funds, private equity firms, or any combination of these (for agencies electing to use the authority in 15 U.S.C. 638(dd)(1)); OR

(iii) Be a joint venture in which each entity to the joint venture must meet the requirements set forth in paragraph (a)(1)(i) or (a)(1)(ii) of this section. A joint venture that includes one or more concerns that meet the requirements of paragraph (a)(1)(ii) of this section must comply with § 121.705(b) concerning registration and proposal requirements

(2) No single venture capital operating company, hedge fund, or private equity firm may own more than 50% of the concern.

(3) If an Employee Stock Ownership Plan owns all or part of the concern, each stock trustee and plan member is considered an owner.

(4) If a trust owns all or part of the concern, each trustee and trust beneficiary is considered an owner.

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

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

**Socially and Economically Disadvantaged Individual.** See 13 CFR 124.103 and 124.104.

**Subcontract.** Any agreement, other than one involving an employer-employee relationship, entered into by an awardee of a funding agreement calling for supplies or services for the performance of the original funding agreement.

**United States.** Means the 50 states, the territories and possessions of the Federal Government, the Commonwealth of Puerto Rico, the District of Columbia, the Republic of the Marshall Islands, the Federated States of Micronesia, and the Republic of Palau.

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

### 3.2 Definitions (Relating to R&D)

**Autopsy Materials.** The use of autopsy materials is governed by applicable Federal, state, and local law and is not directly regulated by 45 CFR part 46.

**Child.** The NIH Policy on Inclusion of Children defines a child as an individual under the age of 18 years (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-010.html). The intent of the NIH policy is to provide the opportunity for children to participate in research studies when there is a sound scientific rationale for including them, and their participation benefits children and is appropriate under existing Federal guidelines. Thus, children must be included in NIH conducted or supported clinical research unless there are scientific or ethical reasons not to include them. This policy is separate from considerations of protections and consent for children to participate in research**.**

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

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

(2) Epidemiologic and behavioral studies.

(3) Outcomes research and health services research.

Note: Studies falling under Exemption 4 for human subjects research are not considered clinical research by this definition.

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

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

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

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

**Human Subjects.** The HHS regulations "Protection of Human Research Subjects" 45 CFR part 46, (administered by OHRP) define a human subject as a living individual about whom an investigator conducting research obtains:

- Data through *intervention* or *interaction* with the individual; or,
- Identifiable private information.

**Individually Identifiable Private Information.** According to its guidance for use of coded specimens, OHRP generally considers private information or specimens to be *individually identifiable* as defined at 45 CFR 46.102(f) when they can be linked to specific individuals by the investigator(s) either directly or indirectly through *coding* systems. Conversely, OHRP considers private information or specimens not to be individually identifiable when they cannot be linked to specific individuals by the investigator(s) either directly or indirectly through coding system.

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

**Intervention** includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. (45 CFR 46.102(f)).

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

**Investigator.** The OHRP considers the term investigator to include anyone involved in conducting the research. OHRP does not consider the act of solely providing coded private information or specimens (for example, by a tissue repository) to constitute involvement in the conduct of the research. However, if the individuals who provide *coded* information or specimens also collaborate on other activities related to the conduct of the research with the investigators who receive such information or specimens, they will be considered to be involved in the conduct of the research. (See OHRP's Guidance on Research Involving Coded Private Information on Biological Specimens.)

**Manufacturing-related R&D as a result of Executive Order 13329.** Encompasses improvements in existing methods or processes, or wholly new processes, machines or systems. Four main areas include:

- Unit process level technologies that create or improve manufacturing processes including:
  - Fundamental improvements in existing manufacturing processes that deliver substantial productivity, quality, or environmental benefits.
  - Development of new manufacturing processes, including new materials, coatings, methods, and associated practices.
- Machine level technologies that create or improve manufacturing equipment, including:
  - Improvements in capital equipment that create increased capability (such as accuracy or repeatability), increased capacity (through productivity improvements or cost reduction), or increased environmental efficiency (safety, energy efficiency, environmental impact).
  - New apparatus and equipment for manufacturing, including additive and subtractive manufacturing, deformation and molding, assembly and test, semiconductor fabrication, and nanotechnology.
- Systems level technologies for innovation in the manufacturing enterprise, including:
  - Advances in controls, sensors, networks, and other information technologies that improve the quality and productivity of manufacturing cells, lines, systems, and facilities.
  - Innovation in extended enterprise functions critical to manufacturing, such as quality systems, resource management, supply change integration, and distribution, scheduling and tracking.
- Environment or societal level technologies that improve workforce abilities, productivity, and manufacturing competitiveness, including:
  - Technologies for improved workforce health and safety, such as human factors and ergonomics.
  - Technologies that aid and improve workforce manufacturing skill and technical excellence, such as educational systems incorporating improved manufacturing knowledge and instructional methods.
  - technologies that enable integrated and collaborative product and process development, including computer-aided and expert systems for design, tolerancing, process and materials selection, life-cycle cost estimation, rapid prototyping, and tooling.

**Private information** includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (for example, a medical record). Private information must be *individually identifiable* (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects. (45 CFR 46.102(f))

- **Coded.** With respect **to private information** or human biological specimens, *coded* means that:

- Identifying information (such as name or social security number) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol or combination thereof (i.e., the code); and
- A key to decipher the code exists, enabling linkage of the identifying information with the private information or specimens.

Research that involves only coded private information/data or coded human biological specimens may not constitute human subjects research under the HHS human subjects regulations (45 CFR 46) if:

- The specimens and/or information/data are not obtained from an interaction/intervention with the subject specifically for the research; and
- The investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain (e.g., the researcher's access to subject identities is prohibited).

Individuals who provide coded information or specimens for proposed research and who also collaborate on the research involving such information or specimens are considered to be involved in the conduct of human subjects research.

(See the following guidance from the Office for Human Research Protections (OHRP) for additional information and examples: http://www.hhs.gov/ohrp/policy/cdebiol.html.)

**Research or Research and Development (R/R&D).** Any activity that is:

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

**Research Involving Vertebrate Animals**

All research involving live vertebrate animals shall be conducted in accordance with the Public Health Service Policy on Humane Care and Use of Laboratory Animals (PHS Policy).

In addition, the research involving live vertebrate animals shall be conducted in accordance with the description set forth in the Vertebrate Animal Section (VAS) of the contractor's technical proposal, as modified in the Final Proposal Revision (FPR), which is incorporated by reference. If using live vertebrate animals, HHS policy requires that offerors address the criteria in the Vertebrate Animal Section (VAS) of the Technical Proposal. Each of the criteria must be addressed in the VAS portion of the Technical Proposal. For additional information see Office of Laboratory Animal Welfare – Vertebrate Animals Section and use Contract Proposal VAS Worksheet. .

**Research Involving Human Subjects**

All research involving human subjects, to include use of identifiable human biological specimens and human data, shall comply with the applicable federal and state laws and agency policy/guidelines for human subject protection.

Exemptions. The following six categories of research meet the basic definition of human subjects research but are considered to be exempt from the HHS human subject regulations:

(1) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as:

(i) Research on regular and special education instructional strategies; or

(ii) Research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

(2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:

(i) Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and

(ii) Any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

(3) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b)(2) of this section, if:

(i) The human subjects are elected or appointed public officials or candidates for public office; or

(ii) Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

(4) Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

(5) Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine:

(i) Public benefit or service programs;

(ii) Procedures for obtaining benefits or services under those programs;

(iii) Possible changes in or alternatives to those programs or procedures; or

(iv) Possible changes in methods or levels of payment for benefits or services under those programs.

(6) Taste and food quality evaluation and consumer acceptance studies,

(i) If wholesome foods without additives are consumed or

(ii) If a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

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

**Research Involving Recombinant or Synthetic Nucleic Acid Molecules.** Any recipient performing research involving recombinant or synthetic nucleic acid molecules and/or organisms and viruses containing recombinant or synthetic nucleic acid molecules shall comply with the National Institutes of Health Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules, dated April 2016 as amended. The guidelines can be found at: https://www.federalregister.gov/documents/2016/04/15/2016-08810/national-institutes-of-health-nih-office-of-science-policy-osp-recombinant-or-synthetic-nucleic-acid.

Recombinant or synthetic nucleic acid molecules are defined as:

(i) Molecules that a) are constructed by joining nucleic acid molecules and b) that can replicate in a living cell, i.e., recombinant nucleic acids;

(ii) Nucleic acid molecules that are chemically or by other means synthesized or amplified, including those that are chemically or otherwise modified but can base pair with naturally occurring nucleic acid molecules, i.e., synthetic nucleic acids; or,

(iii) Molecules that result from the replication of those described in (i) or (ii) above.

**Sex/Gender.** Refers to the classification of research subjects in either or both of two categories: male and female. In some cases, representation is unknown, because sex/gender composition cannot be accurately determined (e.g. pooled blood samples or stored specimens without sex/gender designation). In addition, sex/gender classification is based on the self-reporting of participants enrolled in the research study. Investigators should consider the scientific goals of their study when requesting this information, particularly if the research may include individuals whose gender identity differs from their sex assigned at birth.

**Valid Analysis.** This term means an unbiased assessment. Such an assessment will, on average, yield the correct estimate of the difference in outcomes between two groups of subjects. Valid analysis can and should be conducted for both small and large studies. A valid analysis does not need to have a high statistical power for detecting a stated effect. The principal requirements for ensuring a

valid analysis of the question of interest are: allocation of study participants of both sexes/genders (males and females) and from different racial and/or ethnic groups to the intervention and control groups by an unbiased process such as randomization; unbiased evaluation of the outcome(s) of study participants; and use of unbiased statistical analyses and proper methods of inference to estimate and compare the intervention effects by sex/gender, race, and/or ethnicity.

## 4 PROPOSAL FUNDAMENTALS

Unless otherwise specified, Section 4 applies to both Phase I and Phase II.

### 4.1 Introduction

The proposal must provide sufficient information to demonstrate to the evaluator(s) that the proposed work represents an innovative approach to the investigation of an important scientific or engineering problem and is worthy of support under the stated criteria. The proposed research or research and development must be responsive to the chosen topic, although it need not use the exact approach specified in the topic. Anyone contemplating a proposal for work on any specific topic should determine that (a) the technical approach has a reasonable chance of meeting the topic objective, (b) this approach is innovative, not routine, with potential for commercialization and (c) the proposing firm has the capability to implement the technical approach, i.e., has or can obtain people and equipment suitable to the task.

### 4.2 Offeror Eligibility and Performance Requirements

To receive SBIR funds, each awardee of a SBIR Phase I or Phase II award must qualify as a small business concern (SBC) at the time of award and at any other time set forth in SBA's regulations at 13 CFR 121.701-121.705. Each applicant must qualify as a small business for research or research and development purposes and certify to this on the Cover Sheet (Appendix A) of the proposal. Additionally, each awardee must submit a certification stating that it meets the size, ownership and other requirements of the SBIR Program at the time of award, and at any other time set forth in SBA's regulations at 13 CFR 121.701-705.

For Phase I, a minimum of two-thirds of the research or analytical effort must be performed by the awardee. For Phase II, a minimum of one-half of the research or analytical effort must be performed by the awardee. The percentage of work will be measured by total award dollars.

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

For both Phase I and Phase II, all research or research and development work must be performed by the SBC and its subcontractors in the United States.

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

### 4.3 SBIR/STTR Performance Benchmarks for Progress towards Commercialization

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

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

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

**Phase I to Phase II Transition Benchmark**

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

**Phase II to Phase III Commercialization Benchmark**

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

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

### 4.4 Multiple Principal Investigators (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.

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

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

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

The Life Cycle Certification is required prior to final payment on the Phase I award, prior to receiving 50% of the total award amount on the Phase II award, and prior to final payment on the Phase II award, and may also be required at any other time that has been identified and incorporated into the contract delivery schedule.

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

*Representation Regarding Certain Telecommunications and Video Surveillance Services or Equipment.*

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

### 4.13 Promotional Materials

Promotional and non-project related discussion is discouraged and additional information provided via Universal Resource Locator (URL) links or on computer disks, CDs, DVDs, video tapes or any other medium will not be accepted or considered in the proposal evaluation.

### 4.14 Prior, Current, or Pending Support of Similar Proposals or Awards

A small business concern may not submit both a contract proposal and a grant application for essentially equivalent work (*see definition in Section 3.1*) in response to multiple NIH/CDC SBIR solicitations and funding opportunity announcements. The only exception is that a grant application is allowed to be submitted after a contract proposal has been evaluated and is no longer being considered for award.

It is permissible, with proposal notification, to submit proposals containing essentially equivalent work for consideration under another federal program solicitation in addition to one NIH/CDC solicitation or funding opportunity announcements for the SBIR program. The small business concern must make appropriate disclosures within Appendix A and Appendix C.

**IMPORTANT – It is unlawful to enter into contracts or grants requiring essentially equivalent effort**. If there is any question concerning prior, current, or pending support of similar proposals or awards, it must be disclosed to the soliciting agency or agencies as early as possible.

### 4.15 Reporting Matters Involving Fraud, Waste, and Abuse

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

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

### 4.16 State Assistance and Technical Assistance

*State Assistance*

Many states have established programs to provide services to those small business firms and individuals wishing to participate in the Federal SBIR/STTR Program. These services vary from state to state. Contact your State SBIR Support office at https://www.sbir.gov/state_services for further information.

*Technical and Business Assistance (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. If no Data Rights clause is included in the SBIR contract, the following legend, at a minimum, should be affixed to any data submissions under that award: These SBIR data are furnished with SBIR rights under Funding Agreement No._____(and subcontract No. _____ if appropriate), Awardee Name_____, Address, Expiration Period of SBIR Data Rights_____. The Government may not use, modify, reproduce, release, perform, display, or disclose technical data or computer software marked with this legend for four (4) years. After expiration of the 4- year period, the Government has a royalty-free license to use, and to authorize others to use on its behalf, these data for Government purposes, and is relieved of all disclosure prohibitions and assumes no liability for unauthorized use of these data by third parties, except that any such data that is also protected and referenced under a subsequent SBIR award shall remain protected through the protection period of that subsequent SBIR award. Reproductions of these data or software must include this legend."

## 5 CONTRACT REQUIREMENTS

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

### 5.1 NIH Policy on Enhancing Reproducibility Through Rigor and Transparency

Contractors shall adhere to the NIH policy of enhancing reproducibility through rigor and transparency by addressing each of the four areas of the policy in performance of the Statement of Work and in publications, as applicable: 1) Scientific Premise; 2) Scientific Rigor; 3) Consideration of Relevant Biological Variables, including Sex; and 4) Authentication of Key Biological and/or Chemical Resources. This policy applies to all NIH funded research and development, from basic through advanced clinical studies. See NIH Guide Notice, NOT-OD-15-103 , "Enhancing Reproducibility through Rigor and Transparency" and NOT-OD-15-102 , "Consideration of Sex as a Biological Variable in NIH-funded Research" for more information. In addition, publications are expected to follow the guidance at http://www.nih.gov/research-training/rigor-reproducibility/principles-guidelines-reporting-preclinical-research, whether preclinical or otherwise, as appropriate. More information is available at http://grants.nih.gov/reproducibility/index.htm, including FAQs and a General Policy Overview.

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

a. Before undertaking performance of any contract involving animal-related activities where the species is regulated by the United Sates Department of Agriculture (USDA), the Contractor shall register with the Secretary of Agriculture of the United States in accordance with 7 U.S.C. 2136 and 9 CFR 2.25 through 2.28. The Contractor shall furnish evidence of the registration to the Contracting Officer.

b. The Contractor shall acquire vertebrate animals used in research from a dealer licensed by the Secretary of Agriculture under 7 U.S.C. 2133 and 9 CFR 2.1 2.11, or from a source that is exempt from licensing under those sections.

c. The Contractor agrees that the care, use, and intended use of any live vertebrate animals in the performance of this contract shall conform with the Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals (PHS Policy), the current Animal Welfare Assurance (Assurance), the Guide for the Care and Use of Laboratory Animals (National Academy Press, Washington, DC) and the pertinent laws and regulations of the United States Department of Agriculture (see 7 U.S.C. 2131 et seq. and 9 CFR subchapter A, Parts 1-4). In case of conflict between standards, the more stringent standard shall govern.

d. If at any time during performance of this contract, the Contracting Officer determines, in consultation with the Office of Laboratory Animal Welfare (OLAW), National Institutes of Health (NIH), that the Contractor is not in compliance with any of the requirements and standards stated in paragraphs (a) through (c)above, the Contracting Officer may immediately suspend, in whole or in part, work and further payments under this contract until the Contractor corrects the noncompliance. Notice of the suspension may be communicated by telephone and confirmed in writing. If the Contractor fails to complete corrective action within the period of time designated in the Contracting Officer's written notice of suspension, the Contracting Officer may, in consultation with OLAW, NIH, terminate this contract in whole or in part, and the Contractor's name may be removed from the list of those contractors with Animal Welfare Assurances.

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

### 5.3 Animal Welfare

All research involving live, vertebrate animals shall be conducted in accordance with the Public Health Service Policy on Humane Care and Use of Laboratory Animals (PHS Policy). The PHS Policy can be accessed at: http://grants1.nih.gov/grants/olaw/references/phspol.htm .

In addition, the research involving live vertebrate animals shall be conducted in accordance with the description set forth in the Vertebrate Animal Section (VAS) of the contractor's technical proposal, which is incorporated by reference.

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

a. The Contractor agrees that the rights and welfare of human subjects involved in research under this contract shall be protected in accordance with 45 CFR part 46 and with the Contractor's current Federal-wide Assurance (FWA) on file with the Office for Human Research Protections (OHRP), Department of Health and Human Services. The Contractor further agrees to provide certification at least annually that the Institutional Review Board has reviewed and approved the procedures, which involve human subjects in accordance with 45 CFR part 46 and the Assurance of Compliance.

b. The Contractor shall bear full responsibility for the performance of all work and services involving the use of human subjects under this contract and shall ensure that work is conducted in a proper manner and as safely as is feasible. The parties hereto agree that the Contractor retains the right to control and direct the performance of all work under this contract. Nothing in this contract shall create an agency or employee relationship between the Government and the Contractor, or any subcontractor, agent or employee of the Contractor, or any other person, organization, institution, or group of any kind whatsoever. The Contractor agrees that it has entered into this contract and will discharge its obligations, duties, and undertakings and the work pursuant thereto, whether requiring professional judgment or otherwise, as an independent Contractor without creating liability on the part of the Government for the acts of the Contractor or its employees.

c. Contractors involving other agencies or institutions in activities considered to be engaged in research involving human subjects must ensure that such other agencies or institutions obtain their own FWA if they are routinely engaged in research involving human subjects or ensure that such agencies or institutions are covered by the Contractors' FWA via designation as agents of the institution or via individual investigator agreements (see OHRP Website at: http://www.hhs.gov/ohrp/policy/guidanceonalternativetofwa.pdf ).

d. If at any time during the performance of this contract the Contractor is not in compliance with any of the requirements and or standards stated in paragraphs (a) and (b) above, the Contracting Officer may immediately suspend, in whole or in part, work and further payments under this contract until the Contractor corrects the noncompliance. The Contracting Officer may communicate the notice of suspension by telephone with confirmation in writing. If the Contractor fails to complete corrective action within the period of time designated in the Contracting Officer's written notice of suspension, the Contracting Officer may, after consultation with OHRP, terminate this contract in whole or in part. (End of clause)

## 5.5 Required Education in the Protection of Human Research Participants

NIH policy requires education on the protection of human subject participants for all investigators receiving NIH contract awards for research involving human subjects. For a complete description of the NIH Policy announcement on required education in the protection of human subject participants, the Contractor should access the NIH Guide for Grants and Contracts Announcement dated June 5, 2000 at the following website:

http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html .

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

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

Prior to any substitution of the Principal Investigator or any other individuals responsible for the design and/or conduct of the research under the contract, the Contractor shall provide the following written information to the Contracting Officer: the title of the education program and a one sentence description of the program that has been completed by the replacement.

## 5.6 Inclusion of Women and Minorities in Research Involving Human Subjects

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

All investigators proposing research involving human subjects should read the UPDATED "NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research, Amended November 2017," published in the NIH Guide for Grants and Contracts on October 9, 2001 at the following web site: http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm .

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

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

### 5.7 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.

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: http://www.pubmedcentral.nih.gov .
Additional information is available at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-09-071.html and http://publicaccess.nih.gov .

### 5.17 Technical Data Rights

***Rights in Data Developed Under SBIR Funding Agreement.*** The Act provides for “retention by an SBC of the rights to data generated by the concern in the performance of an SBIR award.”

(1) Each agency must refrain from disclosing SBIR technical data to outside the Government (except reviewers) and especially to competitors of the SBC, or from using the information to produce future technical procurement specifications that could harm the SBC that discovered and developed the innovation.

(2) SBIR agencies must protect from disclosure and non-governmental use all SBIR technical data developed from work performed under an SBIR funding agreement for a period of not less than four years from delivery of the last deliverable under that agreement (either Phase I, Phase II, or follow-on non-SBIR Federal funding agreement) unless, subject to paragraph (b) (3) of this section, the agency obtains permission to disclose such SBIR technical data from the awardee or SBIR applicant. Agencies are released from obligation to protect SBIR data upon expiration of the protection period except that any such data that is also protected and referenced under a subsequent SBIR award must remain protected through the protection period of that subsequent SBIR award. For example, if a follow-on non-SBIR Federal funding award is issued within or after the Phase II data rights protection period and the follow-on non-SBIR Federal funding award refers to and protects data developed and protected under the Phase II award, then that data must continue to be protected through the award protection period. Agencies have discretion to adopt a protection period longer than four years. The Government retains a royalty-free license for Government use of any technical data delivered under an SBIR award, whether patented or not. This section does not apply to program evaluation.

(3) SBIR technical data rights apply to all SBIR awards, including subcontracts to such awards, that fall within the statutory definition of Phase I or II of the SBIR Program, or follow-on non-SBIR Federal funding award, as described in section 4 of the SBIR Policy Directive. The scope and extent of the SBIR technical data rights applicable to follow-on non-SBIR Federal funding awards is identical to the SBIR data rights applicable to Phases I and II SBIR awards. The data rights protection period lapses only:

(i) Upon expiration of the protection period applicable to the SBIR award; or

(ii) By agreement between the awardee and the agency.

### 5.18 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 Technology and Innovation
Office of Science
Centers for Disease Control and Prevention (CDC)

1600 Clifton Road, NE MS H21-8
Atlanta, Georgia 30329
Phone: 404-718-1386
E-mail: TTO@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 2022, Executive Schedule, Level II of the Federal Executive Pay Scale is $203,700.

### 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://grants.nih.gov/grants/peer/guidelines_general/Resource_sharing_plans.pdf
  - Data Sharing Plan http://grants.nih.gov/grants/policy/data_sharing
  - Model Organism Sharing Plan 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

**For NIH Awarding Components:**

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

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

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

### 6.2 Award Decisions

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

- Ratings resulting from the technical evaluation;
- Areas of high program relevance;
- Program balance (i.e., balance among areas of research);

- Availability of funds; and,
- Cost/Price

The Government anticipates that prospective offerors will develop unique proposals in response to the topics of research set forth in this solicitation. The agency is not under any obligation to fund any proposal or make any specific number of contract awards in a given research topic area. The agency may also elect to fund several or none of the proposals received within a given topic area.

### 6.3 Phase I Technical Evaluation Criteria

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

| FACTORS FOR PHASE I PROPOSALS | WEIGHT |
|---|---|
| 1. The soundness and technical merit of the proposed approach.<br>a. Identification of clear, measurable goals (*i.e.*, milestones) that have a reasonable chance of meeting the topic objective in Phase I.<br>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<br>a. Identification of clear, measurable goals (*i.e*., milestones) that have a reasonable chance of meeting the topic objective in Phase II<br>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 14, 2022**. The Government may issue an amendment to this solicitation which publishes its responses to questions submitted. The Government anticipates that responses would be published in sufficient time for interested offerors to consider them prior to submission of a proposal.

## 7.2 Pre-Proposal Conference

HHS will hold a pre-proposal conference, via webinar, on August 24, 2022 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 beta.SAM.gov and the NIH SBIR/STTR webpage following its completion.

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

SBIR Phase I Technical Proposals (Item 1) shall not exceed 50 pages.

SBIR Phase II Technical Proposals (Item 1) shall not exceed 150 pages.

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

Besides the Human Subjects and Clinical Trials Information form, the Technical Proposal shall not exceed the page limits stated above, inclusive of all pages, cover sheet, tables, CVs, resumes, references, pictures/graphics, appendices, attachments, etc. Page margins must be at least one inch on all sides (with the exception of forms provided as appendices to this solicitation). Proposal pages shall be numbered "Page 1 of 50," "Page 2 of 50," and so on. Pages shall be of standard size (8.5" X 11") with a font size of 11 points (or larger). Pages in excess of the page limitation will be removed from the proposal and will not be considered or evaluated.

## 7.4 Submission, Modifications, Revision, and Withdrawal of Proposals

(a) Offerors are responsible for submitting proposals to the electronic Contract Proposal Submission (eCPS) website at https://ecps.nih.gov/ by the date and time specified on the first page of this solicitation.

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

(b) Instructions on how to submit a proposal into eCPS are available at https://ecps.nih.gov/howtosubmit. Offerors may also reference Frequently Asked Questions regarding online submissions at https://ecps.nih.gov/faq.

1. Be advised that registration is required to submit a proposal into eCPS and registration may take several business days to process.

2. The proposal must be uploaded in 3 parts: Technical Proposal, Human Subjects and Clinical Trials Information Form, and Business Proposal.

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

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

The Business Proposal shall consist of Items 3, 4 (if applicable), 5, and 6, as described in Section 8.3 and 8.4. The Business Proposal must consist of a single PDF file. Offerors may also choose to submit an optional Excel Workbook spreadsheet providing a cost breakdown, in addition to the single PDF file.

3. Proposal Naming Conventions

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

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

      An example is provided below:

      - Phase I_XYZ Company_ NCEZID_Topic_014

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

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

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

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

        | | |
        |---|---|
        | Technical Proposal: | XYZ Company_NIAID_TOPIC_033_Technical.pdf |
        | Human Subjects and Clinical Trials Information Form: | XYZ Company_NIAID_TOPIC_033_HumanSubjectsForm.pdf |
        | Business Proposal: | XYZ Company_NIAID_TOPIC_033_Business.pdf |
        | Excel Workbook (Optional): | XYZ Company_NIAID_TOPIC_033_Business.xlsx |

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

        | | |
        |---|---|
        | Technical Proposal: | XYZ Company_NCIRD_TOPIC_031_Technical.pdf |
        | Human Subjects and Clinical Trials Information Form: | XYZ Company_NCIRD_TOPIC_031_ HumanSubjectsForm.pdf |
        | Business Proposal: | XYZ Company_NCIRD_TOPIC_031_Business.pdf |
        | Excel Workbook (Optional): | XYZ Company_NCIRD_TOPIC_031_Business.xlsx |

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

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

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

(d) If an emergency or unanticipated event interrupts normal Government processes so that proposals cannot be received at the eCPS website by the exact time specified in the solicitation, and urgent Government requirements preclude amendment of the solicitation closing date, the time specified for receipt of proposals will be deemed to be extended to the same time of day specified in the solicitation on the first work day on which normal Government processes resume.

(e) Proposals may be withdrawn by written notice at any time before award. A copy of withdrawn proposals will be retained in the contract file.

## 8 PROPOSAL PREPARATION AND INSTRUCTIONS

### 8.1 Introduction

It is important to read and follow the proposal preparation instructions carefully. The requirements for Phase I and Fast Track proposals are different and are outlined below. Pay special attention to the requirements concerning Human Subjects and use of Vertebrate Animals if your project will encompass either item.

### 8.2 Fast Track Proposal Instructions (NIH Only)

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

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

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

### 8.3 Phase I Proposal Instructions

A complete Phase I proposal consists of the following:

**TECHNICAL PROPOSAL**

Item 1: Technical Element

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

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

**BUSINESS PROPOSAL**

Item 3: Pricing Proposal (Appendix C)

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

Item 5: Proof of Registration in the SBA Company Registry
(Refer to Section 4.12 for Directions)

Item 6: Summary of Related Activities (Appendix F)

**IMPORTANT** -- While it is permissible, with proposal notification, to submit identical proposals or proposals containing a significant amount of essentially equivalent work for consideration under numerous federal program solicitations, it is unlawful to enter into contracts or grants requiring essentially equivalent effort. If there is any question concerning this, it must be disclosed to the soliciting agency or agencies as early as possible. Refer to Appendix A and Appendix C.

### 8.4 Phase II Proposal Instructions

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

**TECHNICAL PROPOSAL**

Item 1: Technical Element

- Technical Proposal Cover Sheet (Appendix D)
- Table of Contents
- Abstract of the Research Plan (Appendix B)
- Content of the Technical Element
- Draft Statement of Work (Appendix E)
- Proposal Summary and Data Record (Appendix G)

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

**BUSINESS PROPOSAL**

Item 3: Pricing Proposal (Appendix C)

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

Item 5: Proof of Registration in the SBA Company Registry
(Refer to Section 4.12 for Directions)

Item 6: Summary of Related Activities (Appendix F)

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

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

### 8.5 Technical Proposal Cover Sheet (Item 1)

**For Phase I Proposals, complete the form identified as Appendix A and use it as the first page of the proposal. No other cover sheet should be used.** If submitting a proposal reflecting Multiple Principal Investigators/Project Directors (PIs/PDs), the individual designated as the Contact PI should be entered here.

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

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

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

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

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

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

### 8.6 Table of Contents (Item 1)

Include a Table of Contents. Number all pages of your proposal consecutively. The header on each page of the technical proposal should contain your company name and topic number. The header may be included in the one-inch margin.

### 8.7 Abstract of Research Plan (Item 1)

Complete the form identified as Appendix B

MS Word (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixB.docx)

PDF (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixB.pdf)

Do not include any proprietary information as abstracts of successful proposals will be published by NIH/CDC. The abstract should include a brief description of the problem or opportunity, specific aims, and a description of the effort. Summarize anticipated results and potential commercial applications of the proposed research. Include at the end of the Abstract a brief description (two or three sentences) of the relevance of this research to public health. In this description, be succinct and use plain language that can be understood by a general, lay audience.

### 8.8 Content of Technical Element (Item 1)

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

The Technical Item should cover the following items in the order given below.

**(A) Research Plan for a Phase I Proposal**

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

Discuss the following elements in the order indicated:

1) **Identification and Significance of the Problem or Opportunity.** Provide a clear statement of the specific technical problem or opportunity addressed.

2) **Technical Objectives.** State the specific objectives of the Phase I effort, including the technical questions it will try to answer to determine the feasibility of the proposed approach.

3) **Detailed Approach and Methodology.** Provide an explicit, detailed plan for the Phase I R&D to be carried out, including the experimental design, procedures, and protocols to be used. Address how the objectives will be met and the questions stated in Item b above. Discuss in detail the methods to be used to achieve each objective or task. The plan should indicate what is planned, how, when, and where the work will be carried out, a schedule of major events, the final product to be delivered, and the completion date of the effort. The Phase I effort should determine the technical feasibility of the proposed concept.
   - Address the points discussed in the Section 8.9 Enhancing Reproducibility through Rigor and Transparency.
   - If a project involves vertebrate animals, include a Vertebrate Animals Section, as discussed in Section 8.10 Research Involving Vertebrate Animals.
   - If Section 8.11 Dual Use Research of Concern is applicable to your project, address it here.

4) **Related Research or R&D.** Describe significant research activities directly related to the proposed effort, including any conducted by the Project Director/Principal Investigator (PD/PI), the proposing firm, consultants, or others. Describe how these activities interface with the proposed project and discuss any planned coordination with outside sources. The PD/PI must persuade reviewers of his or her awareness of recent significant research or R&D conducted by others in the same scientific field.

5) **Relationship with Future R&D.**

   a) State the anticipated results of the proposed approach, assuming project success.

   b) Discuss the significance of the Phase I effort in providing a foundation for the Phase II R/R&D effort.

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

7) **Potential Commercial Applications.** Describe why the proposed project is deemed to have potential commercial applications (for use by the Federal Government and/or private sector markets.) Describe the market as it currently exists and how your product may enter and compete in this market. Include the potential barriers to market entry and how you expect to overcome them. Describe the strategy for protecting your innovation (such as status of and/or potential for intellectual property or market exclusivity, etc.).

8) **Senior/Key Personnel and Bibliography of Directly Related Work.** Identify senior/key personnel, including their directly related education, experience, and bibliographic information. Where resumes are extensive, focus on summaries of the most relevant experience or publications. Provide dates and places of employment and some information about the nature of each position or professional experience. Resumes must identify the current or most recent position.

9) **Subcontractors/Consultants.** Identify all investigator/collaborators by name and organization. Involvement of a university or other subcontractors or consultants in the project may be appropriate and is permitted. If such involvement is intended, it should be described in detail, identified in the cost proposal, and supported by appropriate letters from each individual confirming his/her role in the project which must be included.

10) **Multiple PI/PD Leadership Plan *(NIH Only)*.** For proposals designating multiple PIs/PDs, a leadership plan must be included. A rationale for choosing a multiple PI/PD approach should be described. The governance and organizational structure of the leadership team and the research project should be described, including communication plans, process for making decisions on scientific direction, and procedures for resolving conflicts. The roles and administrative, technical, and scientific responsibilities for the project or program should be delineated for the PIs/PDs and other collaborators.

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

11) **Facilities and Equipment.** Indicate where the proposed research will be conducted. One of the performance sites must be the offeror organization. Describe the facilities to be used; identify the location; and briefly indicate their capacities, pertinent capabilities, relative proximity, and extent of availability to the project. Include clinical, computer, and office facilities of the offeror and those of any other performance sites to be used in the project. For facilities other than those of the applicant, a letter must be submitted with the proposal stating that leasing/rental arrangements have been negotiated and will be available for the use of the SBIR applicant.

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

12) **Resource Sharing Plan(s**). NIH considers the sharing of unique research resources developed through NIH-sponsored research an important means to enhance the value and further the advancement of the research. When resources have been developed with NIH funds and the associated research findings published or provided to NIH, it is important that they be made readily available for research purposes to qualified individuals within the scientific community. If the final data/resources are not amenable to sharing (for example, human subject concerns, the Small Business Act provisions (15 U.S.C. 631, et seq., as amended), etc.), this must be explained in the proposal.

    a) **Sharing Model Organisms:** Regardless of the amount requested, all proposals where the development of model organisms is anticipated are expected to include a description of a specific plan for sharing and distributing unique model organisms or state appropriate reasons why such sharing is restricted or not possible. See Sharing Model Organisms Policy, and NIH Guide NOT-OD-04-042.

b) **Genome Wide Association Studies (GWAS):** Regardless of the amount requested, offerors seeking funding for a genome-wide association study are expected to provide a plan for submission of GWAS data to the NIH-designated GWAS data repository, or an appropriate explanation why submission to the repository is not possible. GWAS is defined as any study of genetic variation across the entire genome that is designed to identify genetic associations with observable traits (such as blood pressure or weight) or the presence or absence of a disease or condition. For further information, see Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies, NIH Guide NOT-OD-07-088, and Genome-Wide Association Studies.

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

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

Discuss the following elements in the order indicated:

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

**For Fast Track proposals**: Briefly discuss and summarize the objectives of the Phase I effort, the research activities to be carried out, and the anticipated results.

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

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

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

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

4) **Personnel** - List by name, title, department and organization, the extent of commitment to this Phase II effort, and detail each person's qualifications and role in the project. Provide resumes for all key staff members, describing directly related education, experience, and relevant publications. Describe in detail any involvement of subcontractors or consultants, and provide resumes for all key subcontractor staff. Also, include letters of commitment with proposed consultants confirming the extent of involvement and hourly/daily rate.

5) **Subcontractors/Consultants**. Identify all investigator/collaborators by name and organization. Involvement of a university or other subcontractors or consultants in the project may be appropriate and is permitted. If such involvement is intended, it should be described in detail and identified in the cost proposal. In addition, supported by appropriate letters 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.

   a) **Data Sharing Plan:** Offerors seeking $500,000 or more in direct costs in any year are expected to include a brief 1-paragraph description of how final research data will be shared, or explain why data-sharing is not possible (for example human subject concerns, the Small Business Innovation Development Act provisions, etc.). See Data-Sharing Policy or NIH Guide NOT-OD-04-042.

   b) **Sharing Model Organisms:** Regardless of the amount requested, all proposals where the development of model organisms is anticipated are expected to include a description of a specific plan for sharing and distributing unique model organisms or state appropriate reasons why such sharing is restricted or not possible. See Sharing Model Organisms Policy, and NIH Guide NOT-OD-04-042.

   c) **Genome Wide Association Studies (GWAS):** Regardless of the amount requested, offerors seeking funding for a genome-wide association study are expected to provide a plan for submission of GWAS data to the NIH-designated GWAS data repository, or an appropriate explanation why submission to the repository is not possible. GWAS is defined as any study of genetic variation across the entire genome that is designed to identify genetic associations with observable traits (such as blood pressure or weight) or the presence or absence of a disease or condition. For further information, see Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies, NIH Guide NOT-OD-07-088, and Genome-Wide Association Studies.

9) **Commercialization Plan** – **Limited to 12 pages.** The Phase II portion of Fast-Track proposals and all Direct Phase II proposals must include a Commercialization Plan. Be succinct. There is no requirement for offerors to use the maximum allowable pages allotted to the Commercialization Plan. Provide a description in each of the following areas:

   a) **Value of the SBIR Project, Expected Outcomes, and Impact.** Describe, in layperson's terms, the proposed project and its key technology objectives. Clarify the need addressed, specifying weaknesses in the current approaches to meet this need. In addition, describe the commercial applications of the research and the innovation inherent in this proposal. Be sure to also specify the potential societal, educational, and scientific benefits of this work. Explain the non-commercial impacts to the overall significance of the project. Explain how the SBIR project integrates with the overall business plan of the company.

   b) **Company.** Give a brief description of your company including corporate objectives, core competencies, present size (annual sales level and number and types of employees), history of previous Federal and non-Federal funding, regulatory experience, and subsequent commercialization, and any current products/services that have significant sales. Include a short description of the origins of the company. Indicate your vision for the future, how you will

grow/maintain a sustainable business entity, and how you will meet critical management functions as your company evolves from a small technology R&D business to a successful commercial entity.

c) **Market, Customer, and Competition.** Describe the market and/or market segments you are targeting and provide a brief profile of the potential customer. Tell what significant advantages your innovation will bring to the market, e.g., better performance, lower cost, faster, more efficient or effective, new capability. Explain the hurdles you will have to overcome in order to gain market/customer acceptance of your innovation.

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

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

d) **Intellectual Property (IP) Protection.** Describe how you are going to protect the IP that results from your innovation. Also note other actions you may consider taking that will constitute at least a temporal barrier to others aiming to provide a solution similar to yours.

e) **Finance Plan.** Describe the necessary financing you will require, and when it will be required, as well as your plans to raise the requisite financing to launch your innovation into commercialization and begin the revenue stream. Plans for this financing stage may be demonstrated in one or more of the following ways:

i) Letter of commitment of funding.
ii) Letter of intent or evidence of negotiations to provide funding, should the Phase II project be successful and the market need still exist.
iii) Letter of support for the project and/or some in-kind commitment, e.g., to test or evaluate the innovation.
iv) Specific steps you are going to take to secure non-SBIR follow-on funding.

f) **Production and Marketing Plan.** Describe how the production of your product/service will occur (e.g., in-house manufacturing, contract manufacturing). Describe the steps you will take to market and sell your product/service. For example, explain plans for licensing, internet sales, etc.

g) **Revenue Stream.** Explain how you plan to generate a revenue stream for your company should this project be a success. Examples of revenue stream generation include, but are not limited to, manufacture and direct sales, sales through value added resellers or other distributors, joint venture, licensing, service. Describe how your staffing will change to meet your revenue expectations.

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

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

### 8.9 Enhancing Reproducibility through Rigor and Transparency

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

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

b. Describe the experimental design and methods proposed and how they will achieve robust and unbiased results.

c. Explain how relevant biological variables, including sex, are factored into research designs and analyses for studies in vertebrate animals and humans. For example, strong justification from the scientific literature, preliminary data, or other relevant considerations, must be provided for proposals proposing to study only one sex. If your proposal involves human subjects, the sections on the Inclusion of Women and Minorities and Inclusion of Children can be used to expand your discussion and justify the proposed proportions of individuals (such as males and females) in the sample. Refer to NOT-OD-15-102 for further consideration of NIH expectations about sex as a biological variable.

d. If applicable to the proposed science, briefly describe methods to ensure the identity and validity of key biological and/or chemical resources used in the proposal. Key biological and/or chemical resources may or may not be generated with NIH funds and: 1) may differ from laboratory to laboratory or over time; 2) may have qualities and/or qualifications that could influence the research data; and 3) are integral to the proposed research. These include, but are not limited to, cell lines, specialty chemicals, antibodies, and other biologics.

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

### 8.10 Research Involving Vertebrate Animals

If it is intended that live vertebrate animals will be used during performance of this contract the Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals (authority derived from the Health Research Extension Act of 1985) specifies that certain information is required from offerors in contract proposals submitted to the NIH.

**The following criteria must be addressed in a separate section titled "Vertebrate Animals Section"** within the Detailed Approach and Methodology section of the technical proposal**:**

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

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

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

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

A concise (no more than 1-2 pages), complete description addressing these criteria must be provided. The description must be cohesive and include sufficient information to allow evaluation by reviewers and NIH staff. For more discussion regarding the VAS, see http://grants.nih.gov/grants/olaw/vertebrate_animal_section.htm. For additional guidance see the *Worksheet for Review of the Vertebrate Animal Section under Contract Proposals*, http://grants.nih.gov/grants/olaw/VAScontracts.pdf.

The *PHS Policy on Humane Care and Use of Laboratory Animals* (PHS Policy) requires that offeror organizations proposing to use vertebrate animals file a written **Animal Welfare Assurance** with the Office of Laboratory Animal Welfare (OLAW), establishing appropriate policies and procedures to ensure the humane care and use of live vertebrate animals involved in research activities supported by the PHS. The PHS Policy defines "animal" as "any live vertebrate animal used or intended for use in research, research training, experimentation or biological testing or for related purposes."

In accordance with the PHS Policy, offerors must establish an **Institutional Animal Care and Use Committee (IACUC)**, qualified through the experience and expertise of its members, to oversee the institution's animal program, facilities, and procedures. No PHS award for research involving vertebrate animals will be made to an offeror organization unless that organization is operating in accordance with an approved **Animal Welfare Assurance** and provides **verification that the IACUC has reviewed and approved** the proposed activity in accordance with the PHS Policy. This information should be addressed in the Technical Proposal section on Vertebrate Animals.

Proposals may be referred by the PHS back to the IACUC for further review in the case of apparent or potential violations of the PHS Policy. No award to an individual will be made unless that individual is affiliated with an assured organization that accepts responsibility for compliance with the PHS Policy. Foreign offeror organizations applying for PHS awards for activities involving vertebrate animals are required to comply with PHS Policy or provide evidence that acceptable standards for the humane care and use of animals will be met.

The PHS Policy stipulates that an offeror organization, whether domestic or foreign, bears responsibility for the humane care and use of animals in PHS-supported research activities. This policy implements and supplements the *U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training* and requires that institutions use the *Guide for the Care and Use of Laboratory Animals* as a basis for developing and implementing an institutional animal care and use program, see: http://grants.nih.gov/grants/olaw/Guide-for-the-Care-and-Use-of-Laboratory-Animals.pdf. Methods of euthanasia used will be consistent with the recommendations of the American Veterinary Medical Association (AVMA) Guidelines for the Euthanasia of Animals, unless a deviation is justified for scientific reasons in writing by the investigator, see: https://www.avma.org/KB/Policies/Documents/euthanasia.pdf . This policy does not affect applicable state or local laws or regulations that impose more stringent standards for the care and use of laboratory animals. All institutions are required to comply, as applicable, with the Animal Welfare Act as amended (7 U.S.C. 2131 et sec.) and other Federal statutes and regulations relating to animals. These documents are available from the Office of Laboratory Animal Welfare, National Institutes of Health, Bethesda, MD 20892, (301) 496-7163, e-mail: olaw@mail.nih.gov.

For further information, contact OLAW at NIH, 6705 Rockledge Drive, RKL1, Suite 360, MSC 7982 Bethesda, Maryland 20892-7982 (E-mail: olaw@od.nih.gov; Phone: 301–496–7163). The PHS Policy is available on the OLAW website at: http://www.grants.nih.gov/grants/olaw/olaw.htm.

### 8.11 Dual Use Research of Concern

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

a. Identification of the agents or toxins subject to the DURC policy:
    - Avian influenza virus (highly pathogenic)
    - *Bacillus anthracis*
    - Botulinum neurotoxin
    - *Burkholderia pseudomallei*
    - Ebola virus
    - Foot-and-mouth disease virus
    - *Francisella tularensis*
    - Marburg virus
    - Reconstructed 1918 influenza virus
    - Rinderpest virus
    - Toxin-producing strains of *Clostridium botulinum*
    - Variola major virus
    - Variola minor virus
    - *Yersinia pestis*

b. A description of the categories of experiments in which the identified agents or toxins produces or aims to produce or can be reasonably anticipated to produce one or more of the effects identified in Section 6 of the DURC policy.

c. For projects involving any of the agents listed in the DURC policy and that involve or are anticipated to involve any of the categories of experiments listed in the DURC policy, an indication of whether or not the project meets the definition of "dual use research of concern" in Section 4C of the policy.

d. For projects meeting the definition of "dual use research of concern," a draft risk mitigation plan.

e. Certification that the offeror is or will be in compliance with all aspects of the DURC policy prior to use of pertinent agents or toxins.

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

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

### 8.12 Human Subjects and Clinical Trials Information Form

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

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

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

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

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

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

#### *8.12.1 Human Specimens and/or Data*

If your project does not meet the definition of human subjects research, but involves the use of human data and/or biological specimens, you must provide a justification for your claim that no human subjects are involved. There is a field in the Human Subjects and Clinical Trials Information form to attach this explanation. To help determine whether your research is classified as human subjects research, refer to the Research Involving Private Information or Biological Specimens flowchart.

#### *8.12.2 Human Subjects Research with an Exemption from Federal Regulations*

If **all** of your proposed human subjects research meets the criteria for one or more of the human subjects exemption categories, identify which exemptions you are claiming and justify why your proposed research meets the criteria for the exemptions you have claimed. This justification should explain how the proposed research meets the exemption criteria and should not merely repeat the criteria or definitions themselves. This exemption justification must be attached to the Human Subjects and Clinical Trials Information form using the **"Other Requested Information"** field.

#### *8.12.3 Protection of Human Subjects*

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

- The Department of Health and Human Services (HHS) regulations for the protection of human subjects, 45 CFR part 46, are available on the Office for Human Research Protections (OHRP) Web site at: http://www.hhs.gov/ohrp/index.html .These regulations provide a systematic means, based on established ethical principles, to safeguard the rights and welfare of human subjects participating in research activities supported or conducted by HHS.
- The regulations define a human subject as a living individual about whom an investigator (whether professional or student) conducting research obtains data or identifiable public information through intervention or interaction with the individual, or identifiable private information. In most cases, the regulations
  extend to the use of human organs, tissue, and body fluids from individually identifiable human subjects as well as to graphic, written, or recorded information derived from individually identifiable human subjects. 45 CFR part 46 does not directly regulate the use of autopsy materials; instead, applicable state and local laws govern their use.
- Activities which involve human subjects in one or more of the categories set forth in 45 CFR 46.101(b)(1)-(6) are exempt from complying with 45 CFR part 46. See http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html .

- Inappropriate designations of the noninvolvement of human subjects or of exempt categories of research in a project may result in delays in the review of a proposal.
- In accordance with 45 CFR part 46, offerors considered for award shall file an acceptable Federal-wide Assurance (FWA) of compliance with OHRP specifying review procedures and assigning responsibilities for the protection of human subjects. The FWA is the only type of assurance that OHRP accepts or approves. The initial and continuing review of a research project by an institutional review board shall ensure that: The risks to subjects are minimized; risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result; selection of subjects is equitable; and informed consent will be obtained and documented by methods that are adequate and appropriate. Depending on the nature of the research, additional requirements may apply; see http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46 .111 for additional requirements regarding initial and continuing review. HHS regulations for the protection of human subjects (45 CFR part 46), information regarding OHRP registration and assurance requirements/processes, and OHRP contact information is available at the OHRP Web site (at http://www.hhs.gov/ohrp/assurances/index.html ).
- Offerors may consult with OHRP only for general advice or guidance concerning either regulatory requirements or ethical issues pertaining to research involving human subjects. ONLY the contracting officer may offer information concerning a solicitation.
- The offeror's proposal shall document that it has an approved or active FWA from OHRP, related to the designated IRB reviewing and overseeing the research. When possible, the offeror shall also certify the IRB has reviewed and approved the research. If the offeror cannot make this certification at the time of proposal submission, its proposal must include an explanation. Never conduct research covered by 45 CFR part 46 prior to receiving certification of the research's review and approval by the IRB. If the offeror does not have an active FWA from OHRP, the offeror shall take all necessary steps to obtain an FWA prior to the deadline for proposal submission. If the offeror cannot obtain an FWA before the proposal submission date, the proposal shall indicate the steps/actions the offeror will take to obtain OHRP approval prior to human subjects work beginning. Upon obtaining FWA approval, submit the approval notice to the Contracting Officer. (End of provision)

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

### *B. Instructions to Offerors Regarding Protection of Human Subjects*

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

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

a. Risks to the subjects

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

b. Adequacy of Protection Against Risks

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

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

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

d. Importance of the Knowledge to be Gained

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

**Collaborating Site(s)**

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

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

### *8.12.4 Required Education in the Protection of Human Research Participants*

NIH policy requires education on the protection of human subject participants for all investigators submitting NIH proposals for contracts for research involving human subjects. This policy announcement is found in the NIH Guide for Grants and Contracts Announcement dated June 5, 2000 at the following website: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html . Offerors should review the policy announcement prior to submission of their offers. The following is a summary of the Policy Announcement.

For any solicitation for research involving human subjects, the offeror shall provide the following information as an attachment to the Human Subjects and Clinical Trials Information form **"Other Requested Information"** field:

(1) a list of the names of the principal investigator and any other individuals proposed under the contract who are responsible for the design and/or conduct of the research;

(2) the title of the education program completed (or to be completed prior to the award of the contract) for each named personnel;

(3) a one sentence description of the program(s) listed in (2) above.

This requirement extends to investigators and all individuals responsible for the design and/or conduct of the research who are working as subcontractors or consultants under the contract.

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

If an institution already has developed educational programs on the protection of research participants, completion of these programs also will satisfy the educational requirement.

In addition, prior to the substitution of the principal investigator or any other individuals responsible for the design and/or conduct of the research under the contract, the Contractor shall provide the contracting officer with the title of the education program and a one sentence description of the program that the replacement has completed.

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

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

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

***Inclusion of Women and Minorities in Research Involving Human Subjects***

NIH-conducted and supported clinical research must conform to the NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research in accord with Public Health Service Act sec. 4928 U.S.C. sec 289a-2. The policy requires that women and members of minority groups and their subpopulations must be included in all NIH-conducted or supported clinical research projects involving human subjects, unless a clear and compelling rationale and justification establishes to the satisfaction of the relevant NIH Institute/Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects

or the purpose of the research. The Director, NIH, may determine that exclusion under other circumstances is acceptable, upon the recommendation of an IC Director, based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research.

All investigators proposing research involving human subjects should read the UPDATED "NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research, Amended November 2017," published in the NIH Guide for Grants and Contracts on October 9, 2001 at the following web site:
http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm

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 Two).

Complete the Pricing Item in the format shown in the Pricing Proposal (Appendix C). Some items in the Pricing Proposal may not apply to the proposed project. If that is the case, there is no need to provide information on each and every item. What matters is that enough information be provided to allow us to understand how you plan to use the requested funds if a contract is awarded.

- List all key personnel by name as well as by number of hours dedicated to the project as direct labor.
- While special tooling and test equipment and material cost may be included under Phase I, the inclusion of equipment and material will be carefully reviewed relative to need and appropriateness for the work proposed. The purchase of special tooling and test equipment must, in the opinion of the Contracting Officer, be advantageous to the Government and should be related directly to the specific topic. These may include such items as innovative instrumentation or automatic test equipment. Title to property furnished by the Government or acquired with Government funds will be vested with the HHS Component; unless it is determined that transfer of title to the contractor would be more cost effective than recovery of the equipment by the HHS Component.
- Cost for travel funds must be justified and related to the needs of the project. Describe reason for travel, location of travel, number of travelers, and number of nights of lodging in the Description fields in Appendix C.
- Cost sharing is permitted for proposals under this solicitation; however, cost sharing is not required nor will it be an

evaluation factor in the consideration of a Phase I proposal.

- All subcontractor costs and consultant costs must be detailed at the same level as prime contractor costs in regards to labor, travel, equipment, etc. Provide detailed substantiation of subcontractor costs in your cost proposal. Enter this information in the Explanatory Material section of the on-line cost proposal form.
- **NIH Policy on Threshold for Negotiation of General and Administrative (G&A)/Indirect Costs (IDC) Rates for SBIR proposals** – SBIR offerors who propose a G&A/IDC rate of 40 percent of total direct costs or less will not be required to negotiate Final Indirect Rates with the NIH Division of Financial Advisory Services (DFAS), or other cognizant auditing agency. However, awarding Contracting Officers may require offerors to document how they calculated their IDC rate(s) in order to determine that these costs are fair and reasonable. Furthermore, the Division of Financial Advisory Services (DFAS) will retain the authority to require well-documented proposals for G&A/IDC rates on an *ad hoc* basis. If the SBC has a currently effective negotiated indirect cost rate(s) with a Federal agency, such rate(s) shall be used when calculating proposed G&A/IDC costs for an NIH proposal. (However, the rate(s) must be adjusted for IR&D expenses, which are not allowable under HHS awards.)

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

- **Prior, Current, or Pending Support of Similar Proposals or Awards**.

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

  1) Name and address of the Federal Agency(s) or HHS Component, to which a proposal was submitted, will be submitted, or from which an award is expected or has been received.
  2) Date of proposal submission or date of award.
  3) Title of proposal.
  4) Name and title of principal investigator for each proposal submitted or award received.
  5) Title, number, and date of solicitation(s) under which the proposal was submitted, will be submitted, or under which award is expected or has been received.
  6) If award was received, state contract number.
  7) Specify the applicable topics for each SBIR/STTR proposal submitted or award received.

### 8.14 Reminders

Those responding to this solicitation should note the proposal preparation tips listed below:

- Read and follow all instructions contained in this solicitation, including the instructions in Section 12.0 of the HHS Component to which the firm is applying.

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

- Check that the Project Abstract and other content provided on the cover sheets contain NO proprietary information. Mark proprietary information within the Technical Proposal as instructed in Section 4.18.

- 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)<br>National Center for Advancing Translational Sciences (NCATS) | 1-2 | Scientific and Technical Merit Review: January-February 2023<br>Anticipated Award Date: August-September 2023 |
| National Institutes of Health (NIH)<br>National Cancer Institute (NCI) | 20-35 | Scientific and Technical Merit Review: March-May 2023<br>Anticipated Award Date: August-September 2023 |
| National Institutes of Health (NIH)<br>National Institute on Aging (NIA) | 3-6 | Scientific and Technical Merit Review: January-February 2023<br>Anticipated Award Date: August-September 2023 |
| National Institutes of Health (NIH)<br>National Institute of Allergy and Infectious Diseases (NIAID) | 19-38 | Scientific and Technical Merit Review: March 2023<br>Anticipated Award Date: August 2023 |
| National Institutes of Health (NIH)<br>National Heart Lung and Blood Institute (NHLBI) | 1-5 | Scientific and Technical Merit Review: February-April 2023<br>Anticipated Award Date: July-September 2023 |
| National Institutes of Health (NIH)<br>National Institute on Drug Abuse (NIDA) | 3-4 | Scientific and Technical Merit Review: March 2023<br>Anticipated Award Date: August 2023 |
| Centers for Disease Control and Prevention (CDC)<br>National Center for Emerging Zoonotic and Infectious Diseases (NCEZID) | 1 | Scientific and Technical Merit Review: March 2023<br>Anticipated Award Date: August 2023 |
| Center for Disease Control and Prevention (CDC)<br>National Center for HIV, Viral Hepatitis, STD, and TB Prevention (NCHHSTP) | 1 | Scientific and Technical Merit Review: March 2023<br>Anticipated Award Date: August 2023 |

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

General Questions about the NIH SBIR Program
Email: sbir@od.nih.gov

**Any small business concern that intends to submit an SBIR contract proposal under this solicitation should provide the appropriate contracting officer(s) with early, written notice of its intent, giving its name, address, telephone, e-mail, and topic number(s). If a topic is modified or canceled before this solicitation closes, only those companies that have expressed such intent will be notified.**

### NATIONAL INSTITUTES OF HEALTH (NIH)

#### NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES (NCATS)

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)

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

#### NATIONAL HEART, LUNG, AND BLOOD INSTITUTE (NHLBI)

Allison Cristman
Contracting Officer, Branch Chief
Office of Acquisitions, OM, NHLBI
Phone: (301) 827-7703
E-mail: allison.cristman@nih.gov

**NATIONAL INSTITUTE ON DRUG ABUSE (NIDA)**

Tracy L. Cain
Contracting Officer
NIDA Section, Contracts Management Branch Red
(301) 443-6677
E-mail: tracy.cain@nih.gov

## CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

### NATIONAL CENTER FOR EMERGING ZOONOTIC AND INFECTIOUS DISEASES (NCEZID)

Jennifer Hartnett
Contracts Specialist
Centers for Disease Control and Prevention Office of Financial Resources
Phone: (678)475-4696
E-mail: rju8@cdc.gov

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

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

## 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 023 - Development of Automated Cell Culture Flask Cleaning Instrument**

(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: 1 to 2

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:** Tissue culture flasks, of various sizes are nearly ubiquitous in many life sciences laboratory settings, used as a standard tool to act as the vessel in which a wide variety of living cell types are grown, expanded, manipulated, differentiated, monitored, and maintained. Universally these flasks are assumed to be a consumable product, used once and then discarded, making them in effect a disposable item due to the risk of cross contamination. Depending on the laboratory in question, it is not uncommon for thousands if not tens of thousands of these flasks to be consumed and discarded within a single year. Due to this, these parts have been manufactured with the idea that each flask will be a consumable product and are made from non-biodegradable optically clear virgin polystyrene, including a surface treatment or coating on the interior side where the cell growth/manipulation occurs with a high-density polyethylene vented cap.

Over the last decade, High-Throughput Experimental Sciences (i.e., High-Throughput Screening) have evolved at a very rapid pace, largely enabled by advancement in incredibly complex cellular screening models, and the evolution of detection and miniaturization schemes. Ten years ago, a typical high-throughput assay would yield a single absorbance or fluorescence-based readout. Today, modern screening facilities are commonly running very high-content, data rich assays with optical microscopy- based readouts. With this comes the need for large-scale tissue culture resulting in utilization of tons of plastic flasks in a manual and automated processes, all destined for the landfill.

This initiative seeks to develop an automated piece of instrumentation that can be utilized to clean previously used cell tissue culture flasks, making them suitable for reuse and therefore treated as a resource instead of a consumable. The large quantities of flasks required for high-throughput screening, stem cell differentiation protocols, 3D construction of skin or other tissue models. The relationship of flasks to compound libraries to be screened and cell model complexity can be greater than a 1 to 1 association,

meaning as your compound library grows and model complexity increases, your demand for cell culture flasks increases exponentially, driving costs upwards. Even more so when you apply this in an automated tissue culture setting with stringent requirements, added holders, barcoding, and substantial increase in throughput. Recent studies have shown that we ingest, bathe in, and inhale microplastics daily, plus the permanent layer of plastic now in our fossil record. Any such device to clean flasks for reuse will save money, non-biodegradable parts from adding to the increasing presence of plastic in the environment as help improve human health. Significant time will also be saved with the recent manufacturing delays many industries are experiencing.

**Goals and Specific Objectives**:

The purpose of this project is to treat a cell culture flask not as a disposable product meant to act as a vessel for one batch of cells to grow for harvest for use in one experiment, but instead to potentially be a resource that can be used multiple times. The preliminary goal of this project is to develop a functional prototype of an instrument capable of removing biological reagents, organic material, and any chemical compounds from used flasks of various sizes, but primarily 75, 175, and 225 $cm^2$ growth surface size. The final product will be an instrument or set of instruments that could be integrated as a component of a high throughput cell culture system in an automated fashion, capable of cleaning flasks regardless of the size. The long-term goal of this project is to bring this instrument or process to market to meet the needs of those researchers using high quantities of flasks, for cell-based high throughput screening including complex 3D models and stem cell differentiation.

**Phase I Activities and Expected Deliverables:**

- Develop a prototype instrument or a detailed plan for a device that meets the following specifications:
    - Can remove biological reagents, organic material, and any chemical compounds from used flasks of various sizes, but primarily T75, T175, and T225 flask sizes with vented caps, but ideally all of varying specification shapes and surface treatments;
    - Has the ability to utilize multiple potential cleaning solutions while minimizing the need for large quantities of reagent;
    - Has the capacity to completely dry a cleaned flask;
    - Does not involve any abrasive touching of the interior of the flask, the growth area in particular, that could negatively affect the physical integrity;
    - Has a maximum clean cycle time of 5 minutes total;
    - Demonstrates a cleaning process for flasks to be used for growing and harvesting a variety of cell types with the ability to:
        - Remove between 75% and 99% biological reagent such as trypsin, organic material such as HEK293 or HeLa cells, and chemical compounds/reagents used in cell culture (could verify viability visually under microscope or use traditional cell counting techniques);
        - Eliminate contamination risk due to cleaning process or previous reagent/organic material remnants; can verify by Mycoplasma testing and STR profiling for example;
        - Ensures cell health is not affected by cleaning process or previous reagent/organic material remnants. Can use simple viability assay using Bortezomib as a control for example and observe cell shape/clustering under microscope;
        - Allows reuse, including maintenance of sterility and elimination of cross contamination, of the flask vented cap which allows for gas exchange while incubating.
    - Does not degrade cell health or attachment (for adherent cell lines) with repeated wash cycles, capable of withstanding up to 50 wash cycles total;
    - There should be some ability or plan to quantify a Sterility Assurance Level (SAL), to ensure there is no contamination between uses.
- Cost estimates to manufacture a device capable of meeting the specifications listed above.
- Present Phase I findings and demonstrate the prototype instrument to the NCATS contracts and scientific team via webinar
- Provide NCATS with all data and materials resulting from Phase I Activities and Deliverables.
- Provide a market analysis of the commercial application for the proposed technology.

**Phase II Activities and Expected Deliverables:**

- Build a prototype instrument that meets the Phase I specifications in addition to several others geared towards the device working as part of a larger automated process:
    - Is accessible enough to have a flask automatically loaded into the device by standard laboratory robotic equipment;
    - Has a remote programmatic interface allowing the instrument to be controlled by an external software application through standard laboratory communication protocols (RS-232, TCP/IP, etc.);
    - Can reliably operate for extended periods of time in an automated fashion (overnight usage with a constant flask throughput

limited by the duration of the load/unload time of the device and the cleaning process itself).

- Develop detailed procedures to be able to quantify the instruments cleaning effectiveness:
  - Provide detailed protocols to show the effectiveness of the instrument in removing biological and chemical reagents as well as organic material from a used cell culture flask;
  - Provide detailed protocols to show the effectiveness of the instrument in retaining sterility, cell viability and confluency for a flask washed for reuse.
- In addition to meeting Phase I specifications, demonstrate the ability of the prototype instrument to remove greater than 99% biological reagent such as trypsin, organic material such as HEK293 or HeLa cells, and chemical compounds/reagents used in cell culture (could verify viability visually under microscope or use traditional cell counting techniques);
- Demonstrate the ability of the prototype instrument to run the cleaning procedures as described above in an automated fashion:
  - A set of cell culture flasks should be run for multiple cycles and show no residual biological or chemical contamination from previous uses;
  - The cell viability and confluency data should remain close to constant despite using the same flasks repeatedly;
  - The cell viability and confluency data should be comparable to using new culture flasks;
  - Multiple cross contamination and cell viability detection methods should be tested as described in Phase I.
- Provide a concept for tracking and retaining pertinent information including number of wash cycles the flask has gone through and cell lines grown/harvested from that same flask.
- Develop a robust manufacturing plan for the instrument, using off the shelf OEM components where possible to minimize expense.
- Present Phase II findings and demonstrate the prototype instrument to the NCATS contracts and scientific team via webinar
- In the first year of the contract, provide the program and contract officers with a letter(s) of commercial interest.
- In the second year of the contract, provide the program and contract officers with a letter(s) of commercial commitment
- Provide NCATS with all data and materials resulting from Phase II Activities and Deliverables.
- In the Phase II required commercial development plan, provide information or market analysis on the commercial application for the proposed technology.

**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-22-025.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 446 – Development of Senotherapeutic Agents for Cancer Treatment**

Fast-Track proposals will be accepted.

Direct-to-Phase II proposals will be accepted.

Number of anticipated awards: 3-5

Budget (total costs, per award):

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

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

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

**Summary**

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

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

Several research groups and companies are developing senotherapeutics as agents that exploit senescent cells for therapeutic benefit – though most have not prioritized cancer-centered R&D. Senotherapeutics include senolytics – pharmacologic agents that eliminate senescent cells, senostatics – agents that suppress senescence, and senomorphics – agents that suppress senescent phenotype without cell-killing. A variety of agents have been reported to have senolytic activity and have demonstrated promising results in animal models. Thus, the goal of this contract topic is to support small businesses developing senotherapeutics and catalyze the development of this class of drugs to improve outcomes for cancer patients.

**Project Goals**

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

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

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

**Phase I Activities and Deliverables:**

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

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

**Phase II Activities and Deliverables:**

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

- Conduct structure-activity relationship (SAR) studies, medicinal chemistry, and/or lead biologic optimization (as appropriate).
- Perform animal toxicology and pharmacology studies as appropriate for the agent(s) selected for development.
- Expand upon initial animal efficacy studies in an appropriate model for cancer therapy-induced senescence and conduct experiments to determine whether senotherapeutic agent(s) confer benefits with respect to mitigation of adverse side effects to normal tissues and/or enhanced cancer therapy efficacy.
- Perform other IND-enabling studies as appropriate for the agent(s) under development.

**NIH/NCI 447 – Non-invasive Device Technology Research & Development for Chemotherapy-induced Peripheral Neuropathy Management**

Fast-Track proposals will be accepted.

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

Number of anticipated awards: 1-2

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**

Chemotherapy-induced peripheral neuropathy (CIPN) is a progressive, enduring, and often irreversible adverse effect of taxane, platinum, and vinca alkaloid chemotherapy. For example, paclitaxel which is approved by the FDA for the treatment of ovarian, breast, and lung cancer induces CIPN in an estimated one-third of recipients. For breast cancer alone, this results in an estimated 90,000 new cases of CIPN a year. Considering the other common cancers for which paclitaxel is used, and that cancer patients live longer, in many cases several decades, it is estimated that millions of people live with CIPN today. Damage to the peripheral nervous system underlies CIPN and this induces the long-term symptoms of numbness, tingling, and pain in the hands and feet, affecting the quality of life of cancer survivors, and also increasing the risk of dangerous falls for these patients.

With repair of the nerve damage underlying CIPN as yet out of reach, treatment focuses on modulating nerve activity to allow management of the symptoms. Current approaches with pain-relief drugs and procedural therapies based on common pain management approaches have failed to provide long-term relief to patients. A significant opportunity lies in exploring technologies that allow the development of affordable devices that have the potential to bring recent research advances to the home-care setting. These technologies (neurofeedback, nerve stimulation, neuromodulation, etc.) may be adopted in procedural therapies or wearable devices to manage and reduce CIPN pain in a more targeted and sustained manner.

**Project Goals**

The purpose of this contract topic is to solicit proposals to advance the development and/or application of new non-invasive device technologies to provide effective mitigation of CIPN and bring them to the marketplace. Such technology would improve the functionality of cancer survivors with CIPN, enhancing their quality of life and reducing the risk of further complications like falls. The ideal technology would be designed for effective mitigation of CIPN pain in a non-invasive, cost-effective, accessible manner in the home-care setting so that its long-term use can provide sustained relief to as many cancer survivors as possible. Therapeutics will not be considered under this solicitation.

Activities and deliverables envisaged under this contract topic include the developing of technology prototypes, testing these for clinical efficacy and user adoption/usability using accepted assessment tools, and benchmarking them against current practices. Next steps would include the production and testing of a marketable version of such prototypes in a limited, real-world setting, determining the impact of sustained application, and creating a path towards FDA approval.

*Activities not responsive to announcement:*

The development of pharmacological interventions for CIPN treatment or prevention or the development of stem-cell-based therapies for nervous system repair are considered non-responsive to this announcement.

**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:

- Establish a project team, including proven expertise in pain management related to CIPN, device development, user-centered design, software and hardware expertise, and other areas of expertise as appropriate for the proposed project.
- Using user-centric design principles, develop a cost-effective, non-invasive, and accessible device prototype capable of mitigating CIPN symptoms.
- Conduct studies to evaluate and test user acceptability and feasibility in intended use populations.
- Demonstrate accessibility and ease of use of device in an at-home setting with only minimal support from a health care provider.
- Benchmark the device against current practice for reduction in CIPN pain as described in the medical literature using accepted pain measures, and improvements in appropriate quality of life metrics.
- Offerors may need to establish a collaboration or partnership with a research group or medical facility that can provide relevant patient access; 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, marketable device following appropriate FDA device guidelines.
- Conduct a clinical study of the device using accepted pain measures and user adoption/usability by target patient population to determine clinical efficacy.
- Determine whether sustained periodic use of the technology beyond an initial period provides ongoing clinical benefit.
- Establish a strategy for FDA regulatory approval and insurance and/or CMS reimbursement.

**NIH/NCI 448 – Wearable Devices for Dosimetry of Radiopharmaceutical Therapy**

Fast-Track proposals will be accepted.

Direct-to-Phase II proposals will be accepted.

Number of anticipated awards: 1-3

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**

Dosimetry for radiopharmaceutical therapy (RPT) has the potential to increase tumor control and/or decrease side effects as it is the standard of care in external beam and brachytherapy forms of radiation therapy (RT). Radiation dosimetry is a crucial tool to guide and optimize tumor control and minimize adverse toxicity to normal tissues.

The goal of this contract topic is to accelerate the development of devices that are wearable detectors of radiation emitted from therapeutic radiopharmaceuticals to perform 4D radiation dosimetry for RPT using a single or no SPECT/CT and/or PET/CT scans. A wearable (e.g., clothing-based) integrated dosimetry-sensor also opens the opportunity for out-of-clinic collection of dynamic, continuous data monitoring, which is not possible with current in-hospital SPECT/CT or PET/CT scans. These data have the potential to optimize treatment by delivery of maximum tolerated dose to the organs at risk. They will also enable assessing the efficacy of the dose delivered to the tumors, informing the treatment of individual patients. If some of the tumors receive a suboptimal dose, they might get a boost of external RT. If the dose delivered to all of the tumors is too low to be effective, then the RPT will be discontinued, and other treatment modalities will be used.

Currently, dosimetry procedures involve multiple PET/CT or SPECT/CT whole-body scans that present a challenge for hospital systems and patients. Multiple scans require extra days in the hospital, additional travel, time away from home, and/or anesthesia use as needed for young children. This problem might be solved by wearable dosimeters to be used at home. For example, a procedure could include long underwear-like clothing or Lycra with built-in sensors that collect data on dose and its distribution to be remotely transferred (synchronously or asynchronously) to a treatment planning system.

**Project Goals**

The goal of this concept is to develop wearable technologies (e.g., dosimetry sensor-incorporated clothing) to allow RPT dose to be measured as patients go about their activities of daily living – providing dynamic, rich, time-based dose data for RPT agents that can be correlated with the patient's anatomy. Products that are compatible for use in the pediatric population are strongly encouraged. It is encouraged that products be able to be used across all ages of patients. The scope of proposed activities includes the engineering of new devices and/or integration of existing technology to achieve the goal. Specific supported activities would include device development and production, development of organ dosimetry data over time that is DICOM compatible, development of Q/A methods for the proposed device(s), and optimization of the interface. Proposals must include the clinical indications for the device(s).

The goals of this topic are to design and validate a wearable dosimetry clothing/device array for remote monitoring in a well-defined RPT cancer treatment scenario. Examples of possible devices include clothing that collects dose, development of different dosimeter arrangements that are tailored to specific radiopharmaceuticals, organ at risk, tumor locations, and cancers.

Phase I deliverables will include proof of concept such as a mockup of a proposed sensor array/clothing/wearable with collection of data being performed on a phantom (ideally anthropomorphic). The device can be independent of other methods or work in conjunction with existing treatment planning systems to improve dosimetry. Dose collected must be able to be stored in an electronic file format and demonstrated to the program and contract officers to move to Phase II.

Phase II deliverables will include holding at least one pre-submission meeting with the FDA, developing Q/A and related standard operating procedures, developing the means to scale up production to a clinically and commercially viable solution, being able to perform dosimetry at multiple time points, demonstrating in the first year of Phase II to program and contract officers a letter(s) of commercial interest and in the second year of Phase II providing program and contract officers with a letter(s) of commercial commitment. Capacity for DICOM export of dosimetric RPT data from the device(s) is required.

**Phase I Activities and Deliverables:**

- Generate proof-of-concept data that demonstrate feasibility of the proposed solutions to improve quantitative accuracy and precision in RPT dose measurement.
- In the first year of the contract, provide the program and contract officers with a letter(s) of commercial interest from potential end users, which might include those interested in using the solution as a research tool or in collaborating in a business venture.
- Offerors should specify quantitative technical and commercially relevant milestones, that can be used to evaluate the success of the tool or technology being developed.

- Offerors should develop specifications for robustness and durability of the wearable unit overall, and provide appropriate justification relevant to both the development and commercialization of these technologies.
    - Additional relevant details might include context of use for the device(s); design specifications on the type(s) of radiation activity being detected; anticipated spatial configuration of detectors; methodological basis of detectors; indication of and rationale for time-integrated acquisition; indication of how the unit is powered, the basis for communication between detector elements and means for information output or export; methodology for calculating absorbed dose.
- Quantitative milestones may be relative metrics (e.g. compared to currently used technologies and benchmarks or algorithms and methods) indicating clear advantages of the proposed technologies.
- Build a prototype that demonstrates operability, data transferability, and strong translational potential for use and that demonstrates rigor and reproducibility in benchmark experiments using relevant RPT agents/modalities in appropriate phantoms.
- In the first year of the contract, provide the program and contract officers with a letter(s) of commercial interest.

**Phase II Activities and Deliverables:**

- Demonstrate reliability, robustness, and usability in clinical and/or preclinical RPT delivery measurement.
- Propose a validation plan. Demonstrate system performance and functionality against commercially relevant quantitative milestones.
    - Offerors should specify quantitative technical and commercially-relevant milestones, that can be used to evaluate the commercialization of the tool or technology being developed.
    - Offerors should also provide appropriate justification relevant to both the development and scalable commercialization of these technologies.
    - Quantitative assessment milestones may be relative metrics (e.g. compared to currently used systems), and/or metrics (e.g. accuracy at various dose and radiation types relative to SPECT-CT and/or PET controls; the capacity to record and report dose delivery fine structure; or a method to provide a safety analysis rapidly in an RPT context).
- Show feasibility to be scaled up at a price point that is compatible with market success and widespread adoption by the cancer research and treatment communities.
- In the second year of the contract, provide the program and contract officers with a letter(s) of commercial commitment.
- Documentation of at least one pre-submission meeting with the FDA.

**NIH/NCI 449 – Wearable Technologies to Facilitate Remote Monitoring of Cancer Patients Following 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**

The growing sophistication of wearable device technologies coupled with recent advancements in machine learning, and other complex informatics approaches for biometric data analysis, have created new opportunities to develop tools capable of supporting clinical management of cancer patients during treatment. The goal of this contract topic is to accelerate the combination of wearable sensors, and other remote monitoring technologies, with sophisticated analytical approaches and user interfaces that allow patients to be remotely monitored for cancer- or treatment-related adverse events (*e.g.*, acute chemotherapy-induced toxicities). Such technologies would offer complete solutions (*e.g.,* hardware and software) to allow healthcare providers the ability to monitor a patient in real-time and preemptively mitigate adverse events when needed. A clear opportunity exists to substantially improve patient care and expand the footprint of clinical trials (decentralized) to more patients (*e.g.,* medically underserved, rural, and more).

**Project Goals**

The goal is to improve the availability of remote monitoring tools for patients and their clinical care teams during sensitive periods of cancer treatment. Commercially available activity monitors that rely on accelerometer- and photoplethysmography (PPG)-based sensor technology (*e.g.* Fitbit or Apple Watch) have become increasingly more reliable to track measures like sleep cycles, exercise, fatigue, etc. These devices have expanded even further to include measurement of common vital signs such as heart rate, blood oxygen saturation, electrocardiograms, and more. However, they generally lack the ability to track vital clinical information with sufficient accuracy to serve clinical management teams who monitor a patient's tolerance and overall reaction to therapy. Moreover, validation of data produced by these devices as actionable signal or linking to specific intended uses for cancer patients undergoing treatment is still needed to solidify their clinical use. New remote monitoring approaches are needed to assess a patient's vitality and any deteriorating levels sufficiently early to allow earlier release of patients from costly hospital confinement while ensuring they can return to the clinic in time to manage adverse events. Beyond measurement capabilities, a robust user platform that connects and informs the clinical team while offering patients an intuitive user interface is also required. Commercial wearable devices and the smartphone and tablet apps developed to interface with them have pioneered effective, user-centered designs for the consumer market, thereby paving the way for new platforms that can enable remote clinical monitoring. Another emerging trend that has reduced the technical hurdles for this field is the advancement of novel machine learning and "deep learning" analytical approaches that can help overcome signal-to-noise challenges associated with biological signals measured by non-invasive wearable or ambient monitoring devices.

The expected activities under this topic should combine and validate emerging wearable and/or ambient, passive remote monitoring technologies with suitable analytic approaches focused on a well-defined cancer treatment scenario with documented adverse event risks, where effective remote monitoring is enabled through an appropriate user interface that serves the needs of both patients and clinical care teams, to actively monitor cancer patients during sensitive periods of their care. Fundamentally, this proposed contract topic would require tools, or suites of tools, that report objective clinical information to be delivered to the clinical care team (*e.g.*, clinical decision support), for patients supported in the ambulatory setting. Projects may include activities leading to the development of a new device or hardware, or they may leverage existing devices capable of capturing relevant physiological measurements. The primary goal of this topic is the development of a complete remote monitoring capability that includes software and/or analytics capable of supporting clinical decision-making and patient care.

*Activities not responsive to announcement:*

Tools that don't focus on an identified clinical cohort and associated treatments with at least some assessment of adverse event risks relevant to those patients that could be monitored with the identified wearable technology(s) proposed; approaches that seek to address cancer prevention or early detection of cancer; and applications from teams that don't include clinical collaborators or lack relevant technology development expertise.

**Phase I Activities and Deliverables:**

- Provide a clear description for the patient treatment monitoring scenario being targeted, including a description of the patient population being targeted, the kinds of treatments, and their known and/or suspected adverse effects that are being tracked in current clinical work practices. Examples could include (but are not limited to) conditions like neuropathy, depression, pain, etc. Offerors should provide a description for the anticipated improvement in patient outcomes that are anticipated, should the proposed monitoring technology be successful (as proposed).
- Establish a project team including proven expertise in both the technology and methodology to be developed as well as clinical research.
    - Technology team members should include expertise in sensor technology for physiological monitoring, wireless sensor integration with mobile devices, secure wireless transport of health data using standards-based protocols, secure cloud computing models, bioanalytical technologies, epidemiology, biostatistics/bioinformatics, machine learning, and deep learning, and systems architecture.
    - Clinical team members should include expertise in oncology, nursing, and clinical trials management.
- Select and validate a suitable wearable monitoring device(s) needed to assess required patient measures needed to monitor patient's fitness and detect signs of patient deterioration. Alternatively, describe a plan to build and test a wearable device appropriate for the features/biomarkers to be measured. The offeror must propose detailed quantitative performance benchmarks that will be achieved to demonstrate robust capabilities for each of the attributes being measured and tracked. The demonstration deliverable for Phase I should include testing with at least 5 individuals/patients.
- Design and conduct a needs assessment to ascertain a breadth of relevant use cases and appreciate the potential and challenges for adoption of the proposed technology.

- Develop and validate the analytical methods necessary to assess patients' fitness and detect signs of deterioration while monitoring the selected wearable device(s) in "real world conditions" over extended time periods (at least 72 hours continuous).
- Develop the appropriate data visualization, feedback, and reporting systems for clinical monitoring
- Develop a functional prototype system. Establish user design and user experience wireframes as the basis for the user interface platforms that will ultimately be utilized by the patient being monitored and clinical care team members. The offeror must design a system that provides ease of use, including features that demonstrate user design features that accommodate the often busy and complex work environment for the clinical care team monitoring the patient and also the intuitive and enjoyable ease-of-use features needed to empower the patient being monitored.

**Phase II Activities and Deliverables:**

- Design and perform properly powered clinical studies in relevant cancer populations to establish the clinical utility and performance of the prototype system.
- Conduct usability testing of consumer/patient-facing mobile applications and any associated web portals and care team/researcher-facing user interface features developed in Phase I, including system management, analyses, and reporting applications.
- Engage user testing with at least 30 patients utilizing the wearable monitoring device(s) and at least 3 distinct clinical care teams working with those patients (no members of any one clinical care team can be part of any of the other clinical care teams, to ensure a diversity of "real world" testing demonstrations).
- Establish an appropriate mechanism (e.g., surveys) to receive ongoing feedback from health care providers to refine processes and protocols that will enable successful integration into clinical workflows.
- Develop a scaled manufacturing and production plan for the wearable monitoring device(s) package (inclusive of the user apps and data analysis elements)
- Present an appropriate regulatory plan consistent with intended use.

**NIH/NCI 450 – Technology Platforms for Circulating Tumor-Macrophage Hybrid Cells**

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**

Cell fusion benefits the evolving cancer cell population, and the hybrid cells inherit genotypic and phenotypic characteristics of both the parental cells to help tumor cells survive under selective pressure. Several reports present evidence that macrophages are an important partner in this process and hybrid cells acquire tumor cell proliferation and macrophage migratory capabilities. Tumor-macrophage hybrid cells (TMHCs) are the product of fusion and not a product of genomic instability, paracrine cellular interactions, or phagocytosis of tumor cells by macrophages. TMHCs were found in several solid tumor types of sex-mismatched bone marrow transplant patients confirming that they are fusion hybrids, express several genes associated with tumor invasion and metastasis, exhibit enhanced metastatic potential, and are associated with aggressive clinical behavior, poor outcomes, and survival in every solid cancer tested. Patient-derived TMHCs have been shown to form metastatic lesions in distant organ sites in animal models better than the circulating tumor cells (CTCs). Relative abundance of the TMHCs in blood was reported to be significantly higher compared to CTCs or cancer-associated macrophage-like cells (CAMLs), and more prognostic than the CTCs or CAMLs. Current CTC platforms are not adequate for the characterization of cTMHCs. Affinity-based CTC platforms specifically exclude CD45 expressing cells including hybrid cells with macrophages, monocytes, or bone marrow-derived mesenchymal cells. There is a need for better technology platforms that isolate and enrich circulating TMHCs (cTMHCs) for enumeration and identification. Once sufficiently developed, these technologies should enable downstream omic analysis to understand the origin and role of the TMHCs in cancer progression and metastasis and provide sufficient yield of TMHCs for in vitro drug testing and development of

cell line-derived xenograft (CDx) models.

**Project Goals**

The immediate goals of this contract topic are to support development of platforms to isolate, enrich, enumerate, and identify the cTMHCs in blood from cancer patients or animal models of cancer. Individual project goals should align with the clear unmet need and the deliverables. Offerors are expected to utilize technologies that are common to research and clinical diagnostic labs, and not the highly specialized technologies only available in major research core facilities to establish the platform to facilitate easy adoption of the platforms for clinical applications. In Phase I, offerors are encouraged to develop platforms that combine TMHC's biophysical and/or mechanical properties with the more specific affinity-based strategies to isolate and enrich the cTMHCs. The platform should have the capability to enumerate the cTMHCs. The enrichment is expected to achieve >80% purity, and preserve viability (>50%) of the enriched preparation in sufficient yields to culture and develop *in vitro* models. Offerors must benchmark the platform against flow cytometry or other modalities and demonstrate that cell genotype and phenotype are maintained during culture.

Offerors should optimize the reagents to enable cTMHCs isolation, enrichment, and enumeration and show that they have the freedom to operate/use all reagents and devices needed for the platform; show access to blood samples from cancer patients to conduct studies in Phase II; develop QA/QC for the reagents; establish SOPs; demonstrate potential for reagent scale-up. In Phase II, the offerors are expected to do reagent scaleup; assemble a kit for use on human blood; demonstrate use of the platform using blood samples (n≥20/cancer type) from cancer patients for at least two major cancer types; demonstrate utility of the platform in at least one research model, such as collecting and culturing the cTMHCs and using them for drug testing, developing CDx models and/or conducting one or more of the downstream genome, transcriptome, proteome and/or metabolome analysis; and develop algorithms to determine tissue of origin.

*Activities not responsive to announcement:*

Computational methods that use genomic or epigenomic data to deconvolute and enumerate cTMHCs.

**Phase I Activities and Deliverables:**

- Develop technologies to isolate and enrich cTMHCs from blood
- Integrate the technologies with the approaches to enumerate and confirm identity of the TMHCs
- Show reproducibility and repeatability of the isolation and enrichment
- Develop and establish a QA/QC plan
- Demonstrate that the enriched preparation has >80% purity
- Demonstrate performance of the platform using at least 50 blood samples (1-10 ml) from patients of one cancer type
- Demonstrate that the platform can provide sufficient quantity of cells for downstream cellular phenotyping or molecular analysis
- Establish sample handling and storage conditions prior- to and post- cTMHC enrichment to ensure the enriched cTMHC preparation is useful for downstream analysis
- Develop training modules for lab personnel to perform the isolation, enrichment, enumeration, and identification using the platform
- Develop a design prototype of the integrated platform
- Show access to patient cohorts or clinical trials needed for the robust validation of the technology platforms in Phase II
- Submit protocols, SOPs, designs, performance characteristics, training modules, cost parameters, and time factors to NCI SBIR

**Phase II Activities and Deliverables:**

- Develop a commercial prototype of the platform, including reagent scaleup and assembling a kit for use on human blood
- Demonstrate the use of the platform with blood samples from cancer patients for at least two major cancer types with appropriate consideration for statistical significance
- Demonstrate utility of the platform in at least one research model, such as collecting and culturing the cTMHCs and using them for drug testing, developing CDx models, and/or conducting one or more of the downstream genome, transcriptome, proteome, and/or metabolome analysis; and develop algorithms to determine tissue of origin

- Submit protocols, SOPs, designs, performance characteristics, training modules, algorithms, cost parameters, and time factors to NCI SBIR

**NIH/NCI 451 – 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.

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 and cause of cancer-related mortality in women. In low- and middle-income countries (LMIC), cervical cancer is typically the first or second most common cancer and cause of cancer-related mortality in women due to poor access to preventive services. When pre-cancer or cancer is diagnosed early it is one of the most preventable or treatable forms of cancer. As a result of complex and expensive cytology-based programs in high-income countries, cervical cancer has become a cancer that defines health disparity populations and one that is still a major cause of morbidity and mortality in low-resource settings globally, where a cytology-based screening program may not be feasible.

The World Health Organization (WHO) Global Cervical Cancer Elimination strategy calls for twice-in-a-lifetime screening of at least 70% of women globally with a high-performance test. Realization of that goal given the current commercially available HPV tests is unlikely without new tests coming to market that can be performed and analyzed outside of traditional healthcare settings and are at a price point that is affordable for going to scale in low-resource settings. 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 lower cost than existing tests. Additionally, numerous studies have shown that women across diverse settings can properly collect their own samples for HPV-based cervical cancer screening and that HPV DNA can be detected in a way that is non-inferior to clinician-collected samples.

The overarching goal of the work to be supported by this initiative is therefore to bring needed new alternatives for HPV testing to the market that are both in a form factor and at a price point that will enable testing programs to be established globally.

**Project Goals**

Projects in response to this FOA should first develop a functioning prototype for a portable HPV diagnostic designed for near-patient use. The device should enable rapid detection and genotyping for HPV. 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 to this FOA can propose to modify 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 training needs for its use.

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 as well as 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 should include disposables. Technologies should be sustainable

and affordable by local providers (either low enough in cost to easily replace, have easily replaceable parts/be easy to repair, and/or use parts, reagents, and consumables that are locally available in LMIC supply chains).

Note: This FOA specifically focuses on development of an affordable point of care (POC) HPV diagnostic device to enable scaling up cervical cancer screening programs globally and does not support development of associated devices for self-collection and transport/storage of cervicovaginal specimens.

**Phase I Activities and Deliverables:**

- 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 (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 a well-defined diagnostic device under good laboratory practices (GLP) and/or good manufacturing practices (GMP).
- Perform manufacturing scale-up and production for multi-site and multi-test evaluations, including sites both in the U.S. and at a site in a resource-limited setting.
- Demonstrate the clinical sensitivity and specificity of the device for 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 452 – 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: 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 purpose of this technology-agnostic contract solicitation is to bring highly sensitive cancer-specific imaging agents and technologies capable of imaging 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 which dramatically enhances contrast between very small cancer and normal tissue is acceptable for consideration, which can include software techniques 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. 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. The goal is to build upon existing development successes with activatable diagnostic probes 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 which 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 which 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. Demonstration of success for these activated imaging probes and/or techniques must include: (i) Tumor-specific binding, (ii) Low binding to surrounding normal tissue, (iii) High output efficiency in the "on" state, (iv) very low output in the "off" unbound state, (v) studied Pharmacokinetics/Pharmacodynamics (PK/PD) in an animal model, (vi) Low toxicity.

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.
- Develop and/or 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, with keen interest in eliminating potential false positives and false negatives.
- Acquire institutional IRB approval to perform selected optimized molecular probe dose-escalation safety studies on small number (5 – 10) of healthy human subjects.
- Convene the project team with expertise in imaging science, cancer surgery, and pathology.

- Submit and acquire single IRB approval for recruitment of patients undergoing cancer surgery with the selected molecular probe labeling for the selected cancer to validate the molecular probe's capabilities to identify additional cancers that were not detected by normal white light or palpation.
- 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:**

- Begin clinical validation studies through an approved single IRB at multi-sites requiring a minimum of 15 cancer patients per site with a minimum of 3 multi-centers.
- File regulatory submission with FDA by the end of year-02, following either the 510k or PMA path (as required by FDA for the specific product use and claims sought by the contractor).
- Secure at least one letter of commercial interest from potential customers at the end of year-01.
- Secure two letters of commercial commitment to buy the product from customers at the end of year-02.
- Present phase II findings and demonstrate the system via a webinar at a time convenient to the offeror and NCI program staff.

**NIH/NCI 453 – Digital Tools to Integrate Cancer Prevention Within Primary Care**

Fast-Track proposals will be accepted.

Direct-to-Phase II proposals will be accepted.

Number of anticipated awards: 2-4

Budget (total costs, per award):

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

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

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

**Summary**

Many clinical guidelines rely on Primary Care Providers (PCPs) to assess cancer risk and provide recommendations. For example, the US Preventive Services Task Force (USPSTF) recommends that patients who are concerned about their breast/ovarian cancer risk seek guidance from their PCPs. To date, recognition of some cancer risk factors and incorporation of cancer prevention beyond routine screening, vaccinations, and behavior modification within the primary care workflow has been limited, in part due to time constraints, workflow integration, cognitive overload, and inadequate or delayed communication with patients or with specialists, leaving a missed opportunity for cancer prevention. Thus, there is an unmet need for evidence-based cancer prevention guidelines, cancer risk assessment tools, and recommendations for cancer prevention interventions to be better integrated within the primary care workflow. This is particularly necessary in the case of clinical practices not associated with, or regions without access to, high-risk clinics. A cancer prevention-focused digital platform (including genetic and other risk assessment tools as well as information on oral and locally delivered risk-reducing agents) is needed to help PCPs evaluate a patient's cancer risk, be informed of clinical guidelines and recommendations related to these cancer risks and comprehend and evaluate the benefits and risks of applicable cancer preventive interventions. Developing a digital solution that can be seamlessly integrated within an already existing clinical management workflow will provide the resources and support to help PCPs become more proficient with cancer risk assessments and preventive recommendations, without additional time/resource burdens.

**Project Goals**

The overall goal of this solicitation is to develop a digital platform that provides PCPs with validated cancer risk assessment tools, cancer prevention guidelines, and clinical recommendations based on a patient's risk factors to discuss with their patients. This technology will compile evidence-based tools/guidelines/recommendations related to cancer prevention for multiple cancer types, beyond routine screening and behavioral interventions, into a centralized platform that can be readily integrated within routine primary care workflows so that they do not provide an additional burden on PCPs given the time constraints of clinical management. For example, if a patient with a DCIS diagnosis sees their PCP for clinical management, the PCP could use the digital platform to review risk factors and guideline recommendations with the patient to determine possible management plans for

breast cancer prevention.

The proposed technology should: be designed for updates as new/updated clinical guidelines are released; return cancer risk assessments and facilitate communication of clinical recommendations from PCPs to their patients in real-time as necessary; include information and resources related to a wide scope of cancer preventive interventions; include a provider-facing interface to run risk assessments, review clinical guidelines based on these assessments, and facilitate communication and shared decision making based on the recommendations; include a patient-facing interface with simplified language for patients to input their personal and family history and other risk factors, to provide the necessary information for risk assessment. The patient-facing interface should not provide access to risk assessments or clinical recommendations; this information will be communicated by PCPs. The proposed digital platform should use simplified language to assist with provider communication and facilitate patient comprehension and engagement for shared decision making. Development of the digital platform should incorporate input from both providers and patients from various types of healthcare communities (e.g., academic, community, etc.) and minority and rural populations, to ensure equitable ease of use and uptake.

*Activities not responsive to announcement:*

Platforms that cannot integrate with Electronic Health Records (EHR), platforms focused on a single cancer type, and platforms that do not incorporate a broader scope of cancer prevention (e.g., technology only focused on screening, vaccines, and behavioral interventions) will not be considered responsive to this solicitation.

**Phase I Activities and Deliverables:**

The goal of Phase I is to develop a digital technology that integrates cancer prevention guidelines, cancer risk assessment tools, and applicability of cancer prevention interventions.

Activities:

- Establish a project team with expertise in digital healthcare platforms/EHR, cancer prevention and primary care, software development, user-centric design, patient navigation/engagement as appropriate for this proposed project.
- Complete a systematic review to compile and assess current cancer prevention guidelines and recommendations for multiple cancer types beyond routine screening, vaccines, and behavioral interventions, to include supplemental screening, risk-stratified screening, personal and family history, genetic testing referral and results, ancestry, epidemiologic risk factors, available risk assessment tools, and recommendations from applicable organizations such as the National Comprehensive Cancer Network (NCCN), the USPSTF, and the American Cancer Society (ACS).
- Engage stakeholders and determine clinical consensus in cases of differing recommendations or insufficient data.
- Develop a pilot digital platform that incorporates the compiled research into a tool that PCPs can efficiently use to assess their patients' cancer risks, and effectively communicate these risks and evidence-supported preventive recommendations to their patients.
- Include a patient-facing interface for data collection within the digital platform.
- Include the ability to continuously incorporate new information on cancer risk assessment and recommendations as it is released by the appropriate organizations.
- Ensure privacy protection as required by law.
- Identify at least two clinical settings, including a community-based clinic, where the digital platform may be used and integrated within a primary care practice for pilot user testing.
- Test the feasibility/usability of the digital platform in a sample population of at least 25 PCPs and patients.
- Test the feasibility of the digital platform within an EHR testing environment.

Deliverables:

- A report of the compiled research on cancer prevention including resources/recommendations/guidelines that were incorporated into the technology.
- Pilot technology design.
- Demonstration of technology feasibility and acceptability by PCPs and patients, including in a community setting.
- Technical specifications, including privacy and security protections, as well as an operations/user guide.
- Outline of metrics that can be used to assess the successful application of the technology.

**Phase II Activities and Deliverables:**

The goal of Phase II is to implement the digital technology within EHR systems and evaluate its application in primary care settings.

Activities:

- Develop a plan to implement the digital platform in EHR systems in primary care practice settings, including community clinics.
- Enhance systems interoperability for deployment of digital platform in diverse software environments and provider networks.
- Develop metrics to demonstrate successful use of the digital platform, including comprehension of the information by PCPs primary care providers and by the patients as communicated by their providers.
- Conduct a validation study of the feasibility/acceptability and successful use of the digital platform in an additional population of at least 100 PCPs and patients.
- Prepare a web-based course for training PCPs and patients on the intended use of the digital platform.
- Develop a dissemination plan for the digital platform and the training course.
- Develop a plan for commercialization of the digital platform.

Deliverables:

- Letter(s) of commercial interest provided to the project and contract officers in the first year of the Phase II contract.
- Validation of technology feasibility, acceptability, and successful use by PCPs and patients, including in a community setting.
- Report with metrics demonstrating that PCPs comprehend the information within the technology and that patients understand the information as communicated by their providers. Report should also include analysis from discussions with participating providers and patients to better understand and improve the acceptability of the technology more broadly.
- Finalized user guide and operations manual for use of technology within a range of primary care settings, including community clinics. These documents will include technical specifications, process guides/flow charts for how and by whom the technology will be used, and privacy and security protections.
- Finalized troubleshooting guide as well as frequently asked questions.
- Letter(s) of commercial commitment provided to the project and contract officer.

**NIH/NCI 454 – Software to Evaluate Artificial Intelligence/Machine Learning Medical Devices in Oncology Settings**

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**

There is an unmet need to *develop software tools for evaluating the safety and effectiveness of cancer-related devices that use artificial intelligence and machine learning (AI/ML)* algorithms. The development of such software tools to evaluate real-world performance in oncology settings will facilitate bringing medical devices to market faster, monitoring devices during post-market surveillance, and assessing rapidly developing updates to AI/ML algorithms. Importantly, these tools have the potential to promote trust and transparency among users, which is critical for the adoption of new devices that use AI/ML algorithms in clinical practice. Such software tools may be considered for qualification by the FDA Medical Device Development Tools (MDDT)

Program.

FDA's mission is to protect and promote public health. One of the ways it does this is by helping to speed up innovations that help provide methods to demonstrate safety, effectiveness, or performance of medical devices to encourage streamlined medical device development for patients. The FDA MDDT Program is a mechanism for FDA to qualify tools that companies can use in the development and evaluation of medical devices subject to regulatory decision-making by the Center for Devices and Radiological Health (CDRH). More information about the MDDT Program can be found here.

FDA's MDDT Program collaboration with the NCI SBIR Development Center can help incentivize the small business community to develop and qualify innovative tools for oncology-related regulatory decision-making. These tools can be sold to industry or academia developing new medical devices 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. Potential products that could be MDDTs developed under this topic include software tools for evaluating and monitoring existing AI/ML devices used for patient triage, diagnostic imaging, and radiation treatment planning as well as supporting the development of new devices used for diagnostics and therapeutics; for example, to support the evaluation of devices used to support the oncological workflow by helping the user confirm the absence or presence of cancerous lesions, including evaluation, quantification, follow-up, and documentation of any such lesions.

**Project Goals**

The goal of this contract topic is to stimulate the participation of small businesses in the FDA's MDDT Program to develop and qualify software tools for evaluating and monitoring AI/ML devices in oncology settings. A 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.

The project scope should include a demonstration that the software tool has a reasonable ability to evaluate device safety, effectiveness, and/or performance in a real-world setting. For example, FDA has qualified a modeling software instrument as a MDDT. The software predicts the interactions of medical devices (i.e., medical implants) with the electromagnetic fields in the magnetic resonance imaging environment. The software was validated against actual physical testing of medical device implants. The summary of evidence and qualification for this tool and all other qualified MDDTs can be found here.

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 tool is suitable for qualification consideration through the MDDT Program by submitting a Qualification Plan that includes a proposed MDDT description, context of use, an appropriate plan for collecting evidence to support qualification of the tool for the defined context of use, and qualification criteria to describe how the tool is expected to perform. The result of this phase is a FDA determination on whether to advance the tool to the qualification phase.
>
> **Qualification Phase**: The goal is to determine whether, for the specific context of use, the tool can be qualified based on evidence and justifications provided supporting that the tool operates within the proposed qualification criteria. The data collected according to the Qualification Plan is submitted as the Full Qualification Package and reviewed by FDA for a qualification decision.

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

While not a comprehensive list, several examples of technologies considered responsive to this solicitation include software tools capable of:

- Estimating and reporting the robustness of AI/ML to variation in data acquisition, demographic, or other factors.
- Analyzing AI/ML-based computer-aided triage (CADt).
- Analyzing AI/ML-based computer-aided acquisition and optimization (CADa/o).

- Evaluating specific imaging performance claims and image reconstruction AI/ML-based algorithms in the clinical setting.
- Monitoring AI/ML device performance in the real-world setting over time and for devices that continuously learn from new training data.
- Acquiring data or developing data acquisition methods to support AI/ML evaluation and device comparisons.

Activities that would not be considered responsive to this solicitation include software tools that are not helpful for regulatory decision-making, software that is applicable only to one manufacturer's device, software that is only applicable to FDA Drug Development Tools (DDT) Program, and other software tools considered to be a medical device.

**Phase I Activities and Deliverables:**

- Develop a working prototype of the software tool that meets the criteria defined by the FDA MDDT program.
- Prepare a MDDT Qualification Plan using the MDDT Qualification Plan Submission Template which outlines specific information necessary to submit a MDDT Qualification Plan. For additional details review Qualification of Medical Device Development Tools - Guidance for Industry, Tool Developers, and Food and Drug Administration Staff.
- Demonstrate the suitability of the software tool for use in regulatory decision-making (e.g., demonstrate how the tool supports the safety, effectiveness, or performance of the medical device).
- Submit a complete Qualification Plan to the FDA's MDDT Program. It should include description of the MDDT, context of use, and a detailed plan to collect evidence based on the context of use for qualification of the tool. Use the MDDT Qualification Plan Template for this submission.
- Specify the quantitative technical and commercially relevant milestones that will be used to evaluate the success of the software tool.
- Conduct a pilot usability study of the prototype software tool.
- Develop a strategy/plan which includes a timeline for when you expect to submit a Full Qualification Package for a MDDT.

**Phase II Activities and Deliverables:**

- Test integration of the tool into the particular clinical workflow applicable to the specific medical device(s) that will be monitored.
- Design and conduct a validation study using the tool in a real-world monitoring setting.
- Develop user support documentation to support all applicable potential users of the tool. Provide a report documenting user support resources, including but not limited to, links to online resources and copies of electronic or paper user support resources as appropriate.
- Prepare a Full MDDT Qualification Package which includes specific requirements and activities with respect to the proposed MDDT.
- Submit a Full Qualification Package to the FDA's MDDT Program including the data collected according to the FDA-accepted Qualification Plan. Use the MDDT Qualification Package Template for this submission.
- Engage with FDA to determine if your product is a regulated device or MDDT. If warranted, provide sufficient data to submit a regulatory application to obtain approval for clinical application.

**Frequently Asked Questions:**

1. Who are the potential customers for a MDDT?

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

2. Will FDA or NCI purchase the MDDT?

Offerors must identify the eventual customers for their tool. NCI and the FDA are not potential customers for this product. These tools can be licensed or sold to medical device manufacturers developing new medical devices 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 patient care.

3. Are there examples of MDDTs?

Yes, the MDDT page (Medical Device Development Tools (MDDT) | FDA) lists all qualified MDDTs.

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

You must submit your qualification plan to the FDA by the end of the Phase I contract. CDRH will review Full Qualification Packages submitted at the end of the Phase II contract and make a qualification decision regarding the tool's acceptance as a FDA-qualified MDDT. If awarded, companies are highly encouraged to engage the MDDT Program via email (MDDT@fda.hhs.gov) early on and prior to development of their Qualification Plan for the MDDT Program.

## 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 007 - High Throughput CHIP (clonal hematopoeisis of indeterminate potential) Assay as a Powerful Tool to Study CHIP Related Age Associated Diseases**

Number of anticipated awards: 1 to 3

Budget (total costs, per award): Phase I: $300,000 for 12 months; Phase II: $2,000,000 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 in described for Phase

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:***

Clonal hematopoiesis of Indeterminate Potential (CHIP) has emerged as a potent biological mechanism for multiple aging diseases ranging from cardiovascular disease to blood cancer. Through self-renewing hematopoietic stems cells, the bone marrow continuously regenerates cells of the blood in order to maintain homeostasis. Over time, DNA damage or errors in DNA replication result in the acquisition of somatic mutations in hematopoietic stem cells. The majority of these mutations are of no consequence but certain mutations (e.g., DNMT3A, TET2, ASXL1, JAK2) can confer a selective advantage to multiply and lead to expansion of a clone. By the age of 70, more than 10% of individuals harbor clones that make up an appreciable fraction of peripheral blood. Currently, the only way to screen and detect clonal hematopoiesis in individuals is through DNA sequencing of peripheral blood. Although there is interest in examining the role of clonal hematopoiesis in the context of exceptional health and age-related conditions/diseases, there does not exist a low cost, scalable assay for analyses of clonal hematopoiesis. This represents a considerable methodological gap. Further work is required to develop and validate the CHIP assay for use in human cohort studies and relevant animal models including dogs and non-human primates and CLIA standardization for application in clinical screening. The availability of such an assay, particularly one which could be used in both animal models, epidemiological studies and in clinical research would not only advance our understanding of the role of CHIP in health and disease but also potentially lead to novel lines of translational research. Once developed, such an assay could be further validated for clinical diagnostic purposes and submitted for FDA approval, etc. and translated for use in patient care settings. Importantly, this methodological challenge can be addressed in a timely fashion through modifications to and leveraging of assays systems which are currently under development versus the de novo development of new assays.

***Project goals:***

The purpose of the current concept proposed for SBIR contract solicitation is to develop an inexpensive, high throughput assay to detect CHIP mutations for research purposes, which could eventually be translated into a diagnostic/prognostic assay for use in healthcare settings for patient management. This assay is expected to overcome current challenges and limitations of reliance on existing methods to examine CHIP and provide accessibility to more basic and clinical researchers to better study aging biology (longitudinal /multi time points) in diverse populations to understand CHIP. The assay could potentially be used in clinical setting as a tool for risk stratification/diagnostic/prognostic assay for patient management.

The assay could also enable the discover CHIP based therapeutic targets to develop tailored therapies to patients in a biomarker-enriched fashion.

***Phase I Activities and Expected Deliverables (as applicable):***

- Optimization and Expansion of the current research focused CHIP assay by inclusion of additional CHIP related genes in the assay that may be associated with aging and age- related diseases
- Development of a bioinformatics workflow to analyze and report out the data in both research and clinical settings
- Expansion of CHIP assays with a specific panel of genes as screening, predictive/ prognostic and indicative (disease state - cardiology, oncology/ dementia) tool to obtain FDA approval for potential clinical application in patient management
- Identification of clinical partners to identify clinical biospecimens for clinical validation and demonstration of the performance standards of the developed assays
- Translation of the protocols from the current research lab environment to a CLIA certified sequencing lab to run clinical studies and to support the clinical validity of the test.
- Plans to meet with FDA to understand the requirements of FDA for approval for clinical implementation

***Phase II Activities and Expected Deliverables:***

- Conversion of the research CHIP assay into a CLIA certified CHIP assay to meet regulatory needs of FDA to claim the assay as a screening, predictive/prognostic and companion diagnostic tool
- Meeting with FDA to discuss premarket submission requirements to demonstrate that the device to be marketed meets regulatory criteria, safe and effective.
- Conducting large clinical studies with well-defined end points and a statistical analysis plan to claim the CHIP assay as a screening tool and to show clinical validity. This would also require a Post Market application (PMA) with the FDA. Consideration of an underlying biomarker(s) being measured is highly encouraged
- Designing and conducting clinical studies to demonstrate validity of the CHIP assay to meet the requirement for a prognostic claim (class II in regulatory language) and preparation of a De Novo application for first of its kind test or a 510k application.
- Establishment of studies to claim the CHIP assay as a companion diagnostic tool through clinical studies in which the diagnostic test is used to select a patient population for which the therapeutic product will be safe and effective

**NIH/NIA 008 - Improving Microphysiological Systems for AD/ADRD Therapy Development**

Number of anticipated awards: 2 to 5

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

Fast- Track proposals will be accepted.

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

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:***

Microphysiological systems (MPS) hold the promise to improve and expedite the entire drug development process including both, drug discovery and pre-clinical testing. For example, animal testing is the gold standard for preclinical drug development, however, species differences between animals and humans have resulted in over 85% of AD/ADRD investigational drugs failing in clinical testing, with ~30% failing due to toxicity and ~60% failing due to lack of efficacy. Thus, there is a critical need for the development of more predictive and high-throughput *in vitro* MPS as simple, reproducible, and scalable platforms that recapitulate organ-level functions to be used in different stages of AD/ADRD drug development.

3D MPS models (i.e. organs-on-chips) contain cells in linked chambers perfused with recirculating tissue medium to model organ structures and functions. Unlike 2D in vitro systems, 3D models more accurately mimic the in vivo milieu by recreating the morphology and arrangement of individual and multiple cell types, concentration gradients of signaling molecules and therapeutic agents, and the mechanical forces to the tissue being modeled. Organ-on-chip platforms can contain multi-organ systems such as liver, kidney, gut, BBB, and brain to create complex tissue- tissue or organ-organ interactions to enable drug discovery, ADMET, PK/PD, and efficacy and toxicology analyses. Organ chip platforms can also be derived from patient cells leading towards the development of precision medicine. The use of 3D systems that recreate the human microenvironment can serve as an alternative model to replace, reduce, and refine use of laboratory animals and speed up development of therapeutics.

Properly representing the neurodegenerative microenvironment is particularly critical for testing the effectiveness of therapies for AD/ADRD. The main challenge is engineering 3D systems that recapitulate both the vast complexity of the human brain while emulating the aging-relatedbprocesses that influence disease. This is imperative for heterogeneous and chronic diseases like AD/ADRD. Thus, systems to properly recreate the neurodegenerative microenvironment are essential to advance the discovery and development of effective AD/ADRD therapies. Microphysiological systems will also be critical in allowing for the testing of potential AD/ADRD therapies in a manner that incorporates disparities and differences in the specific pathogenesis across populations.

***Project goals:***

The focus of this topic is the development of 3D human MPS that accurately mimic the AD/ADRD microenvironment, including factors that recapitulate both the vast complexity of the human brain while emulating the heterogeneity of the disease for use in AD/ADRD drug development. The project goal is to produce a system that is validated against known AD/ADRD therapeutic agents and align with human “omic” data from AMP-AD (described below) to demonstrate the system's utility as a predictive tool and screening assay. It is anticipated that the development of 3D systems representative of human AD/ADRD will lead to an increase in the quality and reduction in timelines and costs associated with screening drugs, and enhance efficacy and safety information for regulatory decisions.

Essential characteristics of an in vitro AD/ADRD microsystem should include the following features: 1) multicellular architecture that represents physiologically relevant characteristics of the brain and AD/ADRD pathology; 2) ability to examine multiple aspects of AD/ADRD, such as proteinopathy, neuroinflammation, synaptic dysfunction, neurodegeneration, and metabolic dyshomeostasis; 3) compatibility with high content screening platforms that include multiple molecular read-outs, such as genomic, proteomic, metabolomic, or epigenomic analyses; and 4) reproducible and viable operation with simple and clear protocols. Systems should include physiological structures such as neural networks and BBB. Systems that solely replicate the BBB and transport across the BBB would not be responsive to this solicitation. System development should permit scale-up production such that the system can be reliably reproduced at a cost with reasonable expectation for market success. Eventual utility for such systems may include either the ability to incorporate individual patient stem cells to test patient-specific responses to available agents or to be used for more context-rich and robust high throughput screening assays. Thus, NIH will consider proposals to develop both individualized and high throughput MPS-based assays for this contract topic.

As stated earlier, one project goal is to produce a system that aligns with human “omic” data from AMP- AD (Accelerating Medicines Partnership-Alzheimer’s Disease). The AMP-AD Program supports integrated analyses of large-scale molecular data with network modeling approaches and experimental validation. Over 3,000 human brain samples at all stages of the disease have been evaluated using cutting-edge systems and network biology approaches to integrate multidimensional human “omic” data (genomic,epigenomic, RNAseq, proteomic) with clinical and pathological data. All data, including biological data and analytical methodology, are publicly available through the centralized big data infrastructure AD Knowledge Portal.

***Phase I Activities and Expected Deliverables (as applicable):***

- Develop 3D culture system prototype that recapitulates human AD/ADRD
- System should include:
- Co-culture with multiple cell types, such as neuronal cells, microglia, astrocytes, etc.
- Demonstration of disease heterogeneity, such as such as proteinopathy, neuroinflammation, synaptic dysfunction, neurodegeneration, and metabolic dyshomeostasis
- Can use human AD/ADRD iPSC line that are readily available and well characterized
- Model should be developed using or easily adapted for use with high content screening platforms for sample analysis or be developed for patient-specific testing as a precision medicine tool
- Develop standardized protocol to enable reproducible culture of cells in 3D microenvironment

- Recapitulate tissue-tissue interfaces, spatiotemporal chemical gradients (e.g. oxygen, nutrients, and/or growth factors), and mechanical context of AD/ADRD microenvironment
- Submit a statement to NIA that specifies metrics used and criteria for prediction of clinical efficacy prior to demonstration of accurate prediction of clinical efficacy
- Identify specific biomarkers (e.g. gene expression patterns, cell surface proteins, secreted proteins) that characterize cell types and disease
- Specify criteria for assessing whether the microenvironment is representative of human physiological environment
- Specify metrics that will be used to evaluate efficacy and milestones for desired efficacy
- Demonstrate accurate prediction of clinical efficacy in the developed prototype
- Test at least one AD/ADRD therapeutic agent with a known clinical profile using the developed prototype
- Benchmark performance in developed system against 2D and currently available 3D culture systems

***Phase II Activities and Expected Deliverables:***

- Benchmark performance in developed system against applicable in vivo animal model(s) and known human clinical performance
- Test multiple agents with known clinical profiles in the developed prototype
- Test at least one agent that has proven efficacious in animal trials but not in clinical trials
- Assess genomic, proteomic, metabolomic, and epigenomic profile of the AD/ADRD system
- Use validated markers and/or evaluative criteria from human samples
- Compare to human "omic" data from AMP-AD
- Compare dose-response relationships of known AD/ADRD therapeutic agents
- Demonstrate the ability to scale-up the system for use in AD/ADRD drug development

**NIH/NIA 009 - AI/ML Tool for Visualizing Behavioral and Social Science Research**

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 in described for Phase

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:***

As the Division of Behavioral and Social Research (BSR) launches more and more initiatives to promote behavioral and social science research relevant to Alzheimer's disease (AD) and AD-related dementias (ADRD) it is becoming increasingly clear that a major barrier lies in the challenge of compiling, collating and comprehending the burgeoning literature that characterizes this field. To that end, this initiative would develop a tool that extracts, aggregates, and visually maps variables and causal relationships tested in BSR papers, allowing users to automatically generate a causally structured overview of the literature, explore it in depth, and identify latent connections between variables. Such a tool would be useful not only for portfolio analyses within BSR (and NIA more broadly) but would be useful as a research tool in behavioral and social sciences more broadly.

Behavioral and social science research (BSR) represents an important, cross-disciplinary segment of the health research funded by the NIH, and is key to developing effective new approaches for supporting individuals with cognitive impairment - particularly for mitigating the immense individual and societal burden associated with Alzheimer's disease and related dementias. At its most fundamental level, quantitative research in BSR can be thought of, and conceptually represented, as a network of variables (i.e., characteristics of an individual, group, or environment) and causal relationships between them. Yet currently no tool exists that allows users of BSR research to quickly derive a causal overview of the relevant literature, so that they can uncover promising new associations between variables.

***Project goals:***

Behavioral and social science research (BSR) represents an important, cross-disciplinary segment of the health research funded by the NIH, and is key to developing effective new approaches for supporting individuals with cognitive impairment - particularly for mitigating the immense individual and societal burden associated with Alzheimer's disease and related dementias. At its most fundamental level, quantitative research in BSR can be thought of, and conceptually represented, as a network of **variables** (i.e., characteristics of an individual, group, or environment) and **causal relationships** between them (Babbie, 2013). Yet currently no tool exists that allows users of BSR research to quickly derive a causal overview of the relevant literature, so that they can uncover promising new associations between variables.

To address this need, at least in part, is an educational, AI-based tool for BSR-specific literature visualization and hypothesis discovery, that can be marketed to behavioral science investigators and research institutions that consume scientific research with a particular emphasis on Alzheimer's disease (AD) and AD-related dementia (ADRD). The envisioned tool would extract, aggregate, and visually map variables and causal relationships tested in BSR papers, allowing users to automatically generate a causally structured overview of the literature, explore it in depth, and identify latent connections between variables. This tool would reduce the time for understanding the conceptual structure of the literature from hours to seconds, accelerating scientific discovery. The tool will be particularly relevant for novice AD/ADRD researchers, who can use it to educate themselves on existing BSR research and uncover ways to leverage this research towards improving care outcomes for persons with Alzheimer's disease (PwD) and their caregivers. The tool may also be useful for funding agencies that support BSR research assuming that research grant applications, rather than scientific publications, can serve as input data.

The successful solution will apply Natural Language Processing (NLP) and Machine Learning (ML) techniques to experiment-based papers in scientific journals in disciplines such as psychology, sociology, economics and others— from which causally categorized variables can be extracted and with fairly high accuracy — and coupled the other data to yield causal mapping of the extracted variables.

The goal is to develop an AI-based tool for BSR-specific literature visualization and hypothesis discovery, that might be marketed ultimately to various institutions that consume scientific research, with an emphasis on Alzheimer's disease. Such a tool would likely reduce the time for understanding the conceptual structure of the literature from hours to seconds, accelerating scientific discovery. The tool will be particularly relevant for novice Alzheimer's disease researchers, who can use it to educate themselves on existing BSR research and uncover ways to leverage this research towards improving care outcomes for persons with Alzheimer's disease (PwD) and their caregivers.

***Phase I Activities and Expected Deliverables (as applicable):***

- Production of a Visual Mapping System for faster literature comprehension & hypothesis discovery. A cross disciplinary group of researchers will be needed to craft—and implement—a set of optimal research visualization features:
- grouping of ontologically-related concepts into categories;
- highlighting latent connections between variables;
- producing a topically-organized mapping of Alzheimer's disease research in a given focal area (e.g., care/caregiving, cognitive function, neuropsychiatric testing, etc.)

***Phase II Activities and Expected Deliverables:***

- Broaden the type of science indexed—with an emphasis on Alzheimer's disease—in conjunction with ontology development for more comprehensive literature exploration.
    - Broaden the index developed in Phase I to cover a cross-section of BSR disciplines (e.g., general and economics-based psychology, behavioral medicine and pharmacology, gerontology—and other domains),
    - Include a broader range of research methodologies (i.e., experimental, observational, etc.) than covered in Phase I.
    - Progressively add different disciplines by obtaining access to papers from the top journals in each discipline with a larger, curated index for Alzheimer's disease,
    - Refine an ML model for extracting the variables tested in those papers, and
    - Ontologically categorize the extracted variables.
- Develop user management system for enhanced literature navigability and result accuracy.
    - Provide instant variable and relationship visualization for user-defined input (whether published papers or grant applications), and
    - Include an error reporting module that allows users to identify variables that have been incorrectly extracted by the system, and allowing such data to be fed back into the system within an "active
    - learning" ML pipeline, for optimizing the tool's output accuracy.

- Verify of the tool's efficiency, output comprehensibility, and efficacy for hypothesis discovery.
  - Derive a literature overview to verify the tool's efficiency, output comprehensibility and efficacy for hypothesis discovery
  - Identify papers relevant to specific causal relationships, and
  - Identify potential gaps for which new research is needed and demonstrate the tool's ability to do so more quickly and efficiently compared with other tools such as Google Scholar or PubMed. (The specific measures of speed and efficiency to be determined by the developer.)

## 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 113 - Development of a Simian Immunodeficiency Virus (SIV) and Simian Human Immunodeficiency Virus (SHIV) Database

Only Fast Track proposals **will** be accepted.
Phase I only or Direct-to-Phase II proposals **will not** be accepted.
Number of anticipated awards: 1-2

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

***Background***
A number of key advances in HIV/AIDS research have been accomplished through extensive use of animal models, in particular models of SIV and SHIV infection of various monkey species, including macaques and African green monkeys. Animal models offer obvious advantages for the study of HIV/AIDS, allowing for a more invasive investigation of the disease and preclinical testing of drugs and vaccines. Understanding the advantages and limitations of each of these models is essential for the design of animal studies to guide the development of vaccines and antiretroviral therapies for the prevention and treatment of HIV-1 infection.

To support future research on HIV vaccines and cure, a plethora of SIV and SHIV strains have been molecularly cloned or isolated from infected monkeys and made available to the scientific community through the NIAID-supported AIDS Reagent Program and other resources. However, information about the natural history and pathogenesis as well as the characteristics of a particular SIV or SHIV strain is not easily accessible. In support of future HIV vaccine or cure studies in NHP, it is important that biological data about available SIV and SHIV strains are captured in an easily searchable database or knowledge base that is continuously updated and reviewed.

***Project Goals***
The goal of the SIV/SHIV database is to develop and maintain, for the duration of the project, a database that represents information about SIV and SHIV strains and their biological properties, and a user-friendly web-based interface that enables data search and retrieval using graphic displays. At the end of the project period, the database should be merged with or integrated into one of the other NIH-supported professional repositories that would sustain the data for longer-term use.

***Phase I Activities and Deliverables:***
- Establish a project team with expertise in the areas of knowledge representation, database development and implementation, software engineering, literature search, natural language processing, and HIV/SIV biology. One PhD-level scientist with experience in SIV or SHIV model research must be part of the team.
- Select a commonly used and compatible software application for the data/knowledge base. The data must be presented in a format that can be easily understood and be appropriate for users with a non-expert level of understanding of the data.
- Develop solutions for data hosting, data transfer, and maintenance of data quality and content.
- Develop a scalable and expandable (meta-) data model design to represent the virus strains and biological information. The metadata model should be based on schema.org or include a mapping to schema.org.
- Data collection: Select approximately 15 SHIV and 15 SIV strains from publicly available literature.
- Establish parameters to be entered into the database in collaboration with the Division of AIDS. Examples of parameters include but are not limited to: strain genetic information incl. genetic diversity of virus stocks and clade, history of the origin of each virus, virus titers, the sensitivity of the virus stock to antibody neutralization, other biological

characteristics, doses used for *in vivo* challenges, tropism, barcodes, references, etc.
- Develop a central web-based high-quality data resource with information about the selected 15 SIV and 15 SHIV strains that enables highly innovative data search and retrieval methods.
- Obtain concurrence from the Division of AIDS for the high-quality data resource.
- Deposit the database/knowledge base in a professional data repository that enables inclusion of the database in the NIAID Data Ecosystem.

***Phase II Activities and Deliverables:***
- Curate all SIV and SHIV strains from PubMed literature, other publicly available information sources, and direct submissions from the broader research community into the existing prototype database, using automated methods where possible.
- Expand the existing database to all curated SIV and SHIV strains in collaboration with the Division of AIDS and develop the user interface. The user interface will comprise a graphical component and an Application Programming Interface (API). The SIV/SHIV database will be freely accessible to the scientific community via an Internet website.
- Perform market research and user surveys to develop a user-friendly web-based interface for data search and retrieval.
- Perform periodic data validation of the existing entries, including quality control and quality assurance.
- Obtain concurrence from the Division of AIDS for the expanded database after year 1 of the phase II award and improve the database in a collaborative, iterative process through outreach to the scientific user community.
- Create a website for user access and advertisement of the database in the first year of the phase II contract leveraging the NIAID Data Ecosystem.
- Continuously curate new publicly available literature for newly developed SIV and SHIV strains and maintain the database for another two years. For example, develop (semi-) automated algorithms/systems to keep the database/knowledge base up to date with newly published information, into a self-maintaining dataset, e.g., using artificial intelligence-based knowledge discovery methods.
- Provide, upgrade, and maintain hardware and networking architecture for the database for a widely distributed user network, including international users.
- Establish and track performance metrics to determine utilization and utility of the web portal within the scientific community.
- Integrate the database into an existing larger database or data repository in the last six months of the phase II contract. The larger database for integration will be determined by the Division of AIDS in a timely manner.

***This SBIR contract topic will <u>not</u> support:***
- Lab supplies and animal studies
- Entry of HIV strains into the database
- Viruses other than SIV or SHIV

**NIH/NIAID 114 - Point-of-Care HIV Viral Load, Drug Resistance, and Adherence Assays**

Phase I and Fast Track proposals **<u>will be</u>** accepted.
Direct to Phase proposals II **<u>will not</u>** be accepted.
Number of anticipated awards: 3-5

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

***Background***
A new initiative by the US Government (https://www.hiv.gov/federal-response/ending-the-hiv-epidemic/overview) seeks to reduce the number of new HIV infections in the United States by 75 percent within five years, and then by at least 90 percent within 10 years. Most new infections occur in a limited number of counties and among specific populations. One of the necessities to reduce HIV incidence in the US are point-of-care assays to assist People Living with HIV (PLWH) or people at high risk of HIV infection manage their condition and prevent HIV transmissions among the US population. The solicitation would support two of the four pillars: 1. Treat people with HIV rapidly and effectively to reach sustained viral suppression, and 2. Prevent new HIV transmissions by using proven interventions, including pre-exposure prophylaxis. 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 long-term goals are to propose 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 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 (PLWH) on/off antiretroviral therapy or on PrEP to detect viral spikes during ART therapy, viral rebound during analytical treatment interruption, HIV breakthrough infection during PrEP, or to rule out HIV infection in the presence of an HIV vaccine-induced immune seroreactivity.

- 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
  - o have a minimum sensitivity of <500 RNA copies per mL of HIV-1 or equivalent if a biomarker is used.
  - o at a minimum be able to detect HIV strains circulating in the US but detection can be extended to other HIV-1 subtypes.
  - o have a short diagnostic time to the final result (optimally 20 minutes or less but no longer than 1 hour).
  - o 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. HIV Drug Resistance Monitoring**

- Develop an inexpensive, easy-to-use, POC assay that will detect the presence or absence of five common HIV drug resistance mutations in blood samples from patients failing HAART regimens.
- Must detect HIV resistant variants in blood specimens from HIV-infected individuals with HIV RNA viral loads above 500 copies/mL.
- Methods that detect a set of relevant point mutations and methods that collect full sequences are both acceptable, but the method must be developed for POC testing by trained professionals in clinics.
- For methods that detect point mutations, a set of relevant mutations should be proposed in the application but will be finalized in cooperation with DAIDS program staff.
- The method must be appropriate for use in clinics with a target turnaround time of less than 2 hours and an initial target cost of $100 or less.

**3. 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
  - o PrEP adherence
  - o ART adherence to trigger adherence interventions
  - o The long-tail associated with long-acting ART or PrEP
  - o Blood donations for PrEP or ART drug levels (as a risk indicator of HIV exposure or infection)

All three assays will assist with monitoring HIV viral loads, HIV drug resistance, and adherence to antiretrovirals. The ultimate goal is to increase viral suppression under combination ART and to monitor the effectiveness of PrEP.

***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/NIAID 115 - Development of Diagnostics to Differentiate HIV Infection from Vaccine-Induced Seropositivity**

Phase I and Fast Track proposals **<u>will be</u>** accepted.
Direct-to-Phase II proposals **<u>will not</u>** be accepted.
Number of anticipated awards: 3-5

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

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

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

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

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

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

devices.

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

Since test(s) will also be deployed in low-to-middle-income countries and remote areas, dependency on refrigeration and electricity must be kept to a minimum, and shelf life should be maximized. Special attention must be given to how results are obtained or communicated in order to protect confidentiality and privacy. Finally, production and operating costs should be as low as possible to make it affordable to individuals and institutions, and practical for repeated testing by the end-user.

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

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

***This SBIR contract topic will <u>not</u> support:***
- The design and operation of clinical trials (see https://grants.nih.gov/grants/glossary.htm#ClinicalTrial for the NIH definition of a clinical trial); and
- Testing non-HIV immunogens or studies unrelated to HIV vaccine development efforts.

**NIH/NIAID 116 - Adjuvant Discovery for Vaccines for Infectious and Immune-Mediated Diseases**

Fast-Track proposals **<u>will be</u>** accepted.
Direct-to-phase II proposals **<u>will be</u>** accepted.
Number of anticipated awards: 1-3

Budget (total costs):
Phase I: $300,000/year for up to 2 years;
Phase II: $1,000,000/year with appropriate justification by the applicant for up to 3 years.

***Background***
The goal of this program is to support the screening for new vaccine adjuvant candidates against infectious diseases or for tolerogenic adjuvants for the treatment of autoimmune or allergic diseases. For the purpose of this SBIR, the definition of <u>vaccine adjuvants</u> 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." <u>Tolerogenic adjuvants</u> are defined as compounds that promote immunoregulatory or immunosuppressive signals to induce non-responsiveness to self-antigens in autoimmune diseases or transplantation, or environmental antigens in allergic diseases.

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

In addition, adjuvants may facilitate the development of immunotherapeutics for immune-mediated diseases (e.g., allergic rhinitis, asthma, food allergy, autoimmunity, transplant rejection). The field of tolerogenic adjuvants is still in its infancy. No compounds have been licensed yet in the U.S. and immune-mediated diseases are treated mostly with broadly immunosuppressive drugs or long-term single- or multi-allergen immunotherapy. In contrast to drugs, tolerogenic or immunomodulatory adjuvants may regulate immune responses to specific antigens through a variety of mechanisms, including induction of regulatory T cells or alterations in the profile of the pathogenic lymphocyte response (e.g., Th1 to Th2 or vice versa). For tolerogenic and immune modifying adjuvants, the antigens may originate from environmental (allergy) or endogenous (autoimmunity) sources and may not need to be supplied exogenously together with the adjuvant. When pursuing this approach, the proposal must describe a compelling mechanism by which the adjuvant would modulate an antigen-specific response, and include studies demonstrating altered or suppressed responses against the allergen or autoantigen.

Recent advances in understanding of innate immune mechanisms have led to new putative targets for vaccine adjuvants and for immunotherapy. Simultaneously, progress is being made in the identification of *in vitro* correlates of clinical adjuvanticity, which allows the design of *in vitro* screening assays to discover novel adjuvant candidates in a systematic manner.

The gaps that need to be addressed by new adjuvants include improvements to existing vaccines (e.g., the acellular pertussis vaccine, influenza, etc), and development of vaccines for: emerging and re-emerging threats (e.g., coronaviruses, enteroviruses, MRSE/A, pandemic preparedness); vulnerable 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.

***Project Goal***
The objective of this program is to support the screening for new adjuvant candidates for vaccines against infectious diseases, or for autoimmune and allergic diseases, or transplantation tolerance; their characterization; and early-stage optimization.

***Phase I Activities include, but are not limited to:***
- Optimize and scale-up screening assays to identify new potential vaccine- or tolerogenic adjuvant candidates
- Create targeted libraries of putative ligands of innate immune receptors
- Conduct pilot screening assays to validate high-throughput screening (HTS) approaches for identifying adjuvant candidates
- Develop or conduct *in silico* screening approaches to pre-select adjuvant candidates for subsequent *in vitro* screens and validation

***Phase II Activities include, but are not limited to:***
- High thorough-put screening (HTS) of compound libraries and confirmation of adjuvant activity of lead compounds
- Confirmatory *in vitro* screening of hits identified by HTS or *in silico* prediction algorithms
- Optimization of lead candidates identified through screening campaigns through medicinal chemistry or formulation
- Screening of adjuvant candidates for their usefulness in vulnerable populations, such as the use of cells from cord blood of infants or elderly/frail humans
- Screening of adjuvant candidates in animal models representing vulnerable human populations

***This SBIR will <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 previously identified adjuvants
- The conduct of clinical trials (see https://grants.nih.gov/grants/glossary.htm#ClinicalTrial for the NIH definition of a clinical trial)

**NIH/NIAID 117 - 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.

***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 also could help reduce the dose, frequency, and duration of allergen administration in the context of allergen immunotherapy and reduce adverse allergic reactions, leading to higher acceptance and effectiveness.

New or improved 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 mimics of late-stage adjuvants or adjuvants in licensed vaccines, would offer more flexibility to vaccine developers, for the net benefit of the public.

***Project 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, modulate 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
- Tolerogenic or immune deviating adjuvants for use in the prevention or treatment of immune mediated diseases
- Novel combination adjuvants
- Adjuvants that functionally replicate those used in licensed vaccines

***This SBIR will <u>not</u> 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/grants/glossary.htm#ClinicalTrial 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 118 - Reagents for Immunologic Analysis of Non-mammalian and Underrepresented Mammalian Models**

Fast-Track proposals **<u>will be</u>** accepted.
Direct-to-phase II proposals **<u>will be</u>** accepted.
Number of anticipated awards: 3-6

Budget (total costs):
Phase I: $300,000/year for up to 2 years;
Phase II: $1,500,000 with appropriate justification by the applicant for up to 3 years.

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

Non-mammalian models are easily tractable model systems to study basic, conserved immune defense pathways and mechanisms. For example, characterization of the *Drosophila* Toll signaling pathway facilitated the discovery of mammalian Toll-Like Receptors (TLR), which significantly accelerated progress made in the field of innate immunity. Non-mammalian models can be much more easily adapted to high-throughput screening formats than mammalian organisms. *Caenorhabditis elegans* has been used for whole-organism, high-throughput screening assays to identify developmental and immune response genes, as well as for drug screening. Many non-mammalian species are natural hosts for human pathogens and share many conserved innate immune pathways with humans, such as the NF-κB pathway in mosquitoes, the intermediate hosts for *Plasmodia* parasites. However, studies to better understand immune regulation within non-mammalian models have been constrained by the limited availability of antibodies and other immune-based reagents for use in scientific studies. Certain mammalian models display many features of human immunity but are similarly underutilized due to limited availability of immunologic reagents. For example, the progression of disease that follows infection of guinea pigs with *Mycobacterium tuberculosis*, the causative agent of tuberculosis (TB), displays many features of human TB. While this model has been used for more than 100 years as a research tool to understand and describe disease mechanisms, immunologic analyses are constrained by the limited availability of immunological reagents specific for the guinea pig. Another example is the ferret model, one of the best animal models of human influenza infection, where immunologic studies also have been limited by the lack of immunological reagents. In addition, minks are highly susceptible to SARS-CoV-2 infection with potential for zoonotic pathogen transmission. However, there are almost no reagents available for immunological studies in this species. Lastly, although bats are the natural reservoir and vector for several major zoonotic diseases that cause severe human diseases, the lack of reagents has impeded studies of how bat adaptive or innate immune responses control these pathogens without manifestation of disease.

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

***Phase I Activities must include the following activities:***
- Selection of targets, which may include: immune cell markers; receptors with immune function; or other molecules important for immune function;
- Development of antibodies or other reagents against these targets,
    - If polyclonal antibodies are being developed, the plan also must include the development of monoclonal antibodies;
- Characterization of antibodies or reagents developed (*e.g.,* confirmation of binding to the intended native antigen/immunogen by flow cytometry and other assays) using at least two different assays.

***Phase II Activities must include:***
- Comprehensive evaluation of specificity, functional utility, and cross-reactivity (off-target binding) of antibodies/reagents, which must minimally include evaluation of non-specific binding to cells or unrelated molecules and utility of antibodies/reagents for Western blotting (denatured and native protein), immunoprecipitation, immunohistochemistry and flow cytometry. Screening for cross-reactivity with related molecules on other non-mammalian species or mammalian immune cells;
- Optimization (*e.g.,* secondary modifications/conjugations) of the antibodies/reagents for use in different assays and platforms;
- Scale-up production of the 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 response; or
- Development of novel or refined animal models.

**NIH/NIAID 119 - Adaptation of CRISPR-based *in vitro* diagnostics for rapid detection of select eukaryotic pathogens**

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***
Ultrasensitive field-deployable diagnostic assays are an unmet need for malaria and select neglected tropical diseases (NTDs), as current assays lack the performance needed to achieve disease control and elimination goals. Rapid assays in current use are suboptimal for surveillance to detect the asymptomatic reservoir (malaria), case finding (human African trypanosomiasis), early detection for effective treatment (visceral leishmaniasis), and species differentiation (malaria, cutaneous leishmaniasis, onchocerciasis/*Loa loa*). Nucleic acid tests achieve high sensitivity and specificity but require specialized laboratory equipment and trained personnel, making them unsuitable for resource-constrained settings (RCS). Clustered regularly interspaced short palindromic repeats (CRISPR)-based diagnostics provide analytical sensitivity comparable to PCR, while offering several advantages, including high programmability, and compatibility with low cost, low complexity test formats. Application to infectious diseases has thus far been largely limited to viral and bacterial pathogens.

***Project Goal***
The goal of this solicitation is to adapt CRISPR-based diagnostic technologies to detect select eukaryotic pathogens at the point of need with higher sensitivity and specificity than rapid diagnostic tests (RDTs) in current use. Targeted pathogens should include at least one of the following: *Plasmodium* spp., *Leishmania* spp. (visceral or cutaneous), *Trypanosoma brucei*, *Onchocerca volvulus/Loa loa*. Areas of research will include the development of simplified sample-preparation protocols, robust target enrichment protocols, and a field-amenable readout.

***Phase I activities:***
- Development of initial CRISPR-based diagnostic prototype.
- Demonstration of successful isothermal pre-amplification strategy, if pre-amplification is required to achieve desired sensitivity and specificity.
- Demonstration of successful CRISPR-based target enrichment.
- Development of rapid and low-cost readout.
- Development, integration, and validation of internal process controls.
- Determination of the sensitivity, specificity and other performance characteristics (e.g., time to result, limit of detection, test stability) of the diagnostic.
- Initial testing on laboratory isolates.

***Phase II activities:***
- Continued development and validation of prototype.
- Development of well-defined test platform under good manufacturing practices (GMP).
- 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:***
- Clinical trials (see https://grants.nih.gov/grants/glossary.htm#ClinicalTrial for the NIH definition of a clinical trial).

**NIH/NIAID 120 - Modular Sample Preparation for In-Field Viral Discovery**

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

Number of anticipated awards: 1-2

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

***Background***
In-field surveillance of wildlife and screening at-risk populations in an endemic area are essential for predicting and containing future epidemics/pandemics of viral pathogens. In remote settings or low and/or middle-income countries (LMIC), resources are limited, which makes high volume diagnostic testing challenging. Sample collection and preparation are important components for diagnostics, but the generation of high-quality samples (e.g., RNA, serum) relies on resources (laboratories; centrifugation; electricity) that are typically lacking in a remote setting. There is an urgent need for consistent and reliable in-field sample preparation to generate high-quality analyte(s) for subsequent discovery technologies. Modular systems that allow rapid, simple, high-throughput processing of specimens (e.g., blood, sputum, swabs, urine, feces, tissues) will improve the efficiency of surveillance and screening activities for pathogens with epidemic/pandemic potential.

***Project goal***
The goal of this solicitation is to develop modular, rapid, and reliable sample processing technologies that can be used in combination with an established diagnostic platform (e.g., NGS, LFIA, LAMP) for the detection of viral pathogens with pandemic potential (e.g., Filo-, Bunya-, Corona-, Paramyxo-, Flavi-, Togaviruses). The proposed sample processing technology may employ selective enrichment of pathogens, or their biochemical components, to concentrate samples and to reduce the amounts of interfering substances. The in-field sample processing systems should provide stabilization of the extracted samples to allow for storage in field environments where, for example, refrigeration is not readily available, and/or transport (if needed) prior to diagnostic analysis. Ideally, the modular systems should accommodate high-throughput sample processing for surveillance and screening activities. The final product must be designed to rapidly extract the high-quality analyte(s) from human or animal specimens such as blood, urine, feces, saliva, and swabs, without requiring resources such as laboratories, electricity, or centrifuges.

***Areas of research will include:***
- Development of improved technologies for rapid sample processing in the field, and if appropriate, concentration, storage, and recovery in a form suitable for subsequent diagnostic platforms.
- Development, incorporation, and validation of process controls that will demonstrate that quantity and quality of analyte(s) are sufficient to allow for detection of the pathogen in the diagnostic platform of choice.

***Phase I activities:***
- Development of initial prototype for sample processing system
- Development and validation of appropriate pathogen-capture/enrichment reagents, if appropriate
- Development, incorporation, and validation of process controls that will demonstrate that purity, concentration, and yield of analyte(s) are sufficient for subsequent steps in diagnostics (e.g., library generation for NGS; LFIA; LAMP).
- Demonstration that prototype is capable of capturing the pathogen and/or purifying the analyte(s) of interest using animal or deidentified human samples (e.g., blood, serum, saliva, tissue)

***Phase II activities:***
- Continued development and validation of prototype
- Demonstration that performance and reliability of final product are equal to or better than standard commercial products in generating high quantity and quality analyte (s) using metrics such as yield, concentration, purity, and absence of inhibitors, as required for the subsequent diagnostic platform of interest (e.g., library generation for NGS, LAMP, LFIA).
- Process development for the manufacturing of diagnostic components, including Quality Assurance/Quality Control methods for analyte(s) recovery, characterization, purification, identity, and stability.

***This SBIR will <u>not</u> support:***
- Proposals that are focused on the development of a diagnostic. The development of novel diagnostic platforms is not intended with this solicitation.

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

**NIH/NIAID 121 - Artificial Intelligence to Improve Clinical Microscopy for Diagnosis of Infectious Diseases**

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***
Diagnosis of infectious disease using clinical microscopy applications, such as smear microscopy, is often limited by poor sensitivity and dependence on the expertise of technical staff. Low pathogen burden may be undetected by the human eye or by reader fatigue and in some settings, such as low resource settings, by the lack of adequate number of well-trained technicians.

Advances in image analyses, in particular application of artificial intelligence (AI), have the potential to automate clinical microscopy methods and support more timely and accurate diagnoses. Accurate and sensitive automated AI driven interpretation of clinical microscopy tests, especially smear tests, can address many of the current limitations allowing for improved remote access to care and high throughput testing.

NIAID continues to support and encourage the development of modern tools for diagnosis. Many point-of-care (POC) settings continue to rely on smear and other clinical microscopy tools and improving the reliability of these tools will improve diagnosis, even as new diagnostic technologies are in development. Once developed, image-based AI analysis is inexpensive and amenable to use at the point of care, including in low resource settings.

***Project Goal***
The purpose of this solicitation is to develop Artificial Intelligence (AI) applications to improve clinical microscopy for diagnosis of infections, especially automated smear reading of blood, sputum, stool, or other clinical samples with the goal of improving current, widely used diagnostic tools. Of particular interest are AI applications for identification of bacteria, viruses and parasites in sputum, blood, and other clinical specimens. Examples include: identification of *Mycobacterium tuberculosis (Mtb)* in sputum; blood slide reading for malaria infection or sepsis; stool slide reading to identify schistosomes and soil-transmitted helminth (STH) eggs by species; and applications for detection of sexually transmitted infections, including automated reading of rapid plasma reagin (RPR) tests for syphilis and clue cell identification for bacterial vaginosis.

***Phase I activities may include, but are not limited to:***
- Early development of automated AI tools for identification of infectious agents
- Proof of concept studies
- Initial algorithm training and testing of AI tools with clinical samples or spiked human samples
- Adaptation of existing AI automated imaging tools for use to diagnosis one or more infectious diseases

***Phase II activities may include, but are not limited to:***
- Iterative improvement of existing AI tools for automated clinical microscopy
- Large scale validation of AI tools on clinical samples
- Adaption of AI tools to pair with a POC device
- Assessment of operator use of automated tools

***This SBIR will not support:***
- The design and conduct of clinical trials
- (see https://grants.nih.gov/grants/glossary.htm#ClinicalTrial for the NIH definition of a clinical trial).
- AI applications for detection of abnormal cytology, e.g. pap smear identification of abnormal cells due to HPV infection, identification of abnormal blood cells
- Clinical microscopy for diagnosis of non-communicable disease

**NIH/NIAID 122 - Advanced and Immersive Visualization Tools for Infectious and Immune-mediated Disease Research**

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 for up to 1 year;
Phase II: $1,000,000 for up to 3 years if accept direct to Phase II proposals.

***Background***
The objective of this topic is to support visualization and analysis of large, multidimensional, and complex datasets from basic and clinical research in infectious, immunologic and allergic diseases through the integration of enhanced and immersive three-dimensional (3D) visualization technologies and advanced computational tools.

NIAID-funded extramural and intramural research projects are generating large volumes of complex and diverse datasets. From microbial biomolecular structures and pathogen whole genome sequence data, to clinical data and medical images, the research findings from these studies enhance our understanding of pathogens and infectious and immune-mediated disease pathogenesis. Translating these discoveries into clinical applications accelerates development of novel diagnostics, therapeutics, and vaccines.

As these research datasets continue to expand in size and complexity, the ability of basic and clinical researchers to explore large volumes of data points and ultra-high resolution images is fettered by the bounds of standard computer displays, which are limited to around one to four million pixels. Installation of video walls and multi-panel displays allow users to capitalize on the immense volume and detail in the datasets by visualizing tens of millions of pixels at a time, and facilitate collaborative exploration of data. At the same time, virtual reality (VR) and augmented reality (AR) technology provide immersive experiences with stereoscopic depth information, and unique vantage points that are not possible with a two-dimensional screen. Spreading data out into the third dimension facilitates visualization of much greater amounts of data, and in a more comprehensible way.

Together, these new and emerging 3D visualization technologies help researchers to explore, understand, and communicate complex data. The NIAID seeks to capitalize on these advancing technologies to accelerate new research discoveries from data generated or collected across NIAID extramural and intramural projects from multiple sources and platforms.

At present, the adoption and utilization of 3D technologies, such as large-scale display systems and immersive VR/AR environments, is hindered by a lack of tools that allow for portability and mobility of results outside of the visualization/analysis tool, such that they can be exported or imported in various formats for sharing and interoperability with different types of hardware or traditional visualization methods. At the same time, web-based and/or cloud-enabled tools are needed to facilitate access across device platforms and encourage collaborative research and communication of results. Researchers require new tools with intuitive graphical user interfaces for importing and interacting with large datasets, especially as it applies to unstructured data. Integration of machine learning algorithms into user-friendly tools is necessary for scientists and clinicians to capitalize on the latest data science techniques, without having extensive training in that domain.

This project builds up NIAID's investment across the spectrum of technologies related to advanced visualization, including those that incorporate large-scale, interactive, and immersive 3D experiences. The types of data for these visualization tools includes, but is not limited to, genomics and other -omics datasets, host-pathogen interactions, molecular structures, medical imaging, and clinical data. The rapid response of the scientific community to share SARS-CoV-2 and COVID-19 related data during the COVID-19 pandemic underscores the need for innovative tools that combine advanced or immersive visualization with machine learning to accelerate discovery in basic and clinical research and improve the development of new diagnostics, therapeutics, vaccines, and other technologies that impact the health of millions of people in the United States and around the world.

***Project Goal***
The project goal is to support the development, enhancement or adaptation of innovative, robust, user-focused tools for data visualization and analysis that are applicable to basic and clinical infectious and immune-mediated diseases. The ability to make visualization-focused analytical tools user-friendly for all, and accessible to researchers with less data science domain knowledge, is paramount to deriving insights and communicating research findings.

NIAID encourages proposals aimed at developing and improving tools that integrate new and emerging 3D technologies in visualization, analysis, and communication of research data in infectious and immune-mediated diseases. Project proposals should incorporate user-focused documentation, such as user guides, standard operating procedures (SOPs), and training materials developed along with the visualization/analysis tool for broad use beyond the developer. An optimal outcome would be the creation of a research informatics tool that addresses the challenges of data integration and results sharing, and that incorporates machine learning algorithms along with two or more of the following capabilities:

- 3D visualization in a browser-based environment.
- Support for use with virtual and/or augmented reality head-mounted displays.
- Visualizations that are enhanced through the use of multidimensional, high-resolution displays – suitable for a video wall or other devices with tens of millions of pixels.

***Phase I Activities and Expected Deliverables:***

- Provide an overall plan and justification to develop a new informatics tool or significantly enhance, modify, improve, or adapt existing tools for visualization and integrative analysis of multi-scale data from multiple sources and platforms including publicly available data repositories for infectious and immune-mediated disease research.
- Provide use cases and describe the potential user communities that will benefit.
- Identify public data repositories to be investigated by the analysis tool, and suggest end points of the analyses.
- Assemble a team with appropriate expertise to support design, development, and testing; subject matter experts in infectious disease should be engaged in selection, analysis, and presentation of the data and interpretation of the results.
- Develop an (early) prototype for the tool and perform alpha testing with representatives of the user community.
- Evaluate and report results of alpha testing and address issues based on user feedback.

***Phase II Activities and Expected Deliverables:***

- Further development, enhancement, adaptation, integration, and optimization of the prototype visualization and analysis tool.
- Demonstrate usability by the infectious and immune-mediated diseases research community in a beta testing phase.
- Document feedback, address issues, and finalize the prototype tool.
- If appropriate, plan for and implement deployment of the tool.
- Develop user focused documentation, user guides, SOPs and training materials; algorithms packaged within the application should be transparent, to facilitate reproducibility of results.

***The SBIR will not support:***

- Projects proposing significant data generation for validation and testing of informatics tools.
- Development of wearable device hardware, including VR/AR headmounted displays
- Projects developing wet-laboratory experimental methods, research or technologies
- Projects focused on data "dashboards" that do not incorporate analysis tools

**NIH/NIAID 123 - Data Science Tools for Infectious and Immune-mediated Disease Research**

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 for up to 1 year;
Phase II: $1,000,000 for up to 3 years if accept direct to Phase II proposals.

***Background***

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

Innovation in optimal search and discovery of biomedical data is still lacking. Moreover, non-interoperable data impedes the ability to answer sophisticated biological questions across diverse data types without significant harmonization. Although there is considerable effort in developing standards and data curation programs to address these challenges, they are mostly

manual, expensive, and not scalable.

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

***Project Goal***

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

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

- Increase the findability of data by utilizing information that includes, but is not limited to data, metadata, associated literature, and text;
    - Improve indexing by popular search engines and recommend or discover relevant data sets beyond the original search;
    - Perform automated curation and quality control;
    - Increase data searchability and interoperability multiple resources by application and adoption of community standards and ontologies that may include software pipelines or platforms to automate annotation, markup, or curate datasets not compatible with community standards, formats, or controlled vocabularies;
    - Harmonize clinical data via customized data harmonization pipelines which among other features could combine data sets or un-merge combined data sets;
- Standardize the de-identification, and other privacy-preserving approaches, of individual patient level data and allow the timely sharing of human clinical research data including tools that can assess and minimize the risk of re-identification.
- Develop and improve quantum algorithms that leverage quantum computing to improve computational capabilities to analyze complex molecular and imaging data.

***Phase I Activities***

- Establish a project team composed of experts in software development and as appropriate to the project include but not limited to expertise in statistics, infectious and immune mediated diseases, or clinical research.
- Provide an overall development plan with milestones and deliverables for the proposed tool.
- Provide justification and unique value proposition for the development, adaptation or enhancement of this specific tool in light of the currently available tools.
- Describe the potential user communities and provide relevant use cases.
- Develop an (early) prototype for the tool, perform alpha testing, and address issues from testing and solicit feedback from the appropriate user community.

***Phase II Activities***

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

***The SBIR will not support:***

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

## 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 113 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.

**NIH/NHLBI 114 Device to Permit Continuous Self-Monitoring of Blood Oxygen Saturation During Activities of Daily Living for Individuals at Risk for Desaturation During Physical Exertion**

**Budget and number of awards:**

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

**Number of anticipated awards:** 2 Phase I, 1 Phase II

**Budget (total costs per award):** Phase I: **$300,000** for **12** months, Phase II: **$3,000,000** for **3** years

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

**Summary:**
The need for a new device that patients can use to monitor blood oxygen saturation (SpO2) during activities of daily living (ADL) has never been greater. In addition to more people living with chronic cardiorespiratory diseases than ever before, at least 49.6 million people in the US have tested positive for COVID-19. Changes in lung diffusion capacity place survivors of COVID-19 at risk for persistent oxygen desaturation, especially during physical exertion. Continuous self-monitoring of SpO2 during activities of daily living (ADL) that require physical exertion as well as during independent exercise regimens permit patients to appropriately adjust exertion and supplemental oxygen levels to optimize outcomes and safety.

Increasingly popular, new models of virtual cardiopulmonary rehabilitation and related therapies improve accessibility and reduce barriers to participation and are currently under investigation (NCT04664101, NCT04649736, NCT05003271, NCT04982042,

NCT04634318) or in use for post-COVID and other patient populations. Such solutions must be supported by adequate remote monitoring technology (i.e. pulse oximeters useable during exercise) to maintain safety in the unsupervised, at-home setting. A recent investigation of a "mobile health" exercise prescription for patients with interstitial lung disease (ILD) indicated that ability to self-monitor SpO2 is critical to acceptability and adherence to an at-home program for those prone to desaturation during exercise. An important application for a new home SpO2 monitor is the control of oxygen desaturation due to obstructive sleep apnea, for patients to use during sleep monitoring, a situation that occurs in other than lung diseases.

Unfortunately, currently available pulse oximeters fall short for these applications. Devices used in the clinical setting are not designed for continuous wear and are cumbersome and impractical for exercise and sleep. Consumer-grade fingertip pulse oximeters ($25 to $100), wrist-wearable device sensors such as those included in newer models of Fitbit, Garmin, and Apple fitness trackers ($120 to $800), and smartphone-based sensors are not FDA-approved and do not have algorithms written to control for motion artefact. They also do not continuously sample data from biosensors to detect desaturation during exercise. Rather, device instructions specify measurement at rest during normal, quiet breathing and keeping the measurement location stationary. Despite these limitations, use of home pulse oximetry by patients with cardiopulmonary disorders is increasingly common, consistent with the rapidly expanding paradigm of disease self-management enabled by advances in remote health monitoring technology.

**Project Goals:**

The goal of this Phase I topic proposal is to develop a novel wireless pulse oximeter device for at-home use that is suitable for wear during physical activity and sleep. The device must interface with a wide variety of smartphones and wearable devices, incorporate user-centered design methods, and share data in a way that is easy to understand. It must incorporate accurate hardware and software technology features available to minimize bias and maximize precision and accuracy for continuous monitoring during physical exertion. Such a device will improve the customization of at-home exercise prescriptions and the detection of adverse desaturation events during exercise and other physical ADLs.

**Phase I Activities and Expected Deliverables**

This Phase I award will be used establish the technical merit, feasibility, and commercial potential of the proposed R&D and to determine the quality of performance of the small business awardee organization. The expected milestones and deliverables are as follows:

- The development of a wearable device for patient self-monitoring of SpO2 that is:
  - Wireless
  - Comfortable to wear and does not impede movement of extremities and digits during various modes of physical activity or sleep
  - Capable of interfacing with Android and iPhone smartphone apps and/or other commercially-available wearable fitness/activity trackers for validation of oxygen saturation in real time, so that patient can transmit data to clinical lab or healthcare provider
  - User-friendly and displays data in an easy-to-understand format
  - Incorporates motion-insensitive hardware and software technology features that minimize bias and maximize precision and accuracy for continuous monitoring during physical activity.
- Develop the prototype by testing it on a small group of patients (n=10-20) that desaturate during physical exertion, tested during simulation of common physical ADLs and during exercise of varying type and difficulty. This prototype will be validated against clinically obtained data by DIR laboratory. The diversity of subjects needs to be considered in measurement of oxygen saturation with the proposed pulse oximeter

**Phase II Activities and Expected Deliverables**

The Phase II award will be used to continue the R&D efforts initiated in the Phase I award. The expected milestones and deliverables are as follows:

1. Further refining prototype and accompanying smartphone app by conducting focus group studies for usability and durability to optimize user interface and data output.
2. Conduct clinical trials.
3. Apply for FDA authorization.
4. Work to develop commercialization for large-scale distribution.

Offerors are advised to plan travel to NHLBI in Bethesda, Maryland. Offerors are expected to plan meetings at project initiation, at mid-project to determine what iteration is necessary, and at project completion. The contracting DIR lab offers to perform a clinical trial at no cost to the awardee.

**NATIONAL INSTITUTE ON DRUG ABUSE (NIDA)**

NIDA is the lead federal agency supporting scientific research on drug use and its consequences. Our mission is to advance science on the causes and consequences of drug use and addiction and to apply that knowledge to improve individual and public health through: 1) strategically supporting and conducting basic and clinical research on drug use, its consequences, and the underlying neurobiological, behavioral, and social mechanisms involved; and 2) ensuring the effective translation, implementation, and dissemination of scientific research findings to improve the prevention and treatment of Substance Use Disorders (SUDs) and enhance public awareness of addiction as a brain disorder.

***NIDA Topics***

This solicitation invites proposals in the following areas:

**NIH/NIDA 167 - Cause of Death Elucidated (CODE) in Drug Overdose: research and development of new postmortem toxicology screening devices that are portable, rapid, accurate, affordable, and accessible**

Fast-Track Proposals will be accepted
Direct-to-Phase II proposals will be accepted
Number of Anticipated Awards: 3-4

Budget (total costs, per award):
Phase I: up to $400,000 for up to 12 months
Phase II: up to $2,000,000 for up to 2 years

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

***Background***

Over 840,000 individuals in the US have died from drug overdoses from 1999 to 2021, and, distressingly, the rate of fatal overdoses has been accelerating in recent years (https://nida.nih.gov/drug-topics/trends-statistics/overdose-death-rates). The enormous death toll has strained the resources needed to track the drug epidemic accurately. Over the past 20 years, approximately 20% of drug overdose death records did not specify the drug involved. Because drug overdose mortality counts describing specific drugs are regularly underreported, this severely hinders accurate monitoring of death rates, which then curbs public health authorities' ability to identify threats in a timely manner and to implement effective interventions or care in communities impacted by drug overdoses.

Currently, suspected drug overdoses represent more than 1 in 6 death investigations, and both coroner and medical examiner offices are facing overwhelming caseloads that require comprehensive toxicology analysis. Therefore, there is a critical and immediate need to improve the workflow in suspected fatal overdose cases with new postmortem toxicology screening tools.

***Project Goal***

The National Institute on Drug Abuse (NIDA) is soliciting proposals from small business concerns (SBC) to develop new postmortem toxicology screening devices that are portable, rapid, accurate, affordable, and accessible.

The technologies for toxicology screening devices may be based on mass spectroscopy, infrared spectroscopy, Raman spectroscopy, or immunoassay. Novel emerging technologies are also encouraged, as long as they satisfy this solicitation's intent to deliver user-friendly, cost-efficient, rapid, portable and accurate toxicology screening devices into the marketplace.

Projects to address this topic require multidisciplinary efforts to succeed and, therefore, the project team must possess the technical/scientific expertise to engineer the devices and the experience in product development.

***Scientific/Technical Scope***

Proposals should aim to develop working prototypes by the end of Phase II and should describe a clear plan to achieve this goal.

Table 1 describes the features of an ideal postmortem toxicology screening device (A) to be developed as the result of this solicitation, with two commonly used platforms in postmortem toxicology testing (B and C) as comparators.

Table 1. Product Value Proposition for Novel Forensic Toxicology Testing Device

| Features | Ideal Postmortem | Automated | LC/MS-MS |
|---|---|---|---|

| | Toxicology Screening Device A | Immunoassay Analyzer B | C |
|---|---|---|---|
| | | | |
| **Must Haves** | | | |
| Capability to identify >500 drugs and drug metabolites | Yes | Yes | Yes |
| Capability to analyze samples of whole blood | Yes | Yes | Yes |
| Device consumables stable at room temperature | Yes | Yes | Yes |
| | | | |
| **Performance Benefits** | | | |
| Cost of device | $5 - $25,000 | > $100,000 | > $300,000 |
| Type of analysis | Semi-quantitative | Qualitative | Quantitative |
| Test kit format | Test devices and reagents | Same plus controls | Same plus controls |
| End-user profile | Non-professional in the field conditions | Non-professional/ Professional in laboratory | Professional in laboratory |
| Training needs | ≤ 2 hours | 1 day | Weeks |
| Sample preparation steps | ≤ 3 | 3 | 3 |
| Need to transfer a precise volume of sample | No need for precise volume | Need precise volume | Need precise volume |
| Time to obtain results | ≤ 60 minutes | 20 minutes | 2 - 3 days |
| Device weight | < 25 pounds | 100 pounds | > 200 pounds |
| Operating conditions | 10-35°C; 25-80% RH | 20-25°C; 30% - 50% RH | 20-25°C; 30% - 50% RH |
| Power requirement | Connect to power outlet and runs on rechargeable battery with > 1 hour life | Connect to power outlet | Connect to power outlet |
| Biological sample transport required | No | Yes | Yes |
| Need for calibration with standards | Annual | Annual | Daily |
| | | | |
| **Delighters** | | | |
| Data storage | Cell phone communication and data storage | LIMS | LIMS |
| Disposable | Yes | No | No |

All proposed products must meet the Must Haves requirements listed in Table 1. In cases when the postmortem toxicology screening devices cannot be designed to meet any one of the Must Haves, such devices may not be a viable option to compete in the marketplace. Therefore, an ideal postmortem toxicology screening device must have the capability to detect and identify >500 drugs or drug metabolites in samples of decedent's whole blood and utilize consumables that are stored under room temperature conditions. While it may not be possible to completely reduce to practice the identification of the desired number of drugs and drug metabolites during the life of this SBIR contract, the description of proposed technology/product should clearly demonstrate that it is technically feasible to expand and increase the number of identified molecules to be >500 with further development, which may be beyond the duration of this SBIR contract. The prototype devices should be able to identify specific drugs of interest that are listed in the 2021 ANSI/ASB Standard for the Analytical Scope and Sensitivity of Forensic Toxicological Testing of Blood in Medicolegal Death Investigations, namely, those under the drug classes of barbiturates, benzodiazepines /sedatives, cannabinoids, dissociatives, cocaine, opioids, and sympathomimetics amines. For the Must Haves listed in Table 1, there is no expectation of quantitate and/or qualitative improvements in these parameters. Therefore, for the proposed prototypes that can be designed to meet these Must Have features, the focus of the project should be on improving the Performance Benefits and, possibly, Delighter categories.

The Performance Benefits describe features that differentiate a proposed prototype from existing comparators. The best combination of Performance Benefit features for a proposed prototype optimizes its performance and utility in postmortem toxicology screening. The proposed features of a prototype may approach or exceed those of an ideal postmortem toxicology screening device described in Table 1. While it may not be possible to completely reduce to practice the desired Performance Benefits in this SBIR contract, the description of the technology should clearly demonstrate that it is technically feasible.

For Performance Benefits features, an ideal toxicology screening device should:

- be cost-competitive; the design of the proposed prototype should give consideration to the final product having manufacturing costs that should not exceed $25,000;
- deliver at least semi-quantitative (e.g., ranges of concentrations) results on drug concentrations. The cut off values for blood screen are presented in the 2021 ANSI/ASB Standard for the Analytical Scope and Sensitivity of Forensic Toxicological Testing of Blood in Medicolegal Death Investigations; for example, amphetamine (25 ng/mL), and fentanyl (1 ng/mL);
- deliver results in less than 60 minutes;
- be < 25 pounds for use in field conditions (e.g., death scene investigation): capable of operating on power outlet or on rechargeable battery with > 1 hour life and capable of operating in environments of 10-35°C and 25-80% relative humidity (RH). Field use would eliminate the need for transport of biological samples;
- be simple enough to be used by non-professionals with < 2 hours of training, should not require precise volume of sample and should reduce or eliminate the need for controls and calibration with standards.

In the description of the value proposition, Delighters provide unexpected benefits that exceed customer expectations, resulting in very high customer satisfaction, thus, positively affecting the new product's commercialization prospects. For the features in the Delighter category, an ideal toxicology screening device could be able to transmit and store data on cell phones. Additionally, ideal devices could be envisioned as disposable if they are used up or if they are damaged, since the cost of repair or maintenance would be more than the cost of the replacement device. While the absence of Delighter features does not hurt purchase and uptake, their presence improves likelihood of purchase and uptake.

The proposed prototypes for a novel toxicology screening device may not be able to incorporate all features of ideal device listed in Table 1. However, the SBC-offerors should strategically incorporate the listed features to bring the proposed device closer to the ideal.

***Phase 1 activities may include:***

- Develop software and methods
- Develop sample preparation methods consistent with the product platform
- Develop a proof-of-concept prototype product

***Phase 2 activities may include:***

- Finalize prototype
- Determine performance characteristics
- Conduct validation testing
- Design of scale-up manufacturing

***Impact***
A postmortem toxicology screening device will improve the overall monitoring of specific drugs involved in fatal overdose cases.

***Commercialization Potential***
If successful through all phases, these devices could be commercialized and marketed directly to the coroner offices, medical examiner offices, and laboratories that perform toxicology testing. Following the successful completion of this contract, SBC may consider lead applications that extend beyond the forensic toxicology markets.

***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.

## CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

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

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 030 - Developing an Over-the-Counter Diagnostic Test for Valley Fever**

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 **$1,838,436** 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***
Valley fever, also known as coccidioidomycosis, is an infectious fungal disease that can result in substantial illness and death. People can get Valley fever by breathing in the microscopic fungal *Coccidioides* spp. spores from the air. Infections range from: a) an asymptomatic, subclinical infection, to b) a symptomatic, protracted, but usually self-limited, pulmonary illness presenting as pneumonia, to c) a progressive and often life-threatening extra-thoracic disseminated infection. In southwestern U.S. endemic regions, Valley fever infections are responsible for up to one-third of community acquired pneumonia cases, and the annual economic impact is approximately $1.5 billion. Experts estimate that up to 150,000 infections occur in the United States each year.

Other endemic areas include parts of Mexico, Central America, and South America, and there is evidence that the geographic range is expanding.

Currently, no therapy is curative, and a preventative vaccine does not exist. Like many fungal diseases, early detection is critical to successful treatment. In addition, because symptoms of Valley fever are indistinguishable from those caused by other types of community-acquired pneumonia (CAP), over 70% of patients with Valley fever go through multiple rounds of unnecessary treatments with antibiotics before getting a correct diagnosis. The COVID-19 pandemic demonstrated the utility of at home diagnostic tests as valuable tools for identifying infected individuals. An over-the-counter (OTC) diagnostic test for coccidioidomycosis would not only save lives and improve outcomes for people who are at risk of developing severe infections but would also prevent thousands of unnecessary prescriptions of antibiotics that are often prescribed empirically for patents with all types of pneumonia.

***Project Goals***

The goal is to develop a simple and fast diagnostic test for Valley Fever, intended for OTC use outside of a clinical laboratory. Dipsticks and Lateral Flow Assays (LFAs) that can detect antibody or antigen in capillary fingerstick blood, saliva or other self-collected samples are examples of how such a test could be achieved. An adaptation of the already developed LFA for use with self-collected specimens can also be considered. The test should generate results that can be interpreted without the requirement of sophisticated equipment, such as a visually observable color change or appearance of a positive indicator as commonly seen in CLIA-waived* test platforms. Each individual test should include an internal positive control, insensitive to inhibitors. External positive and negative controls should also be provided, which could be accomplished through inclusion with a kit of multiple tests, or as otherwise appropriate to sufficiently control for the associated production lot. *(Clinical Laboratory Approved Amendment – CLIA)

***Phase I Activities and Expected Deliverables***

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

1.) A physical prototype suitable for further testing or, if the already developed platform is adapted, a detailed protocol describing how the test will be done.

2.) Preliminary assessment of the prototype's ability to detect *Coccidioides* spp. infection using laboratory-generated mock specimens. Examples may include blood spiked with purified antigen, antibodies, or serum from patients with coccidioidomycosis or other relevant samples.

3.) Preliminary assessment of the prototype's specificity using laboratory-generated mock samples representing other endemic fungi such as histoplasmosis and blastomycosis. Data from biological replicates performed on different days should be provided.

4.) A report summarizing progress including both raw and summary data. The report should include a summary of performance specifications observed, including a description of samples included, such as the sample origin and prior storage conditions, as well as a description of the test methodology used. The report should also include raw data results for individual replicates and controls.

***Impact***

Early diagnosis is critical to successful treatment of fungal diseases. Unfortunately, Valley fever is challenging to diagnose and current laboratory capacity is limited. Existing tests currently require specialized methods performed in a CLIA validated laboratory, and cross-reactivity with infections caused by other fungal pathogens remains an issue. A sensitive and specific test that is widely available OTC would help improve early detection and treatment, thus reducing morbidity and mortality.

***Commercialization Potential***

If successful through all phases, this technology would result in an OTC diagnostic test that could be commercialized and marketed. Demand would be driven by increasing awareness of Valley fever, and by recommendations made by public health authorities to consider testing to reap the benefits of early detection.

## 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/

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

### CDC/NCHHSTP 054- School Illness-Related Absenteeism and Learning Modality Surveillance

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 **$1,838,436** 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***
The impact of the COVID-19 pandemic on schools was unprecedented. Concerns over illness transmission in schools led to school closures causing immense economic strain as well as health impacts on students and parents. These impacts are estimated to be long-lasting and substantial and have exacerbated existing inequities. Some estimates note a loss of $128-188 billion to annual GDP due to pandemic-related unfinished learning.

CDC was tasked with identifying and tracking school learning modes and outbreaks within schools. However, the current system is not adequate for ongoing surveillance because it relies on a combination of web scraping and calling school districts. To ensure that schools can remain open, continued investment in safety preparedness must occur and reliable data is paramount to this effort.

Data on school absences, reasons for absences, outbreaks, and school closures, can all be important for local, state, and federal public health agencies seeking to understand the impact of known illnesses, such as influenza, and the emergence of new infections, such as was seen with SARS-CoV-2. Data on early indicators, such as absences, could be early indicators of an emerging risk to a community, even before cases start to appear in emergency department or other traditional healthcare system databases. However, these data must be shared quickly (i.e., within a day or two) to be of use for these purposes. These data can also help the educational system know whether they need to shift to a virtual or hybrid learning modality, plan for increased student or staff absences, or make other changes.

At the current time, only a few systems collect any parts of these data. To our knowledge, no systems provide the ability to share collected data with local, state, or federal public health agencies in real-time and without personal identifiers. With more than 17,000 school districts in the US, having many districts across the country using the same system, and sharing data

in real-time with public health, could allow for the de facto creation of a public health surveillance system using school-related data.

***Project Goals***

The long-term intent of this project is to create a new system for collecting and rapidly sharing information on school learning modality, outbreaks, and/or early warning signs such as absenteeism with local, state, or federal public health agencies. The goals of this Phase 1 project are to: (1) identify existing school data collection systems; (2) evaluate these systems using CDC's framework for evaluating public health surveillance systems as to how well they meet the needs of schools and public health agencies; (3) propose a design for a new system to meet these needs (i.e., collecting and rapidly sharing information on school learning modality, outbreaks, and/or early warning signs such as absenteeism with local, state, or federal public health agencies); and (4) describe how data from multiple school districts could be aggregated to create a state or national surveillance system.

***Phase I Activities and Expected Deliverables***

1. Identify existing, similar systems. Describe the operation of the systems including purpose, context, integration with other systems, and components. Describe the resource needs of current systems. Gather and report credible evidence on the performance of the current system (for example describe simplicity, flexibility, data quality, and representativeness).
2. Evaluate existing systems against CDC's framework for evaluating public health systems to determine their timeliness and completeness for sharing with public health agencies.
3. Propose a design for a new system. Describe system requirements. Describe ability of proposed system to meet goals of timely sharing with public health agencies.
4. Generate conclusions and recommendations including:
    - Detailed cost and time estimate for design of new system.
    - Expected timeline(s) for system development, testing, and deployment.
    - Detailed descriptions of system scalability (both addition of variables and roll-out to additional school districts) should the need arise. This should include time and cost estimates.
    - Expected cost to consumers/government for system usage.

***Impact***

Local, state, and federal public health agencies currently have no school-level surveillance system that collects these data in real-time. The development of such a system could provide public health with early signals for disease outbreaks leading to earlier implementation of prevention efforts at the school level, situational awareness for learning modalities allowing for identification of districts in need of public health support, and an existing system that may be scaled-up for additional data collection should the need arise. Public health agencies must be positioned to respond to the needs of schools more rapidly and have the ability to maintain situational awareness of school operations in emergencies.

***Commercialization Potential***

The more than 17,000 school districts in the US collect large amounts of data daily on absences and other information, but few use systems that make the collection of these data easy and quick to share with public health agencies. Such a system would be of great benefit to the government, public health, and education agencies. If the system is flexible and user friendly, school-systems would be incentivized to use the system. Alignment with government data modernization efforts would increase public sector uptake.

## 13 APPENDICES

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

MS Word (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.docx)
PDF (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.pdf)

### APPENDIX B — ABSTRACT OF RESEARCH PLAN - USE FOR A PHASE I AND A PHASE II PROPOSAL

MS Word (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixB.docx)
PDF (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixB.pdf)

### APPENDIX C — PRICING PROPOSAL - USE FOR A PHASE I AND A PHASE II PROPOSAL

MS Word (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixC.docx)
PDF (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixC.pdf)

### APPENDIX D — PHASE II TECHNICAL PROPOSAL COVER SHEET - USE FOR A PHASE II PROPOSAL

MS Word (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixD.docx)
PDF (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixD.pdf)

### APPENDIX E — STATEMENT OF WORK SAMPLE FORMAT - USE FOR A PHASE II PROPOSAL

MS Word (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixE.docx)
PDF (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixE.pdf)

### APPENDIX F — SUMMARY OF RELATED ACTIVITIES - USE FOR A PHASE I AND A PHASE II PROPOSAL

MS Word (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixF.docx)
PDF (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixF.pdf)

### APPENDIX G — PROPOSAL SUMMARY AND DATA RECORD - USE FOR A PHASE II PROPOSAL

MS Word (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixG.docx)
PDF (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixG.pdf)

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

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

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

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

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

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

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

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

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

DISCLAIMER: Reference to these software packages neither constitutes nor should be inferred to be an endorsement or recommendation of any product, service, or enterprise by the National Institutes of Health, any other agency of the United States Government, or any employee of the United States Government. No warranties are stated or implied.

**APPENDIX I.1 — 52.204-24 Representation Regarding Certain Telecommunications and Video Surveillance Services or Equipment.**

REPRESENTATION REGARDING CERTAIN TELECOMMUNICATIONS AND VIDEO SURVEILLANCE SERVICES OR EQUIPMENT (OCT 2020)

The Offeror shall not complete the representation at paragraph (d)(1) of this provision if the Offeror has represented that it "does not provide covered telecommunications equipment or services as a part of its offered products or services to the Government in the performance of any contract, subcontract, or other contractual instrument" in paragraph (c)(1) in the provision at 52.204-26, Covered Telecommunications Equipment or Services—Representation, or in paragraph (v)(2)(i) of the provision at 52.212-3, Offeror Representations and Certifications-Commercial Items. The Offeror shall not complete the representation in paragraph (d)(2) of this provision if the Offeror has represented that it "does not use covered telecommunications equipment or services, or any equipment, system, or service that uses covered telecommunications equipment or services" in paragraph (c)(2) of the provision at 52.204-26, or in paragraph (v)(2)(ii) of the provision at 52.212-3.

(a) *Definitions.* As used in this provision—

*Backhaul, covered telecommunications equipment or services, critical technology, interconnection arrangements, reasonable inquiry, roaming, and substantial or essential component* have the meanings provided in the clause 52.204-25, Prohibition on Contracting for Certain Telecommunications and Video Surveillance Services or Equipment.

(b) *Prohibition*.

(1) Section 889(a)(1)(A) of the John S. McCain National Defense Authorization Act for Fiscal Year 2019 (Pub. L. 115-232) prohibits the head of an executive agency on or after August 13, 2019, from procuring or obtaining, or extending or renewing a contract to procure or obtain, any equipment, system, or service that uses covered telecommunications equipment or services as a substantial or essential component of any system, or as critical technology as part of any system. Nothing in the prohibition shall be construed to—

(i) Prohibit the head of an executive agency from procuring with an entity to provide a service that connects to the facilities of a third-party, such as backhaul, roaming, or interconnection arrangements; or

(ii) Cover telecommunications equipment that cannot route or redirect user data traffic or cannot permit visibility into any user data or packets that such equipment transmits or otherwise handles.

(2) Section 889(a)(1)(B) of the John S. McCain National Defense Authorization Act for Fiscal Year 2019 (Pub. L. 115-232) prohibits the head of an executive agency on or after August 13, 2020, from entering into a contract or extending or renewing a contract with an entity that uses any equipment, system, or service that uses covered telecommunications equipment or services as a substantial or essential component of any system, or as critical technology as part of any system. This prohibition applies to the use of covered telecommunications equipment or services, regardless of whether that use is in performance of work under a Federal contract. Nothing in the prohibition shall be construed to—

(i) Prohibit the head of an executive agency from procuring with an entity to provide a service that connects to the facilities of a third-party, such as backhaul, roaming, or interconnection arrangements; or

(ii) Cover telecommunications equipment that cannot route or redirect user data traffic or cannot permit visibility into any user data or packets that such equipment transmits or otherwise handles.

(c) *Procedures.* The Offeror shall review the list of excluded parties in the System for Award Management (SAM) (https://www.sam.gov) for entities excluded from receiving federal awards for "covered telecommunications equipment or services".

(d) *Representation.* The Offeror represents that—

(1) It □ will, □ will not provide covered telecommunications equipment or services to the Government in the performance of any contract, subcontract or other contractual instrument resulting from this solicitation. The Offeror shall provide the additional disclosure information required at paragraph (e)(1) of this section if the Offeror responds "will" in paragraph (d)(1) of this section; and

(2) After conducting a reasonable inquiry, for purposes of this representation, the Offeror represents that—

It □ does, □ does not use covered telecommunications equipment or services, or use any equipment, system, or service that uses covered telecommunications equipment or services. The Offeror shall provide the additional disclosure information required at paragraph (e)(2) of this section if the Offeror responds "does" in paragraph (d)(2) of this section.

(e) *Disclosures.*

(1) Disclosure for the representation in paragraph (d)(1) of this provision. If the Offeror has responded "will" in the representation in paragraph (d)(1) of this provision, the Offeror shall provide the following information as part of the offer:

(i) For covered equipment—

(A) The entity that produced the covered telecommunications equipment (include entity name, unique entity identifier, CAGE code, and whether the entity was the original equipment manufacturer (OEM) or a distributor, if known);

(B) A description of all covered telecommunications equipment offered (include brand; model number, such as OEM number, manufacturer part number, or wholesaler number; and item description, as applicable); and

(C) Explanation of the proposed use of covered telecommunications equipment and any factors relevant to determining if such use would be permissible under the prohibition in paragraph (b)(1) of this provision.

(ii) For covered services—

(A) If the service is related to item maintenance: A description of all covered telecommunications services offered (include on the item being maintained: Brand; model number, such as OEM number, manufacturer part number, or wholesaler number; and item description, as applicable); or

(B) If not associated with maintenance, the Product Service Code (PSC) of the service being provided; and explanation of the proposed use of covered telecommunications services and any factors relevant to determining if such use would be permissible under the prohibition in paragraph (b)(1) of this provision.

(2) Disclosure for the representation in paragraph (d)(2) of this provision. If the Offeror has responded "does" in the representation in paragraph (d)(2) of this provision, the Offeror shall provide the following information as part of the offer:

(i) For covered equipment—

(A) The entity that produced the covered telecommunications equipment (include entity name, unique entity identifier, CAGE code, and whether the entity was the OEM or a distributor, if known);

(B) A description of all covered telecommunications equipment offered (include brand; model number, such as OEM number, manufacturer part number, or wholesaler number; and item description, as applicable); and

(C) Explanation of the proposed use of covered telecommunications equipment and any factors relevant to determining if such use would be permissible under the prohibition in paragraph (b)(2) of this provision.

(ii) For covered services—

(A) If the service is related to item maintenance: A description of all covered telecommunications services offered (include on the item being maintained: Brand; model number, such as OEM number, manufacturer part number, or wholesaler number; and item description, as applicable); or

(B) If not associated with maintenance, the PSC of the service being provided; and explanation of the proposed use of covered telecommunications services and any factors relevant to determining if such use would be permissible under the prohibition in paragraph (b)(2) of this provision.

(End of provision)

**APPENDIX I.2 — 52.204-25 Prohibition on Contracting for Certain Telecommunications and Video Surveillance Services or Equipment.**

PROHIBITION ON CONTRACTING FOR CERTAIN TELECOMMUNICATIONS AND VIDEO SURVEILLANCE SERVICES OR EQUIPMENT (AUG 2020)

(a) Definitions. As used in this clause—

Backhaul means intermediate links between the core network, or backbone network, and the small subnetworks at the edge of the network (e.g., connecting cell phones/towers to the core telephone network). Backhaul can be wireless (e.g., microwave) or wired (e.g., fiber optic, coaxial cable, Ethernet).

Covered foreign country means The People's Republic of China.

Covered telecommunications equipment or services means-

(1) Telecommunications equipment produced by Huawei Technologies Company or ZTE Corporation (or any subsidiary or affiliate of such entities);

(2) For the purpose of public safety, security of Government facilities, physical security surveillance of critical infrastructure, and other national security purposes, video surveillance and telecommunications equipment produced by Hytera Communications Corporation, Hangzhou Hikvision Digital Technology Company, or Dahua Technology Company (or any subsidiary or affiliate of such entities);

(3) Telecommunications or video surveillance services provided by such entities or using such equipment; or

(4) Telecommunications or video surveillance equipment or services produced or provided by an entity that the Secretary of Defense, in consultation with the Director of National Intelligence or the Director of the Federal Bureau of Investigation, reasonably believes to be an entity owned or controlled by, or otherwise connected to, the government of a covered foreign country.

Critical technology means-

(1) Defense articles or defense services included on the United States Munitions List set forth in the International Traffic in Arms Regulations under subchapter M of chapter I of title 22, Code of Federal Regulations;

(2) Items included on the Commerce Control List set forth in Supplement No. 1 to part 774 of the Export Administration Regulations under subchapter C of chapter VII of title 15, Code of Federal Regulations, and controlled—

(i) Pursuant to multilateral regimes, including for reasons relating to national security, chemical and biological weapons proliferation, nuclear nonproliferation, or missile technology; or

(ii) For reasons relating to regional stability or surreptitious listening;

(3) Specially designed and prepared nuclear equipment, parts and components, materials, software, and technology covered by part 810 of title 10, Code of Federal Regulations (relating to assistance to foreign atomic energy activities);

(4) Nuclear facilities, equipment, and material covered by part 110 of title 10, Code of Federal Regulations (relating to export and import of nuclear equipment and material);

(5) Select agents and toxins covered by part 331 of title 7, Code of Federal Regulations, part 121 of title 9 of such Code, or part 73 of title 42 of such Code; or

(6) Emerging and foundational technologies controlled pursuant to section 1758 of the Export Control Reform Act of 2018 (50 U.S.C. 4817).

Interconnection arrangements means arrangements governing the physical connection of two or more networks to allow the use of another's network to hand off traffic where it is ultimately delivered (e.g., connection of a customer of telephone provider A to a customer of telephone company B) or sharing data and other information resources.

Reasonable inquiry means an inquiry designed to uncover any information in the entity's possession about the identity of the producer or provider of covered telecommunications equipment or services used by the entity that excludes the need to include an internal or third-party audit.

Roaming means cellular communications services (e.g., voice, video, data) received from a visited network when unable to connect to the facilities of the home network either because signal coverage is too weak or because traffic is too high.

Substantial or essential component means any component necessary for the proper function or performance of a piece of equipment, system, or service.

(b) Prohibition.

(1) Section 889(a)(1)(A) of the John S. McCain National Defense Authorization Act for Fiscal Year 2019 (Pub. L. 115-232) prohibits the head of an executive agency on or after August 13, 2019, from procuring or obtaining, or extending or renewing a contract to procure or obtain, any equipment, system, or service that uses covered telecommunications equipment or services as a substantial or essential component of any system, or as critical technology as part of any system. The Contractor is prohibited from providing to the Government any equipment, system, or service that uses covered telecommunications equipment or services as a substantial or essential component of any system, or as critical technology as part of any system, unless an exception at paragraph (c) of this clause applies or the covered telecommunication equipment or services are covered by a waiver described in FAR 4.2104.

(2) Section 889(a)(1)(B) of the John S. McCain National Defense Authorization Act for Fiscal Year 2019 (Pub. L. 115-232) prohibits the head of an executive agency on or after August 13, 2020, from entering into a contract, or extending or renewing a contract, with an entity that uses any equipment, system, or service that uses covered telecommunications equipment or services as a substantial or essential component of any system, or as critical technology as part of any system, unless an exception at paragraph (c) of this clause applies or the covered telecommunication equipment or services are covered by a waiver described in FAR 4.2104. This prohibition applies to the use of covered telecommunications equipment or services, regardless of whether that use is in performance of work under a Federal contract.

(c) Exceptions. This clause does not prohibit contractors from providing—

(1) A service that connects to the facilities of a third-party, such as backhaul, roaming, or interconnection arrangements; or

(2) Telecommunications equipment that cannot route or redirect user data traffic or permit visibility into any user data or packets that such equipment transmits or otherwise handles.

(d) Reporting requirement.

(1) In the event the Contractor identifies covered telecommunications equipment or services used as a substantial or essential component of any system, or as critical technology as part of any system, during contract performance, or the Contractor is notified of such by a subcontractor at any tier or by any other source, the Contractor shall report the information in paragraph (d)(2) of this clause to the Contracting Officer, unless elsewhere in this contract are established procedures for reporting the information; in the case of the Department of Defense, the Contractor shall report to the website at https://dibnet.dod.mil. For indefinite delivery contracts, the Contractor shall report to the Contracting Officer for the indefinite delivery contract and the Contracting Officer(s) for any affected order or, in the case of the Department of Defense, identify both the indefinite delivery contract and any affected orders in the report provided at https://dibnet.dod.mil.

(2) The Contractor shall report the following information pursuant to paragraph (d)(1) of this clause:

(i) Within one business day from the date of such identification or notification: the contract number; the order number(s), if applicable; supplier name; supplier unique entity identifier (if known); supplier Commercial and Government Entity (CAGE) code (if known); brand; model number (original equipment manufacturer number, manufacturer part number, or wholesaler number); item description; and any readily available information about mitigation actions undertaken or recommended.

(ii) Within 10 business days of submitting the information in paragraph (d)(2)(i) of this clause: any further available information about mitigation actions undertaken or recommended. In addition, the Contractor shall describe the efforts it undertook to prevent use or submission of covered telecommunications equipment or services, and any additional efforts that will be incorporated to prevent future use or submission of covered telecommunications equipment or services.

(e) Subcontracts. The Contractor shall insert the substance of this clause, including this paragraph (e), in all subcontracts and other contractual instruments, including subcontracts for the acquisition of commercial items.

(End of clause)

**APPENDIX I.3 — 52.204-26 Covered Telecommunications Equipment or Services-Representation**

COVERED TELECOMMUNICATIONS EQUIPMENT OR SERVICES-REPRESENTATION (OCT 2020)

(a) *Definitions.* As used in this provision, "covered telecommunications equipment or services" and "reasonable inquiry" have the meaning provided in the clause 52.204-25, Prohibition on Contracting for Certain Telecommunications and Video Surveillance Services or Equipment.

(b) *Procedures.* The Offeror shall review the list of excluded parties in the System for Award Management (SAM) (https://www.sam.gov) for entities excluded from receiving federal awards for "covered telecommunications equipment or services".

(c) (1) *Representation.* The Offeror represents that it □ does, □ does not provide covered telecommunications equipment or services as a part of its offered products or services to the Government in the performance of any contract, subcontract, or other contractual instrument.

(2) After conducting a reasonable inquiry for purposes of this representation, the offeror represents that it □ does, □ does not use covered telecommunications equipment or services, or any equipment, system, or service that uses covered telecommunications equipment or services.

(End of provision)