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 2021-1

Closing Date: October 26, 2020, 5:00 PM Eastern Daylight Time

Participating HHS Components:

- The National Institutes of Health (NIH)
- The Centers for Disease Control and Prevention (CDC)

IMPORTANT

Deadline for Receipt: Proposals must be received by October 26, 2020, 5:00 PM Eastern Daylight Time.

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

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

Please go to https://www.sbir.gov/sites/default/files/SBIR-STTR_Policy_Directive_2019.pdf to read the SBIR/STTR Policy Directive issued by the Small Business Administration for further information.

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1 INTRODUCTION

The National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) invite small business concerns (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. This is a rapidly evolving situation and NIH 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 020	Yes	No	No	Development of Remote Rare Disease Patient Care Environment through Immersive Virtual Reality
NIH/NCATS 021	Yes	No	No	Platform for Rapidly Deployable Autonomous Laboratory
NIH/NCI 413	Yes	Yes	No	Next Generation 3D Tissue Culture Systems with Tertiary Lymphoid Organs
NIH/NCI 414	Yes	No	Yes	Synthetic Biology Gene Circuits for Cancer Therapy
NIH/NCI 415	Yes	Yes	No	Applicator-Compatible Electronic Brachytherapy Sources for Cancer Radiotherapy
NIH/NCI 416	Yes	Yes	Yes	Self-Sampling Devices for HPV-Testing-Based Cervical Cancer Screening
NIH/NCI 417	Yes	Yes	No	Quantitative Imaging Software Tools for Cancer Diagnosis and Treatment Planning
NIH/NCI 418	Yes	Yes	No	3D Spatial Omics for Molecular and Cellular Tumor Atlas Construction
NIH/NCI 419	Yes	Yes	No	Understanding Cancer Tumor Genomic Results: Technology Applications for Providers
NIH/NCI 420	Yes	No	No	Single-Cell "Unbiased Discovery" Proteomic Technologies
NIH/NCI 421	Yes	Yes	No	Quantitative Biomimetic Phantoms for Cancer Imaging and Radiation Dosimetry
NIH/NCI 422	Yes	Yes	No	Spatial Sequencing Technologies with Single Cell Resolution for Cancer Research and Precision Medicine

TOPIC NUMBER	PHASE I ALLOWED?	FAST TRACK ALLOWED? (A Phase I proposal and a Phase II proposal submitted simultaneously)	DIRECT TO PHASE II ALLOWED? (Includes only a Phase II Proposal)	TOPIC TITLE
NIH/NCI 423	Yes	Yes	No	Software to Address Social Determinants of Health in Oncology Practices
NIH/NCI 424	Yes	Yes	No	Digital Tools to Improve Health Outcomes in Pediatric Cancer Survivors
NIH/NCI 425	Yes	Yes	No	Information Technology Tools for Automated Analysis of Physical Activity, Performance, and Behavior from Images for Improved Cancer Health
NIH/NCI 426	Yes	Yes	No	Tools and Technologies for Visualizing Multi-Scale Data
NIH/NCI 427	Yes	No	No	De-Identification Software Tools and Pipelines for Cancer Imaging Research
NIH/NCI 428	Yes	Yes	No	Cloud-Based Multi-Omic and Imaging Software for the Cancer Research Data Commons
NIH/NCI 429	Yes	Yes	No	Advanced Manufacturing to Speed Availability of Emerging Autologous Cell-Based Therapies
NIH/NHLBI 111	Yes	Yes	Yes	Oxygen Delivery Device Innovations
NIH/NHLBI 112	Yes	Yes	Yes	Intramyocardial Suture Annuloplasty System (“SCIMITAR” devices)
NIH/NIAID 087	Yes	Yes	No	Point-of-Care HIV Viral Load, Drug Resistance, and Adherence Assays
NIH/NIAID 088	Yes	Yes	No	Therapeutic Targeting of Intracellular HIV-1 Proteins or Nucleic Acids
NIH/NIAID 089	Yes	Yes	No	Particle-based Co-delivery of HIV immunogens as Next-generation HIV Vaccines
NIH/NIAID 090	Yes	Yes	No	Sequence-based Assays to Quantify the Replication-Competent HIV Reservoir
NIH/NIAID 091	Yes	Yes	Yes	Adjuvant Development for Vaccines and for Autoimmune and Allergic Diseases
NIH/NIAID 092	Yes	Yes	Yes	Adjuvant Discovery for Vaccines and for Autoimmune and Allergic Diseases
NIH/NIAID 093	Yes	Yes	Yes	Production of Adjuvants Mimics
NIH/NIAID 094	Yes	Yes	Yes	Reagents for Immunologic Analysis of Non-mammalian and Underrepresented Mammalian Models
NIH/NIAID 095	Yes	Yes	No	Improving Technologies to Make Large-scale High Titer Phage Preps

TOPIC NUMBER	PHASE I ALLOWED?	FAST TRACK ALLOWED? (A Phase I proposal and a Phase II proposal submitted simultaneously)	DIRECT TO PHASE II ALLOWED? (Includes only a Phase II Proposal)	TOPIC TITLE
NIH/NIAID 096	Yes	Yes	No	Development of priority diagnostics for Chagas disease
NIH/NIAID 097	Yes	Yes	Yes	Pediatric Formulations of Select Second Line Drugs for Treating Tuberculosis
NIH/NIAID 098	Yes	Yes	Yes	Group A Streptococcus Vaccine Development
NIH/NIAID 099	Yes	Yes	No	Rapid, Point-of-Care Diagnostics for Hepatitis C Virus
NIH/NIAID 100	Yes	Yes	Yes	Informatics Tools (Data Science Tools) for Infectious, Immune, and Allergic Research
CDC/CPR 006	Yes	No	No	Developing Innovative Specimen Packaging Approaches to Improve Transit Success Rates
CDC/NCEZID 024	Yes	No	No	Device Development for Microbial Surface Sampling, Field Extraction and Collection
CDC/NCEZID 025	Yes	No	No	Development of a Diagnostic Testing Platform to Assess Antibiotic Activity on Microbial Communities
CDC/NCEZID 026	Yes	No	No	Intradermal Delivery Human Rabies Vaccine Using Dissolvable Microneedles
CDC/NCEZID 027	Yes	No	No	Interactive Phone-Based Video Game to Promote Handwashing Behavior Among Children
CDC/NCHHSTP 050	Yes	No	No	Agnostics Computer Vision Solution for Highly Integrated Robotic Platforms
CDC/NCHHSTP 051	Yes	No	No	Microfluidics for Genetic and Serological Characterization of hepatitis C Virus Infection

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

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

2 PROGRAM DESCRIPTION

2.1 Objectives

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

The basic design of the NIH/CDC SBIR program is in accordance with the Small Business Administration (SBA) SBIR Program Policy Directive dated May 2, 2019. 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.*

Commercialization stage without SBIR funds

The small business concern to pursue, with non-SBIR funds, the commercialization objectives resulting from the outcomes of the research or R&D funded in Phases I and II. Projects may be funded by non-Federal sources of capital, or may be funded by follow-on non-SBIR Federal funding agreements.

The competition for SBIR Phase I and Phase II awards satisfies the competition requirements of the Competition in Contracting Act. Therefore, for an agency that wishes to fund an SBIR 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, NHLBI, and NIAID), 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 I-Corps™ at NIH participation runs concurrently with the performance of the SBIR Phase I research.

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

- Chief-Level Corporate Officer
  (CEO of the SBIR awardee company strongly preferred)
- Industry Expert
  (internal, such as a Business Development Manager or Board Member, or external, such as a consultant or mentor with the National Innovation Network)
- Program Director/Principal Investigator (PD/PI)
  (or, in the case that PD/PI is also the CEO, an additional technical/scientific expert)

To successfully complete the I-Corps™ at NIH Program, the entire I-Corps™ team must be deeply committed and dedicated to the time-intensive curriculum. Each team member should plan to spend at least 20 hours per week on I-Corps™ activities for the full

duration of the 8-week program. In-person attendance of all 3 team members is mandatory for a 3-day immersion 'kickoff' workshop and a 2-day closing workshop, location to be determined (within the United States), where team members will give presentations as well as participate in lectures and training sessions. There will also be weekly webinar sessions and requirements to get "out of the lab" and gather information by conducting at least 100 discovery interviews with potential customers, strategic partners, and other third-party stakeholders.

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

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

Application Process

The first step in the I-Corps™ at NIH application process is submitting an additional, separate "Appendix C – Contract Pricing Proposal," in your Business Proposal. Specify "I-Corps" in the "Title of Proposal" field. This separate budget must not exceed $55,000 in total direct costs – indirect costs may not be included. Of that amount, $22,000 must go towards covering workshop registration fees, which should be listed in field 4.e. OTHER of Appendix C. Remaining budget should be allocated as appropriate to cover personnel time for the I-Corps™ team members – at least 20 hours per week for 8 weeks for the 3 team member roles discussed above – as well as travel costs to participate in the in-person workshops and conduct on-site customer development interviews within the U.S.

Dates, times, and locations for NIH/CDC 8-week cohorts in 2021 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 2021 with travel to Los Angeles, California for a three day workshop in April and travel to Bethesda, Maryland for a two day workshop in May.

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

The second step in the I-Corps™ application process will take place several months into Phase I project performance, when the Government will notify companies with the I-Corps™ contractual option and allow them the opportunity to prepare a brief application to be considered for I-Corps™ selection, subject to availability of funds. The estimated deadline for this application is early January 2021 and the application will consist of components such as those discussed below:

- *Executive Summary of Predicate SBIR/STTR Phase I Contract and Team (1 page only)*
- *I-Corps™ Team and Project Plan (up to 5 pages)*
    - *I-Corps™ Team*

      Description of the I-Corps™ team; indication of commitment to meet time-intensive requirements; discussion of team's willingness to modify/refine the overall commercialization strategy based on knowledge gained during the course of the I-Corps™ Program.
    - *Potential Commercial Impact*

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

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

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

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

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

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

2.6 Grant Opportunity - Phase IIB Competing Renewal Awards and Commercialization Readiness Pilot (CRP) Program (INFORMATION ONLY)

Phase IIB Competing Renewal Awards: Some NIH Institutes/Centers (ICs) offer Phase II SBIR/STTR awardees the opportunity to apply for Phase IIB Competing Renewal grant awards. Phase II contract awardees are eligible to apply for Phase IIB grants offered by those participating NIH ICs. The Phase II contract must be completed prior to award of a Phase IIB grant, although the Phase II contract need not be completed prior to application. Phase IIB Competing Renewal grant awards are available for those projects that require extraordinary time and effort, including those requiring regulatory approval or development complex instrumentation, clinical research tools, and behavioral interventions. NIH ICs that accept Phase IIB applications, either through the Omnibus SBIR/STTR grant funding opportunity announcements or other specific funding opportunity announcements, are listed in the PHS 2020-2 SBIR/STTR Program Descriptions and Research Topics for NIH, CDC, and FDA. Additional requirements and instructions (e.g., submission of a letter of intent) are available in the specific IC research topics section and in the NIH Targeted Funding Opportunities that allow Phase IIB applications.

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

2.7 Awarding Components

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

National Institutes of Health (NIH) Components:

National Center for Advancing Translational Sciences (NCATS)

National Cancer Institute (NCI)

National Heart, Lung, and Blood Institute (NHLBI)

National Institute of Allergy and Infectious Diseases (NIAID)

Centers for Disease Control and Prevention (CDC) Components:

Center for Preparedness and Response (CPR)

National Center for Emerging Zoonotic and Infectious Diseases (NCEZID)

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

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

Phase II to Phase III Commercialization Benchmark

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

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

4.4 Multiple Principal Investigators

The NIH provides offerors the opportunity to propose a multiple Principal Investigator (PI) model on research and development contracts. The multiple PI model is intended to supplement, and not replace, the traditional single PI model. Ultimately, the decision to submit a proposal using multiple PIs versus a single PI is the decision of the investigators and their institutions. The decision should be consistent with and justified by the scientific goals of the project. At least one proposed PI must be primarily employed with the applicant, as discussed in Section 4.2 "Offeror Eligibility and Performance Requirements."

4.5 Joint Ventures and Limited Partnerships

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

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

Small businesses that are owned in majority part by multiple venture capital operating companies (VCOCs), hedge funds, or private equity funds **are** eligible to submit proposals for opportunities under this solicitation, but **are required to submit a "SBIR Application VCOC Certification" at time of their application submission** per the SBIR Policy Directive. Download the "SBIR Application VCOC Certification.pdf" at the NIH SBIR Forms webpage. Answer the 3 questions and check the certification boxes. The authorized business official must sign the certification. The signed SBIR Application VCOC Certification must be submitted as part of the Pricing Proposal.

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

4.7 Conflicts of Interest

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

4.8 Market Research

Base SBIR award funding will not support any market research or studies of the literature that will lead to a new or expanded statement of work. Literature searches where the commercial product is a database are acceptable. However, refer to Section 2.5 I-Corps™ at NIH and Section 4.16 State Assistance and Technical Assistance for potential opportunities for specialized supplemental funding to support commercialization efforts.

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

4.9 Debriefing

An unsuccessful offeror that submits a written request for a debriefing within 3 calendar days of being notified that its proposal was not selected for award will be provided a debriefing in accordance with the Awarding Component's processes. The written request should be sent to the Awarding Component's point of contact that provided such notification to the offeror. Be advised that an offeror that fails to submit a timely request is not entitled to a debriefing, although untimely debriefing requests may be accommodated at the Government's discretion.

4.10 Phase I Award Information

Number of Phase I Awards. The Topic Description indicates the number of Phase I contract awards anticipated by the Awarding Component. No Phase I contracts will be awarded until evaluation of all eligible proposals for a specific topic is completed.

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

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

4.11 Phase II Award Information

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

Type of Funding Agreement. Each Phase II proposal selected for award will be funded under negotiated contracts. Phase II contracts may be either firm fixed price or cost-reimbursement type. A firm-fixed-price contract establishes a payment amount that is not subject to adjustment on the basis of the contractor's actual costs in performing the contract. A cost-reimbursement contract provides for payment of allowable incurred costs, up to the ceiling amount established in the contract.

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

4.12 Registrations and Certifications

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

Proposing firms must be registered in the System for Award Management (SAM) at https://www.sam.gov. The registration should reflect "Purpose of Registration: All Awards" and not "Purpose of Registration: Federal Assistance Awards Only."

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

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

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

All applicants to the SBIR and STTR programs are required to register at the SBA Company Registry **prior to proposal submission** and **attach proof of registration**. Completed registrations will receive a unique SBC Control ID and .pdf file. If applicants have previously registered, you are still **required to attach proof of registration**. The SBA Company Registry recommends verification with SAM (see above) but a SAM account is not required to complete the registration. In order to be verified with SAM, your email

address must match one of the contacts in SAM. If you are unsure what is listed in SAM for your company, you may verify the information on the SAM site.

Follow these steps listed below to register and attach proof of registration to your application:

- Navigate to the SBA Company Registry.
- If you are a previous SBIR/STTR awardee from any agency, search for your small business by Company Name, EIN/Tax ID, DUNS, or Existing SBIR/STTR Contract/Grant Number in the search fields provided. Identify your company and click "Proceed to Registration".
- If you are a first-time applicant, click the New to the SBIR Program? link on lower right of registry screen.
  - Fill out the required information on the "Basic Information" and "Eligibility Statement" screens.
  - Press "Complete Registration" on the lower right of the "Eligibility Statement" screen and follow all instructions.
- Download and save your SBA registry PDF locally. The name will be in the format of SBC_123456789.pdf, where the 9-digit number reflects your firm's SBC Control ID.

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

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

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

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

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

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

Representation Regarding Certain Telecommunications and Video Surveillance Services or Equipment.

All offerors must complete and submit FAR Provision 52.204-24 as part of your Business Proposal, which is attached and incorporated as Solicitation APPENDIX I.1.

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/hotline/ and the mailing address is:

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

4.16 State Assistance and Technical Assistance

State Assistance

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

Technical and Business Assistance

NIH offers distinct technical assistance programs to NIH and CDC SBIR and STTR Phase I and Phase II awardees. These programs offer specialized, strategic business training and provide access to a vast network of industry experts which is made possible by the efficiencies of scale accomplished through providing this service through the Government.

If you wish to utilize your own technical assistance provider, you are required to include these costs in your budget and to provide a detailed budget justification. 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.

Refer to Section 8 for how to include this in your Pricing Proposal. Please note, if funds are requested to utilize your own technical assistance vendor and an award is made, the awardee is not eligible to apply for the NIH-provided technical assistance program for the phase awarded.

Technical assistance is limited to services that comply with 15 U.S.C. § 638(q):

> To provide small business concerns engaged in SBIR or STTR projects with technical and business assistance services, such as access to a network of scientists and engineers engaged in a wide range of technologies, product sales, IP protections, market research, market validation, development of regulatory plans, manufacturing plans, or access to technical and business literature available through on-line data bases, for the purpose of assisting such concerns in—
>
> (A) making better technical decisions concerning such projects;
>
> (B) solving technical problems which arise during the conduct of such projects;
>
> (C) minimizing technical risks associated with such projects; and
>
> (D) developing and commercializing new commercial products and processes resulting from such projects.

4.17 Payment

The Government shall make payments, including invoice and contract financing payments, by electronic funds transfer (EFT). As a condition to any payment, the contractor is required to register in the System for Award Management (SAM).

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

Advance payments may be requested, and approved on a case-by-case basis, and are dependent on Agency procedures. Offerors should indicate the need for advanced payments in Appendix C – Contract Pricing Proposal, Section III. If you are notified that your proposal is being considered for award, communicate with the point of contact named in that notification regarding procedures for requesting advanced payment.

4.18 Proprietary Information

Information contained in unsuccessful proposals will remain the property of the applicant. The Government may, however, retain copies of all proposals. Public release of information in any proposal submitted will be subject to existing statutory and regulatory requirements. If proprietary information is provided by an applicant in a proposal, which constitutes a trade secret, proprietary commercial or financial information, confidential personal information or data affecting the national security, it will be treated in confidence, to the extent permitted by law. This information must be clearly marked by the applicant with the term "confidential proprietary information" and identified by asterisks (*).

For Phase I proposals, also note each page number that contains proprietary information in the appropriate field in Appendix A. For Phase II proposal, please include the following language at the beginning of the "Content of the Technical Element" section of the proposal: "These data shall not be disclosed outside the Government and shall not be duplicated, used, or disclosed in whole or in part for any purpose other than evaluation of this proposal. If a funding agreement is awarded to this applicant as a result of or in connection with the submission of these data, the Government shall have the right to duplicate, use, or disclose the data to the extent provided in the funding agreement and pursuant to applicable law. This restriction does not limit the Government's right to use information contained in the data if it is obtained from another source without restriction. The data subject to this restriction are contained on pages __ of this proposal."

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

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

5 CONTRACT REQUIREMENTS

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

5.1 NIH Policy on Enhancing Reproducibility Through Rigor and Transparency

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

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

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

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

5.3 Animal Welfare

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

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

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

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

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

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

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

5.5 Required Education in the Protection of Human Research Participants

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

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

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

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

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

5.6 Inclusion of Women and Minorities in Research Involving Human Subjects

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

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

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

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

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

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

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

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

5.8 Clinical Trial Registration and Results Information Submission

The Contractor conducting clinical trials, funded wholly or partially through the NIH extramural and intramural programs, shall ensure that its NIH-funded clinical trials are registered at, and summary results information is submitted to, www.clinicaltrials.gov for public posting. See NIH Guide Notice NOT-OD-16-149 dated September 16, 2016.
All NIH-funded clinical trials shall be registered and results information submitted to www.clinicaltrials.gov regardless of study phase, type of intervention, or whether they are subject to the regulation 42 CFR Part 11. Clinical trials subject to the regulation are called "applicable clinical trials."

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

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

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

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

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

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

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

5.9 Single Institutional Review Board (sIRB)

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

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

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

Exceptions to the NIH Single IRB Policy

The Contractor may request an exception in the following instances:

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

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

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

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

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

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

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

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

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

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

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

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

5.11 Copyrights

With prior written permission of the Contracting Officer, the awardee may copyright material developed with HHS support. HHS receives a royalty-free license for the Federal Government and requires that each publication contain an appropriate acknowledgment and disclaimer statement.

5.12 Technical Data Rights

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

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

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

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

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

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

5.13 Patents and Invention Reporting

Small business firms normally may retain the principal worldwide patent rights to any invention developed with Government support. The Government receives a royalty-free license for its use, reserves the right to require the patent holder to license others in certain limited circumstances, and requires that anyone exclusively licensed to sell the invention in the United States must normally manufacture it domestically. To the extent authorized by 35 USC 205, the Government will not make public any information disclosing a Government-supported invention to allow the awardee to pursue a patent.

The reporting of inventions is accomplished by submitting information through the Edison Invention Reporting System for those Awarding Components participating in "Interagency Edison", or iEdison. The NIH has developed the iEdison electronic invention reporting system to assist contractors in complying with invention reporting requirements. NIH requires contractors to use iEdison, which streamlines the reporting process and greatly reduces paperwork. Access to the system is through a secure interactive Web site to ensure that all information submitted is protected.

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

This should be done prior to any publication or presentation of the invention at an open meeting, since failure to report at the appropriate time is a violation of 35 U.S.C. 202, and may result in loss of the rights of the small business concern, inventor, and Federal Government in the invention. All foreign patent rights are immediately lost upon publication or other public disclosure unless a United States patent application is already on file. In addition, statutes preclude obtaining valid United States patent protection after one year from the date of a publication that discloses the invention.

If no invention is disclosed or no activity has occurred on a previously disclosed invention during the applicable reporting period, a negative report shall be submitted to the Contracting Officer.

Inquiries or information about invention reporting or requirements imposed by 37 CFR 401 may also be directed to:

Office of Policy for Extramural Research Administration,
Division of Extramural Inventions and Technology Resources,
National Institutes of Health (NIH)
6705 Rockledge Drive, MSC 7980
Bethesda, MD 20892-7980
Phone: (301) 451-4235
Fax: (301) 480-0272
E-mail: hammerslaa@mail.nih.gov

5.14 Salary Rate Limitation

None of the funds appropriated shall be used to pay the direct annual salary of an individual at a rate in excess of Executive Schedule, Level II of the Federal Executive Pay Scale. Effective January 2020, Executive Schedule, Level II of the Federal Executive Pay Scale is $197,300.

5.15 Other Contract Requirements

The outline that follows is illustrative of the types of generally-applicable clauses required by the Federal Acquisition Regulations that will be included in contracts resulting from this solicitation. This is not a complete list of clauses to be included, nor does it contain specific wording of these clauses. An award document reflecting all contract requirements applicable to your proposal will be made available prior to award.

a. **Technical Progress Reporting.** Contractors will be required to submit periodic technical progress reports throughout the period of performance, to be specified by the Awarding Component. On fixed-price contracts, payments may be tied to delivery and acceptance of these technical progress reports. For all contracts, final payment will not be made until all reports and deliverables included in the contract have been delivered and accepted by the Government.

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

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

b. **Inspection.** Work performed under the contract is subject to Government inspection and evaluation at all reasonable times.

c. **Audit and Examination of Records.** The Contracting Officer and the Comptroller General, or a fully authorized representative of either, shall have the right to examine and audit all records and other evidence sufficient to reflect properly all costs claimed to have been incurred or anticipated to be incurred directly or indirectly in performance of this contract.

d. **Basic Information Systems Security.** The Contractor shall utilize defined security controls to provide at least a minimum level of protection for covered contractor information systems. See FAR clause 52.204-21 Basic Safeguarding of Covered Contractor Information Systems for applicability and specific requirements.

e. **Default.** The Government may terminate the contract if the contractor fails to perform the work contracted.

f. **Termination for Convenience.** The contract may be terminated at any time by the Government if it deems termination to be in its best interest, in which case the contractor will be compensated for work performed and for reasonable termination costs.

g. **Disputes.** Any dispute concerning the contract which cannot be resolved by agreement shall be decided by the Contracting Officer with right of appeal.

h. **Acknowledgement of Federal Funding.** The Contractor shall clearly state, when issuing statements, press releases, requests for proposals, bid solicitations and other documents describing projects or programs funded in whole or in part with Federal money: (1) the percentage of the total costs of the program or project which will be financed with Federal money; (2) the dollar amount of Federal funds for the project or program; and (3) the percentage and dollar amount of the total costs of the project or program that will be financed by nongovernmental sources.

i. **Items Unallowable Unless Otherwise Provided.** Unless authorized in writing by the Contracting Officer, the costs of the following items or activities shall be unallowable as direct costs: purchase or lease of any interest in real property; special rearrangement or alteration of facilities; purchase or lease of any item of general purpose office furniture or equipment regardless of dollar value; travel to attend general scientific meetings; foreign travel; non-expendable personal property with an acquisition cost of $1,000 or more.

j. **Continued Ban on Funding Abortion and Continued Ban on Funding of Human Embryo Research.** The Contractor shall not use contract funds for (1) any abortion; (2) the creation of a human embryo or embryos for research purposes; or (3) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero under 45 CFR 46.204(b) and Section 498(b) of the Public Health

Service Act (42 U.S.C. 289(b)). The term "human embryo or embryos" includes any organism, not protected as a human subject under 45 CFR 46 as of the date of the enactment of this Act, that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells. Additionally, Federal funds shall not be used for the cloning of human beings.

k. **Use of Funds for Conferences, Meetings and Food.** The Contractor shall not use contract funds (direct or indirect) to conduct meetings or conferences in performance of this contract without prior written Contracting Officer approval. In addition, the use of contract funds to purchase food for meals, light refreshments, or beverages is expressly prohibited.

l. **Use of Funds for Promotional Items.** The Contractor shall not use contract funds to purchase promotional items. Promotional items include, but are not limited to: clothing and commemorative items such as pens, mugs/cups, folders/folios, lanyards, and conference bags that are sometimes provided to visitors, employees, grantees, or conference attendees. This includes items or tokens given to individuals as these are considered personal gifts for which contract funds may not be expended.

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

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

o. **Equal Opportunity for Workers with Disabilities.** The contractor will not discriminate against any employee or applicant for employment because he or she is physically or mentally handicapped.

p. **Anti-Kickback Procedures.** The contractor is prohibited from offering or accepting any money, gifts, things of value, etc. for the purpose of improperly obtaining or rewarding favorable treatment in connection with a federal contract or subcontract and shall have procedures in place to prevent and detect violations.

q. **Covenant Against Contingent Fees.** No person or agency has been employed to solicit or secure the contract upon an understanding for compensation except bona fide employees or commercial agencies maintained by the contractor for the purpose of securing business.

r. **Gratuities.** The contract may be terminated by the Government if any gratuities have been offered to any representative of the Government to secure the contract**.**

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

t. **Employment Eligibility Verification.** The contractor shall be enrolled as a Federal Contractor in E-Verify and verify all employees assigned to the contract as well as all new employees hired by the contractor.

u. **Needle Exchange.** The Contractor shall not use contract funds to carry out any program of distributing sterile needles or syringes for the hypodermic injection of any illegal drug.

v. **Limitation on Use of Funds for Promotion of Legalization of Controlled Substances.** The Contractor shall not use contract funds to support activities that promote the legalization of any drug or other substance included in schedule I of the schedules of controlled substances established under section 202 of the Controlled Substances Act, except for normal and recognized executive-congressional communications. This limitation shall not apply when the Government determines that there is significant medical evidence of a therapeutic advantage to the use of such drug or other substance or that federally sponsored clinical trials are being conducted to determine therapeutic advantage.

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

x. **Anti-Lobbying.** Pursuant to the current appropriations act, except for normal and recognized executive legislative relationships, the contractor shall not use any contract funds for (i) publicity or propaganda purposes; (ii) the preparation, distribution, or use of any kit, pamphlet, booklet, publication, radio, television or video presentation designed to support or defeat legislation pending before the Congress or any State legislature, except in presentation to the Congress or any State

legislature itself; or (iii) payment of salary or expenses of the Contractor, or any agent acting for the Contractor, related to any activity designed to influence legislation or appropriations pending before the Congress or any State legislature.

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

z. **Restriction on Pornography on Computer Networks.** The contractor shall not use contract funds to maintain or establish a computer network unless such network blocks the viewing, downloading, and exchanging of pornography.

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

bb. **Subcontracts for Commercial Items**. Contracts resulting from this solicitation will include FAR clause 52.244-6 (Aug 2019), which can be referenced here.

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

6 METHOD OF EVALUATION

All proposals will be evaluated and judged on a competitive basis. Each proposal will be judged on its own merit. The Agency is under no obligation to fund any proposals or any specific number of proposals in a given topic. It may also elect to fund several or none of the proposed approaches to a given topic.

6.1 Evaluation Process

Using the technical evaluation criteria specified below, a panel of experts knowledgeable in the disciplines or fields under review will evaluate proposals for scientific and technical merit. For NIH, this peer review panel will be composed of experts from outside the Awarding Component, in accordance with 42 CFR 52h. For CDC, this panel may be composed of internal governmental scientific and technical experts. The review panel provides a rating for each proposal and makes specific recommendations related to the scope, direction and/or conduct of the proposed research.

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

- Resource Sharing https://grants.nih.gov/grants/peer/guidelines_general/Resource_sharing_plans.pdf
  - Data Sharing Plan http://grants.nih.gov/grants/policy/data_sharing
  - Model Organism Sharing Plan http://grants.nih.gov/grants/policy/model_organism/
  - Genome Data Sharing http://gds.nih.gov/
- Human Subject Protection http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html
- Data Safety Monitoring Plan http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html
- Inclusion of Women and Minorities http://grants.nih.gov/grants/funding/women_min/women_min.htm
- Inclusion of Children https://grants.nih.gov/grants/funding/children/children.htm
- Animal Welfare http://grants.nih.gov/grants/oer_offices/olaw.htm
- Biohazards/Select Agents/Recombinant DNA http://grants.nih.gov/grants/guide/notice-files/not95-209.html
- Dual Use Research of Concern: http://phe.gov/s3/dualuse/Documents/oversight-durc.pdf

For NIH Awarding Components:

For NIH Awarding Components, the peer review technical evaluation panel will also determine whether each proposal is technically acceptable, meaning that it demonstrates sufficient technical understanding and capabilities to perform the technical objectives set forth in the solicitation. <u>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.</u>

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

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

6.2 Award Decisions

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

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

- Availability of funds; and,
- Cost/Price

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

6.3 Phase I Technical Evaluation Criteria

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

FACTORS FOR PHASE I PROPOSALS	WEIGHT
1. The soundness and technical merit of the proposed approach. a. Identification of clear, measurable goals (*i.e.*, milestones) that have a reasonable chance of meeting the topic objective in Phase I. b. Demonstration of a Strong Scientific Premise for the Technical Proposal. (*I.e.*, Sufficiency of proposed strategy to ensure a robust and unbiased approach, as appropriate for the work proposed. Adequacy of proposed plan to address relevant biological variables, including sex, for studies in vertebrate animals and/or human subjects.)	25%
2. The potential of the proposed research for technological innovation – whether the end product or technology proposed would offer significant advantages over existing approaches, methodologies, instrumentation, or interventions currently utilized in research or clinical practice.	25%
3. The potential of the proposed research for commercial application - whether the outcome of the proposed research activity will likely lead to a marketable product or process considering the offeror's proposed methods of overcoming potential barriers to entry in the competitive market landscape.	20%
4. The qualifications of the proposed Principal Investigators, Project Directors, supporting staff and consultants, and the appropriateness of the leadership approach (including the designated roles and responsibilities, governance, and organizational structure).	20%
5. The adequacy and suitability of the proposed facilities, equipment, and research environment.	10%

Technical reviewers will base their conclusions only on information contained in the proposal. It cannot be assumed that reviewers are acquainted with the firm or key individuals or any referenced experiments. Relevant supporting data such as journal articles, literature, including Government publications, etc., should be contained or referenced in the proposal and will count toward the page limit.

6.4 Phase II Technical Evaluation Criteria

Phase II proposals (those included in Fast Track submissions and those subsequently submitted by contractors who are awarded a Phase I contract under this solicitation) will be evaluated based on the criteria outlined below – subfactors are considered to be of equal importance:

FACTORS FOR PHASE II PROPOSALS	WEIGHT
1. The soundness and technical merit of the proposed approach a. Identification of clear, measurable goals (*i.e.*, milestones) that have a reasonable chance of meeting the topic objective in Phase II b. Demonstration of a Strong Scientific Premise for the Technical Proposal. (*I.e.*, Sufficiency of proposed strategy to ensure a robust and unbiased approach, as appropriate for the work proposed. Adequacy of proposed plan to address relevant biological variables, including sex, for studies in vertebrate animals and/or human subjects.)	25%
2. The potential of the proposed research for technological innovation – whether the end product or technology proposed would offer significant advantages over existing approaches, methodologies, instrumentation, or interventions currently utilized in research or clinical practice.	25%
3. The potential of the proposed research for commercialization, considering the offeror's Commercialization Plan, the offeror's record of successful commercialization for other projects, commitments of additional investment during Phase I and Phase II from private sector or other non-SBIR funding sources, and/or any other indicators of commercial potential for the proposed research.	25%
4. The qualifications of the proposed Principal Investigators, Project Directors, supporting staff and consultants, and the appropriateness of the leadership approach (including the designated roles and responsibilities, governance, and organizational structure).	15%
5. The adequacy and suitability of the facilities and research environment.	10%

Technical reviewers will base their conclusions only on information contained in the proposal. It cannot be assumed that reviewers are acquainted with the firm or key individuals or any referenced experiments. Relevant supporting data such as journal articles, literature, including Government publications, etc., should be contained or referenced in the proposal and will count toward the page limit.

7 PROPOSAL SUBMISSION

7.1 Questions

Offerors with questions regarding this solicitation must submit them in writing to the Contracting Officer point of contact identified in Section 10 of this solicitation for the Awarding Component that is responsible for the Topic of interest to the offeror. To ensure that the Government has sufficient time to respond, questions should be submitted by **September 4, 2020**. 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 11, 2020** 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://register.gotowebinar.com/register/3908910480225516044. 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/sbirsttr by the date and time specified on the first page of this solicitation.

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

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

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

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

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

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

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

3. Proposal Naming Conventions

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

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

An example is provided below:

- Phase I_XYZ Company_ NCEZID_Topic_014

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

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

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

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

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

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

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

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

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

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

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

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

8 PROPOSAL PREPARATION AND INSTRUCTIONS

8.1 Introduction

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

8.2 Fast Track Proposal Instructions (NIH Only)

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

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

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

8.3 Phase I Proposal Instructions

A complete Phase I proposal consists of the following:

TECHNICAL PROPOSAL

Item 1: Technical Element

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

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

BUSINESS PROPOSAL

Item 3: Pricing Proposal (Appendix C)

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

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

Item 6: Summary of Related Activities (Appendix F)

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

8.4 Phase II Proposal Instructions

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

TECHNICAL PROPOSAL

Item 1: Technical Element

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

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

BUSINESS PROPOSAL

Item 3: Pricing Proposal (Appendix C)

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

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

Item 6: Summary of Related Activities (Appendix F)

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

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

8.5 Technical Proposal Cover Sheet (Item 1)

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

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

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

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

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

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

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

8.6 Table of Contents (Item 1)

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

8.7 Abstract of Research Plan (Item 1)

Complete the form identified as Appendix B

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

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

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

8.8 Content of Technical Element (Item 1)

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

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

(A) Research Plan for a Phase I Proposal

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

Discuss the following elements in the order indicated:

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

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

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

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

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

   a) State the anticipated results of the proposed approach, assuming project success.
   b) Discuss the significance of the Phase I effort in providing a foundation for the Phase II R/R&D effort.

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

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

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

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

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

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

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

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

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

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

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

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

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

Discuss the following elements in the order indicated:

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

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

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

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

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

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

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

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

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

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

7) **Resources** - List/describe all equipment, facilities and other resources available for this project, including the offeror's clinical, computer and office facilities/equipment at any other performance site that will be involved in this project. Briefly state their capacities, relative proximity and extent of availability to this effort. (Any equipment specifically proposed as a cost to the contract must be justified in this section as well as detailed in the budget. Equipment and products purchased with Government funds shall be American-made, to the extent possible. Title to the equipment will vest in the Government.)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8.9 Enhancing Reproducibility through Rigor and Transparency

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

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

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

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

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

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

8.10 Research Involving Vertebrate Animals

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

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

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

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

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

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

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

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

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

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

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

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

8.11 Dual Use Research of Concern

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

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

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

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

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

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

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

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

8.12 Human Subjects and Clinical Trials Information Form

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

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

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

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

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

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

8.12.1 Human Specimens and/or Data

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

8.12.2 Human Subjects Research with an Exemption from Federal Regulations

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

8.12.3 Protection of Human Subjects

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

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

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

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

B. Instructions to Offerors Regarding Protection of Human Subjects

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

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

a. Risks to the subjects

- Human Subjects Involvement, Characteristics, and Design
  - Briefly describe the overall study design in response to the solicitation.
  - Describe the subject population(s) to be included in the study; the procedures for assignment to a study group, if relevant; and the anticipated numbers of subjects for each study group.
  - List any collaborating sites where human subjects research will be performed, and describe the role of those sites and collaborating investigators in performing the proposed research.
- Study Procedures, Materials, and Potential Risks
  - Describe all planned research procedures (interventions and interactions) involving study subjects; how research material, including biospecimens, data, and/or records, will be obtained; and whether any private identifiable information will be collected in the proposed research project.
  - For studies that will include the use of previously collected biospecimens, data or records, describe the source of these materials, whether these can be linked with living individuals, and who will be able to link the materials.

- Describe all the potential risks to subjects associated with each study intervention, procedure or interaction, including physical, psychological, social, cultural, financial, and legal risks; risks to privacy and/or confidentiality; or other risks. Discuss the risk level and the likely impact to subjects.
- Where appropriate, describe alternative treatments and procedures, including their risks and potential benefits. When alternative treatments or procedures are possible, make the rationale for the proposed approach clear.

b. Adequacy of Protection Against Risks

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

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

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

d. Importance of the Knowledge to be Gained

- Discuss the importance of the knowledge gained or to be gained as a result of the proposed research.
- Discuss why the risks to subjects are reasonable in relation to the importance of the knowledge that may reasonably be expected to result.

- Note: If a test article (investigational new drug, device, or biologic) is involved, name the test article and state whether the 30-day interval between submission of offeror's certification to the Food and Drug Administration (FDA) and its response has elapsed or has been waived and/or whether the FDA has withheld or restricted use of the test article.

Collaborating Site(s)

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

8.12.4 Required Education in the Protection of Human Research Participants

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

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

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

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

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

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

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

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

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

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

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

Your Inclusion discussion may include multiple Inclusion Enrollment Reports for each study proposed. The Inclusion Enrollment Report is embedded into the **Appendix H.3 Study Record Form**. To access the Inclusion Enrollment Report, click the button "Add Inclusion Enrollment Report" at the end of "Section 2 – Study Population Characteristics" within the **Appendix H.3 Study Record**

Form. The Study Record form is itself an attachment to the **Appendix H.2 Human Subjects and Clinical Trials Information Form.**

Inclusion of Women and Minorities in Research Involving Human Subjects

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

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

Information Required for ALL Clinical Research Proposals

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

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

The proposal must include the following information:

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

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

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

In addition to the above requirements, solicitations for **NIH defined Phase III clinical trials** require that: a) all proposals and/or protocols provide a description of plans to conduct analyses, as appropriate, to detect significant differences in intervention effect by sex/gender, racial/ethnic groups, and relevant subpopulations, if applicable; and b) all contractors to report annually cumulative

subject accrual, and progress in conducting analyses for sex/gender and race/ethnicity differences. See the NIH Guide for definitions of Significant Difference and NIH-Defined Phase III Clinical Trial: http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm .

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

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

  OR

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

  OR

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

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

Inclusion of Children in Research Involving Human Subjects

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

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

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

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

Justifications for Exclusion of Children

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

- The objective of the solicitation is not relevant to children.
  - There are laws or regulations barring the inclusion of children in the research to be conducted under the solicitation.

- The knowledge being sought in the research is already available for children or will be obtained from another ongoing study, and an additional study will be redundant. You should provide documentation of other studies justifying the exclusion.
- A separate, age-specific study in children is warranted and preferable. Examples include:
  - The relative rarity of the condition in children, as compared with adults (in that extraordinary effort would be needed to include children); or
  - The number of children is limited because the majority are already accessed by a nationwide pediatric disease research network; or
  - Issues of study design preclude direct applicability of hypotheses and/or interventions to both adults and children (including different cognitive, developmental, or disease stages of different age-related metabolic processes); or
  - Insufficient data are available in adults to judge potential risk in children (in which case one of the research objectives could be to obtain sufficient adult data to make this judgment). While children usually should not be the initial group to be involved in research studies, in some instances, the nature and seriousness of the illness may warrant their participation earlier based on careful risk and benefit analysis; or
  - Study designs aimed at collecting additional data on pre-enrolled adult study subjects (e.g., longitudinal follow-up studies that did not include data on children);
  - Other special cases justified by the offeror and found acceptable to the review group and the Institute Director.

Definition of a Child

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

The definition of child described above will pertain to this solicitation (notwithstanding the FDA definition of a child as an individual from infancy to 16 years of age, and varying definitions employed by some states). Generally, State laws define what constitutes a "child," and such definitions dictate whether or not a person can legally consent to participate in a research study. However, State laws vary, and many do not address when a child can consent to participate in research. Federal Regulations (45 CFR 46, subpart D, Sec.401-409) address DHHS protections for children who participate in research, and rely on State definitions of "child" for consent purposes. Consequently, the children included in this policy (persons under the age of 21) may differ in the age at which their own consent is required and sufficient to participate in research under State law.

8.12.6 Data and Safety Monitoring in Clinical Trials

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

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

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

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

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

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

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

a Data Safety Monitoring Board (DSMB). The establishment of a DSMB is optional for Phase I and Phase II clinical trials.

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

For any proposed clinical trial, NIH requires a data and safety monitoring plan (DSMP) that is commensurate with the risks of the trial, its size, and its complexity. Provide a description of the DSMP, including:

- The overall framework for safety monitoring and what information will be monitored.
- The frequency of monitoring, including any plans for interim analysis and stopping rules (if applicable).
- The process by which Adverse Events (AEs), including Serious Adverse Events (SAEs) such as deaths, hospitalizations, and life threatening events and Unanticipated Problems (UPs), will be managed and reported, as required, to the IRB, the person or group responsible for monitoring, the awarding IC, the NIH Office of Biotechnology Activities, and the Food and Drug Administration.
- The individual(s) or group that will be responsible for trial monitoring and advising the appointing entity. Because the DSMP will depend on potential risks, complexity, and the nature of the trial, a number of options for monitoring are possible. These include, but are not limited to, monitoring by a:
    - PD/PI: While the PD/PI must ensure that the trial is conducted according to the approved protocol, in some cases (e.g., low risk trials, not blinded), it may be acceptable for the PD/PI to also be responsible for carrying out the DSMP.
    - Independent safety monitor/designated medical monitor: a physician or other expert who is independent of the study.
    - Independent Monitoring Committee or Safety Monitoring Committee: a small group of independent experts.
    - Data and Safety Monitoring Board (DSMB): a formal independent board of experts including investigators and biostatisticians. NIH requires the establishment of DSMBs for multi-site clinical trials involving interventions that entail potential risk to the participants, and generally, for all Phase III clinical trials, although Phase I and Phase II clinical trials may also need DSMBs. If a DSMB is used, please describe the general composition of the Board without naming specific individuals.

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

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

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

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

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

b. The reporting of summary results information (including adverse events) no later than 1 year after the completion date for registered applicable clinical trials involving drugs that are approved under section 505 of the Food, Drug and Cosmetic Act (FDCA) or licensed under section 351 of the PHS Act, biologics, or of devices that are cleared under section 510k of FDCA.

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

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

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

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

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

1. The Contractor shall register and submit results information to ClinicalTrials.gov as outlined in the NIH policy on the Dissemination of NIH-Funded Clinical Trial Information and according to the specific timelines stated in the policy (this can be a brief statement);
2. Informed consent documents for the clinical trial(s) shall include a specific statement relating to posting of clinical trial information at ClinicalTrials.gov; and
3. The Contractor has an internal policy in place to ensure that clinical trials registration and results reporting occur in compliance with NIH policy on the Dissemination of NIH-Funded Clinical Trial Information requirements.

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

8.12.8 Plan for Single Institutional Review Board (sIRB)

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

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

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

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

EXCEPTIONS TO THE SINGLE INSTITUTIONAL REVIEW BOARD (sIRB) POLICY

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

1. For sites for which Federal, state, or tribal laws, regulations or policies require local IRB review (policy-based exceptions):
    a. The Offeror shall identify any site that meets the requirements for the Single IRB policy but is required to have local IRB review because of a federal, state, or tribal law, regulation or policy; and
    b. The Offeror shall provide specific citation for policy-based exceptions.

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

Post-Award Exception Requests

For any post-award changes that necessitate an exception request, such as the addition of a new domestic site that may be unable to use the sIRB Contractor shall contact their Contracting Officer (CO). For policy-based exceptions, the Contractor shall provide the appropriate citation to verify the requirement for local IRB review for the newly added site(s) to the CO. For *other exceptions* , the Contractor shall provide compelling justification to the CO to be reviewed by the NIH Exceptions Review Committee (ERC) (see **Steps to Request an *Other Exception* to the sIRB Policy** above). For time limited exceptions, Contractor shall provide the parent contract number to the CO.

Notice of Approval or Disapproval of *Other Exception* Requests

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

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

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

All research projects (both NIH-funded and non-NIH-funded) involving recombinant or synthetic nucleic acid molecules that are conducted at or sponsored by an entity in the U.S. that receives any support for recombinant or synthetic nucleic acid research from NIH shall be conducted in accordance with the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines) (see http://osp.od.nih.gov/biotechnology/nih-guidelines). All NIH-funded projects conducted abroad that involve research with recombinant or synthetic nucleic acid molecules must also comply with the NIH Guidelines. In addition to biosafety and containment requirements, the *NIH Guidelines* delineate points to consider in the development and conduct of human gene transfer clinical trials, including ethical principles and safety reporting requirements (see Appendix M of the *NIH Guidelines*).

Prior to beginning any clinical trial involving the transfer of recombinant or synthetic nucleic acid molecules into humans, the trial must be registered with the NIH Office of Science Policy (OSP) and, if applicable, reviewed by the NIH Recombinant DNA Advisory Committee (RAC). If this contract involves a human gene transfer trial raising unique and/or novel issues, the trial may be discussed by the RAC in a public forum (see Appendix M-I-B of the *NIH Guidelines* for the specific criteria for the selection of protocols for RAC review and discussion). Approval of an Institutional Biosafety Committee (IBC) and the Institutional Review Board (IRB) are necessary before the Contracting Officer's Representative (COR) and Contracting Officer (CO) may approve the

protocol prior to the start of the research. IBC approval may not occur until the protocol registration process with NIH is complete. If the trial is reviewed by the RAC, IBC approval may not occur before the RAC has concluded its review of the protocol and the protocol registration process with NIH is complete.

For human gene transfer research, Appendix M-I-C-4 of the NIH Guidelines requires any serious adverse events (SAEs) that are both unexpected and possibly associated with the human gene transfer product to be reported to NIH OSP and an IBC within 15 days, or within 7 days if the event was life-threatening or resulted in a death. A copy of the report must also be filed with the COR and CO. SAE reports must also be submitted within their mandated time frames to the IRB, Food and Drug Administration (FDA), and, if applicable, the Health and Human Services (HHS) Office for Human Research Protections (OHRP). In addition, annual reports must be submitted to NIH OSP covering certain information about human gene transfer protocols. Further information about the content of these reports can be found in Appendix M-I-C-3 of the *NIH Guidelines* . Additional information on the requirements that pertain to human gene transfer can be found in a series of Frequently Asked Questions at: http://osp.od.nih.gov/office-biotechnology-activities/biosafety/institutional-biosafety-committees/faq .

Failure to comply with the *NIH Guidelines* may result in suspension, limitation, or termination of the contract for any work related to recombinant or synthetic nucleic acid research or a requirement for the CO to approve any or all recombinant or synthetic nucleic acid molecule projects under this contract. This includes the requirement for the institution to have an IBC registered with NIH OSP that complies with the requirements of the *NIH Guidelines* . Further information about compliance with the *NIH Guidelines* can be found on the NIH OSP web site: at: http://osp.od.nih.gov/office-biotechnology-activities/rdna_ibc/ibc.html

8.12.10 Human Stem Cell Research

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

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

8.13 Content of the Pricing Proposal (Item Two).

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

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

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

  SBCs are reminded that only actual G&A/IDC costs may be charged to projects. If awarded at a rate of 40 percent or less of total direct costs, the rate used to charge actual G&A/ID costs to projects cannot exceed the awarded rate unless the SBC negotiates an indirect cost rate(s) with DFAS.

- Offerors submitting proposals may include the amount of up to $6,500 per year for a Phase I and up to $50,000 per Phase II project (across all years) for technical assistance as discussed and outlined in Section 4.16 of the solicitation. Include a detailed description of the technical or business assistance that your vendor/s will provide, including the name of the vendor/s and the expected benefits and results of the technical or business assistance provided. A letter of support from the vendor describing their qualifications and services to be provided is recommended.

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

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

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

8.14 Reminders

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

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

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

Check that the Project Abstract and other content provided on the cover sheets contain NO proprietary information.

Mark proprietary information within the Technical Proposal as instructed in Section 4.23.

Check that the header on each page of the technical proposal contains the company name and topic number.

9 SUMMARY OF HHS COMPONENTS ANTICIPATED NUMBER OF AWARDS

HHS COMPONENTS	ANTICIPATED NO. OF AWARDS	ANTICIPATED TIME OF AWARD
National Institutes of Health (NIH) National Center for Advancing Translational Sciences (NCATS)	1-6	Scientific and Technical Merit Review: February-April 2021 Anticipated Award Date: July-September 2021
National Institutes of Health (NIH) National Cancer Institute (NCI)	44-77	Scientific and Technical Merit Review: March-May 2021 Anticipated Award Date: August-September 2021
National Institutes of Health (NIH) National Heart, Lung, and Blood Institute (NHLBI)	4-5	Scientific and Technical Merit Review: February-April 2021 Anticipated Award Date: July-September 2021
National Institutes of Health (NIH) National Institute of Allergy and Infectious Diseases (NIAID)	28-47	Scientific and Technical Merit Review: March 2021 Anticipated Award Date: August 2021
Center for Disease Control and Prevention (CDC) Center for Preparedness and Response (CPR)	1	Scientific and Technical Merit Review: Anticipated Award Date: August 2021
Centers for Disease Control and Prevention (CDC) National Center for Emerging Zoonotic and Infectious Diseases (NCEZID)	4-5	Scientific and Technical Merit Review: Anticipated Award Date: August 2021
Center for Disease Control and Prevention (CDC) National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (NCHHSTP)	2	Scientific and Technical Merit Review: Anticipated Award Date: August 2021

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

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

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

NATIONAL INSTITUTES OF HEALTH (NIH)

NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES (NCATS)

Rieka Plugge
Contracting Officer
NIDA Office of Acquisition
Phone: (301) 827-7515
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NATIONAL CANCER INSTITUTE (NCI)

Rosemary Hamill
Procurement Analyst
Office of Acquisitions, OM, NCI
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NATIONAL HEART, LUNG, AND BLOOD INSTITUTE (NHLBI)

Joanna Magginas
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NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES (NIAID)

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

CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

For general administrative SBIR program questions, contact:

Office of Science, Office of Technology and Innovation

Sean David Griffiths, M.P.H.
SBIR Program Manager
Office of Technology and Innovation
Office of Science
Phone: 404-639-4641
Fax: 404-639-4903
E-mail: SBIR@cdc.gov

Mim Kelly, PhD
Office of Technology and Innovation
Office of Science
Phone: 404-639-4784
Fax: 404-639-4903
Email: SBIR@cdc.gov

CENTER FOR PREPAREDNESS AND RESPONSE (CPR)

Michael Crow
Contracting Officer
Centers for Disease Control and Prevention
Office of Financial Resources
Phone: (770) 488-3208
E-mail: WYV2@cdc.gov

NATIONAL CENTER FOR EMERGING ZOONOTIC AND INFECTIOUS DISEASES (NCEZID)

Priscilla Turner
Contracting Officer
Centers for Disease Control and Prevention
Office of Financial Resources
Phone: (770) 488-2821
E-mail: PBTurner@cdc.gov

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

Sherrie Randall
Contracting Officer
Centers for Disease Control and Prevention
Office of Financial Resources
Phone: (770) 488-2866
E-mail: iom2@cdc.gov

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://nnlm.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:

020 Development of Remote Rare Disease Patient Care Environment through Immersive Virtual Reality

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

Number of anticipated awards: 1 to 3

Budget (total costs, per award): Phase I: $325,000 for 9-12 months; Phase II: $2,000,000 for 2 years

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

Summary:

The objective of this contract is to develop a multi-modal virtual reality environment for remote use enabling physicians and healthcare providers to guide rare disease patient therapy while automatically obtaining crucial health metrics.

Genetic and rare diseases are often chronic debilitating disorders for which patients require life-long individualized care, and which frequently require longer and more frequent visits with their physicians and healthcare providers than for typical patients. Given the small numbers of patients with each rare disease and few specialists with expert knowledge about these disorders, an understanding of the clinical characteristics and course of a rare disease often resides with patients and caregivers who are geographically scattered throughout the country. . Thus, there is a need for rare disease patients to receive active feedback pertaining to their health and disease progression, as well as to engage patients to positively enable the healing process. Engagement of rare disease physicians and healthcare providers can also be a challenge given the frequent lack of measurable outcome assessment tools to monitor patients over the long-term for both disease progression and the benefits of therapeutic intervention, and the need for seamless coordination with a multi-disciplinary care team.

Additionally, rare diseases disproportionately affect children and adolescents, and the repetitive often boring nature of physical and occupational therapies can lead to disengagement and a lack of motivation to continue these interventions outside of the clinic. Rare disease patients may also be located far from expert medical centers, have difficulty with travel due to the severity of their conditions, and in the event of National emergencies (i.e. pandemics), many rare disease patients experience disproportionate interruptions in medical care. These issues are especially difficult for rare disease patients in rural or low-income communities ("medical deserts"). While current video-conferencing capabilities enable communication, they lack the interpersonal connections between healthcare providers and patients, and the ability to accurately assess

functional measures over the course of treatment, such as joint mobility, forces/timing of physical movement, global activity, or accurate assessment of heart/respiratory rate. Thus, there is a critical need for rare disease patients to have the ability to remain home with continued access to high-quality teletherapy and remote monitoring.

To address the needs for user engagement and remote metrics for rare disease patients, physicians, therapists and healthcare providers are collaborating to develop an immersive VR environment for physical and occupational therapy and rehabilitation. The experience provides a remote medium to monitor user pain, discomfort, mobility, and biometrics during a prescribed therapeutic exercise session. Research has indicated that immersion afforded by VR can reduce pain and discomfort in the physical medicine and rehabilitation context. However, perception of immersion is highly individualized and context-dependent to the patient. To address the needs for user engagement and remote metrics, physicians, therapists and healthcare providers are working with developers to advance an immersive VR environment for physical and occupational therapy and rehabilitation. Efforts in game design mechanics through multi-modal immersion such as haptic feedback vests, olfactory masks, and other emerging technologies are being investigated to understand how to best design healthcare experiences for emotional engagement and interpersonal connection. These metrics can provide a remote medium for physicians and therapists to understand patient movement and engagement in therapy protocols. Now, these efforts should evolve into an interactive environment so physicians and healthcare providers and rare disease patients can meet remotely and still receive quality care.

Project Goals:

The purpose of this project is to create a virtual reality therapy environment for remote use enabling physicians and healthcare providers to provide quality care for rare disease patients outside of their offices or clinic settings. Offerors will address the current limitations with teletherapy by creating features to guide patients and gather relevant metrics necessary for physicians and healthcare providers. We want to address the challenges of disengagement and frustration by creating a stimulating, enjoyable and easy to use virtual environment for rare disease patients.

To this end, the goal of this project is to translate rare disease patient care into virtual reality through (1) automated health metrics utilizing an immersive virtual reality systems motion capture, (2) remote healthcare provider-patient interaction through virtual avatars in a 6 degrees of freedom (6-DoF) environment, and (3) a series of games that are customizable by the healthcare provider for physical, functional, cognitive, or behavioral exercises for the rare disease patient to be played independently.

An optimal outcome would be the creation of a system for physicians and healthcare providers to adopt beyond shelter in place that would have the following benefits:

- Increase physician and healthcare provider accessibility to rare disease patients through virtual clinics and at-home meetings.
- Increase rare disease patient motivation and engagement to therapy protocol through gamification.
- Monitor and document compliance with therapy protocols through remote capture.
- Optimize healthcare provider time by automating analysis of patient specific health metrics.
- Personalize rare disease patient therapeutic exercises through a tunable environment for both the patient and physician.
- Provide real-time rare disease patient feedback through web-based analytic dashboards.
- Provide engagement through virtual environments to aid in physical, functional, cognitive or behavioral exercises.
- Enable a standardized platform for collecting remote health data.

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

Phase I Activities and Expected Deliverables:

- An immersive virtual reality environment with a minimum of the following capabilities:
    - An avatar representation for remote patient- healthcare provider interaction.
    - A WebXR instance of the experience through the Unity Game Engine to enable usage on any VR device through the world-wide web.
    - Sensing capabilities to perform runtime health analytics for physician observation.

- An analytics dashboard for patient- healthcare provider interpretation both in and outside of the virtual environment.
    - An algorithm for automated runtime health informatics to provide rare disease patient engagement, discomfort, kinematics, dynamics, and muscle force estimation.
    - Representations of functional assessment for the patient's avatar in immersive virtual reality through force vectors and heatmaps.
    - A modular dashboard for representations of targeted health informatics.
    - Verification of secure and ethical data practices for remote data collection.
- A method of personalized gamification for physician prescribed exercises.
    - A customizable background environment to change the audio-visual stimuli of the user's virtual health experience.
    - An adaptive input system to enable the addition of immersive peripherals such as haptic feedback vests, olfactory masks, gaze-based systems, and custom controllers for accessibility and variable immersion.
    - A physical exercise game for physicians to record desired movements and prescribe them to patients.
    - A mindfulness exercise game for healthcare providers to record desired breathing patterns and mediation lengths and prescribe them to patients.

- Assemble appropriate expertise in their teams to meet statement of work goals, which could include clinicians, occupational therapists, physical therapists and other appropriate subject matter experts depending on the deliverables of the contract.

- Provide NCATS with all data and materials resulting from Phase I Activities and Deliverables.

Phase II Activities and Expected Deliverables:

- Build a prototype virtual experience that meets the Phase I specifications.
- Provide a test plan to evaluate every feature of the virtual experience.
- Provide NCATS with all data from each executed test to properly evaluate each test condition.
- Develop a robust web server for the virtual experience, using compliant secure components and minimizing expense where possible.
- Provide NCATS with all data resulting from Phase II Activities and Deliverables.
- Assemble appropriate team/expertise to perform deliverables of the contract
- Provide NCATS with all data and materials resulting from Phase II Activities and Deliverables.

021 Platform for Rapidly Deployable Autonomous Laboratory

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

Number of anticipated awards: 1 to 3

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

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

Summary:

The unprecedented 2020 COVID-19 pandemic and subsequent physical distancing has led critical experimentation for developing novel diagnostic techniques and potential therapeutic interventions to nearly grind to a halt. This is due to the reliance on people to be physically present in a laboratory. The contract proposed here is to develop a next generation therapeutic discovery or diagnostic platform consisting of distributed, Artificial Intelligence (AI)-enabled, fully automated pieces of instrumentation that are capable of functioning in an autonomous fashion and directly linked to virtual cloud-based resources. The type of instrumentation required will depend upon the kind of experiment to be performed. Regardless of the

experiment type, the instrumentation should be geared towards therapeutic discovery or a diagnostic technique such as an ELISA assay, the resultant experimental data could be ingested in real time to a cloud-based virtual research organization (VRO). The VRO model proposed would greatly improve safety with little or no loss of productivity. A key challenge for rapid development of diagnostics and therapeutics has been the inability to acquire, harmonize, store, analyze and share data generated during experimentation. Through this concept, a platform would be created to make data accessible to researchers anywhere on the globe in near real-time to help respond to a fast-changing pandemic or other healthcare crisis where time is of the essence.

Project Goals:

The goals of this project are to develop a platform comprised of three core components:

1. Distributed, modular, next generation autonomous laboratories that focus on areas such as high throughput screening (HTS) for drug discovery, next generation sequencing (NGS), high content imaging (HCI), polymerase chain reaction (PCR) diagnostics and others.
2. A cloud based VRO that each distributed automated laboratory is directly connected to.
3. Federated AI, potentially most critical, is the integration of the physical laboratories with the virtual cloud environment such that AI methods can be utilized to generate hypotheses based on previous experiments that could then be tested in the physical laboratory environment.

This distributed and iterative approach would allow for the on demand initiation of a physical experiment, which could conceivably be a HTS run in one location along with NGS at another, the generation and analysis of data, with each experiment performed further expanding the available data to be used for more efficient and accurate AI models which can then initiate new experiments. It would be possible to compile and quickly perform a relational analysis of multiple relevant data types ingested into the cloud-based VRO from different distributed autonomous laboratories, as well as use AI generated hypotheses to trigger new experiments in order to broaden the dimension of discovery in a shorter time frame. The modular nature of this approach will also allow the entire platform to quickly add or scale up additional resources as required to respond to emerging pathogens or other biological scientific needs.

Phase I Activities and Expected Deliverables:

- Develop a prototype Platform for Rapidly Deployable Autonomous Laboratory comprised of three components:
    - Modular instrumentation with the following characteristics:
        - Must be used in typical laboratory operations such as HTS, NGS, HCI, PCR, etc.
        - Must use standard laboratory instrumentation communication protocols to communicate with other devices such as RS-232, TCP/IP, CAN bus, etc.
        - Must use ethernet based protocols to communicate with cloud-based environments such as TCP/IP, MQ Telemetry Transport (MQTT); commonly used for the Internet of Things (IoT); Advanced Message Queuing Protocol (AMQP), etc.
        - Must have a comprehensive application program interface (API) allowing for full control of the instrument, ranging from initiating the execution of an instrument specific protocol, to monitoring the status of the device, reporting results, reporting device faults with ability to recover, etc.
        - Must be able to communicate with other pieces of instrumentation to develop functional laboratory platforms.
        - Must include an instrument which generates data as the result from laboratory operations such as HTS, NGS, HCI, PCR, etc.
        - Must include consideration for a sample transport device.
        - Ideally will utilize modular components which are easily replaced when required.

- A cloud based VRO that each distributed automated laboratory is directly connected to with the following core capabilities:
    - Infrastructure:
        - A scalable, cloud-based architecture residing in a major cloud service provider such as Amazon Web Services (AWS), Microsoft Azure, Google Cloud Platform (GCP), etc. The offeror should be able to demonstrate access (via an executed license) to the cloud service.
    - Data Storage, Access, and Catalog
        - Distributed data storage via services such as S3, Azure and Google storage etc.
        - Storage Class memory technology to be able to access data in real-time.
        - Data access API for simplified interface such as the use of 'PUT' and 'GET' requests.
        - A Data Catalog accessible via an API and keep tracks of all data sources and their respective metadata.
    - Data Extraction, Aggregation, Integration, and Harmonization:
        - Ability to integrate simultaneous data connections from multiple concurrent sources.
        - Enable connections to multiple types of databases and makes data available to users through a single access point.
    - Secure collaboration:
        - Multiple users should be able to visualize and work on the same data in a collaborative platform.
        - Remote Binding to ensure device control is handled securely and safely
        - Complaint with the following industry best-practice certifications, attestations, alignments, and frameworks such as:
            - SSAE18 SOC 2 Type II
            - ISAE 3000 SOC 2 Type II
            - FedRAMP Moderate (Ideally, but not required for Phase I)
    - Interoperability and Open Architecture
        - Store data in open source formats and expose REST APIs to interoperate with third-party and open source tools
- Integration of the physical laboratories with the virtual cloud environment to allow for:
    - Federated AI and Machine Learning (ML) such that AI and ML methods can be utilized to generate hypotheses based on previous experiments that could then be tested in the physical laboratory environment.
    - Accessibility from external collaborator laboratories for use of the VRO and ability to remotely run experiments and process data into the VRO cloud environment
    - Adherence to appropriate safety protocols and procedures for physical control is mandatory of the above requirement within the VRO for anyone to be able to remotely control instrumentation.

    - Ability to scale, publish and share instrument services/functionality i.e. laboratory as a service (LaaS)

- Provide cost estimates to develop a proof of concept platform capable of meeting the specifications listed above.

- Provide NCATS with all data resulting from Phase I Activities and Deliverables.

Phase II Activities and Expected Deliverables:

- Build a prototype platform that meets the Phase I specifications.
- Provide a test plan to evaluates all components of the platform, from the instrumentation performing some laboratory operation, to the data being sent securely to the VRO and finally with that data being used to propose and initiate a new experiment to be run on the platform.
- Demonstrate that the platform is scalable to potentially hundreds of pieces of instrumentation in a distributed fashion.
- Provide NCATS with all data resulting from Phase II Activities and Deliverables.

NATIONAL CANCER INSTITUTE (NCI)

The NCI is the Federal Government's principal agency established to conduct and support cancer research, training, health information dissemination, and other related programs. As the effector of the National Cancer Program, the NCI supports a comprehensive approach to the problems of cancer through intensive investigation in the cause, diagnosis, prevention, early detection, and treatment of cancer, as well as the rehabilitation and continuing care of cancer patients and families of cancer patients. To speed the translation of research results into widespread application, the National Cancer Act of 1971 authorized a cancer control program to demonstrate and communicate to both the medical community and the general public the latest advances in cancer prevention and management. The NCI SBIR program acts as NCI's catalyst of innovation for developing and commercializing novel technologies and products to research, prevent, diagnose, and treat cancer.

It is strongly suggested that potential offerors do not exceed the total costs (direct costs, facilities and administrative (F&A)/indirect costs, and fee) listed under each topic area.

Unless the Fast-Track option is specifically allowed as stated within the topic areas below, applicants are requested to submit only Phase I proposals in response to this solicitation.

NCI Phase IIB Bridge Award

The National Cancer Institute would like to provide notice of a recent funding opportunity entitled the SBIR Phase IIB Bridge Award. This notice is for informational purposes only and is not a call for Phase IIB Bridge Award proposals. This informational notice does not commit the government to making such awards to contract awardees.

Successful transition of SBIR research and technology development into the commercial marketplace is difficult, and SBIR Phase II awardees often encounter significant challenges in navigating the regulatory approval process, raising capital, licensure and production, as they try to advance their projects towards commercialization.

The NCI views the SBIR program as a long-term effort; to help address these difficult issues, the NCI has developed the SBIR Phase IIB Bridge Award under the grants mechanism. The previously-offered Phase IIB Bridge Award was designed to provide additional funding of up to $4M for a period of up to three additional years to facilitate the transition of SBIR Phase II projects to the commercialization stage. The specific requirements for the previously offered Phase IIB Bridge Award can be reviewed in the full RFA announcement: https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-20-033.html.

In FY2011, the NCI expanded the Phase IIB Bridge Award program to allow previous SBIR Phase II contract awardees to compete for SBIR Phase IIB Bridge Award grants. Provided it is available in the future, the Phase IIB Bridge Award program will be open to contractors that are successfully awarded a Phase II contract (or have an exercised Phase II option under a Fast-Track contract). NIH SBIR Phase II contractors who satisfy the above requirements may be able to apply for a Phase IIB Bridge Award under a future Phase IIB Bridge Award grant funding opportunity announcement (FOA), if they meet the eligibility requirements detailed therein. Selection decisions for a Phase IIB Bridge Award will be based both on scientific/technical merit as well as business/commercialization potential.

NCI Topics

This solicitation invites proposals in the following areas. Offerors may propose clinical studies, as appropriate.

413 Next Generation 3D Tissue Culture Systems with Tertiary Lymphoid Organs

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 9 months

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

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

Summary

Tertiary lymphoid organs (TLOs) are lymph node-like structures that form in tissues in the presence of chronic inflammation in response to molecular and pathological damage from exposures (both internal and external). The purpose of their formation is an active area of study, but they likely form to fight damage at the tissue level while also collecting, processing, and delivering and presenting tissue- and tumor- antigens to primary and secondary lymphoid organs. TLOs are characterized by many of the same morphological features as lymph nodes. These morphological features include germinal center B-cell zones, T-cell follicles, and high endothelial venules (HEVs) through which immune cells traffic into/out of the TLO. TLOs are also populated with many of the same cell types as lymph nodes, including mesenchymal derived follicular dendritic cells that recruit lymphocytes and assist in the formation of the morphological features; and hematopoietic stem cell derived antigen presenting dendritic cells (DCs), macrophages, central and effector memory lymphocytes, etc. TLOs are found within almost all tumors and may play a critical gatekeeping role in the ability for T cells to access the tumor microenvironment and participate in immune surveillance. Recent studies show that intra-tumoral TLOs can sequester cytotoxic T cells, and ectopic TLO formation immediately adjacent to the tumor margin prevents the infiltration of T lymphocytes (TILs) into tumor.

While TLOs are likely to play a critical role in the ability of the immune system to mount an immune response to tumor neoantigens, and also control effector cell access to tumor cells, TLO containing in vitro models do not exist and in vivo approaches to induce TLOs in animal models are extremely limited. Therefore, there is a need for more efforts to develop both intra and ectopic tumor associated TLO models to understand their role in the development of cancer, immune tolerance, tumor immune evasion, and antitumor immunity. Generating these 3D systems with TLOs that are viable for longer periods is challenging but once established using right elements that best represent the biology and pathology, they can be valuable tools for obtaining insights in basic and translational research in cancer, autoimmune diseases and chronic inflammatory and infectious diseases. Establishing TLO containing 3D systems that survive for a longer duration is not only important for understanding the immune system's role in keeping cancers in check but also for unraveling how immune system may contribute ques for cell transformation, cancer development and progression, and all these processes require a longer interaction of the immune system with the tissue cells.

Project Goals

The goal is to advance the development of next generation 3D tissue/tumor cell culture systems that develop and maintain self-assembled TLOs for months. There are several potential research uses for 3D culture models that incorporate TLOs, including: 1) studying immune system's role in clearing autophagy, apoptosis and/or necrosis mediated tissue damage; 2) studying immune system's role in prevention, initiation and development of cancer as well as metastasis, 3) studying interactions among immune cells and tumor cells in the tumor microenvironment, 4) serving as an innovative and simple in vitro approach for identifying neoantigens that are collected, processed and displayed by the antigen presenting cells in the TLOs, 5) studying movements and interactions of TILs in tumors, and 6) facilitate development of personalized immunotherapy.

The activities and deliverables in the solicitation will focus on the development of 3D tissue cultures that contain self-assembling TLOs with key morphological and functional characteristics. Critical morphological characteristics of the TLOs are B cell and T cell zones. Offerors will be required to interrogate the functional aspects of the TLOs including tumor antigen presentation by DCs within the TLO, and activation and expansion of T cells and B cells. This topic will require developers to establish a 3D culture system representing at least one tumor type and develop 3D cultures from multiple donors. Furthermore, the activities will require that the offerors evaluate the longevity of TLOs in vitro, and ideally demonstrating that a 3D culture systems containing TLOs can be maintained for a minimum of 2 months, with a preference for longer periods of 8-10 months, to allow testing the utility of the established systems, particularly for studying tumor microenvironment interactions.

Responsive proposals must develop 3D culture systems containing TLOs using human tumor and immune tissue. Offerors must propose to use tumor tissue and immune cells from the same donor for each 3D system's development. The immune cells must be differentiated and/or obtained using progenitors with tumor cells providing the cues for their differentiation and activation. The stromal-like cells, to improve structural organization and functionality of the TLOs, must be differentiated/obtained from mesenchymal stromal cells. Preference may be given to systems that use matrices from human sources. Systems that use matrices from non-human sources will be of low priority. Offerors will not be required to develop new 3D tissue culture systems to respond to the solicitation, and companies that have expertise in building 3D culture

systems and previously built 3D culture systems through a previous NCI SBIR contract opportunity or other opportunities will be eligible to compete for this topic assuming their proposals meet all of the requirements laid out in this solicitation.

Activities not responsive to announcement:

3D systems 1) without functional immune cells, 2) that are simply made by incubating the 3D systems with peripheral blood mononuclear cells (PBMCs) to allow infiltration of immune cells, 3) made using immune cells not properly allowed to mature, differentiate and activate using the cues from the tissue/tumor cells used for creating the 3D system, and 4) 3D systems with TLOs made using synthetic polymer-based dendritic cells

Phase I Activities and Deliverables:

- Project team: Establish a project team with proven expertise in development of 3D complex tissue models, immunology, clinicians with access to patient samples, including subject matter experts in the tumor(s) being studied
- Identify appropriate cell types needed to create the 3D systems
- Show resources and expertise needed to mature, differentiate and/or activate the cells needed for creating 3D systems containing TLOs
- Create the 3D systems with TLOs representing at least one cancer type (such as pancreas, breast, prostate, lung, colon or liver)
- Show that the 3D systems can be developed reproducibly, by showing that the developed systems maintain genotypic and phenotypic characteristics for at least a month. Determine growth and expansion of cells and continued maintenance of genotype and phenotype in different compartments of the 3D systems
- Characterize the cells in the 3D system: Show that the mesenchymal derived follicular dendritic cells can recruit immune cells and form TLOs in the 3D systems. Determine antigen presenting capacity of dendritic cells, and central and effector memory cells divide, expand and maintain the TLOs. Analyze T cell receptor excision circles and kappa-deleting recombination excision circles to determine half-life of the T/B cell clonotypes and number of cell divisions, and T cell and B cell receptor sequencing to determine suitability of the T/B cells for forming TLOs that represent the TLOs present in tumor/tissue that is being created
- Show access to samples needed to conduct comparative analysis in phase II
- Establish workflows for creation and maintenance of 3D systems, and morphological and molecular characterization of the 3D systems and component cells
- Submit a detailed statement of performance characteristics along with SOPs for establishing and characterizing the 3D systems to NCI.

Phase II Activities and Deliverables:

- Create 3D systems with intra and/or ectopic TLOs.
- Improve viability and show that the 3D systems' viability is for a minimum of 2 months with a preference for longer periods of 8-10 months and reproducibility is > 75%.
- Characterize the interactions in the microenvironment - such as genotypic (chromatin accessibility, mutation, structural changes, etc.), epigenetic (methylation, histone modification, etc.) and phenotypic (gene expression, chemokines, cytokines, morphological, function, etc.) changes- among immune cells, endothelial cells and epithelial cells using physicochemical, biological, immunocytochemical/histochemical imaging methods.
- Compare the 3D systems' physicochemical and functional characteristics with the characteristics of TLO containing tissues/tumors from humans
- Compare antigens displayed by the TLO-DCs in 3D systems with antigens displayed by the circulating migratory DCs in blood from experimental animals or cancer patients with respective cancer type(s)
- Compare microenvironment interactions displayed by the 3D systems with the data from in vivo models
- Demonstrate utility of the 3D systems for quickly collecting neoantigens in vitro: Identify antigens displayed by the dendritic cells (TLO resident or migratory dendritic cells) in the 3D system

- Assess utility of the 3D systems for determining drug/immunotherapy response
- Assess how the location and duration of TLO (intra or ectopic) alter infiltration and movement of TILs
- Establish QC and QA parameters to increase reliability of the 3D systems and create a commercial prototype of the 3D tissue/tumor culture system
- Submit final SOPs, QC/QA parameters, performance characteristics, and characterization and antigen data

414 Synthetic Biology Gene Circuits for Cancer Therapy

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

Direct-to-Phase II proposals will be accepted

Number of anticipated awards: 3 - 5

Budget (total costs, per award):

Phase I: up to $400,000 for up to 9 months

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

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

Summary

Gene therapy has come of age over the past few years. One of the most promising anticancer approaches in the clinic is chimeric antigen receptor (CAR)-T cell therapy. However, the pioneering first-generation products now on the market for B-cell malignancies, that target a single cancer antigen, have major limitations. First, all normal B cells expressing CD19 are eliminated by the therapy meaning that normal B cell functions are lost. Second, patients may lose expression of the CD19 CAR-T target antigen, rendering the malignant tumor cells invisible to the immune system tasked with its destruction. Third, the therapies can trigger toxicities that are hard to predict and control, such as cytokine release syndrome. By combining computer science logic with biology, scientists have developed synthetic gene circuit technologies to redirect genetic events within cells to enable the resulting therapies to sense and adapt to their environment, or be controlled to avoid the safety and efficacy pitfalls that limited first-generation products. For example, new CAR-T approaches involve the delivery to T cells of gene circuits based on Boolean logic that can produce tumor cell killing only when two (or more) cancer antigens are expressed on cancer cells but not on normal cells, preserving normal B cell function.

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

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

Project Goals

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

The activities that fall within the scope of this solicitation include the development of the gene circuits designed and created using synthetic biology approaches into cancer therapies through engineering immune cells ex vivo, or by delivering directly

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

Phase I Activities and Deliverables:

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

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

Phase II Activities and Deliverables:

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

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

415 Applicator-Compatible Electronic Brachytherapy Sources for Cancer Radiotherapy

Fast-Track proposals will be accepted.

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

Number of anticipated awards: 1-3

Budget (total costs, per award):

Phase I: up to $400,000 for up to 9 months

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

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

Summary

This solicitation calls for the development of electronic devices to replace current radiation sources for use in the clinic allowing for implementation using existing high dose rate (HDR) applicators. The goal is to leverage the full, existing radiation therapy infrastructure (training and applicator set investment) to provide radioactive source-free (e.g., iridium) brachytherapy. Submissions will be responsive if the proposed electronic brachytherapy sources are substitutable for radioactive sources currently in use in the clinic via use with unmodified commercial applicator sets.

Brachytherapy, in surface, intracavitary and interstitial forms, using small radioactive sources is a critical component of global radiation therapy and is a mainstay in the cure for diseases like cervical cancer, sarcoma, and recurrent cancer. It is used in both adult and pediatric patient populations. The methods used are proven, affordable, and offer unique advantages to patients in terms of dosimetry - even relative to particle therapy. However, the permanent radioactivity of sources creates issues and costs related to safety and security that electronic devices would not present. Turning an electronic device off causes the radiation emission to cease. In addition, electronic sources may present unique, new advantages for dosimetric control of radiation.

To be responsive to this FOA submissions must develop and test devices that can be employed using existing brachytherapy infrastructure. In this context, the proposed devices must be compatible with the current applicators available on the market. Applicator set examples can have paths with small radii of curvature and include ring and ovoid sets and tandem and ovoid sets for cervical cancer, catheters for prostate cancer, head and neck cancer and sarcoma, and even devices allowing ocular, skin, and nasopharyngeal deployment. Use of these devices is critical so as to take advantage of infrastructure and established safety and efficacy data.

Project Goals

This contract solicitation seeks to stimulate research, development, and commercialization of innovative devices to replace and enhance the radiation space currently occupied by radioactive sources in brachytherapy. To apply for this topic, offerors should:

- Develop an appropriate electronic device and control system to allow integration into the clinic.
- Measure and define the radiation characteristics of the device: output spectrum, stability, dose rates possible, and similar capacities for modulation of dose.
- Validate that the planned (final) device will be deployed in a clinical setting using existing brachytherapy devices (applicator sets). Devices must be able to move around curves and cannot depend on waveguides.

Activities not responsive to announcement:

1. Approaches requiring new infrastructure (patient applicator modifications, treatment planning system standards changes, imaging protocol modifications) are not appropriate for this solicitation.

2. Penetration of radiation in tissue must be equal to or greater than 1 cm and energy of the beam produced must be equal or greater to 250 kV. Devices unable to achieve these energy output constraints or greater will be considered non-responsive.

Phase I Activities and Deliverables:

- Establishment of a project team that includes necessary expertise in: electronic devices capable of delivering radiation that are small in size (physics/engineering); software development for device control and operation, user-centered design for interface design, radiation/clinical oncology delivery and processes, medical devices regulations and manufacturing process expertise. Medical knowledge of brachytherapy practice and delivery is required.
- Develop a fully functional prototype that can be used with existing HDR medical devices (tandems, rings, sarcoma catheters, partial breast devices).
    - Confirm (documentation to be reported) that the device delivers dose at an energy and dose rate required of this announcement (penetration of radiation in tissue must be equal to or greater than 1 cm and energy of the beam produced must be equal or greater to 250 kV).
    - Demonstrate device stability in a model (phantom) of clinical use (motion, temperature, normal handling, dose rate, energy, with repetition). The device needs to be able to tolerate a 30 cm drop onto a solid surface without measurable change to the radiation delivered by the device.
    - Develop standard operating procedures to confirm dose delivery/validation of device function and stability. These must allow NIST traceability to be achieved in phase II.
- Perform in vitro efficacy studies in relevant cancer cell line(s) with normal tissue and standard brachytherapy source device controls.
- Develop user documentation for use of the device.
- Document a telephone call(s) and/or meeting(s) with the FDA discussing the process to achieve an IND and related approvals.

Phase II Activities and Deliverables:

- Develop a device/technology/process to scale up manufacture and calibration of devices centrally so that once produced and sold they are easy to deploy and utilize – test this via making multiple devices that may be calibrated to within 5% dose delivery of each other or better (ideally within 1%).
- Refinement process development for construction of final product by
    - Data for the successful scale-up of production of device
    - Data documenting the completion of process analytics for production and calibration, including demonstrating the ability to be calibrated in a stable fashion to NIST standards at the factory and in the field,
    - Demonstrating the formal, finalized process to allow general production unit's dosimetric verification
    - Documentation demonstrating the completion of safety interfaces and procedures for clinical implementation
- Demonstrate the ability to use a commercial and/or in-house robust and standards-based treatment planning system (TPS) with this device.
    - Treatment plans should be able to be taken from the TPS and put into the delivery system so as to control the "delivery" of the plan to a patient in standard fashion.
    - If an in-house system is developed, appropriate FDA approval processes must take place and demonstration that this TPS can properly interact with at least two leading TPS systems must be documented (plan import and export).
    - Published interface data and standards compliance for all interfaces so that a commercial TPS vendor "could" provide services to the device with their TPS.
- Demonstration of continued, close communication with the FDA in years one and two to initiate the trials and processes needed to achieve full IND approval. Trials should be at least in the process of IRB review.
- In the second year of the contract, provide the program and contract officers with a letter(s) of commercial commitment.

416 Self-Sampling Devices for HPV-Testing-Based Cervical Cancer Screening

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 9 months

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

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

Summary

All currently recommended screening tests for cervical cancer require a clinic visit and a clinical provider (physician/nurse practitioner/physician assistant)-conducted per-speculum examination for sample collection for the screening method (HPV testing and/or Pap smear cytology). An alternative that has been explored is self-collection of samples ('self-sampling') by women themselves for HPV testing, an approach that offers several benefits including ease of collection at a time/place of women's choosing and without a need for appointment or speculum examination. However, most current sampling devices have not incorporated consumer-friendly/user-centric design principles; therefore, it has been challenging to demonstrate acceptable accuracy given the variations in collection type and the expected decrement in yield of cellular material when performing self-sampling versus a clinician-collected sample from the cervix directly. Therefore, there exists a significant need for development and evaluation of novel devices for self-collection. The proposed contract topic solicitates the

development and evaluation of novel self-collection devices, including activities leading to manufacturing and regulatory approval.

Project Goals

The overall goal of the contract solicitation is to facilitate the commercial development and regulatory approval pathway for novel self-sampling devices for HPV-testing-based cervical cancer screening. In particular, companies are expected to propose designing and manufacturing of devices for self-collection and transport/storage of cervicovaginal specimens and to demonstrate their clinical accuracy with a goal to seek FDA clearance via the 510(K) pathway (substantial equivalence with a predicate device for safety and efficacy; NCI will provide access to the predicate device that is being evaluated in an ongoing trial). The type of novel self-sampling devices that fall within the scope of this solicitation can be, but not be limited to, cytobrush-like, broom-like, or tampon-like devices and when applicable may include the following accessories: (i) Transport media (e.g., dry-swab, paper-based, fluid-based), independent or in conjunction with the collection devices, and (ii) shipment protection (with or without the transport media) to prevent contamination and maintain sample integrity during transport. Please note that technologies that involve collection approaches that are designed to be performed without patient participation are NOT considered appropriate for development under this contract topic.

Phase I Activities and Deliverables:

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

- Using user-centric design principles, develop the prototype self-sampling device, transport media and shipment kits for evaluation.
- Conduct studies to establish analytical performance (analytical sensitivity, specificity) and other performance characteristics (e.g., limit of detection, consistency, reproducibility).
- Conduct studies to evaluate and test user acceptability and feasibility in both intended use populations (i.e., women who are likely to miss regular cervical cancer screening and may therefore be appropriate candidates for home-based self-sampling) as well as average-risk populations.
- Conduct initial clinical testing with at least one of the current FDA-approved HPV testing assays to determine the clinical performance measures (e.g., concordance with clinician-collected sample, clinical sensitivity and specificity).
- 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 self-sampling 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
- Demonstrate the clinical sensitivity and specificity of the device for self-sampling by performing multi-site and multi-test evaluations
- Establish a strategy for FDA regulatory approval and insurance and/or CMS reimbursement

417 Quantitative Imaging Software Tools for Cancer Diagnosis and Treatment Planning

Fast-Track proposals will be accepted.

Direct-to-Phase II proposals will NOT be accepted

Number of anticipated awards: 2-3

Budget (total costs, per award):

Phase I: up to $400,000 for up to 9 months

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

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

Summary

Quantitative imaging software tools developed in academic settings are typically developed for specific research purposes and are often validated only within the home institution. However, for such software tools to become widely useful in the clinical oncology community, the tools require rigorous validation at multiple sites, and with dynamic interplay between the tool developer and the clinician end users (radiologists, oncologists) to further refine, optimize, and validate the tool. The goal of this solicitation is to support commercial development by small businesses of new, or existing quantitative imaging (QI) software tools with utility to radiologists who rely on patient medical images for accurate cancer diagnosis and radiation treatment planning. QI tools can be developed *de novo* for commercial purposes under this solicitation. Alternatively, existing tools can be advanced toward commercialization, and candidates include several well developed tools produced by the NCI Quantitative Imaging Network (QIN; see https://imaging.cancer.gov/programs_resources/specialized_initiatives/qin/tools/default.htm) for the purpose of quantifying or predicting response to cancer therapy in human clinical trials. Within QIN, teams of academic researchers have been developing and optimizing tools of various functions for eventual deployment into clinical trials. Possible paths for commercialization of existing QIN tools include small business partnership (with a QIN team or other academic institution) to take the lead in translating an academic QI tool into clinical validation, or for the academic institution to form a new small business for the purpose of QI tool commercialization.

Project Goals

Commercialization by small businesses is expected to produce robust, well documented and well supported software tools after iterative optimization and validation through quality management controls. Furthermore, the software tool will function on several hardware vendor platforms for the common cancer medical imaging modalities (CT, MRI, ultrasound, PET). Under this solicitation, NCI will not support development of software usable on only one vendor platform. The QI tools are intended to have improved cancer detection capabilities, diagnostic accuracy, and utility for radiation treatment planning and cancer treatment decisions to provide the potential for widespread impact on the clinical community.

The small business offeror will be required to specify a cancer imaging use case (e.g. an imaging modality, a specific cancer type, and cancer diagnosis versus monitoring versus radiation treatment planning) to focus on, and will need to clearly describe deidentified medical image data sets and their source for the purposes of conducting the proposed research. Quantitative milestones - with performance targets that define success – should be provided for each project objective.

Phase I Activities and Deliverables:

- Convene the project team with expertise in medical image software design, informatics, radiology, and medical oncology or radiation oncology to review and finalize the software design
- Build Alpha software prototype
- Evaluate Alpha software performance via retrospective analysis of deidentified medical image data sets
- Refine software as needed, and repeat software evaluation via retrospective analysis of deidentified medical image data sets
- Perform small-scale Usability testing, requiring a minimum of 10 end users at 5 different sites
- Develop plans for a pre-regulatory submission dialogue with the FDA, to be completed before submission of a SBIR Phase II proposal, so that FDA requirements can be included in the SBIR Phase II research plan

Phase II Activities and Deliverables:

- Refine, and build the Beta version of the software based on Phase I results
- Perform large-scale Usability testing, requiring a minimum of 30 end users at 15 sites
- Refine software as needed
- Evaluate software performance via retrospective analysis of deidentified, retrospective medical image data sets

- Evaluate software performance with statistical significance via analysis of newly collected medical images in an IRB-approved, prospective clinical trial
- 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 two letters 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

418 3D Spatial Omics for Molecular and Cellular Tumor Atlas Construction

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 9 months

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

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

Summary

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

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

Project Goals

The goal is to advance the development and dissemination of imaging workflows capable of omics-level measurements in thick tissue resections or whole biopsy cores that can scale for use in atlas building initiatives. Proposals should enable interrogation in a manner that combines high resolution (preferably single-cell) -omics level data (i.e. genomics, transcriptomic, proteomic, metabolomic, etc.) with information about 3D native tumor architecture (i.e. extracellular matrix, vasculature, higher order structure, etc.).

Proposals that are within scope of this solicitation may combine existing, new, or improved assay components into an improved imaging workflow. Examples of existing, new, or improved components include imaging technologies or modalities, tissue clearing methodologies, imaging probes and/or detection reagents, cyclic staining or targeting procedures, and/or unique combinations of imaging and multi-omic measurement platforms. A minimal workflow will provide a 3D view of multiplexed omics data without the need for reconstruction from 2D tissue slices. The ability to concurrently acquire additional information regarding native tumor architecture would be considered a strength (e.g. second harmonic imaging or

alternative technology). Offerors should benchmark their proposed workflow against current state-of-the-art imaging workflows and demonstrate a decrease in overall assay time while maintaining a similar or increased capacity for omic-scale analysis.

Activities not responsive to announcement:

It is anticipated that proposals may include the development of new algorithms, visualization tools, and analysis software to facilitate data handling, analysis and visualization of results. However, applications that are solely software-based will be considered not responsive.

Phase I Activities and Deliverables:

- Establish a project team with proven expertise in development of high-resolution cellular imaging systems and multi-modal data analysis, including subject matter experts in the tumor(s) being imaged and the -omics measurements being proposed.
- Define relevant use cases for the technology including, but not limited to, what tissues can be analyzed, what imaging resolution can be expected, what -omic measurement(s) will be completed, desired throughput of the system, and identification of benchmark technologies.
- Prepare a report that specifies quantitative technical and commercially relevant milestones that can be used to evaluate the success of the technology versus current state-of-the-art 3D high resolution imaging platforms. Quantitative milestones may be relevant metrics (i.e. compared to benchmarks, alternative assays) or absolute metrics (i.e. minimum number of proteins or genes detected, metrics related to repeatability of the assay). Metrics regarding total assay time (including tissue preparation, cyclic staining (if relevant), and imaging processing/analysis) are expected.
- Generate proof-of-concept dataset that addresses the use case above using resection tissue or biopsy cores from solid human cancers or from a generally accepted mammalian cancer model (i.e. PDX, xenograft, GEMM) that demonstrates the ability to capture and visualize molecular -omics measurements in 3D.
- Prepare a report summarizing the performance of the system against the quantitative technical milestones indicated above. Include any plans to modify the platform based upon performance against stated milestones.
- Develop and provide preliminary Standard Operating Procedures for system use, including a validated list of reagents addressing the use case identified above.
- Present phase I findings and demonstrate the functional prototype system to an NCI evaluation panel via webinar.

Phase II Activities and Deliverables:

- Generate proof-of-concept dataset that demonstrates the ability to quantify the 3D native tumor architecture (i.e. extracellular matrix, vasculature, higher order structure, etc) in addition to the capabilities optimized in Phase I.
- Generate datasets representative of at least three solid tumor types (thick resections or whole biopsies).
- Provide a report that documents the reliability, robustness and usability of the system for the purpose of generating large scale molecular and cellular atlas building.
- Provide a report to benchmark system performance (including total assay time) and functionality against the commercially relevant quantitative milestones proposed in Phase I. Report should demonstrate feasibility for scale up at a price point that is compatible with market success.
- Provide Standard Operating Procedures for system use, including a validated list of reagents for each of the three demonstration tumor types. Include documentation for troubleshooting new tumor or tissue types to demonstrate the system can be utilized beyond the tumor types proposed.
- Provide a roadmap for development of a turnkey system.

419 Understanding Cancer Tumor Genomic Results: Technology Applications for Providers

Fast-Track proposals will be accepted.

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

Number of anticipated awards: 2-3

Budget (total costs, per award):

Phase I: up to $400,000 for up to 9 months

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

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

Summary

Next-generation sequencing (NGS)–based technology has lowered the cost of testing for genomic alterations in a patient's cancer and is now commercially available from many diagnostic laboratories and covered by an increasing number of insurers. Due to increasing numbers of approved or investigational targeted therapies for cancer, patients are more routinely undergoing tumor or somatic tissue NGS testing at the time of diagnosis or progression. Oncology providers, particularly in low resource settings, need tools to interpret, appropriately utilize, and communicate with patients about NGS somatic test results. Unfortunately, the uptake of NGS testing in cancer care has grown faster than the oncology field's understanding of somatic and tumor testing, and the dire shortage of genetic counselors has only served to exacerbate the problem. Many oncologists and other cancer providers lack time or expertise to interpret the results of NGS testing, and to counsel patients meaningfully about test implications. Published data indicate that providers are often at a loss for how to interpret somatic testing and have few resources for assistance, especially in low resource community settings. Yet, patients' decisions about whether to undergo NGS tumor testing, and understanding of their test results can have profound medical, psychological and familial implications. Furthermore, NGS testing creates added responsibilities for the patient's health care provider team beyond interpretation and communication of results to patients, such as guiding follow-up management, and facilitating communication to family members. Oncology health care providers have traditionally not been trained in the use of tumor or somatic testing technologies; yet, they are increasingly advised by professional societies to consider NGS testing and determine how to inform patients about these tests and the generated results. Resources are needed to help providers: (i) evaluate the need for somatic/tumor testing for their individual patients, (ii) understand, interpret and explain test findings, and (iii) communicate with their patients both before testing (to obtain truly informed consent) and after testing (to explain results). The need is particularly acute in low-resource settings where patients are more often treated by primary care physicians or other providers without access to tumor boards or experts in Precision Oncology. In settings without access to genetic consultants, clinicians face unique challenges communicating with patients about tumor test results that are suggestive of incidental germline findings. Tools are needed to provide high quality information and interpretation of patient NGS test results to health care providers in communities with limited access to genetic counselors, to enhance utilization of NGS testing in such areas, and to assist with point of care decision-making by clinicians. Such tools must be integrated with current care models and be easily accessible to providers given time constraints and other realities of medical practice. These tools must also provide complex information in a clear format so that providers can facilitate patient understanding and improve patient engagement in informed decision-making about their health. Companies should incorporate field testing, including patient and provider input into the design of these tools, to ensure utility and uptake.

Project Goals

The goal is to design and develop tools, technologies, or products to: (i) inform oncologists and other health care providers treating cancer patients in settings with low access to genetic counselors about NGS testing and current NCCN guidelines, (ii) help such providers evaluate the need for NGS somatic testing for their cancer patients, (iii) assist providers with interpretation of NGS results (including distinguishing between somatic and incidental germline findings), and (iv) help providers communicate NGS results to their patients. Interpretation of NGS results must be personalized for individual patients. Tools that cater to settings with limited or no access to genetic counselors are encouraged. Tools should: (i) assist providers with communicating test results in a clear and lay-friendly manner, to aid patients' treatment or life planning decisions; (ii) inform providers about genetic counseling resources for their patients; (iii) offer options for video and telephone guidance, especially for patients located in remote settings; (iv) incorporate perspectives of populations experiencing disparities in cancer outcomes, such as minority, underserved and rural communities; and (v) identify strategies for enhancing access to tools for understanding cancer genomic test results. In addition, contractors must evaluate, pilot and disseminate the tool.

Some recommended practices for tool development include:

1. Including patients' and families' perspectives in deciding when, whether and how to communicate specific genetic findings, and when to offer genetic counseling and confirmatory testing based on counseling. This could be accomplished using the principles and elements of a design thinking approach focused on designing the communication strategies for oncology care providers from the perspective of the patients, in an agile, iterative way.

2. Considering a range of cancer treatment scenarios to elicit a broad range of provider needs that can inform tool development. This range includes pediatric, adolescent and young adult as well as adult cancer types.
3. Assembling trans-disciplinary teams that include but are not limited to geneticists, genetic counselors, behavioral researchers, psychologists, oncologists as well as patient navigators, patient advocates, and user experience designers to inform development and validation of tools.
4. Planning for pilot implementation testing of the tool in clinical or other applicable settings as the tool is developed.

The following would be considered out of scope:

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

Phase I Activities and Deliverables

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

Deliverables for this Phase include:

- Prototype design
- Demonstration of the tool and practicality of use by end users
- Provide technical specifications as well as an operations/user guide for the tool to NCI
- Outline of metrics that can be used to assess the successful application of the tool

Phase II Activities and Deliverables

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

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

Deliverables and activities include:

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

420 Single-Cell "Unbiased Discovery" Proteomic Technologies

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

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

Number of anticipated awards: 3-5

Budget (total costs, per award):

Phase I: up to $400,000 for up to 9 months

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

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

Summary

This proposal is for the development of high-throughput, single-cell, unbiased (*i.e.* untargeted) discovery proteomic technologies to advance our knowledge in cancer development and progression, to enable robust cancer biomarker discovery and clinical application. So far, the identification of genomic changes in cancer has led to successful therapy-biomarker matches. It has also become integral to the design of clinical trials of molecularly targeted agents. However, it has only

succeeded in identifying "actionable" abnormalities in a minority of cancer patients, and robust predictive biomarkers are still lacking for key targeted therapeutics. Since proteins are the targets of most anti-cancer therapies, and potentially meaningful changes at the proteomic level are not always present at the genomic level, it is becoming increasingly clear that the cancer proteome is an underexplored domain with significant potential for novel biomarker discovery. To date, the contribution of cancer tissue proteomics to biomarker discovery has been hampered by the requirement for substantial amounts of tissue and the need for more sensitive and high-throughput techniques. The current bulk proteomic analysis does not account for the heterogeneity within a tumor, or the proteomic profiling of rare or low-abundance cells. Single-cell proteomic technologies will have this capacity and will facilitate the development of better diagnosis and more efficient, individualized treatment. Although it is too early to predict the ultimate form and potential of such technology, some initial steps towards high-throughput single-cell proteomic approaches have already been taken. For example, researchers in the mass spectrometry field are rethinking sample preparation (cell lysis, protein purification, digestion and clean-up) and separation approaches to reduce sample losses during processing, to be able to quantify over a thousand proteins in single cells. New innovative proteomic approaches that use the principles of parallel-in-space fluorescence imaging (developed for next-generation DNA sequencing) are also being developed.

Project Goals

The short-term goal of this concept is to stimulate the development of unbiased (i.e. untargeted) discovery proteomic technologies with the capacity to identify proteins in a single cell with a typical size (~10 μm in diameter).

The mid-term goal is to provide efficient research tools with the ability to generate more complete and accurate human cancer proteome information without relying on antibodies or inferring proteomes from mRNA sequencing. Protein sequencing at the single-cell level will allow a better understanding of tumor heterogeneity and microenvironment. Single-cell proteomics will also enable capturing proteomic information from rare and low-abundant cells such as circulating tumor cells and migratory dendritic cells. This will open the door to new biomarker and therapeutic target discoveries in cancers.

The long-term goals also include providing efficient clinical tools for precision medicine by matching patients to therapies based on their proteomic results from clinically relevant samples; earlier cancer detection with the ability to better differentiate healthy normal cells from cancerous cells by adding proteomic information to the genomic and transcriptomic data; and better assessment of treatment response and monitoring with the capacity to get more precise clonal information.

Activities not responsive to announcement:

- Technologies that are solely based on computational approaches
- Bulk proteomic technologies using bioinformatic approaches to deconvolve different cell and clone types in the bulk tumor sample
- Targeted methods for identifying and quantifying proteins including, but not limited to, antibody-based methods
- Technologies incapable to identify and quantify at least 500 proteins in a single cell

Phase I Activities and Deliverables:

Phase I activities should generate proof-of-concept data that demonstrates the capability of the technology to identify and quantify, at least, 500 proteins in a single cell with a typical size (*i.e.* ~10 μm in diameter):

- Benchmark the new technology against existing approaches.
- Provide an analytical validation report that describes the studies performed for analytical validation of your technology and its performance characteristics including:
    - Accuracy
    - Reproducibility
    - Repeatability
    - Sensitivity for low and high abundance protein
    - Specificity for low and high abundance protein
    - Single-cell proteome depth of coverage.
- Address signal-to-noise issues by evaluating and interpreting "noise" of the measurements.

- Deliver detailed SOPs related to the sample preparation and sequencing protocols used for your single-cell proteomic technology to NCI for evaluation. Note: SOPs for isolation of single cells are not required.
- Describe the potential pitfalls of the experimental measurements.
- Develop a proof-of-principle prototype.
- Present assay performance and validation results and demonstrate the workflow of the technology during NCI SBIR site visit.

Phase II Activities and Deliverables:

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

- Demonstrate that the technology is identifying and quantifying at least 500 proteins in a single cell with a typical size (*i.e.*~10 µm in diameter)
- Demonstrate system performance and functionality by adopting commercially relevant quantitative milestones:
  - Offerors should specify quantitative technical and commercially-relevant milestones that can be used to evaluate the success of the tool or technology being developed.
  - Offerors should also provide appropriate justification relevant to both the development and commercialization of these technologies.
  - Quantitative milestones may be relative metrics (*e.g.* compared to benchmarks, alternative assays or minimization of the pitfalls of the experimental measurements described in phase I) or absolute metrics (*e.g.* minimum level of detection in a clinically meaningful indication).
- Demonstrate that the technology can analyze the proteomes from the routinely collected cancer samples (fresh, frozen, fixed tissue and/or blood samples).
- Report the throughput of the technology and the cost of the proteomic analysis of a single cell
- Show feasibility to scale up the technology at a throughput compatible with widespread adoption by the clinical research community.
- Establish QA/QC parameters at every step of the process to ensure reliability of results generated by your technology.
- Develop a working prototype kit/tool/device for the single-cell proteomic technology (*e.g.* a sample preparation product and/or a protein sequencing product) and/or establish a marketing partnership/alliance with an established strategic business partner (*e.g.* diagnostic or device company)

421 Quantitative Biomimetic Phantoms for Cancer Imaging and Radiation Dosimetry

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 9 months

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

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

Summary

Oncologists are reliant on patient imaging to support clinical decision making and treatment planning for many types of cancer. Therefore, there is a constant need to develop, optimize, and validate new quantitative imaging and dosimetry tools and methods to improve and better inform diagnosis and treatment.

Phantoms are widely used in medical imaging for instrument tuning, quality control, and scientific research. Traditional phantoms are vessels manufactured from man-made materials (e.g., acrylic, resins, etc.) that are filled with solutions containing an agent or tracer compound used in a modality-specific imaging application (e.g., MRI, SPECT, CT, PET systems). Due to their bulk, phantoms are typically not concurrently scanned with the patient.

Recent technologies in the tissue engineering and biomimetics sector offer opportunities for construction of phantoms from tissue-equivalent materials with formulations that better represent the unique characteristics of organs commonly afflicted with cancers (e.g., brain, liver, breast, skin, bone, pancreas). Unique physical and chemical features can be engineered into tissue biomimetic systems with high precision, such as calibrated patches, zones, or gradients of varying stiffness, density, oxygenation, pH, temperature, etc. Bio-engineered matrixes may also incorporate fiducials and imaging agent(s) at known concentrations that can serve as a standardized reference from which quantitative dosimetry data in a tissue-equivalent context can be compared to data obtained by imaging these agents in the patient. Proper calibration and inter-comparison of scanners and imaging devices located in different institutions is crucial for clinical research rigor.

Project Goals

The goal of this concept is to stimulate growth in development of scalable quantitative tissue-equivalent technologies that would benefit patients who rely on cancer imaging modalities for diagnosis, dosimetry, and treatment. By prompting availability of new commercialized "smart-phantoms," the solicitation has potential to catalyze scientific discovery in the broader cancer community wherein these commercialized devices could be used by researchers traditionally without access to tissue engineering biomimetic technologies. Small business development of Quantitative Biomimetic Phantoms (QBP) as organ-specific surrogates have potential to accelerate computational testing of sequences and algorithms to derive new quantitative radiomic and dosimetric data from cancer patients.

The activities that fall within the scope of this solicitation include development and application of QBP devices that represent or simulate specific tissue types or organ sites. QBP devices are to provide the means to objectively detect, measure, and spatially resolve imaging probe(s) in the context of the QBP device's tissue-equivalent environment(s) using either single- or multi-modal cancer imaging scanner systems. Examples of appropriate activities include pre-clinical feasibility and durability studies of the QBP device as a calibrated quantitative analysis tool that can improve quantitative accuracy and precision in imaging data obtained from the corresponding tissue type(s) or organ site(s) the QBP is intended to simulate. Phase I activities should generate data to confirm the feasibility and potential of the QBP technology(ies) to provide quantitative measurements of probes from cancer imaging systems.

Phase I Activities and Deliverables

- Define the cancer imaging modality or application(s) the QBP device(s) or combined device-computational approaches addresses (such as MRI, SPECT, CT, PET). Multimodal applications are suitable, but not required;
- Define the tissue type(s) or organ site(s) the QBP device is intended to simulate. Offerors may propose to deliver a QBP device that represents only one distinct tissue/organ site, or one that has representation of multiple distinct tissues or organs;
- Define the key tissue type or organ specific physical characteristics the QBP device is intended to simulate;
- Generate proof-of-concept data that demonstrate the means to objectively detect, measure, and spatially resolve imaging probe(s) in the context of the QBP device's tissue-equivalent environment(s) using the respective cancer imaging scanner(s);
- Demonstrate feasibility of the QBP device as a calibrated quantitative analysis tool to improve quantitative accuracy and precision in imaging and/or dosimetry data obtained from the corresponding tissue type(s) or organ site(s) the QBP is intended to simulate.
    - Offerors should specify quantitative technical and commercially-relevant milestones, that can be used to evaluate the success of the tool or technology being developed. Offerors should also provide appropriate justification relevant to both the development and commercialization of these technologies.
    - Quantitative milestones may be relative metrics (e.g. compared to benchmarks, assays and/or algorithms to detect and measure the probe analyte), and/or absolute metrics (e.g. minimum level of detection).

Phase II Activities and Deliverables

- Demonstrate reliability, robustness, and usability in clinical and/or basic cancer research, dosimetry, and/or treatment planning;

- 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 success 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 benchmarks, assays and/or algorithms to detect and measure the probe analyte), and/or absolute metrics (e.g. minimum level of detection);
- Demonstrate rigor and reproducibility in benchmark experiments using relevant cancer imaging scanners or systems;
- Demonstrate the QBP device and associated computational tools provide a calibrated and quantitative reference to assess radiometric characteristics relevant to cancer imaging and/or dosimetry of the tissue type(s) or organ site(s) the QBP device is intended to simulate;
- Show feasibility to be scaled up at a price point that is compatible with market success and widespread adoption by the cancer research community;
- 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

422 Spatial Sequencing Technologies with Single Cell Resolution for Cancer Research and Precision Medicine

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: $400,000 for 9 months

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

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

Summary

It is commonly viewed that cancer originates from an accumulation of mutations in oncogenes and tumor suppressors such that cell growth becomes unregulated and invasive. The identification of genomic, epigenomic, and transcriptomic changes in cancer has led to precise classification, biomarker discovery, and mechanical understanding of cancer, and has played an essential part in cancer diagnosis, monitoring, and treatment. However, the up-to-now bulk sequencing without spatial information has limitations on the understanding of the tumor cells with neighbor cells and the tumor microenvironment. For example, limitations on detecting the heterogeneity within a tumor. This limitation has important clinical consequences. For example, cancer is often composed of multiple clones, and the most aggressive clone is difficult to identify and target, and it may not be the one that metastasizes. New sequencing techniques adding spatial resolution to the molecular information could provide a deeper understanding of the relationship between a cell's genotype or gene expression program and its morphology and interaction with local environment, therefore further our knowledge in cancer development and progression for better diagnosis and more efficient, individualized treatment.

Project Goals

The short-term goal of this concept is to stimulate the development of technologies that generate sequence information from slides without losing the histological context of the targets. These technologies must have the capability to identify thousands of genes in a tissue sample and must be able to select, visualize and compare sequences in areas of interest.

The long-term goal is to provide research and/or clinical tools to improve cancer early detection, diagnosis, prognosis for precision medicine. Such tools can be used to identify location of aggressive/mutated clones within the tumor; differentiate between the center and infiltrating edges of the tumor; find correlation between molecular changes and cytology or atypia;

evaluate molecular changes in the stroma infiltrated by the tumor verse stroma outside the tumor; and discover epithelial mesenchymal transition.

The activities that fall within the scope of this solicitation include the development of technologies that can sequence the DNA or the RNA within fresh frozen or fixed normal and tumor cells without destroying their spatial context, and it can be used to directly link spatial features to particular genetic elements in native tissue or organoid specimens; integration of image modalities with cellular sequencing data; cellular mapping and characterization of tumor sequence with the spatial distribution of the original microenvironment including the complex organization of different cell types that are tightly regulated by the interplay of the individual cells. Contractors are not required to obtain whole genome/transcriptome data for all the cells on the entire slide but are required to demonstrate improved capabilities of the technology compared with existing special sequencing technologies.

Activities not responsive to announcement:

Technologies that are solely based in computational development are not appropriated for this solicitation. In situ and single cell technologies that do not have the capability of discovering new sequence variation in intact tissues would also not be considered as responsive.

Phase I Activities and Deliverables:

Phase I activities should generate data to confirm the feasibility and potential of the technology to obtain unbiased sequence (DNA and/or RNA) information directly from fixed or fresh tissue sections preserving the spatial distribution of the oligonucleotides in the tissue sample.

- Demonstrate sensitivity, resolution, reliability, robustness and usability in basic and/or clinical cancer research.
- If it is for RNA sequencing, it should be able to reveal RNA splicing and post-transcriptional modifications (e.g. methylation) while preserving their spatial context.
- For DNA sequencing it should indicate how the sequence information is being used to determine Single Nucleotide Variation (SNV), Copy Number Variation (CNV), Methylation patterns, Gene rearrangements/translocations, Microsatellite Instability etc. while preserving the spatial context
- Develop a computational platform to visualize spatial sequencing information (if applicable).
- Provide the technology workflow and a working protocol, including the instrumentation, reagents and time needed for running samples, as well as estimations on speed of data generation and analysis.

Phase II Activities and Deliverables:

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

- 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 success of the tool or technology being developed.
  - Offerors should also provide appropriate justification relevant to both the development and commercialization of these technologies.
  - Quantitative milestones may be relative metrics (e.g. compared to published benchmarks, alternative assays), or absolute metrics (e.g. minimum level of detection in a clinically meaningful indication)
- Demonstrate the utility of the technology with benchmark experiments obtained across a range of generally accepted patient cancer tissues and/or cell types (as appropriate).
- Show feasibility to scale production of the technology at a price point that is compatible with market success and widespread adoption by the basic research community and or clinical labs (as appropriate).

423 Software to Address Social Determinants of Health in Oncology Practices

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 9 months

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

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

Summary

This solicitation builds on work performed in response to previous solicitations that developed information technology to support financial hardship, patient navigation, informal caregiving and care coordination. These areas of research remain NCI priorities; small business researchers who want to conduct research in these areas are encouraged to apply to the omnibus SBIR solicitation: https://sbir.cancer.gov/funding/opportunities/SBIR-STTR-omnibus-solicitation.

Social determinants of health (SDH) are the health-affecting circumstances in which people are born, grow up, live and work. Examples of SDH that adversely affect health include food insecurity, financial strain, housing instability, social isolation, and transportation-related barriers. Addressing SDH within healthcare improves access to preventive care and improves treatment adherence. Accountable care organizations and other hospital systems have saved over $4.5 million by addressing food insecurity, reduced healthcare costs by 40% after establishing housing partnerships, and reduced inpatient and outpatient spending by 53% and 23%, respectively. Several large organizations, including CMS, CDC, HRSA and Kaiser Permanente, have invested in programs to address SDH. These programs are aimed at addressing SDH in primary care, not in oncology practices. Cancer patients are more likely to worry about their standard of living and experience food insecurity compared to individuals without cancer; these patients are less likely to receive appropriate and timely cancer treatment and have poorer survival. Recently, the American Cancer Society published a blueprint to understand and address SDH in cancer patients.

The first step in addressing SDH is to conduct a patient assessment. The National Academy of Medicine (NAM) has identified several domains and validated measures of SDH that can be used in electronic health records (EHRs). For example, for the domain of social connections and social isolation, NAM identified the NHANES III measure (consisting of four questions) and for the domain of financial resource strain, it identified the measure of overall financial resource strain (consisting of one question). Another relevant activity is the Protocol for Responding to and Assessing Patients' Assets, Risks, and Experiences (PRAPARE) assessment tool that includes16 core measures and 4 optional measures; this tool can be used in EHRs.

The next step after conducting a systematic patient assessment is to address the relevant SDH need(s) in a timely manner. Because most interventions to address SDH are delivered by community-based social service providers (e.g. food banks), a clinician's role is typically limited to referral and appropriate follow-up. A recent market analysis by NORC showed high variability in the level of sophistication of SDH-related systems and their functionalities; this analysis identified several needs, including better patient engagement, better analytic tools, improved collaboration with behavioral health professionals, and scalability of approaches to share data among healthcare providers and community organizations. There is a need for well-designed IT that supports systematic SDH assessment, appropriate referral, and follow-up of cancer patients in oncology practices in a manner that reduces the burden on patients, clinicians, and practices.

Project Goals

The goal of this concept is to solicit proposals that develop and evaluate software to address SDH in oncology practices. The software will be cancer-specific and developed in close collaboration with oncology practices. The software should be designed to support and enhance existing clinical workflows and reduce the burden of SDH data collection and synthesis in care settings. It will support appropriate evidence-based clinical actions, including referral, to address identified patient needs. The software will meet current IT interoperability standards, using FHIR (Fast Healthcare Interoperability Resources) when feasible, and privacy standards.

The activities that fall within the scope of this solicitation include assessment of the current landscape of electronic SDH screening instruments and clinical decision support (including referrals to community-based social service providers); collaboration with oncology practices to understand existing workflows and IT architecture (including existing strategies for collection and use of SDH data); develop software with at least 5 existing, valid SDH measures; conduct usability studies of end-users: clinicians, patients, and community-based service providers; conduct an impact evaluation of the software on clinical workflows, care delivery processes, use of community resources, user satisfaction, and patient outcomes; and, identify an approach to scale the software beyond the initial set of oncology practices and SDH measures.

Activities not responsive to announcement:

Developing software that only screens for SDH without supporting appropriate clinical actions triggered by the screening (including referral to relevant community resources); software that does not work with validated SDH screening instruments; software that is either not integrated into the workflow or the existing IT architecture; software that does not incorporate the current standards and requirements of interoperability, cybersecurity and patient privacy; not working in partnership with oncology practices to identify the most relevant SDH measures and related clinical tasks; software not designed to reduce the patient- and clinician-level burden of performing SDH-related tasks.

Phase I Activities and Deliverables

- Establish a project team with expertise in the areas of software development, cybersecurity, user-centered design, SDH screening and implementation, oncology, health services and disparities research, community-based social services, community engagement and/or patient advocacy, as appropriate for the proposed project.
- Conduct a focused environmental scan of existing software to screen and address SDH, as well as a targeted literature review on the accuracy of screening instruments and effectiveness of interventions for identified patients. The new software should screen for at least 5 SDH measures and use FHIR standards.
- Conduct key informant interviews with members of at least two oncology practices to understand what is currently being done to address SDH, how IT systems are currently configured, how SDH data are collected and analyzed, and how new software would help.
- Develop a prototype of the software. The design requirements of the software should ensure it can be used in a variety of cancer care delivery sites, ranging from academic clinics to community oncology practices, which care for diverse patient populations, including under-served cancer patients. Further, the design requirements should include compatibility with diverse IT architectures and the ability to work across IT systems.
- Conduct pilot usability testing of the prototype with at least 25 persons who represent the end-users including but not limited to: oncology care team members, patients and community-based service providers.
- Propose an approach to modify the software based on user feedback prior to implementation in Phase II.
- Present Phase I findings and demonstrate prototype to an NCI Evaluation Panel via webinar.

Phase II Activities and Deliverables

- Establish a project team with expertise in the areas of software development, cybersecurity, user-centered design, SDH screening and implementation, oncology, health services and disparities research, implementation science, and statistical methods for validation/evaluation, as appropriate for the proposed project.
- Provide a report detailing the approach to integrate the software in existing workflows and IT systems, and to evaluate the software, while considering the requirements of inter-operability, cybersecurity and patient privacy protection.
- Develop appropriate human subjects protection/IRB submission packages and document approval of research plan.
- Develop final study design including aims, participant characteristics (e.g. end users), recruiting plans, inclusion and exclusion criteria, measures, primary and secondary endpoints, design and comparison conditions (if appropriate), power analyses and sample size, and data analysis plan.
- Implement and evaluate the software in at least three oncology practices. The evaluation includes user satisfaction with software, impact of software on care delivery processes and patient outcomes, lessons learned, and recommended modifications to the software, as appropriate.
- Provide a report documenting the results of the software evaluation.
- Identify an approach to scale the software beyond the initial set of oncology practices and SDH measures.
- Provide study progress reports quarterly, documenting recruitment and enrollment, retention, data quality assurance and control measures, and relevant study specific milestones.
- Develop user support documentation to support all applicable potential users of the technology, including but not limited to clinicians, patients, and healthcare systems.
- Prepare a tutorial session for presentation via webinars describing and illustrating the technology and intended use.
- 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.
- Present Phase II findings and demonstrate the validated software to an NCI Evaluation Panel via webinar.

424 Digital Tools to Improve Health Outcomes in Pediatric Cancer Survivors

Fast-Track proposals will be accepted.

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

Number of anticipated awards: 2-4

Budget (total costs, per award):

Phase I: up to $252,131 for up to 9 months

Phase II: up to $1,680,879 for up to 2 years

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

Summary

An estimated 11,060 new cases of cancer were expected to be diagnosed among children ages 0 to 14 years and approximately 70,000 among adolescent and young adults (AYAs) between ages 15 and 39 in 2019. Advances in diagnostic capabilities and treatment have resulted in increased survival rates, with more than 80% of children and AYAs surviving 5 years or more after their cancer diagnosis. This has led to exponential growth in the number of survivors of pediatric cancers. However, survival often comes at the cost of many life-altering late and long-term effects and other unique challenges including the following:

- Adverse long-term and late effects including higher risk of secondary cancers, premature/accelerated aging, cardiotoxicity, endocrine dysfunction, reproductive and developmental issues like infertility, neurocognitive defects (e.g. learning disabilities), and psychosocial issues (e.g. anxiety and depression), poor mental and physical health (e.g. impaired stress management), poor health habits (e.g. alcohol use, physical activity levels), developmental issues, impaired/delayed social development
- Challenges in coordinating care across multiple clinical teams, especially the transition from pediatric to adult care providers
- Need for better care models to improve monitoring for recurrence of primary cancer and screening for early detection of secondary tumors and
- Need for better care models to improve monitoring and management of symptoms arising from long-term adverse effects of cancer treatments

Childhood cancer survivorship care is complex and improved care models are urgently needed. The increased use of digital tools in medical care can be leveraged to improve health outcomes and survivorship in these cancer survivors. This contract topic encourages innovative approaches to improve the quality of health outcomes for long-term childhood and adolescent cancer survivors.

Project Goals

The goal of this solicitation is to stimulate the development and evaluation of innovative digital tools (software, database systems, digital platforms and/or mobile applications) that are integrated with existing EHRs or other clinical IT systems and that support delivery of patient-centered, coordinated, high-quality care to pediatric cancer survivors. To accomplish these goals, the offerors should build a system/tool/app with one of the following two capabilities:

- Creation and implementation of survivorship care plans including integration of National Academy of Medicine, Children's Oncology Group and other relevant long- term follow-up and care guidelines for survivors of childhood and adolescent cancer, OR
- Integration of accountability tools, checklists, and reminders that improve follow-up care adherence and clinical workflow

Additionally, the following capabilities will also be required:

- Seamless coordination of care across healthcare systems either from oncology-based practice to primary care setting or from pediatric to adult care setting
- Remote collection of data from a patient to support and reinforce remote screening and monitoring, symptoms management and disease prevention, behavior modification and personalized intervention patient-reported outcomes
- Secure bi-directional communication between clinical teams and the patients and caregivers that meets HIPAA requirements
- Adopting current interoperability standards such as FHIR
- Integration of technology into clinical workflows

The tools can optionally be integrated with wearables and other devices for cancer recurrence screening and early detection of secondary tumors, monitoring symptoms and adverse effects, and support behavior or other lifestyle modifications needed to improve patient outcomes. The tool must support bi-directional communication; it may be focused on either patient/caregiver tasks or clinical team tasks. The design requirements must include protection of patient privacy and adherence to all relevant regulations.

Activities not responsive to announcement:

This solicitation is focused on development of integrated tools including software, database systems, digital platforms and/or mobile applications-based approaches. The following topic areas are not supported:

- Drug development
- New in vitro, in vivo, or ex vivo diagnostics for symptoms and cancer monitoring
- Digital tools focused on adult cancer survivors

Phase I Activities and Deliverables

- Establish a project team with expertise in the areas of software development and implementation, human-centered design, health communication, pediatric oncology, pediatric cancer survivorship, primary care, behavioral science, health services, care delivery and clinical workflows.
- Perform an environmental scan of relevant, existing software systems and apps designed to support the delivery of pediatric survivorship care, especially during the transitions of care, and identify major gaps that need to be addressed.
- Conduct a small number of key informant interviews with childhood and adolescent cancer survivors, adult caregivers, pediatric oncology providers, and primary care providers to further refine and prioritize areas of unmet needs.
- Develop a functional prototype of the tool with at least one of the following system capabilities and specifications:
    - Creation and implementation of survivorship care plans including integration of National Academy of Medicine, Children's Oncology Group and other relevant long- term follow-up and care guidelines for survivors of childhood and adolescent cancer. Potential features for this type of tool may include:
        - A personal healthcare information management tool (dashboard or other innovative tool) on treatment summary, individualized survivorship care plan including associated risk factors and screening recommendations, key symptom indicators, and prompt survivor to share critical information with their care provider
        - Support module to educate patients and their adult caregivers about the disease, treatments and the potential impact of disease and treatments on a patient's life. This module will also list the relevant clinicians, their contact information, and their roles in managing the patient's care.
        - Seamless coordination of care across healthcare systems such as from oncology-based practice to primary care setting or from pediatric to adult care setting
    - Integration of accountability tools, checklists, and reminders that improve follow-up care adherence and clinical workflow. Potential features of this type of tool include:

        - A personal healthcare information management tool (dashboard or other innovative tool) with all these features
        - A psycho-social health information management tool (dashboard or other innovative tool) to track key factors associated with Quality of Life (QOL) outcomes in cancer survivors
        - Front-end mobile application(s) to facilitate scheduling, tracking and monitoring of care delivery processes, including referrals and the outcome of a referral; communications between patients and clinicians or between clinicians; and survivor support
        - Interfaces with healthcare delivery systems to facilitate remote patient monitoring, communications, and resource provisions (e.g. content management for tailored caregiver support).
- In addition, all tools should include all the following capabilities and specifications:
    - Seamless coordination of care across healthcare systems from oncology-based practice to primary care setting or from pediatric to adult care setting
    - Remote collection of individual health data to support and reinforce efficacious remote screening and monitoring, symptoms management and disease prevention, behavior modification and personalized intervention patient-reported outcomes.
    - Secure bi-directional communication between clinical teams and the patients and caregivers
    - Adopt current interoperability standards such as FIHR
    - Integration into clinical workflows
- The information management tool (dashboard or other innovative tool) needs to have a either patient/caregiver-facing and/or clinician-facing interface and the ability to download and upload relevant information as it becomes available.
- The tool must adhere to relevant data and security standards for collection, transmission, and storage of data that ensure patient and caregiver privacy as required by relevant federal and state laws and regulations.
- Data adaptation for mobile application(s) as needed.
- Conduct a pilot usability testing of the protype tool with at least 25 potential users.
- Present Phase I findings and demonstrate functional prototype to an NCI Evaluation Panel.

Phase II Activities and Deliverables

- Establish a project team for Phase II activities and outcomes. This team should include personnel with training and research experience in chronic disease patient clinical trial or intervention design, implementation, and statistical methods for validation/evaluation as appropriate for the proposed project. Provide a report outlining team member credentials, specific project roles, and timelines for performance.
- Evaluate specific IT customization requirements to support hardware, software, or communications system integration of the technology into the target clinical, health system or service, or other relevant software environment in preparation for validation. Provide a report documenting the specific IT customization requirements and timelines for implementation.
- Evaluate, enhance as necessary and provide documentation that the technology and communications systems maintain compliance with HIPAA, data security, privacy, and consent management protocols as required for the proposed project.
- Enhance systems interoperability for deployment in diverse software environments and provider networks. Provide a report detailing communication systems architecture and capability for data reporting as appropriate for the proposed project.
- Test the integration of the technology into the target clinical, health system or service, or other relevant software environment in preparation for validation. Provide a report documenting the results of system testing and timelines for troubleshooting.

- Develop user support documentation to support all applicable potential users of the technology. 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.
- Design and conduct a validation and evaluation study, including:
  - specify study aims, participant characteristics, recruiting plans, inclusion and exclusion criteria, measures, primary and secondary endpoints, design and comparison conditions (if appropriate), power analyses and sample size, and data analysis plan;
  - develop appropriate human subjects protection / IRB submission packages and documentation of approval for the research plan; and
  - provide study progress reports quarterly, documenting recruitment and enrollment, retention, data quality assurance and control measures, and relevant study specific milestones.
- Present finding and demonstrate functional product to NCI evaluation panel in a webinar.
- In the first year of the contract, provide the program and contract officers with a letter(s) of commercial commitment.

425 Information Technology Tools for Automated Analysis of Physical Activity, Performance, and Behavior from Images for Improved Cancer Health

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 9 months

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

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

Summary

The exponential rise in availability of digital still and video imagery has created enormous opportunities for health researchers. However, software tools for automated image analysis in health are lacking. The goal of this topic is to stimulate development of software for automated analysis of physical activity, performance, and behavior in still and video images for clinical, home monitoring and public health applications. *Physical activity* refers to movement and postures such as ’walking’, ‘sitting’ or ‘standing up'. *Performance* refers to quantitative measures of function such as walking speed or timing of a sit stand test. *Behavior* refers to identification of specific actions such as ‘taking a pill’ or ‘playing soccer’.

Existing software tools emphasize counting and tracking customers (e.g. TraxSales), monitoring transportation behavior (e.g. TRAF-SYS), and security concerns in the private and defense sectors (e.g. DARPA Minds Eye Program). Additionally, emerging research is attempting to develop automated tools to assess sports performance and human performance capture for entertainment applications. In contrast, health-oriented applications are poorly developed, limited to a few publicly available image management and annotation tools. While larger companies are entering this sector (e.g. Microsoft AZURE), they also lack focus on health applications. Finally, advances in machine learning and AI research further support the potential for new products in this area.

Project Goals

This SBIR contract topic is designed to attract proposals for new and innovative image analysis tools to extract information concerning physical activity, performance and behavior. Each of these interrelated elements of human action have distinct associations with health and health monitoring needs. Examples include but are not limited to: 1) Automated assessments of gait, walking speed, and other medically-relevant performance parameters in the clinic; 2) Enabling in-home monitoring of compliance with medication and physical therapy regimens; and 3) Improved evaluation of physical activity in transportation or park settings. Potential image sources include, but are not limited to: wearable cameras, stationary cameras, smart phones, social media, Photovoice projects, and archives of street images from Google Street View or Gigapan. Applicants will be

asked to specify the use case for their project and identify the source of images. Images may be from pre-existing sources or may be collected as part of the project. Collaboration with relevant subject matter experts and computer vision specialists is required to insure use of best possible analytical approaches. The tools developed must provide solutions for protecting sensitive or personally identifiable information available in the images.

The long-term goal of the project is to develop software that can automatically extract data from images concerning people and their activities. Advances in security, loss prevention, assessment of human behavior in retail environments, and automated measurement of human performance in sport and animation domains along with growing capacity of computers to identify and count objects via advances in artificial intelligence and machine learning suggest that algorithms are available that could be applied to health questions. Data from these algorithms could help multiple aspects of cancer prevention and control from primary prevention such as improved evaluation of interventions to encourage physical activity, to enhanced epidemiological studies, to automation in monitoring of symptoms and response to treatment for disease affecting physical performance, to improved compliance with cancer treatments or physical rehabilitation regimens. This interplay could advance health research and lead to improved commercial products for diverse applications.

Proposals addressing biomedical images such as MRIs, microscopy, or DEXA will not be deemed responsive to the call.

Phase I Activities and Deliverables:

- Establish a project team including proven expertise in: image analysis, including recognizing human actions and event segmentation; algorithms for data extraction, e.g. machine learning or neural networks; image data storage and manipulation; secure transmission of health data (if needed); user interface development; and topic-specific expertise in the appropriate behavioral science and public health domains.
- Develop a precis of the proposed tool and carry out structured interviews or one or more focus groups aimed at defining specific subject matter needs.
- Create or identify an open access image data source. Examples include, but are not limited to, cell phone images, SenseCam data, the AMOS archive of webcam images, Photovoice collected image libraries, and security video.
- Develop a functional prototype system from planned Phase I characteristics that includes:
- Capacity to extract data from at least one image type involving human physical activity, performance or behavior,
- Capacity to combine both automatic and manual detection and counting of intended aspects of physical activity, performance and behavior via a graphical user interface on a desktop computer, laptop computer, and/or tablet.
- Conduct a usability study with at least 15 users not affiliated with the study team and in several distinct user groups
- Provide a report including a detailed description and/or technical documentation of the proposed tool including plans for managing large numbers of image files, specific data resources and file formats targeted, details of the algorithmic approaches to be used and an assessment of potential bias in training image data sets, and approaches to be used to assess performance of the software tools. Comparison with gold standard measures such as human data extraction is an important part of validating the approach.
- Describe hardware and any additional software required for use of the tool.
- Present phase I findings and demonstrate the functional prototype system to an NCI evaluation panel via webinar.

Phase II Activities and Deliverables:

- Describe and document protocols and guidance for investigators working with imaging to insure appropriate informed consent, risk assessment, and data management.
- Present Phase II findings and demonstrate the software system to an NCI evaluation panel via webinar
- Improve and expand the capacity of the software to identify aspects of physical activity, performance, and behavior
- Develop or refine data extraction algorithms
- Further test reliability and validity of data extraction via new methods or new image file sources;
- Create a library of open access test images for additional algorithm training efforts;
- Propose and implement a cycle of usability testing incorporating user center design principles to enhance software ease and efficiency of use;

- Develop systems documentation where applicable to support the software and bioinformatic methods.
- In the first year of the contract, provide the program and contract officers with a letter(s) of commercial interest.
- In the second year of the contract, provide the program and contract officers with a letter(s) of commercial commitment.

426 Tools and Technologies for Visualizing Multi-Scale Data

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 9 months

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

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

Summary

Emerging single-cell and in situ technologies are facilitating the characterization of normal, diseased, stromal, and immune cells in human tissues. Coupling these data with imaging modalities that provide information about tissue composition, gross organ structure, and metabolism while incorporating longitudinal clinical data can improve our understanding of the development and evolution of disease. Several recent initiatives have focused on generating 'atlases' that integrate multi-scale maps to facilitate our understanding of health and disease. These include the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, the Human BioMolecular Atlas Program (HuBMAP), the Human Cell Atlas (HCA) initiative, and the Human Tumor Atlas Network (HTAN). Additionally, the rapid advancement of single-cell genomic- and imaging-based technologies has expanded the use of these tools in individual research projects supported by the NIH and NCI.

Spatial atlas mapping efforts seek to analyze and integrate multi-scale and multi-modal data sets to generate cohesive multi-dimensional maps of normal and diseased tissues and provide them in a user-friendly environment for the research and clinical communities. Tumor atlases may include single-cell resolution data describing the tumor itself, the tumor microenvironment, and the immune milieu. A major challenge to realizing the full potential of tumor atlases is the lack of tools for the visualization of data across scales and modalities. The purpose of this contract topic is to incentivize small businesses to *develop technologies that allow integrative multi-scale data visualization to facilitate building and sharing of atlases.*

Project Goals

The goal of this project is to promote integrative visualization of multi-scale data. Potential tools or technologies would include, but are not limited to:

- Web-based or containerized visualization tools that allow seamless traversal across scales of heterogenous or integrated datasets from genetic to molecular to cellular to tissue scales
- Virtual Reality / Augmented Reality systems that let users interact with and manipulate multi-scale data in novel ways, using efficient interaction paradigms
- Visualization tools and methods for intuitive display of high-dimensional multi-scale data and metadata in context, such as integration of cell and tissue image data with accessible genomic profile information
- Visualization tools and methods that display and / or capture the heterogenous quality, uncertainty, or provenance of integrated data sets
- Tools that combine existing visualization sources to facilitate and construct multi-scale visualizations

For this project, data scales are defined as:

1. Genomic (e.g., DNA sequence, epigenetic state)

2. Molecular/subcellular (e.g., RNA abundance, protein abundance, intracellular structures)
3. Cellular (e.g., cell-state, cell-type)
4. Tissue (e.g., tissue morphology, histology, metabolic state)
5. Individual patient (e.g., clinical data, exposure, microbiome)
6. Population (e.g., epidemiological)

Activities not responsive to announcement:

Work that would not fall under this topic include: (1) approaches for visualization at a single scale and (2) approaches that focus on analysis and do not include data visualization as the major component.

Phase I Activities and Deliverables:

The goal of Phase I is to develop proof-of-concept or prototype tools, technologies, or products for visualizing multi-scale biomedical data. Activities and deliverables include:

- Identify and define at least three scales of data (as defined above) that will be part of the Phase I visualization tool.
- Identify relevant use cases for the proposed tool.
- Identify one or more user communities this visualization tool will support. Communities include: (1) basic researchers, (2) computational researcher, (3) clinicians / clinical researchers, and (4) the public.
- Identify and justify development of a tool or technology for visualization of multi-scale data, including the rationale for the selection of data scales and user communities.
- Describe the current state of the art technologies, if any, for visualizing the selected data scales.
- Develop a minimal viable product for visualizing multi-scale data capable of ingesting and visualizing the relevant data types.
- Carryout initial alpha-testing by the appropriate user communities to solicit user feedback.
- Specify and justify quantitative milestones that can be used to evaluate the success of the tool or technology being developed.

Phase II Activities and Deliverables:

The goal of Phase II is an optimized commercial tool or technology for visualizing multi-scale biomedical data. Deliverables and activities include:

- Revise the minimal viable product based on user feedback to add features or functionalities and increase the use-ability and stability of the tool or technology.
- Expand the tool or technology to support the integrative multi-scale visualization of at least four scales of data defined above.
- Make the tool or technology compatible with a wide-range of web browsers and / or operating systems as applicable.
- Carryout beta-testing by the appropriate user communities to solicit additional user feedback.
- Further revise the visualization tool or technology based on user feedback focusing on the transitions between data scales and preserving the relationship of data across scales.
- Develop SOPs and user documentation.

427 De-Identification Software Tools and Pipelines for Cancer Imaging Research

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

Direct-to-Phase II proposal will NOT be accepted

Number of Anticipated Awards: 3-5

Phase I: up to $400,000 for up to 9 months

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

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

Summary

Imaging data is a core component in the development of the National Cancer Data Ecosystem, important in areas from basic research to diagnostics and surveillance. Sharing of any data collected from patients, however, requires first the removal of Protected Health Information (PHI) and personally identifiable information (PII) which can be used to identify the individual from whom the data were collected. Image de-identification, or anonymization, refers to the removal of PHI /PII from imaging data. In digital pathology PHI can be found in the label slide as well as the file header. In clinical imaging, where images are commonly in the DICOM (Digital Imaging and Communication in Medicine) format, PHI is contained in the header of each image file and at times PHI may be embedded in the image itself. For example, the imaging acquisition software may insert PHI in the image field, or the patient may be wearing identifiable jewelry or a personal tag that may be captured in an image. Both the file header and the image field itself must be examined for information that could link the file to a specific individual. In headers, PHI is found in patient identifier fields, such as patient name, patient number, date of birth, etc., and at times in fields not intended to contain such information. In addition, in certain instances, individuals may be identifiable by PII obtained through 3D reconstruction of the face or body surface from tomographic data such as computed tomography or magnetic resonance imaging (MRI). The complexity of the de-identification problem dictates that a substantial amount of human curation is required to ensure proper and complete removal of PHI from images. The need for extensive human participation in the de-identification process impedes the generation of anonymized image collections suitable for public distribution and sharing, including deposition into components of the National Cancer Data Ecosystem like The Cancer Imaging Archive (TCIA) (https://cancerimagingarchive.net) and the Imaging Data Commons of the Cancer Research Data Commons. The goal of this concept is to support the development of software tools that comprehensively de-identify images by removing PHI and PII from image files generated by clinical imaging and/or WSI modalities while retaining metadata relevant to providing interoperability.

Project Goals

While multiple tools exist to remove protected data from image files, particularly DICOM radiology files (https://link.springer.com/article/10.1007/s00330-015-3794-0), they may not thoroughly remove PHI from unexpected DICOM fields or from the image field itself. In addition, other image formats such as proprietary WSI files and other microscope image formats also contain PHI. Proper de-identification of patient imaging files requires careful analysis and remediation of two components of those files: the header and the image field. The goal of this contract topic is to support development and sustainment of software tools and pipelines for image de-identification, specifically for images produced by radiologic and pathology imaging modalities. Within that goal, the following objectives should be met: 1) Removal of PHI from expected fields in multiple imaging formats, 2) Scanning for PHI in fields not designed for their insertion, identification and subsequent removal, 3) Scanning of imaging data for PHI and PII, identification, labeling and subsequent resolution, and 4) Produce processed images that meet a threshold level of de-identification. Brute force methods for de-identification (e.g., erasing of all header information) are not acceptable. A successful de-identification algorithm would not simply remove data from all elements, but simultaneously remove PHI while retaining information required for research studies.

While fully automated image de-identification tools are desired, the proposed solutions should provide a capability to flag suspicious cases that require human intervention for human-in-the-loop remediation. Furthermore, in order to broaden the community of users and developers, offerors are encouraged to consider leveraging open standards to the degree that is possible and does not prevent from the development of commercial solutions. Moreover, the de-identification algorithms should be vendor agnostic particularly for WSI file type, where each vendor has their proprietary format. In addition, development of cloud-ready solutions is also encouraged.

To build upon existing resources in medical image de-identification, , the TCIA de-identification knowledge base (https://wiki.cancerimagingarchive.net/x/ZwA2) could serve as a foundation.. The final delivery in each phase would require the vendor providing their de-identification tool to NCI for a final validation. For this purpose, NCI, possibly in collaboration with TCIA or another contractor, will need to run the tool on selected validation datasets that would include PHI in various places in the header and the image field and confirm that the developed tool has successfully de-identified the collection. Offerors must identify the eventual customers for this tool. While NCI may be a potential future customer, this is not assured or certain. Offerors are expected to get their own datasets. NIH or the TCIA will not provide data with PHI to the offeror. The TCIA database has free downloadable imaging and digital pathology collections that provide examples of the final product. In general, NCI encourages the development of deidentification tools for developing imaging or digital pathology databases. This contract is not meant to be a service contract to the NCI to deidentify images for TCIA or NCI. Successful companies must provide a version of the software developed as part of this contract along with a user manual to NCI for user acceptability testing. A user acceptance testing (UAT) report will be provided back to the company.

Phase I Activities and Deliverables:

- Identify different clinical imaging or WSI file types and the fields that contain PHI (i.e. conduct landscape analysis)
- Ability to recognize and open multiple clinical imaging or WSI file formats
- Display PHI field variable values
- Remove or alter PHI field values
- Produce a log of removed and altered PHI and PII parameters
- Delivery of tool along with required software documentation and user manual to NCI for acceptance testing/validation study
- Include funds in budget ($15K) to present phase I findings and for NCI to complete User Acceptance Testing/validation study.

Phase II Activities and Deliverables:

- Detect PHI in non-PHI fields (e.g., comment fields that may contain PHI)
- Alert user, allow user to edit detected field
- Detection of PHI within image
- Masking of PHI and PII within image
- Masking of PII that may be obtained through 3D reconstruction or other manipulation of the image collection
- Generation of de-identified images with provenance of process
- Flag and report suspicious cases and allow for human-in-the-loop remediation
- Validation with a test data set should demonstrate successful PHI/PII removal from image and image file meta data for ≥95% test files
- Include funds in budget ($20K) to present phase I findings and for NCI to complete User Acceptance Testing/validation study.
- Statistical analysis of validation testing will be provided to NCI
- In the first year of the contract, provide the Program and Contract officers with a letter(s) of commercial interest

428 Cloud-Based Multi-Omic and Imaging Software for the Cancer Research Data Commons

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 9 months

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

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

Summary

The cancer research field has become intensely focused on the generation of high-throughput datasets to better understand cancer and ultimately to inform the development of better treatment and prevention tools. NIH and NCI have supported numerous programs including The Cancer Genome Atlas (TCGA), The Cancer Imaging Archive (TCIA), Therapeutically Applicable Research to Generate Effective Treatment (TARGET), and Clinical Proteomic Tumor Atlas Consortium (CPTAC) to generate a wealth of multi-modal data to be leveraged by the cancer research community. However, we are still

limited in our ability to draw insights and meaningful interpretations from these datasets, which include multi-omics, imaging, and clinical data, and by challenges in integration across disparate datasets. To address these challenges, NCI has created the Cancer Research Data Commons (CRDC) as part of the National Cancer Data Ecosystem recommended by the Cancer Moonshot[SM] Blue Ribbon Panel (BRP). The CRDC brings together data with cloud computing infrastructure to provide secure access to various data types across scientific domains, allowing users to analyze, share, and store results by leveraging the storage and elastic compute of the cloud.

The primary goal of this contract topic is to solicit commercial sector participation in the CRDC to develop strong commercial cloud-based analytic tools, specifically on multi-omics and/or imaging analysis, that can be disseminated and sustained within the cancer research community. To that end, leveraging of open standards to the extent that is possible is highly encouraged. The SBIR contract funding mechanism will offer the opportunity for small business participants to contribute solutions to address unmet challenges of big data analysis that are not currently provided by existing tools in the CRDC by developing and extending tools and resources to integrate into the rapidly evolving CRDC. Through this contract topic, NCI seeks to enable wider engagement of the CRDC community which includes researchers, and clinicians by offering enhanced data analysis capabilities, visualization tools, and data access and sharing platforms.

Project Goals

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

Activities not responsive to announcement:

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

Phase I Activities and Deliverables:

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

Key activities and deliverables include:

- Establish a project team composed of experts in software development, cloud infrastructure, big data informatics (e.g. proteogenomics, imaging), project management, team communication, and user-centered design.
- Design specification for the development/extension of cloud-based informatics tools to operate in the Cancer Research Data Commons.
- Develop an early phase prototype.
- Demonstrate the feasibility of CRDC integration through DCF. Example of feasibility qualification include, but not limited to, user authentication using Fence to access datasets stored in at least one CRDC repository such as Genomic Data Commons and Proteomic Data Commons, which exist now and providing authorization to datasets the user has access to. More nodes, such as Imaging Data Commons, are expected to be available for feasibility testing by the end of 2020.

- Conduct a pilot usability testing by at least 25 users
- Provide a report on the results of the first round of usability testing and the approach to modify the prototype based on this user feedback.
- Present Phase I results and future system development plan to NCI staff.

Phase II Activities and Deliverables:

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

Key activities and deliverables include:

- Enhance, beta test, and finalize prototype development.
- Provide detail plans for implementation of technical assistance and delivery of tool(s) within CRDC.
- Demonstrate CRDC integration through DCF by successfully providing access to data within CRDC and performing large-scale multi-omics and/or imaging data analysis using offeror's tools or resources. Examples of large-scale data analysis include, but are not limited to, demonstration of integration and interoperability of user-provided data with available datasets such as CPTAC from CRDC to perform comparative analyses.
- Conduct usability testing using at least 100 users

429 Advanced Manufacturing to Speed Availability of Emerging Autologous Cell-Based Therapies

Fast-Track proposals will be accepted.

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

Number of anticipated awards: 2-4

Budget (total costs, per award):

Phase I: up to $400,000 for up to 9 months

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

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

Summary

Current manufacturing processes for autologous cell-based cancer therapies are complex, slow, labor intensive, and expensive. These involve highly personalized methods requiring leukapheresis followed by ex vivo manipulation of cells before a therapy can be administered to the patient. While autologous cell-based therapies offer great promise for cancer treatment, there is growing concern that current manufacturing methods are unable to support the delivery of these treatments to the large numbers of patients eligible to receive them. In particular, the cell processing period between cell isolation and therapeutic administration, referred to as 'vein-to-vein' time, currently takes from 3-8 weeks. Using current methods, medical center laboratories that provide cell-based therapy often have the capacity to treat only 2-8 patients per month, which is insufficient to meet the high demand of clinical trials. Moreover, given that cell-based cancer therapy is still in its nascent stages, higher patient throughput is likely to accelerate the iterative bench-to-bedside-to-bench research that will be needed to improve and mature this treatment modality. Advanced manufacturing approaches that can process multiple cell therapies for several patients in parallel could substantially improve the availability of emerging autologous cell-based therapies. Achieving this complex, multi-step, parallel processing is likely to require automated systems that can continuously control and monitor critical quality attributes of the engineered cells. Such systems must also be capable of optimizing and maintaining the desired physiological and immunological status of the expanded cells in a multiplexed fashion, while overcoming issues of cell senescence and exhaustion. A further challenge may involve miniaturization of cell culturing processes to achieve greater efficiency and higher throughput as compared to current approaches. It is expected that advanced manufacturing technologies will decrease both the cost and time required to deliver emerging autologous cell-based therapies to a greater number of patients, including those patients with rapidly progressing disease for whom autologous therapies may not currently be feasible.

Project Goals

The overall goal of this solicitation is to stimulate the development of advanced manufacturing technologies that substantially improve the speed and cost of producing autologous cell-based therapies. Technical solutions are expected to involve parallel processing (i.e., multiplexing) of individual cell-based therapies, although other approaches are encouraged. New technologies must produce cell-based products of equal or superior quality as compared to current manufacturing methods. In addition, the NCI encourages system design features that enable rapid and iterative customization to support bench-to-bedside-to-bench research. For example, technologies may involve a modular engineering approach in which the system can be readily adapted as the critical quality attributes of cell-based products are refined over time based on new clinical research. Proposals submitted under this topic must involve a collaboration between technology developers and clinical researchers with experience developing and treating patients with autologous cell-based cancer therapies. Phase I projects will be expected to involve feasibility testing of the proposed advanced manufacturing technology. A key activity during the Phase I project is to benchmark the novel advanced manufacturing approach against the current manufacturing method for a specific autologous cell-based product. More specifically, the research plan must include validating the proposed novel manufacturing approach against a process that has been used to produce product for clinical trials by demonstrating comparability of products with respect to specific critical quality attributes. Phase II projects will be expected to conduct full-scale parallel processing to demonstrate a substantial increase in the speed and cost of producing autologous cell-based therapies. It is anticipated that most offerors will propose to study T-cell-based immunotherapy products, although other cell types are also encouraged (e.g., NK cells). Advanced manufacturing approaches may involve genetic engineering and optimization as appropriate for the cell-based therapy product, but the primary goal is to achieve substantial cost and throughput improvements for the overall vein-to-vein process. Projects proposing to use allogeneic cell-based therapies for technology validation will not be considered responsive under this solicitation.

Phase I Activities and Deliverables:

- Provide proof of collaboration with an engineer(s), immunologist(s) and clinician(s) that has experience developing high throughput systems and/or treating patients with autologous cell-based cancer therapies;
- Establish assays and/or metrics, especially functional comparability and quality attributes, for benchmarking the approach against current manufacturing methods;
- Establish defined specifications to enable integrated high throughput parallel manufacturing at faster speed and lower cost than current manufacturing methods;
- Develop an early prototype device or technology for integrated high throughput autologous-cell manufacturing that include specifications designed to substantially reducing the speed, as well as any cost savings based on the new manufacturing approach;
- Demonstrate the suitability of the approach to manufacture a minimum of two cell products in parallel
- Demonstrate pilot-scale beta-testing of the approach comparing it against appropriate benchmarking technology
- Demonstrate the immunological functionality of the cells based on the previously identified functional comparability assays and/or metrics, and compare cell function to appropriate benchmarking technology;
- Establish cell culturing technology compatible with high throughput production and technology to monitor the cells

Phase II Activities and Deliverables:

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

NATIONAL 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:

111 Oxygen Delivery Device Innovations

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: **$2,000,000** for **2** years

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

Summary

The Portable Oxygen Concentrators (POCs) currently on the market do not meet the needs of the advanced stage lung disease population or those trying to participate in routine activities for a higher quality of life. The majority of POCs deliver a pulsed oxygen flow up to 3 liters per minute, synchronized with the breathing cycle, but at higher levels of oxygen needs, the pulsed mode is insufficient for routine exertion such as housework or tending to children. Current POCs that deliver a higher, continuous flow of oxygen (up to 10 liters per minute) are too heavy to carry in a shoulder bag or backpack; the user cannot carry a bag or child while also toting a heavy POC around. Also, most of the currently available POCs are not designed to easily or remotely adjust the oxygen flow-based on need. Different modes of remote access are needed to allow for flexibility in adjusting the oxygen flow of the device.

This solicitation aims to support the development and commercialization of a light weight continuous flow Portable Oxygen Device that is available for clinical and investigational care of patients.

Project Goals

The goal of this project is to develop a lightweight, Portable Oxygen Device, with a continuous flow of oxygen of at least 5 liters per minute, and provide pulsed oxygen at a rate equivalent to 5 liters per minute of continuous flow. Remote control of the device to allow adjustments without taking the POC off and allow for use on domestic and international travel.

The final device features should include but are not limited to:

- The flow rate must be adjustable between 1 and 5 liters per minute, both for continuous and pulsed flow options.

- The oxygen delivery system must be light, with a maximum total weight of 5 pounds, so the user can easily carry it hands-free.

- If powered by a battery, the battery must last a minimum of 2 hours at the continuous flow rate of 5 liters per minute.

- The POC system must provide a means to remotely control the flow of oxygen during activity at least 30 feet away. The remote control must enable adjustment easily, without having to remove it from the backpack or bag.

- The POC system must include functional means for the user to control flow rate via a wired or wireless (e.g., Bluetooth, WiFi) connection, as the user needs. The wired controller may be a device attached to a shoulder/waist strap positioned for easy, one-hand access, or on a smart wearable device like a wristband. The wireless controller may be an app residing on a cell phone (e.g., iPhone, Android) or on a smart wearable (e.g., FitBit, iWatch). The app must utilize open source code or otherwise be publicly accessible to ensure it can be maintained by others in the event the awardee ceases to do so.

Miscellaneous Requirements:

- The oxygen delivery system shall sound an alarm when running low in battery, oxygen or if other types of malfunction occurs.

- The oxygen delivery system must operate at the minimum performance level up to 10,000 feet of elevation. Ideally, the oxygen delivery system will be FAA approved for use on commercial airlines for domestic and international travel.

- The oxygen delivery system must comply with all applicable FDA medical device product regulations based on its device class.

Offerors are encouraged to include concrete milestones in their proposals, along with detailed research and development plans, risk analysis, and contingency plans, both for Phase I and Phase II.

Phase I Activities and Expected Deliverables

A Phase I awardee must develop at least one working prototype demonstrating proof of concept for the design. The awardee must perform a formal risk analysis, design a feasible concept, develop a prototype, and demonstrate it has the potential to meet the ultimate requirements of the NHLBI intramural lab.

Below is a list of specific milestones:

- **Conception and ideation**. Identify POC subsystems and determine areas of potential improvement based on user needs, come up with engineering concepts.

- **Risk assessment**. Narrow down ideas based on a detailed risk matrix to objectively compare the ideas based on numerically rated cost, performance, and technology characteristics.

- **Engineering Analysis**. Do mathematical and technical analysis of proposed POC subsystems. Create a report detailing the concepts and hypotheses. Make 3D-CAD conceptual models.

- **Minimum Viable Prototype Design**. Create physical mockups, software, or electronic breadboard to get data and determine real-world feasibility. Create lean prototypes to validate key performance metrics. An example would be making a breadboard of a wireless communication system that could detect a button being switched on and off from 50 feet away.

- **Engineering Design**. Use MVPs and initial data to design final prototype that should meet all functional requirements.

- **Prototype**. Build a prototype according to the engineering design. Design and run a series of tests to determine if prototype achieved the functional requirements. Write final report detailing the development and prototype results, with details regarding outlook, key learnings, remaining technology risks, user assessments, and potential impact of the project on state of the art POC technology moving into Phase II.

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.

Consideration for transition to Phase II funding will include progress toward regulatory clearance. Consideration may include the status of the contractor's interactions with the Food and Drug Administration (FDA); therefore, contractors are encouraged to provide a detailed report of pre-IDE interactions with the FDA identifying requirements for IDE development under Phase II, including the summary of mutual understanding, if available.

Phase II Activities and Expected Deliverables

Phase II will move past the prototype stage to production grade product development and subsequent FDA approval/compliance and manufacturing. The timeline shall be detailed and allow for the completion and validation of the product development and engineering design controls within 24 months.

In addition to meeting all requirements for Phase I, a Phase II award would allow commercial introduction of the device(s) together or independently as 510(k) devices substantially equivalent to marketed predicate devices, or under a *de novo* designation of lower risk. If this is not feasible, the Phase II deliverable would be all testing and regulatory development for the device to be used in human investigation in the United States, under Investigational Device Exemption (IDE), along with devices sufficient to test on 30 human subjects. All communications with FDA related to the device must be recorded and provided to NHLBI.

This Phase II development will likely require specialized engineering, regulatory, and manufacturing expertise related to engineering design controls, fluid control, electric motors, electromechanical engineering, pneumatics, zeolite adsorbents, chemical engineering, firmware/embedded software development, power electronics, battery systems, quality engineering, medical device development, FDA compliance, and/or wireless communication electronics. Any recipients of this NIH grant should be well versed in these areas of engineering or have identified subcontractors who have the requisite industry experience.

Below is a list of specific milestones:

- Ensure stakeholder feedback is incorporated into any Phase I prototypes that are developed. Meet with NHLBI DIR lab to review all elements and finalize design documentation.

- Refine and generate final 3D-CAD model. Iteratively build a model from custom-manufactured goods, test, update risk assessments, adapt software, and improve the 3D-CAD model. Prepare Design Master Record documentation

- Assess required standards test; perform altitude test; confirm software verification; send prototypes to 3rd-party testing houses; select initial sources and production tooling; design verification reports; perform a design review and audit.

- Complete all final documentation requirements, including Quality Plan, Mfg. Assembly Procedures, and Supplier QAs. The output will be three things: a documentation package, secured production sources, and manufacturing infrastructure; together, they must allow the product to be officially produced.

- To ensure that the device conforms to defined user needs and intended uses, test production units under actual or simulated use conditions.

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.

112 Intramyocardial Suture Annuloplasty System ("SCIMITAR" devices)

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): Phase I: **$400,000** for **12** months; Phase II: **$3,000,000** for **3** years:

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

Summary:

Tricuspid valve regurgitation is a common malignant disease with few attractive mechanical treatment options. Secondary tricuspid regurgitation frequently accompanies secondary mitral valve regurgitation and confers a worse prognosis.

NHLBI has developed the Suture via Coronary sinus with Interstitial myocardial navigation for MItral and Tricuspid Annular Reduction (SCIMITAR) procedure to accomplish dual-valve annuloplasty via interstitial navigation of heart muscles entered through heart veins. Clinical evaluation will require the development of purpose-built SCIMITAR devices.

This **contract** solicitation aims to support the development and commercialization of an transcatheter SCIMITAR system.

Project Goals:

The project goal is to develop a SCIMITAR (Suture via Coronary sinus with Interstitial Myocardial navIgation for MItral and Tricuspid Annular Reduction) system implants and delivery catheters. SCIMITAR creates a figure-of-eight loop around the left ventricular myocardial base and inside the right ventricular myocardial wall that narrows both mitral and tricuspid annulis. SCIMITAR implantation requires device or guidewire traversal sequentially from the coronary sinus, through the basal interventricular septum, into the wall of the posterior right ventricle at the base, and through the basal right ventricular free wall to its anterior extent. A tension element is implanted along the SCIMITAR trajectory and countertraction is applied from the free limbs in the coronary sinus and right heart re-entry point near the anteroseptal commissure of the tricuspid valve.

The goals are to develop and commercialize specific catheter tools to accomplish a SCIMITAR annuloplasty. The tools work together as a suite of catheters.

Offerors are encouraged to include concrete milestones in their proposals, along with detailed research and development plans, risk analysis, and contingency plans, both for Phase I and Phase II.

Phase I Activities and Expected Deliverables

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

Below is a list of required characteristics for the specified device system. The system presupposes that an off-the-shelf or purpose-built guidewire has navigated the intramyocardial SCIMITAR trajectory.

- Able to exchange the SCIMITAR guidewire for a permanent tension element, without contributing to or precipitating centripetal (cameral) pull-through

- Incorporating a coronary artery protection element, to protect entrapped (circumflex) coronary artery branches from extrinsic compression.

- Able to deliver a tension countertraction element through the coronary sinus on one limb and the right atrial or right ventricular reentry site on the other limb
- Incorporating an adjustable intravascular lock
- Allowing early removal or at least tension interruption using transcatheter techniques as an emergency bail-out
- Preferred embodiments allow late transcatheter tension adjustment (days to months after the first implantation procedure)
- Incorporating radiopaque markers. Preferred embodiments indicate the perimeter of the implant as a reflection of applied tension
- Preferred embodiments incorporate elements to protect entrapped coronary sinus ("left ventricular") pacemaker or cardiac resynchronization therapy leads from damage
- Safe for body and brain MRI at a minimum 1.5T field strength according to contemporary FDA guidelines

Offerors are advised to plan travel to NHLBI in Bethesda Maryland, and are expected to plan meeting at project initiation, mid-project to determine what iteration is necessary, and at project completion.

Consideration for transition to Phase II funding will include progress toward regulatory clearance. Consideration may include the status of the contractor's interactions with the Food and Drug Administration (FDA); therefore, contractors are encouraged to provide a detailed report of pre-IDE interactions with the FDA identifying requirements for IDE development under Phase II, including the summary of mutual understanding, if available. NHLBI encourages contractors to consider requesting designation to the FDA's Expedited Access for PMA Devices (EAP) program (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM393978.pdf) during the Phase I award period.

Phase II Activities and Expected Deliverables

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

All communications with FDA related to the contracted device must be recorded and provided to NHLBI.

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

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:

087 Point-of-Care HIV Viral Load, Drug Resistance, and Adherence Assays

Fast Track proposals will be accepted.
Direct to Phase II will **not** be accepted.
Number of anticipated awards: 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 the HIV incidence in the US because funds can only be spent domestically and not abroad.

Project Goals

The long-term goal is 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 should include the capacity to connect results to healthcare providers.
- 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 in the presence of an HIV vaccine-induced immune sero-reactivity.
- Assays should be capable of detecting infection in at least one of the following groups: acutely infected people who may have no antibody response and low viral loads; Pre-Exposure Prophylaxis (PrEP) users who may have a very low viral load and a delayed antibody response; vaccine-induced sero-reactive people who will have antibody present even during acute infection; and/or ART-treated people after loss of viral suppression.

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

2. 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 turn-around-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
    - PrEP adherence
    - ART adherence to trigger adherence interventions
    - The long-tail associated with long-acting ART or PrEP
    - 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:

- 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, hair (for drugs) dependent on the application
- Preliminary studies to determine the assay feasibility
- Define process controls
- Establish potential for commercialization

Phase II activities:

- 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 quality control program to enable longitudinal measurements in compliance with Good Clinical Laboratory Practice
- Finalization of the commercialization plan

This SBIR contract topic will <u>not</u> support:

- The conduct of clinical trials

088 Therapeutic Targeting of Intracellular HIV-1 Proteins or Nucleic Acids

Fast Track Proposals <u>will</u> be accepted.
Direct to Phase II will **not** be accepted.
Number of anticipated awards: 2

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

Background

During the HIV life-cycle, multiple viral nucleic acids and proteins are expressed inside the infected cell. All are critical to support assembly, release, and maturation of the virus. Considering each HIV gene product has a defined role in the life-cycle, therapeutically targeting one or more may be an effective strategy to obtain a sustained viral remission. Small molecule inhibitors have been approved for the inhibition of reverse transcriptase, protease, and integrase. Attempts to develop small molecule inhibitors to other intracellular HIV proteins have not been successful since these proteins lack an active site to be targeted for binding, which renders them as "undruggable".
Therapeutic targeting of intracellular HIV proteins or nucleic acids may be an effective strategy for shutting down viral replication, preventing cellular transmission, and may ultimately lead to sustained viral remission. Recent advances in chemoproteomic platforms have resulted in the discovery of druggable hotspots on proteins previously considered to be undruggable. These hotspots can be targeted with small-molecule compounds with the goal of inhibiting protein function. Macromolecules have been developed as therapeutics, which are effective at targeting intracellular proteins. This class of drugs, which include intracellular antibodies, antibody fragments, disordered peptides, and stapled peptides are capable of inhibiting protein function and disrupting protein-protein interactions. The selective targeting of intracellular proteins for ubiquitination and degradation in the proteasome is an effective strategy for removing a protein from the cell and provides an approach, which is different from inhibition. Therapeutic targeting of HIV structural and regulatory proteins may be an effective strategy for inhibiting viral replication and assembly. Alternatively, targeting HIV accessory proteins may restore host anti-viral activities.

The identification of detailed RNA structures (mRNA, noncoding RNAs, and micro RNAs) now allows the design of drugs, which are capable of binding to RNA with high selectivity and specificity or otherwise influence RNA biology resulting in disruption of the HIV life cycle. This strategy has the potential to expand the use of drugs beyond inhibiting functional activity, by preventing the translation of mRNAs, so that the targeted HIV protein is never expressed. In addition, HIV RNA can also be modified by tagging RNA nucleotides with side chains (adducts), especially at the hairpin loop where nucleotides are free.

Project Goals

The goal of this contract solicitation is to support the development of therapeutics which target intracellular HIV proteins or nucleic acids (DNA, RNA) with the goal of inhibiting their function and ultimately HIV replication.

Phase I activities may include:

- Designing, optimizing, and testing strategies for the development of therapeutics, which target intracellular HIV proteins or HIV nucleic acids
- Performing proof-of-concept studies to demonstrate that therapeutics target intracellular HIV proteins or HIV nucleic acids
- Evaluating the ability of the proposed therapeutics to inhibit HIV proteins/nucleic acids and disrupt HIV host protein/RNA interactions in relevant cell lines and primary cells
- Exploring off-target effects
- Performing proof-of-concept studies in small animal models

Phase II activities may include:

- Optimizing delivery to target HIV-infected cells with minimal off-target effects
- Evaluating organ toxicity, immune responses/adverse events, and pharmacokinetic/pharmacodynamic parameters in nonhuman primates
- Performing IND-enabling studies in consultation with the FDA

The SBIR contract topic will <u>not</u> support:

- Development of small molecules to inhibit HIV enzyme activity
- Molecules that enhance latency reversal
- Therapeutic targeting of HIV surface proteins, such as HIV Envelope

089 Particle-based Co-delivery of HIV immunogens as Next-generation HIV Vaccines

Fast Track Proposals <u>will</u> be accepted.
Direct to Phase II will **not** be accepted.
Number of anticipated awards: 2-4

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

Background

A major focus of HIV vaccine research has been the development of immunogens that elicit broadly neutralizing antibody responses targeting the envelope protein (Env). While the field has predominantly focused on immunogen design and soluble

antigens, the targeted and controlled delivery of antigens and optimal antigen-adjuvant formulations has not received much attention and is a gap in the HIV field that needs to be addressed. Lipid- and polymer-based nanoparticle platforms have been shown to induce HIV-specific antibody and cellular immune responses in animal studies. HIV immunogens delivered via particle-based modalities may elicit better and improved humoral and cellular immune responses. Specifically, multivalent/repetitive antigenic display on particle-based carriers may allow for higher avidity interactions and stimulate a diverse set of B cells. Consequently, such multivalent antigen display may mediate efficient engagement and activation of B cells, promoting stimulation of lower avidity cells from the germline antibody repertoire thereby enhancing affinity maturation resulting in superior antibody responses characterized by improved breadth, potency, and durability. Additionally, the ability of nanoparticles to target specific cells and release antigens in a controlled and sustained manner without the complications of viral vector toxicity and anti-vector immune responses makes nanoparticles a promising alternative to viral vectors. Altogether, for elicitation of potent, protective and durable immune responses, HIV immunogen design and particulate delivery of antigens should remain mutually inclusive and should converge for the development of HIV vaccine candidates capable of effectively inducing B/T-cell activation.

Project Goal

Tailored immunogens (such as Envs, monomers, native and/or native-like trimers, nucleic acids/RNA such as mRNAs, self-amplifying RNAs) combined with an effective multivalent antigenic display on nanoparticles for delivery may provide a strategy to promote strong and long-lived neutralizing antibody responses against HIV and direct affinity maturation toward HIV neutralizing antibodies. The primary goal of this SBIR is to solicit proposals that cover the following activities.

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

- Engineering, fabricating nanoparticle platforms/systems and approaches (such as synthetic and/or self-assembling particles and/or conjugating technologies to attach antigen to nanoparticles and/or immunogens to adjuvants and/or encapsulating antigens) for delivering existing and/or novel HIV immunogens (such as Envs, monomers, native and/or native-like trimers, nucleic acids/mRNA/self-amplifying RNAs) that can enhance formulation codelivery, stability and scalability.
- Augmenting HIV vaccine development by enhanced presentation, trafficking and targeting the antigen presentation for the induction of broad humoral and cellular immune responses.
- Developing and evaluating particulate systems (such as synthetic and/or self-assembling and/or covalent chemical attachment and/or encapsulation/condensation of an antigen) that can facilitate co-delivery and/or co-formulation of HIV antigens (such as Envs, monomers, native and/or native-like trimers, nucleic acids/RNA) with adjuvants (such as existing, licensed, biosimilar novel adjuvants/TLR agonists).
- Developing optimal parameters/conditions for incorporation of HIV antigen(s) in nanoparticulate formulation.
- Assessing the effects of modulating particle size, shape, surface properties, composition and modulus/elastic properties of particulate delivery system components on immune responses.
- Conducting pre-formulation/formulation studies on particulate antigen combinations to understand the interactions and compatibility of components (excipients, buffers, pH) and effect on antigen epitope integrity and its performance.
- Developing assays and test methods to analyze and characterize molecular properties of the particulate-antigen formulations through *in vitro* (biophysical, physicochemical, binding assays) and/or *in vivo* testing (small animal studies).
- Developing assays to quantify encapsulation efficiency, immunogen release and expression.
- Studying conditions for controlling particle size and size distribution, charge, composition, and aggregation.
- Conducting mixing, compatibility, studies and short-term stability studies on antigen-adjuvanted formulations.
- Evaluating particulated formulation technologies for fabrication and development of HIV vaccine development.

- Testing for batch-to-batch reproducibility and consistency of particulate formulations for manufacturing, impact of changes in scale, size of the batches.
- Conducting studies whether the particulated formulations can be subjected to sterile filtration and assessing the composition of components after sterilization.
- Developing an efficient process for early-stage/pre-clinical studies, which could be adapted to scale-up studies and which can subsequently lead to the production of clinical-grade material in conformance with current good manufacturing practices (cGMP).
- Evaluating the immunogenicity and effectiveness of particle-based HIV protein and nucleic acid/RNA vaccine candidates using different co-delivery strategies such as, but not limited to, co-administration, colocalization, encapsulation, surface adsorption of antigens (vs. soluble antigen) in animal models.
- Investigating the influence of heterologous prime-boost vaccination strategies on targeting B cell activation and maturation.
- Investigating the effects of route of immunization, dose, dosage form, and dose-sparing capacity of particulate formulations on the particle distribution and kinetics of immunogen immune response.

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

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

090 Sequence-based Assays to Quantify the Replication-Competent HIV Reservoir

Fast Track Proposals will be accepted.
Direct to Phase II will **not** be accepted.
Number of anticipated awards: 1-2

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

Background

Despite effective antiretroviral therapy (ART), HIV-1 persists in all infected individuals as proviral DNA within long-lived memory CD4+ T cells. Early studies on PBMC from HIV-infected donors on suppressive ART demonstrated that a subset of proviruses could be induced to replicate in tissue culture. This replication-competent HIV reservoir constitutes the primary barrier for curing HIV infection. In this context, the number of full-length (intact) HIV proviruses represents the upper limit of the replication-competent HIV reservoir whereas infectious units per million (IUPM) measured by the Quantitative Viral Outgrowth Assay constitute the lower limit of this reservoir of interest.

To measure success, the design of HIV cure strategies should be accompanied by the development of fast and reliable assays that accurately measure changes in the replication-competent HIV reservoir. In addition, for practical reasons, HIV reservoir assays should only require small sample sizes, either a few million cells or a tissue biopsy. Recently, several assays have been developed to replace the time-consuming Quantitative Viral Outgrowth Assay, but validation for clinical applications and commercial purposes is lagging behind.

Project Goal

The overall goal of this project is to develop and commercialize sequence-based HIV reservoir assays for clinical HIV cure interventions. Specifically, the assay should be designed as an analytical tool to monitor the size of the replication-competent HIV reservoir in clinical research and if successful, in prospective clinical trials. Essential characteristics for commercially applicable HIV reservoir assays are reproducibility, low labor intensity, medium-to-high throughput performance, and correlation with the replication-competent HIV reservoir. When designing the requested assays, it needs to be also taken into consideration that besides internal sequence deletions, lethal mutagenesis, such as G-A hypermutations, stop codons within the HIV open reading frames and nonfunctional LTR promoters could also present blockades in the HIV replication cycle.

An additional goal of this project is to develop secondary assays that are not tissue culture-based and discriminate between actively transcribed and latent full-length proviruses. Applicants also need to provide a plan for evaluation how their assay correlates with the Quantitative Viral Outgrowth Assay and other recently developed HIV reservoir assays, such as the Tat/Rev Induced Limiting Dilution Assay (TILDA), and why their assay is superior to similar reservoir assays. **The ultimate goal of this project is to develop an assay that accurately measures the size of the HIV reservoir defined as the "barrier" to the HIV cure, which needs to be eliminated to prevent viral rebound.**

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

- Developing medium-to-high throughput sequence-based assays that accurately reflect the size of the replication-competent reservoir.
- Developing standardized controls for the sequence-based assays.
- Confirming that the sequences detected correspond to full-length HIV proviruses.
- Determining the following assay parameters:
    - Specificity: Will the assay only detect full-length proviruses?
    - Sensitivity: Will the assay detect small levels of full-length proviruses? What is the dynamic range and is it adequate?
    - Interference: will components in the assay sample interfere with the assay (for example, blood anticoagulants, such as heparin)?
    - Robustness: Can the assay cope with small changes in the assay sample/equipment/operator?
    - Accuracy: Is the assay capable of accurately determining the absolute number of full-length proviruses?

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

- Determining the utility of the assay for clinical samples.
- Testing clinical samples from diverse cohorts of HIV+ individuals with varying levels of residual viral reservoirs.
- Validating the developed assays under CLIA and ICH harmonized Good Clinical Practices.
- Determining that the assays qualify for FDA regulatory submissions.
- Determining assay performance for different HIV subtypes and drug-resistant strains.
- Determining assay performance in tissues versus blood.

- Demonstrating that the assay can measure changes in the size of the latent HIV reservoir in response to an intervention.

091 Adjuvant Development for Vaccines and for Autoimmune and Allergic Diseases

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

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

Background

The goal of this program is to support the preclinical development of novel vaccine adjuvant candidates against infectious diseases or of tolerogenic adjuvants for immune-mediated diseases. For the purpose of this SBIR, vaccine adjuvants are defined according to the U.S. Food and Drug Administration (FDA) as "agents added to, or used in conjunction with, vaccine antigens to augment or potentiate, and possibly target, the specific immune response to the antigen". Tolerogenic adjuvants are defined as compounds that promote immunoregulatory or immunosuppressive signals to induce non-responsiveness to self-antigens in autoimmune diseases, or environmental antigens in allergic diseases.

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

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

Adjuvanticity may be obtained with a single immunostimulatory (or immunoregulatory/tolerizing) compound or formulation, or with a combination adjuvant. For this solicitation, a combination-adjuvant is defined as a complex exhibiting synergy between individual adjuvants, such as: overall enhancement or tolerization of the immune response depending on the focus and nature of the vaccine antigen; potential for adjuvant-dose sparing to reduce reactogenicity while preserving immunogenicity or tolerizing effects; or broadening of effector responses, such as through target-epitope spreading or enhanced antibody avidity.

Project Goal

The goal of each project will be to accelerate the pre-clinical development and optimization of a single lead adjuvant candidate or a select combination-adjuvant for prevention of human disease caused by non-HIV infectious pathogens, for the treatment of autoimmune or allergic diseases, or transplantation. The adjuvant products supported by this program must be studied and further developed toward human licensure with currently licensed or new investigational vaccines and may not be developed as stand-alone agents.

Phase I Activities:

Depending on the developmental stage at which an adjuvant is entered into the program, the offeror may choose to perform one or more of the following:

- Optimization of one candidate compound for enhanced safety and efficacy. Studies may include:
    - Structural alterations of the adjuvant
    - Formulation modifications (adjuvant alone or in combination with antigen(s))
    - Optimization of immunization regimens
- Development of novel combinations of previously described individual adjuvants, including the further characterization of an adjuvant combination previously shown to enhance or tolerize immune responses synergistically
- Preliminary studies in a suitable animal model to evaluate: immunologic profile of activity; immunotoxicity and safety profile; protective or tolerizing efficacy of a lead adjuvant:antigen/vaccine combination

Phase II Activities:

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

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

Areas of Interest:

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

This SBIR will not support:

- The further development of an adjuvant that has been previously licensed for use with any vaccine unless such an adjuvant is use as a component of a novel combination adjuvant as defined above
- The conduct of clinical trials (see https://osp.od.nih.gov/wp-content/uploads/2014/11/NIH%20Definition%20of%20Clinical%20Trial%2010-23-2014-UPDATED_0.pdf for the NIH definition of a clinical trial)
- The discovery and initial characterization of adjuvant candidates
- The development of adjuvants or vaccines to prevent or treat cancer
- Development of platforms, such as vehicles, or delivery systems that have no immunostimulatory or tolerogenic activity themselves
- The 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 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.

092 Adjuvant Discovery for Vaccines and for Autoimmune and Allergic Diseases

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

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

Background

The goal of this program is to support the screening for new vaccine adjuvant candidates against infectious diseases or for tolerogenic adjuvants for autoimmune or allergic diseases. For the purpose of this SBIR, the definition of vaccine adjuvants follows that of the U.S. Food and Drug Administration (FDA): "Agents added to, or used in conjunction with, vaccine antigens to augment or potentiate and possibly target the specific immune response to the antigen." Tolerogenic adjuvants are defined as compounds that promote immunoregulatory or immunosuppressive signals to induce non-responsiveness to self-antigens in autoimmune diseases or transplantation, or environmental antigens in allergic diseases.

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

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

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

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

Program Goal

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

Phase I Activities 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:

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

This SBIR will not support

- The development of immunostimulatory compounds or formulations as stand-alone immunotherapeutics (i.e., without a specific antigen/pathogen-specific vaccine component) unless the putative adjuvant is used to modulate or suppress the response against an allergen or autoantigen. In this case, the proposal must include assays to demonstrate the effect of the treatment with an adjuvant on specific allergens or autoantigens.
- The testing of newly identified immunomodulatory compounds or formulations in cancer models
- The further development of previously identified adjuvant
- The conduct of clinical trials (see https://osp.od.nih.gov/wp-content/uploads/2014/11/NIH%20Definition%20of%20Clinical%20Trial%2010-23-2014-UPDATED_0.pdf for the NIH definition of a clinical trial)

093 Production of Adjuvants Mimics

Fast-Track proposals will be accepted.
Direct-to-phase II proposals will be accepted.
Number of anticipated awards: 3-5

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

Background

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

Program Goal

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

Phase I Activities must include at least the following 2 activities:

- Development of one or more adjuvant/adjuvant formulations that is based on or similar to an adjuvant with a proven clinical track record of high adjuvanticity
- Preclinical testing to assure immune potency and safety

Phase II Activities include, but are not limited to:

- Establishment of an immunological profile of the lead product
- Pharmacological and toxicological studies in appropriate animal models
- Validation of product
- Scale-up production
- Development of a marketing plan

This SBIR will not support

- Development of aluminum-based adjuvants as marketable products, unless the aluminum-component is used as a co-adjuvant or carrier
- Discovery of novel immunostimulatory compounds
- Commercial development of adjuvants that do not have the ability or potential to activate human immune cells
- Development of adjuvant mimics that would violate existing patents

094 Reagents for Immunologic Analysis of Non-mammalian and Underrepresented Mammalian Models

Fast-Track proposals will be accepted.
Direct-to-phase II proposals will be accepted.
Number of anticipated awards: 3-5

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, sharks, zebrafish), nematodes, marine echinoids) or in specific underrepresented mammalian models (guinea pig, ferret, 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 the limitations noted above. For example, the progression of disease that follows infection of guinea pigs with *Mycobacterium tuberculosis*, the causative agent of tuberculosis (TB), displays many features of human TB. While this model has been used for more than 100 years as a research tool to understand and describe disease mechanisms, immunologic analyses are constrained by the limited availability of immunological reagents specific for the guinea pig. Another example is the ferret model, one of the best animal models of human influenza infection, where immunologic studies also have been limited by the lack of immunological reagents.

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 underrepresented mammalian models. Non-mammalian models are limited to arthropods, amphibians, fish (e.g., jawless, sharks, zebrafish), nematodes, and marine echinoids. Underrepresented mammalian models are limited to guinea pig, ferret, 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 polycloncal 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 intended antigen/immunogen)

Phase II Activities must include, but are not limited to:

- Comprehensive evaluation of specificity and functional utility 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.

In addition, *Phase II Activities may include, but are not limited to:*

- 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

This SBIR will not support:

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

095 Improving Technologies to Make Large-scale High Titer Phage Preps

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

The rapid emergence of antibiotic resistance in both Gram-positive and Gram-negative bacteria has limited our ability to treat certain infections, leading to an urgent need for new antimicrobial agents and the development of novel approaches to combat bacterial infections. In recent years, there has been an increasing number of reports in which bacteriophages (phages) have been used in a clinical setting to treat infections caused by drug resistant bacteria. However, the use of phage has been largely limited to eIND or compassionate use situations, making it difficult to make definitive conclusions regarding their clinical efficacy. In addition, there are significant roadblocks to testing phage therapy in a clinical setting, including:

- Absence of generalizable procedures to manufacture high titer phage stocks suitable for use in clinical studies.
- Knowledge gaps related to the stability and formulation for specific phages and combinations thereof.

Project Goal

The goal of this solicitation is to develop generalizable procedures and necessary tools to manufacture and purify stable high titer phage stocks suitable for use in clinical trials. The tools and methods should be applicable to phage that could be used to

treat mycobacteria or one of the ESKAPE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter species*).

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

- Identification and development of robust tools and methods to produce and purify high titer phage stocks suitable for use in clinical trials.
- Development of methods to ensure the stability of high titer phage stocks.
- Investigation and development of novel formulations and methodologies that advance the use of high titer phages.

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

- Demonstration that methods developed in Phase 1 are not limited to particular types of phages or phages which grow on specific bacterial pathogens.
- Demonstration that stability methods developed in Phase 1 will be suitable for use with phage cocktails in addition to be suitable for use with single phages.

This SBIR will not support:

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

096 Development of priority diagnostics for Chagas disease

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

Chagas disease (CD) is endemic in Latin America and is a growing public health concern in the U.S. where there are an estimated 300,000 cases. CD progresses from a brief acute phase to a prolonged asymptomatic chronic phase, with 20-30% of those infected developing serious cardiac or gastrointestinal complications. Early diagnosis is important, as the two drugs used to treat CD, benznidazole and nifurtimox, are highly effective if given early but show uncertain efficacy and increasing toxicity with increasing duration of infection and patient age. Currently available diagnostic assays have suboptimal sensitivity and specificity, and a positive diagnosis can require multiple confirmatory tests. The extensive genetic diversity of *Trypanosoma cruzi*, the parasite responsible for CD, likely contributes to this assay discordance. A reliable clinical test of cure (ToC) to gauge treatment efficacy is also lacking, as there are currently no known biomarkers that would provide an early indication of treatment success.

Project Goal

The purpose of this solicitation is to develop one of the following: *i)* a rapid point-of-care diagnostic assay with sensitivity greater than standard serological tests, and appropriate for use during both the acute and chronic phases; or *ii)* a biomarker-based ToC to evaluate treatment outcome during the chronic phase of infection that does not require months or years to definitive results.

Both assays should be able to detect all circulating strains of *T. cruzi*. Additionally, there should be no cross-reactivity with other parasites (i.e. *Leishmania*, *T. rangeli*). Offerors may need to establish a collaboration or partnership with a medical facility or research group in the US or overseas that can provide relevant positive control and patient samples; offerors must provide a letter of support from the partnering organization(s) in the proposal.

Phase 1 activities may include but are not limited to:

- Identification of appropriate biomarkers for prototype diagnostic test.
- Determination of sensitivity, specificity and other performance characteristics (e.g. time to result, limit of detection, cross reactivity, test stability, feasibility for newly infected, chronically infected, and resolved infected clinical samples) of the diagnostic test.
- Performance of initial testing on laboratory isolates.
- Performance of further testing on isolates from across the geographic range of the parasite.

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

- Further characterization of appropriate biomarkers for a prototype diagnostic.
- Further optimization of the assay platform technology and validation of assay reproducibility.
- Testing of de-identified clinical samples from diverse cohorts with varying levels of infection.
- Final validation testing and scale-up manufacturing of test kits.

This SBIR will not support:

- The design and conduct of clinical trials (see http://www.niaid.nih.gov/researchfunding/glossary/pages/c.aspx#clintrial for the NIH definition of a clinical trial).
- Development of assays and/or technologies for research use only.
- Development of diagnostic assays that only identify one or a small subset of circulating strains of *T. cruzi*.

097 Pediatric Formulations of Select Second Line Drugs for Treating Tuberculosis

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

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

Background

Tuberculosis (TB) is the world's leading infectious killer and rates of multi and extensively drug resistant TB (MDR/XDR TB) are increasing. In 2018, an estimated 1.1 million children became ill with TB and an estimated 234,000 children died from the disease. Current TB drug dosing and administration for pediatric TB cases is inadequate, leading to poor adherence, potentially suboptimal drug levels and the development of drug resistant TB. Pediatric formulations of first line TB drugs Isoniazid, Rifampicin (rifampin), Pyrazinamide and Ethambutol are currently available or under development. Treatment of MDR/XDR requires the use of second line TB drugs. However, for many of these drugs, pediatric friendly formulations do not exist. Adult tablets are often cut and administered to children in juice or other palatable substances such as food, which may inactivate these drugs. For MDR and XDR TB, long term treatment is required (18-24 months) and for rapidly growing children frequent dose adjustments may be required, so flexible dose formulations which allow personalization based on weight, age and nutritional status are particularly desirable. Additionally, formulations stable under ambient conditions and suitable for use in resource-limited countries are desirable.

Project Goal

The purpose of this solicitation is to develop innovative, pediatric-friendly, oral formulations for select second line drugs that are approved for treatment of TB. This solicitation specifically targets the development of pediatric formulations for the oxazolidinones (e.g. linezolid), clofazimine, fluoroquinolones, para-aminosalicylic acid (PAS), cycloserine, and the nitroimidazoles Delaminid and Pretomanid. Examples of the types of oral formulations that may address these needs include but are not limited to: oral thin films; porous, chewable matrix systems (scorable "taffy" based on patient weight); candy-like formulations, including gummies and jellybeans; inhaled formulations and easy to dissolve tablets. Ideally, the final product should be stable at room temperature and ready for testing in bioequivalence and pharmacokinetic/pharmacodynamic studies.

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

- Develop prototype formulations for one or more of the following second line TB drugs: the oxazolidinones (e.g. linezolid), clofazimine, fluoroquinolones, para-aminosalicylic acid (PAS), cycloserine, and the nitroimidazoles Delamanid and Pretomanid.
- Develop analytical assays to characterize chemical composition, purity and stability of prototype formulations
- Assess the pharmacokinetic profile and safety of the formulations in appropriate systems or animal models
- Conduct or develop drug potency assays for bioequivalence studies

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

- Scale-up formulations for further preclinical studies
- Conduct additional pharmacology and toxicology evaluations of the formulations in appropriate systems or animal models
- Conduct bioequivalence studies

This SBIR will not support:

- The design and conduct of clinical trials (see http://www.niaid.nih.gov/researchfunding/glossary/pages/c.aspx#clintrial for the NIH definition of a clinical trial).

- Proposals that include formulation of first line TB drugs (Isoniazid, Rifampicin (rifampin), Pyrazinamide and Ethambutol).

098 Group A Streptococcus Vaccine Development

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 one year;
Phase II: $2,500,000 for up to 3 years.

Background

Group A *Streptococcus* (GAS) infection is a global health threat due to its high morbidity and mortality. No licensed GAS vaccines are available, and few candidates have been evaluated clinically. There is a critical need for the development of a safe and effective GAS vaccine. While recent advances in the field of GAS vaccine development have led to many important vaccine candidates, most are at the stages of basic research and early preclinical development.

Project Goals

The overall goal of this solicitation is to develop safe and effective GAS candidate vaccines that are suitable for future product and clinical development. Proposals should establish proof-of-concept for and/or support preclinical development of a candidate vaccine to combat GAS, as well as standardize methods to evaluate immunity, protection, and safety of the candidate vaccine(s). Proposals that significantly advance a candidate vaccine toward clinical development are highly encouraged.

Phase I activities may include but are not limited to:

- Identification and evaluation of novel or improved vaccine candidate(s)/formulation(s) using in vitro and/or in vivo studies
- Development and standardization of in vitro surrogate assays to evaluate induction of immunity and protection
- Development and validation of in vivo proof-of-concept studies to demonstrate protection in animal models
- Development, standardization and validation of assays to evaluate the safety of the vaccine candidate(s)

Phase II activities may include but are not limited to:

- Additional testing and process development of the lead vaccine candidate(s) in the product development pathway leading to IND-enabling studies, including but not limited to testing to improve safety, efficacy, and quality assurance/quality control
- Preclinical testing in animal, including non-human primate, models
- Pilot lot cGMP manufacturing, as appropriate, for further refinement of the vaccine candidate(s)
- Stability and toxicology studies, as appropriate, for later stages of the vaccine product development pathway

This SBIR will not support:

• The design and conduct of clinical trials
(see https://osp.od.nih.gov/wp-content/uploads/2014/11/NIH%20Definition%20of%20Clinical%20Trial%2010-23-2014-UPDATED_0.pdf for the NIH definition of a clinical trial).

099 Rapid, Point-of-Care Diagnostics for Hepatitis C Virus

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

Infection rates of hepatitis C virus (HCV) in the USA have steadily risen since 2010. There are approximately 2 million people chronically infected with HCV in the USA, and it is estimated that up to 45,000 acute infections occur annually. Spontaneous clearance of HCV occurs in 15-47% of acutely infected individuals; the remaining will develop chronic HCV (defined as viremic for 6 months or greater). Globally, there are an estimated 71 million people with chronic HCV; it is estimated that as many as 50% may be unaware of their infection.

In 2016, the World Health Organization established a goal for eliminating HCV infection as a major public health threat by 2030, defined by reductions in incidence (by 90%) and mortality (by 65%). In order to achieve these goals, a new point-of-care (POC) diagnostic that is sensitive, specific, simple, rapid, and cost-effective is critical to more readily connect infected individuals with treatment and case management efforts. While the current HCV diagnostic process utilizes assays that are highly sensitive and specific, it requires at least two tests that can take up to a week or more for results. An initial positive point-of-care screen for anti-HCV antibodies in blood is followed by a viral load test performed in a centralized laboratory. Either the same sample is reflex tested, or the patient must supply an additional sample. The delay in diagnosis can have a significant impact on follow-up care, initiation of treatment, and potential transmission of the virus in at-risk groups (such as persons who inject drugs). Simplified POC testing for active, viremic HCV infections would allow patients to receive their result in a single visit and allow for rapid care planning and management with their physician.

Project Goal

The purpose of this solicitation is to develop a POC diagnostic for primary health-care settings to detect active, viremic HCV infections in a single visit and to confirm cure following treatment.

The diagnostic should be rapid (e.g. results ideally in 1 hour or less), simple (require minimal equipment or training to perform), cost-effective, and have the same or better sensitivity and specificity characteristics as similar FDA-approved diagnostic tests currently available for HCV. Additionally, the diagnostic should be able to detect all HCV genotypes, exhibit no cross-reactivity with endogenous substances or exogenous factors, and ideally utilize sample types that are minimally invasive (such as capillary whole blood).

Offerors may need to establish a collaboration or partnership with a medical facility or research group in the US that can provide relevant positive control and patient samples; offerors must provide a letter of support from any partnering organization(s) in the proposal.

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

- Identification of appropriate diagnostic targets (antigen, biomarkers, nucleic acid sequences, etc.) for a POC diagnostic to detect active, viremic HCV infections.
- Development of the prototype POC diagnostic platform (lateral flow system, instrument, etc.) to detect active, viremic HCV infections.
- Determination and/or optimization of the sensitivity, specificity and other performance characteristics (e.g. time to result, limit of detection, test stability) of the prototype POC diagnostic.
- Initial testing using clinical laboratory isolates with multiple genotypes.
- Initial testing using HCV clinical samples or matrices spiked with known quantities of HCV.

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

- Further characterization of diagnostic targets for the POC diagnostic to detect active, viremic HCV infections.
- Advanced development of the prototype POC diagnostic platform to detect active, viremic HCV infections.
- Optimization of the sensitivity, specificity, and other performance characteristics (e.g. time to result, limit of detection, test stability).
- Validation of assay reproducibility.
- Testing clinical samples from diverse cohorts with varying infecting genotypes and varying case history (acute or chronic).
- GMP manufacturing of test components and final validation studies.

This SBIR will not support:

- The design and conduct of clinical trials (see http://www.niaid.nih.gov/researchfunding/glossary/pages/c.aspx#clintrial for the NIH definition of a clinical trial).
- Proposals that are focused on serological assays that solely detect antibodies against HCV.
- Proposals that do not have the ultimate goal of detecting and identifying an active, viremic HCV infection in human clinical samples.

100 Informatics Tools (Data Science Tools) for Infectious, Immune, and Allergic Research

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

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

Background

Data intense infectious, immune, and allergic basic and clinical research projects are generating unprecedented amounts of complex and diverse data sets and beginning to accelerate research in infectious, immune, and allergic diseases ranging from basic understanding of the pathogen and disease to developing new and improved therapeutic interventions and diagnostics and identifying precise, molecular signatures for clinical application. Yet, increasing the use and re- use of these diverse and complex data sets by basic and clinical scientists studying infectious, immune and allergic diseases remains challenging.

Challenges include the availability of innovative, user focused data ready environments that co- locates data and computational tools for managing, sharing, accessing, integrating, visualizing and analyzing diverse and complex data sets generated or collected across NIAID extramural and intramural projects from multiple sources and platforms. Critical to this data ready environment is the continuous development, enhancement and adaptation of informatic tools (*machine*

learning algorithms, computational and software tools, and mathematical modeling methods) which will extract knowledge from these data sets and drive discovery.

This project builds up NIAID's significant investment in bioinformatics capacity and data science and most recent NIAID's data science activities that are directed to enhancing a data ready environment and leveraging data science activities also across NIH. Examples include piloting a NIAID Data Ecosystem Prototype, enhancing the interoperability of currently supported NIAID data repositories, participating with other ICs in a trans-NIH FOA on Database Repositories that has the potential to increase interoperability across NIH data repositories and trans-NIH FOA focused on developing training modules for rigor and reproducibility of data, key to equipping basic and clinical scientists with skills for generating high quality reproducible data sets.

Project Goals

The project goal is to support the development, enhancement or adaptation of innovative, robust, user focused informatic tools (*machine learning algorithms, computational and software tools, and mathematical modeling methods*) for use in infectious, immune, and allergic diseases basic and clinical research to improve the management, visualization, integration and analysisof large, complex and diverse data sets from multiple sources, platforms and environments including publicly available data repositories.

Integrative analysis of data sets (genomic and other omics data, clinical as EHR and clinical trial, surveillance, social, environmental, etc.) and performing advanced and predictive analytics are powerful approaches to begin to extract knowledge from data sets that can catalyze discovery in basic and clinical research and improve the development of therapeutic interventions. Development of user-focused tools that meet the informatic needs of the infectious, immune, and allergic diseases basic and clinical research community is of high priority. Therefore, it is expected that user focused documentation as user guides, SOPs, and training materials also be developed along with the informatics tool for broad use beyond the developer.

Phase I activities:

- Provide an overall product development plan for the informatic tool and identify the specific set of milestones proposed in this application related to the overall product development plan.
- Provide justification for the development, adaptation or enhancement of this specific informatic tool in light of the currently available informatic tools.
- Develop, significantly enhance, modify, improve, or adapt existing informatic tools for visualization and integrative analysis of multi-scale data from multiple sources and platforms including publicly available data repositories for infectious, immune and allergic diseases research.
- Develop, significantly enhance, modify, improve, or adapt existing informatic methods for systems level modeling of multiple scale diverse data sets and from multiple sources.
- Develop an (early) prototype for the informatics tool, perform alpha testing, and address issues from testing and evaluate with appropriate user community to solicit user feedback. Describe the potential user(s) communities and provide two relevant use cases.

Phase II activities:

- Further development, enhancement, adaptation, and optimization of the prototype informatic tool.
- Beta test the informatic tool with the appropriate user communities and use cases, demonstrating the usability of the tool by the infectious, immune or allergic community.
- Document and implement feedback, address issues and feedback, modify the informatic tool, if appropriate, and finalize the prototype for the informatics tool
- Develop user focused documentation, user guides, SOPs and training materials

This SBIR contract topic will <u>not</u> support:

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

CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

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

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

CDC Role:

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

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

CENTER FOR PREPAREDNESS AND RESPONSE (CPR)

The mission of the Center for Preparedness and Response (CPR) is protecting Americans by advancing public heath preparedness and response capabilities at home and abroad. CPR has primary oversight and responsibility for all programs that comprise CDC's public health preparedness and response portfolio. Through an all-hazards approach to preparedness, focusing on threats from natural, biological, chemical, nuclear, and radiological events, CPR helps the nation prepare for and respond to urgent threats to the public's health. CPR carries out its mission by emphasizing accountability through performance, progress through public health science, and collaboration through partnerships.

CPR's Web site: https://www.cdc.gov/cpr/index.htm

CPR's Topic

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

006 Developing Innovative Specimen Packaging Approaches to Improve Transit Success Rates

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

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

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

Background

Maintaining the integrity of clinical and laboratory specimens from the collection (self-collected or collected by a healthcare professional) to analysis is critical. As such, the performance of any laboratory test is dependent on several pre-analytical phases, including using suitable containers and applying appropriate packaging methods to avoid any possible leakage. During specimen packaging, it is critical to account for various transit factors to ensure shipping personnel and laboratory staff are not exposed to hazardous material. Transit challenges that may result in leaky specimens may also result in rejection for testing, which would require the recollection of clinical specimens thereby delaying timely diagnosis and patient

management. During emergencies, opportunities to re-collect specimens may not be available due to potential health risks, inaccessibility, or death among affected individuals.

Though smaller leak-proof specimen containers utilize O-rings to prevent leakage, the COVID-19 pandemic has highlighted potential operational challenges with maintaining specimen integrity resulting from underlying environmental or human-related factors on larger specimen volumes. Some polypropylene specimen tubes (e.g. Viral Universal Transport Medium tubes used for swab collections) are not currently designed to withstand increased cabin pressure that may occur during transportation by air. As air cabin pressure changes, gases expand, including, the trapped air inside a specimen tube. The expanded air may result in the loosening of the screw cap that alleviates the internal pressure. This may result in specimen leakage. Currently, the United Nations packaging recommendations for Category A or B infectious materials suggest the use of parafilm as a layered barrier on screw caps to reduce the risk of leakage. However, for parafilm to serve as a leak-proof seal it must be stretched around the container cap in the same direction as it closes. This introduces the possibility of additional human error into the specimen processing workflow.

Second, based on the principles of application torque the overtightening of a container cap may strip the threaded closure leading to unintended leaks. Similarly, loosely tightening a cap may render the same result. Currently, re-training healthcare staff on specimen handling is a traditional intervention method used to prevent packaging-related issues and improve quality assurance practices. However, constantly rotating staff (as experienced during emergencies) increases the prevalence of human error, further impacting aspects of the quality management cycle on preserving specimen integrity. As such, overcoming environmental and/or human-prone challenges are critical to facilitate timely patient care, enable a rapid public health response, prevent loss of valuable and sometimes irreplaceable specimens, and protect the handling personals from exposure to hazardous materials.

Project Goals

The primary goal of this proposal is to develop a technical capability that improves the integrity of specimen packaging through transit. Like a 'tamper-proof' cap on prescription pill bottles, the innovation must provide a physical or visual indication to the handling personnel, re-assuring that the specimen is secure from leakage. The innovation may also consider the principles of torque and develop approaches that prevent the handler from over-tightening or loosely tightening a cap for both small and large volume specimen collection containers. The innovation should not increase the physical efforts needed to close specimen containers. This innovation may offer a low-cost advanced safety capability to current specimen collection containers or provide new specimen container alternatives to promote safe packaging of various specimen types. Further, a successful proposal must take into consideration the dependability on supply chain processes to support commercialization potential.

Phase I Activities and Expected Deliverables

During the Phase I period, the activities can include, but are not limited to:

1. Conduct a technical assessment of currently used specimen collection containers in various transport environments to determine physical or functional properties that may result in leaks and other specimen challenges associated with containers (e.g., material of container, external pressure, external vibration, torque, temperature changes, etc.).
2. Identify functional gaps and provide specific technical improvements that may be applied to existing specimen collection containers or for the development of new specimen containers to promote safe packaging of different clinical and laboratory specimen types (e.g., cerebral spinal fluid, OP/NP wash, swabs, serum, whole blood, urine, culture) and prevent leakage and other challenges through various transport environments.
3. Develop a technical prototype for existing or new specimen collection containers that includes a safety feature to prevent leakage through various modes of transportation.

Impact

The Institute of Medicine report "To Err Is Human: Building a Safer Health System," among others, highlights the impact logistical, laboratory, or medical errors may have on public health and patient care. Specimen leakages pose increased health risks to shipping and laboratory personnel, further raising public health concerns on the spread of disease. Improving safety measures on specimen collection containers may promote public health safety, ensure specimen integrity to enable accurate laboratory result reporting, and supports the timely diagnosis for critical patient management during emergencies. The impact of this innovation on public health may be evaluated both during non-emergent and emergency scenarios to measure its effectiveness in preventing disease spread and patient outcome.

Commercialization Potential

This innovation has the potential of commercialization as an ‘add-on’ custom packaging safety feature to existing specimen collection products or a new specimen container alternative. Like the development of the ‘tamper-proof’ safety cap on prescription pill bottles, this capability offers a mechanism to prevent specimen leakage and unintentional exposure during transit resulting from poor packaging practices or environmental factors.

NATIONAL CENTER FOR EMERGING ZOONOTIC AND INFECTIOUS DISEASES (NCEZID)

The mission of the National Center for Emerging and Zoonotic Infectious Diseases aims to prevent disease, disability, and death caused by a wide range of infectious diseases. NCEZID focuses on diseases that have been around for many years, emerging diseases (those that are new or just recently identified), and zoonotic diseases (those spread from animals to people). Work is guided in part by a holistic "One Health" strategy, which recognizes the vital interconnectedness of microbes and the environment. Through a comprehensive approach involving many scientific disciplines, better health for humans and animals and an improved our environment can be attained.

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

NCEZID Topic

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

024 Device Development for Microbial Surface Sampling, Field Extraction and Collection

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

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

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

Background

Surfaces touched by patients and healthcare workers, such as bedrails, tables, medical equipment and toilet sites, are not often cleaned properly and can contribute to the spread of organisms such as Clostridioides difficile, Acinetobacter baumannii, methicillin-resistant Staphylococcus aureus (MRSA) and other antibiotic resistant organisms. When infections repeatedly occur in healthcare settings, epidemiologists and hospital staff typically investigate and search for a potential source of the infection by sampling with swabs (for small surfaces; 4in^2) and wipes or sponges (for larger surfaces; 100 – 200 in^2), sending them to a laboratory to extract the organisms from the sampling device, and for detection of the organisms by culture or by a direct molecular detection assay such as polymerase chain reaction (PCR) or whole genome sequencing. Laboratory extraction methods are often labor intensive and require expensive equipment and time.

With the advent of rapid detection instruments such as the MinION for metagenomic sequencing, microfluidic devices, and "Lab on a Chip" portable detection instruments, the detection of microbes in the field will soon be routinely possible. However, direct detection of target organisms in the field is challenged by low bioburden environmental samples, thus requiring the need for samples to be concentrated and tested in the laboratory using culture-dependent methods. Novel strategies are needed that can elute and concentrate samples from the environmental sampling tool for direct detection of target organisms while at the field location. All manipulations need to be completed while maintaining integrity of the sample, i.e., aseptically and without cross-contamination of samples. Responders investigating the potential release of a biothreat agent also face the same concerns and, in a bio-terrorism event, rapid detection guides decisions to protect public health and safety.

This research topic aims at development of a novel device for environmental sampling of a large area and direct elution and concentration in the field for detection of target organisms and/or broader delineation of microbial populations with either molecular assays or culture assays.

Project Goals

The goal of this project is to develop a novel sampling device that can efficiently collect microorganisms from a solid surface and to extract and concentrate the organisms from the device and into a vial or tube in the field. The extracted sample will be used to detect organisms with both culture and culture-free assays. Since organisms in healthcare settings are typically found in low numbers, the sampling devices must be efficient at recovering vegetative cells and spores from surfaces and able to sample a large surface area (100 in^2 to 200 in^2 or greater) without drying out. Wipes or sponges that are pre-moistened with a

wetting agent containing a surfactant or disinfectant neutralizer recover organisms better than if dry, therefore the device should be made available pre-moistened and able to maintain stability and shelf life for at least 1 year or, be available dry and able to be pre-moistened easily prior to sampling on-site.

Recommended criteria for the device include: easily operated; packaged as sterile and pre-moistened OR be easily pre-moistened aseptically at the sampling site; the device can be sealed aseptically to prevent contamination; able to easily extract the collected organisms from the sampling device without need for a laboratory (i.e., at the sampling site) into a vial or tube for storage until detection is available; final extraction volume must not exceed 2-3 mL. (if the sample can be concentrated to a smaller volume without losing sensitivity, this would be optimum); effective at collecting and eluting organisms, recovering the same $\log_{10}$ level of organisms known to be present on a surface; and, low cost (<$15 each device).

Phase I Activities and Expected Deliverables

Develop prototype sampling, elution and concentration device.

Test efficiency of recovery by placing known quantities of *Staphylococcus aureus,* and *Acinetobacter baumannii* cells and *Clostridioides difficile* spores (or *Bacillus spp.* Spores, if anaerobe chamber is not available) onto surfaces, then use the device to recover the cells and spores. Efficiency will be determined by a quantitative microbial culture and qPCR, then compared to number of cells and spores placed on surface

Impact

A successful novel sampling and extracting device will enable rapid response during a public health investigation resulting from transmission of infections due to contaminated environmental surfaces, whether from drug resistant bacteria in a healthcare facility or as the result of an intentional release of a bio-threat agent.

This device, coupled with a field deployable rapid detection device, will eliminate the need to ship samples to a laboratory for analysis, thereby allowing for detection of target organisms in hours rather than days. Reduced sample analysis time will enable faster public health decisions, saving lives.

Commercialization Potential

The commercialization potential is high. A successful device may be used for detection of multiple organisms in a variety of field settings, whether in a healthcare setting, a biothreat public health scenario, or a pharmaceutical manufacturing facility requiring environmental monitoring. A successful device could be used for traditional culture detection, as well as for next generation molecular detection. The device would save money and time for rapid detection of organisms by enabling field detection or readying and optimizing samples for laboratory detection methods.

025 Development of a Diagnostic Testing Platform to Assess Antibiotic Activity on Microbial Communities

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

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

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

Background

Antimicrobial susceptibility testing relies on standardized microbiological techniques assessing growth of pure cultures on either solid or liquid media with various concentrations of antibiotics. The inhibition of growth is predictive of treatment success and reported by the clinical laboratory to guide therapy. Although this has been the standard for decades, such testing often fails to estimate treatment outcome when an infection is caused by multiple strains or species of bacteria or yeast (i.e., mixed infection), especially if the infection involves a community of microorganisms growing on a surface (i.e., biofilm). Examples of such infections include lung infections in patients with cystic fibrosis, mixed wound or bone infections, and mixed infections involving implanted prosthetic material. In such infections traditional antibiotic susceptibility testing fails to account for the impact of an antibiotic on overall microbial community. Microbial communities can involve cooperative (or antagonistic) communication between members, recruitment of secondary pathogens, and biofilm matrix effects – all of which can impact inherent drug resistance that is not reflected in traditional susceptibility testing methods and results.

Project Goals

The specific goals of this project are to develop a standardized diagnostic platform for use in a clinical laboratory for taking primary clinical specimens (e.g., sputum, stool) and determining the microbial community-level susceptibility/antibiogram of an infection. The second goal is to construct laboratory-developed test methodologies/models or significantly adapt commercial platforms for use in parallel and in comparative assessments with standard clinical isolate-level antibiotic susceptibility testing (AST) analysis. All should have the potential to be validated for use in the clinical setting for treatment decisions.

Phase I Activities and Expected Deliverables

It is anticipated that such development will require dedicated and highly refined approaches specific to primary specimen and pathogen combinations. The technical merit or feasibility of the proposed methodology should be assessed through initial bench-top (*in vitro*) studies with focus on one such specimen-pathogen combination and associated/community and matrix attributes. These studies should be designed to provide a proof-of-concept, and expected deliverables would include a determination of the efficacy of the approach by monitoring community dynamics in the process as well as testing comparative panels of such pathogens in parallel by standard reference methodologies.

a) Produce data useful for informing clinical treatment decisions

b) Document the *in vitro* kinetics being used as a marker of susceptibility

c) Define medium/matrix composition

d) Define potential host factors that affect microbial growth or antibiotic activity *in vivo*

e) Define metabolites of microbial communities that affect microbial growth or antibiotic activity *in vivo*

f) Establish standard methodologies to arrive at a quantitative measurement of minimum inhibitory concentration

g) Establish back-end detection/verification of target pathogen activity

h) Incorporate appropriate methods for specimen processing.

Impact

This project has the potential to impact antibiotic stewardship and therapy practice using available primary specimens to produce a rapid, more clinically relevant estimation of potential drug efficacy including reduction in potential resistance development. Generation of such a system or model may also identify and highlight the relative disparities that exist with reference-based testing and help redefine clinical practice. The broad use of such a system also may have profound impact on directing future drug-specific design by incorporating such considerations (and associated underlying mechanisms thereof) during the drug development phase.

Commercialization Potential

The commercialization potential of such technology is high with a potential for wide-scale use including patenting of processes, universal enrichment/growth media, matrix inhibitors and/or community parameterization. If the design involves laboratory-developed test protocols, kitting of reagents, developed controls, and/or mock communities, these may also provide additional avenues for commercialization. Development of such tools may be employed as front-end, value-added adaptation for commercial platforms. Regardless, this SBIR has potential to impact other settings involving intellectual property rights extended to preserving microbial community strata formulations for modeling biological interactions.

026 Intradermal Delivery of Human Rabies Vaccine Using Dissolvable Microneedles

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

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

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

Background

Although just a handful of deaths occur each year in North America and Europe, the barriers to access life-saving rabies vaccines are evident by the estimated 59,000 human deaths in the developing world every year. Exposures to rabid animals are frequent worldwide, but cost, remote locations, lack of cold chain, and other cultural and social factors remain obstacles to vaccination in most high-risk rabies regions. With proper post-exposure prophylaxis (PEP) almost all rabies deaths are preventable. The majority of these deaths occur in Africa and Asia where canine rabies remains enzootic and availability of rabies biologics for PEP is limited. New, cost-effective strategies are required to overcome the current challenges in rabies prevention.

Currently, human rabies vaccine is delivered in a 1 ml intramuscular (IM) dose. This necessitates using a needle by a trained professional, bulky packaging, and maintenance of cold-chain. We propose a SBIR topic to deliver human rabies vaccine via the intradermal (ID) route using dissolvable microneedles. Microneedles can be administered directly by the patient eliminating the need for trained medical personnel, needles and sharps disposal, as well as flat packaging. Numerous studies have indicated that intradermal delivery of rabies vaccine is dose sparing and more effective than intramuscular delivery. In addition, the current ACIP-recommended regimen for rabies pre- and post-exposure prophylaxis is complex, requiring multiple boosters over a one-month period. Ensuring multiple boosters is especially difficult to achieve in remote settings where human rabies exposures often occur. Other regimens exist for both IM and ID, further confounding the situation, especially in developing countries where governments are hesitant to approve new vaccines. By simplifying the regimen using a microneedle patch, vaccine delivery will be dose sparing and save lives by reaching more people in need of rabies PEP.

Project Goals

The goal of this project is to develop dissolvable microneedles to deliver human rabies vaccine that can induce protective immunity.

Phase I Activities and Expected Deliverables

1. Formulation of rabies vaccine suitable for dissolvable microneedle delivery
2. Development of a dissolvable microneedle device containing rabies virus vaccine
    i. Selection of microneedle material
    ii. Optimization of micromolding
    iii. In vitro analysis of antigen dose present in the final device

Impact

An intradermal rabies immunization by dissolvable microneedles will not only simplify mass pre-exposure prophylaxis (pediatric vaccination in remote areas such as the Amazon jungle or pre-exposure vaccination of soldiers deployed to rabies endemic countries) but will also potentially simplify regimens and reduce time for post-exposure vaccine administration. Adaptation of microneedle technology to rabies vaccine will simplify the administration of human rabies vaccine currently provided mostly via intramuscular administration and will exclude necessity of trained personnel to perform vaccination. A microneedle patch will eliminate injuries associated with vaccination using sharp needles and will eliminate re-use of needles and potential for spread of blood-borne pathogens. Rabies vaccine dissolvable microneedle administration with a continuous release vaccine formulation, will represent a paradigm shift in rabies pre- and post-exposure prophylaxis, ultimately allowing for one microneedle administration to stimulate adequate immune response in recipients.

Commercialization Potential

Intradermal delivery Human Rabies Vaccine using dissolvable microneedles will generates a novel delivery method for human rabies vaccine allowing for results analysis and to make recommendations for further work toward licensing, IND submission, and manufacturing.

027 Interactive Phone-Based Video Game to Promote Handwashing Behavior Among Children

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

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

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

Background

Hand hygiene is one of the simplest, most effective interventions to limit the spread of communicable disease such as gastrointestinal or respiratory illness. As part of the response to the COVID-19 pandemic, a range of non-pharmaceutical interventions are being promoted as key prevention strategies. This includes frequent handwashing with soap and water and frequent use of hand sanitizers. Engagement in frequent handwashing is being promoted among multiple populations as part of the coronavirus response. Polling conducted over the course of the coronavirus response has indicated that the general public is engaging in handwashing behavior and perceive handwashing to be an effective strategy for coronavirus prevention.

A range of factors can influence whether an individual engages in handwashing. This can include knowledge of the benefits, perceptions of risk for illness, access to supplies or infrastructure to engage in handwashing, norms, and hygiene related habits. Interventions to promote community handwashing behavior have targeted these drivers through social marketing or health communication campaigns, or educational interventions. Several of these interventions have been focused on promoting handwashing behavior among youth and children. Children and youth have been prioritized for interventions aimed at promoting handwashing behavior because children often engage in inadequate hygiene related behaviors and are often in congregate settings where there is potential to spread infection easily. Additionally, if children are educated early about the importance of handwashing, and this behavior becomes a life-long habit, it could result in future health benefits.

To date, however, few interventions focused on promoting handwashing behavior have utilized “gamification” as an approach. Gamification has been used broadly in public health to promote a range of health promotion behaviors in both adults and children. Games can make learning about a health behavior more fun, can keep individuals more engaged with a health promoting behavior, and can allow for behavioral monitoring and feedback that can further reinforce the behavior into routine activities. Games have been used, for example, to promote exercise behavior among children. Games work by going beyond increasing knowledge, and incorporate strategies to incentivize health promotion behavior, provide opportunities for feedback, can allow for monitoring, and can utilize video and animation to provide real-time feedback on behaviors. Developing an innovative, interactive, phone-based game to promote handwashing behavior could be used as an innovative strategy to promote handwashing behavior among children and to help sustain frequent handwashing behavior over the lifespan.

Project Goals

The purpose of this project is to develop an interactive, phone-based game to promote handwashing behavior among children.

Phase I Activities and Expected Deliverables

It is expected that the development of a complete, functional, prototype of the video game would be accomplished during this project period. This would include the game story line, the graphics, the scientific content, and all other functionalities to make the game compelling and fun for the user. As part of the development of the functional prototype, aspects of human-centered design strategies will be used to assess and improve the usability of the game.

Impact

As handwashing is one of the key non-pharmaceutical interventions being promoted during the coronavirus response, it is critical to identify innovative strategies to promote this behavior and to encourage sustained engagement in these behaviors.

The impact of this game could result in increases in handwashing behavior which could result in decreases in infection of not just respiratory illness associated with coronavirus, but also for a wider range of other communicable diseases.

Commercialization Potential

Educational games for children are widely promoted through phone-based app stores and educational games for children are also available through a range of toy companies. As more and more children are using tablets as part of their school-work activities, this educational game could be marketed toward school districts to be included on these tablets and incorporate the game into routine activities children complete on their school tablets. The game could also be marketed toward a range of parent groups, such as PTAs, as an educational tool parents can utilize within the home to promote handwashing behavior among children. As many of the games developed to promote healthy behaviors among children allow for real-time monitoring by an administrator, this functionality would be of interest to parents and educators who can monitor child engagement with the materials as well as monitor their completed handwashing behavior. The game could also be marketed to pediatrician offices which could load it on waiting room tablets allowing children to utilize the game to learn about proper handwashing behavior, and could give pediatricians real-time feedback to follow-up on information learned from the game to provide directed health education to both parents and children about handwashing.

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

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

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

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

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

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

050 Agnostics Computer Vision Solution for Highly Integrated Robotic Platforms

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

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

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

Background

Molecular and serological surveillance for infectious diseases often involves high sample throughput and reproducibility. High volume sample processing is also very frequently associated with a higher end user risk of exposure and human error. Automated solutions significantly reduce exposure and human error, while increasing sample throughput and performance. Fully automated, walk-away (load-and-go) platforms are usually designed to further limit the end user exposure by limiting the hands-on requirements for the initial setup. End user errors can still happen at the load stage when working with highly, or even moderately, integrated solutions due to densely labware-populated setups. Developing an agnostic, vendor cross-over, computer vision approach that could validate the initial labware, reagents and sample setup during runtime, is likely to eliminate human errors in reference and clinical laboratories.

Project Goals

The specific goals of this project include the following:

1. Develop an agnostic deck verification tool for use with robotic platforms by different vendors
2. Develop a cross-over solution for validation of integrated devices in complex automated platforms
3. The solution should be sufficiently portable to be included in a single installer package
4. The solution should be easily scalable to add multiple high definition cameras
5. The solution should have recording capabilities for spinning/moving devices
6. The recording capabilities should be able to record during runtime to monitor run progress
7. The solution should be easily trainable to accommodate newly developed methods

8. The solution should log records per run/process
9. The solution should provide optical volume verification
10. User facial recognition is highly desirable but not indispensable
11. The solution should be Windows compatible (7 or higher)

Phase I Activities and Expected Deliverables

1. Hardware specifications (cameras and accessory drives, if applicable)
2. Schematic representation of the workflow for deck and integrated devices setup validation
3. Specifications for training set for new workflows
4. Schematic diagram of the training module and learning approach used by the solution to incorporate new workflows
5. Minimal requirements for device controller

Impact

This solution is expected to significantly reduce errors during setup/runtime by *de facto* preventing run failures and hardware crashes. As a result, minimal disruption in production environments for molecular and serological testing would be experienced. The deck verification piece expected for this solution should be easily implemented in small automated units, allowing small labs to validate the initial setup and preventing major runtime failures.

Commercialization Potential

This solution will likely have a large spectrum of users including reference and clinical laboratories as well as core facilities.

051 Microfluidics for Genetic and Serological Characterization of hepatitis C virus Infection

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

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

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

Background

Timely identification of incident cases is critical for the detection of hepatitis C virus (HCV) transmission networks. In addition, detection of serological markers for viral hepatitis aids to establish high risk individuals who are often positive for multiple markers. Identification of high-risk individuals and their corresponding contacts improves outbreak investigations, molecular surveillance and patient's linkage to care. However, identification of all necessary serological markers and simultaneous genetic characterization of hepatotropic viruses requires multiple diagnostic tools. Implementation of all these diagnostic tools is time consuming, cumbersome and requires highly trained laboratory personnel. Thus, development of a "universal" platform for both genetic characterization and serological marker detection for viral hepatitis will simplify and improve identification of incident and high-risk cases. CITE-SEQ coupled to amplicon deep sequencing is a viable alternative for simultaneous identification of serological markers and viral characterization.

Advanced molecular characterization of infectious agents often relies on next-generation sequencing (NGS) approaches to accurately obtain DNA fingerprints required to establish genetic relatedness among viral strains. Generation of DNA libraries suitable for NGS involves several lengthy, cumbersome and error-prone lab processes. Often, standard operating procedures (SOPs) are devised for manual library preps, leading to small sample throughput, cross contamination and delay in reporting. Automated solutions for DNA library preps are commercially available. However, such automated approaches are expensive and require expertise to implement custom workflows. Microfluidic chips are an alternative to complex automated laboratory methods without the initial investment required for conventional automated solutions. Microfluidic chips are also small and user friendly allowing easy implementation and requiring minimal training. There are no commercially available microfluidic

chips capable of performing all laboratory steps required to generate DNA libraries suitable for Illumina sequencers, including CITE-SEQ for detection of serological markers. This project aims to develop a microfluidic chip capable of extracting nucleic acids and generating Illumina DNA libraries from clinical samples, suitable for advanced genetic and serological characterization, relying on a CITE-Amplicon SEQ approach for detection of hepatitis C virus infection.

Project Goals

The specific goals of this project include the following:

1. Develop a CITE-SEQ approach for the identification of serological HCV markers (IgM, IgG and core antigen)
2. Develop a microfluidic chip for genetic characterization of HCV using deep amplicon sequencing
3. Develop a microfluidic chip suitable for the HCV CITE-SEQ approach

Phase I Activities and Expected Deliverables

1. An engineering model for the corresponding microfluidic chip(s) is required
2. Draft protocols for the CITE-SEQ approach suitable for microfluidics is required
3. Draft protocol for HCV deep sequencing genetic characterization for microfluidics is required

Impact

Availability of commercial microfluidic solutions for HCV genetic and serological characterization is likely to shorten reporting time and increase sample processing capacity. Additionally, microfluidic approaches significantly reduce risk of exposure and end user error and require minimal training for the operator. As a result, outbreak investigations and molecular surveillance should considerably improve.

Commercialization Potential

Microfluidic approaches for HCV characterization will aid state and reference laboratories conducting outbreak investigations, contributing to a better understanding of transmission networks.

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)

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

Fillable PDF (https://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixH.2.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://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixH.3.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 (AUG 2019)

(a) Definitions. As used in this provision—

Covered telecommunications equipment or services, Critical technology, and Substantial or essential component have the meanings provided in clause 52.204-25, Prohibition on Contracting for Certain Telecommunications and Video Surveillance Services or Equipment.

(b) Prohibition. 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. Contractors are not prohibited 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.

(c) Representation. The Offeror represents that—

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.

(d) Disclosures. If the Offeror has responded affirmatively to the representation in paragraph (c) of this provision, the Offeror shall provide the following information as part of the offer—

(1) All covered telecommunications equipment and services offered (include brand; model number, such as original equipment manufacturer (OEM) number, manufacturer part number, or wholesaler number; and item description, as applicable);

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

(3) For services, the entity providing the covered telecommunications services (include entity name, unique entity identifier, and Commercial and Government Entity (CAGE) code, if known); and

(4) For equipment, 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).

(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 2019)

(a) Definitions. As used in this clause—

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).

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

(b) Prohibition. 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 Federal Acquisition Regulation 4.2104.

(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)