

**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 2020-1

Closing Date: October 23, 2019, 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 23, 2019, 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 to submit research proposals under this Small Business Innovation Research (SBIR) Contract Solicitation. Firms with the capability to conduct research and development (R&D) in any of the health-related topic areas described in [Section 12.0](#), and to commercialize the results of that R&D, are encouraged to participate.

This solicitation contains opportunities to submit a proposal under a variety of different Topics, which are summarized below. Some Topics allow for only a Phase I proposal to be submitted at this time. Some Topics allow for only a Phase II proposal to be submitted, through the ‘Direct to Phase II’ process. Some Topics allow for ‘Fast Track’ proposals, which include both a Phase I proposal and a Phase II proposal. For more information on the three-phase program and 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 019	Yes	No	No	Alternatives to commercially available cell culture insert membranes and manufacturing techniques
NIH/NCI 397	Yes	Yes	No	Manufacturing Innovation for the Production of Cell-Based Cancer Immunotherapies
NIH/NCI 398	Yes	Yes	No	Development of Senolytic Agents for Cancer Treatment
NIH/NCI 399	Yes	Yes	No	Combinatory Treatment Utilizing Radiation to Locally Activate Systemically Delivered Therapeutics
NIH/NCI 400	Yes	Yes	No	Sensing Tools to Measure Biological Response to Radiotherapy
NIH/NCI 401	Yes	Yes	No	Quantitative Biomimetic Phantoms for Cancer Imaging
NIH/NCI 402	Yes	Yes	No	Artificial Intelligence-Aided Imaging for Cancer Prevention, Diagnosis, and Monitoring
NIH/NCI 403	Yes	Yes	No	Spatial Sequencing Technologies with Single Cell Resolution for Cancer Research
NIH/NCI 404	Yes	Yes	No	Subcellular Microscopy and -Omics in Cancer Cell Biology
NIH/NCI 405	Yes	Yes	No	Intra-Tumor Sensing Technologies for Tumor Pharmacotyping
NIH/NCI 406	Yes	Yes	No	Software for Patient Navigation Through the Cancer Care Continuum
NIH/NCI 407	Yes	Yes	No	Cloud-Based Software for the Cancer Research Data Commons

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 408	Yes	Yes	No	Tools and Technologies for Visualizing Multi-Scale Data
NIH/NCI 409	Yes	Yes	No	Software for Automated Analysis of Images for Improved Cancer Health
NIH/NCI 410	Yes	Yes	No	Cancer Clinical Trials Recruitment and Retention Tools for Participant Engagement
NIH/NCI 411	Yes	Yes	No	De-Identification Software Tools for Cancer Imaging Research
NIH/NCI 412	Yes	Yes	No	Software Enabling Data Integration from Wearable Sensors for Cancer Patients
NIH/NHLBI 109	Yes	Yes	Yes	Transcatheter trileaflet tricuspid suture repair system
NIH/NHLBI 110	Yes	Yes	Yes	MRI myocardial biopsy system
NIH/NIAAA 018	No	Yes	Yes	Alcohol Biosensor Development for Continuous Alcohol Consumption Monitoring
NIH/NIAAA 019	Yes	No	No	Data Science Tools for Accelerating Alcohol Research
NIH/NIAID 076	Yes	Yes	No	Co-delivery and Formulation of Adjuvants for HIV Vaccine Development
NIH/NIAID 077	Yes	Yes	No	Particle-based Co-delivery of HIV immunogens as Next-generation HIV Vaccines
NIH/NIAID 078	Yes	Yes	No	Sequence-based Assays to Quantify the Replication-Competent HIV Reservoir
NIH/NIAID 079	Yes	Yes	No	Small Molecule Targeting of HIV RNA
NIH/NIAID 080	Yes	Yes	Yes	Adjuvant Discovery for Vaccines against Infectious or Immune-mediated Diseases
NIH/NIAID 081	Yes	Yes	Yes	Adjuvant Development for Vaccines against Infectious or Immune-mediated Diseases
NIH/NIAID 082	Yes	Yes	Yes	Production of Adjuvants
NIH/NIAID 083	Yes	Yes	Yes	Reagents for Immunologic Analysis of Non-mammalian and Underrepresented Mammalian Models
NIH/NIAID 084	Yes	Yes	No	Antiviral drugs to cure chronic hepatitis B virus infection

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 085	Yes	Yes	No	Broad spectrum antibody against human enteroviruses
NIH/NIAID 086	Yes	Yes	No	Development of rapid fungal diagnostics for select endemic dimorphic fungi
CDC/NCCDPHP 043	Yes	No	No	Objective Measurement of Opioid Withdrawal in Newborns
CDC/NCEH 002	Yes	No	No	Web-Based Platform for Flooding Vulnerability and HealthCare Access
CDC/NCEZID 021	Yes	No	No	Assay to Detect and Quantify E. Coli O157 in Water Samples
CDC/NCEZID 022	Yes	No	No	Device Development for Microbial Surface Sampling Field Extraction and Collection
CDC/NCEZID 023	Yes	No	No	Diagnostic Testing Platform to Assess Antibiotic Communities of Cystic Fibrosis Patients
CDC/NCIRD 034	Yes	No	No	Accelerating Time to Detection of Legionella in Environmental Samples

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

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

2 PROGRAM DESCRIPTION

2.1 Objectives

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

The basic design of the NIH/CDC SBIR program is in accordance with the Small Business Administration (SBA) SBIR Program Policy Directive dated 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 Three Phase Program

The SBIR program consists of three separate phases.

Phase I: Feasibility

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

Phase II: Full R/R&D Effort

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

Phase III: Commercialization stage without SBIR funds

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

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

2.3 Fast Track Proposals (NIH Only)

If a Topic notes that Fast Track proposals will be accepted, a Phase I proposal and a Phase II proposal may be submitted simultaneously. As described in Section 8.2 “Fast Track Proposal Instructions,” a Fast Track submission consists of one complete Phase I proposal and one complete Phase II proposal, separately paginated. The Phase I proposal and Phase II proposal will be separately evaluated as set forth in Section 6.0 “Method of Evaluation.”

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

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

Refer to the table in Section 1.0 “Introduction” and [Section 12.0](#) “Research Topics,” for notation of Topics allowing Fast Track proposals.

2.4 Direct to Phase II Proposals

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 funding sources (not SBIR/STTR Phase I funding) may submit a Phase II only proposal. Direct to Phase II awards allow a SBC 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 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, NIAAA, and NIAID).

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 cohort consisting of up to 24 companies, split amongst current grant and contract SBIR Phase I award recipients throughout the NIH. 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 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 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 from April 5, 2021 to May 25, 2021 with travel to Los Angeles, California for a workshop April 5-8, 2021 and travel to Bethesda, Maryland for a workshop May 24-25, 2021.

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 December 2020 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 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 awarding component selection committee will consider the ability of the proposed I-Corps™ effort to increase the overall success of the Phase I research project. (Specific criteria will be discussed in the notification provided by the Government containing finalized application due dates and cohort participation dates.)

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

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

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

2.6 Grant Opportunity - Phase IIB Competing Renewal Awards (INFORMATION ONLY)

Some NIH Institutes/Centers (ICs) offer Phase II SBIR/STTR awardees the opportunity to apply for Phase IIB Competing Renewal grant awards. Phase II contract awardees are eligible to apply for Phase IIB grants offered by those participating NIH ICs. The Phase II contract must be completed prior to award of a Phase IIB grant, although the Phase II contract need not be completed prior to application. Phase IIB Competing Renewal grant awards are available for those projects that require extraordinary time and effort in the R&D phase and may or may not require FDA approval for the development of such projects, including drugs, devices, vaccines, therapeutics, and medical implants related to the mission of the IC. Some ICs have announced this opportunity through the NIH Guide for Grants and Contracts (see link below), and some are using this Omnibus SBIR/STTR Grant Solicitation. Prospective applicants are **strongly encouraged** to contact NIH staff prior to submitting an application. Additional requirements and instructions (e.g., submission of a letter of intent) are available in the specific IC research topics section and in the specific [IC Program Funding Opportunity Announcements](#).

The following NIH ICs will accept applications for Phase IIB Competing Renewal awards: NIA, NIAAA, NIAID (SBIR only), NICHD (SBIR only and only Competing Renewals of NICHD-supported Phase II awards), NIDA (SBIR only), NIDCD, NIDDK (only Competing Renewals of NIDDK-supported Phase II awards), NEI (SBIR only), NIGMS (SBIR only), NIMH (SBIR only), NCATS (SBIR only and only Competing Renewals of NCATS-supported Phase II awards), and ORIP (SBIR only and only Competing Renewals of ORIP-supported Phase II awards). NCI offers Phase IIB opportunities that focus on the commercialization of SBIR-developed technologies. Contact the NCI SBIR Development Center at 301-594-7709, NCISBIR@mail.nih.gov for additional information. NHLBI offers Phase IIB Competing Renewals that focus on the commercialization of technologies requiring regulatory approval through the NHLBI Phase IIB Bridge Awards and the Phase IIB Small Market Awards: <https://www.nhlbi.nih.gov/grants-and-training/funding-opportunities-and-contacts/small-business->

[program](#) Contact NHLBI nhlbi_sbir@mail.nih.gov for additional information. NINDS accepts Phase IIB SBIR/STTR Competing Renewal applications through specific opportunities that focus on the commercialization of SBIR and STTR developed technologies. These opportunities can be found on the NINDS Funding Opportunities webpage: <https://www.ninds.nih.gov/Funding/Find-Funding-Opportunities> Contact Stephanie Fertig, M.B.A., at fertigs@ninds.nih.gov for additional information.

2.7 Awarding Components

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

National Institutes of Health (NIH) Components:

National Center for Advancing Translational Sciences (NCATS)

National Cancer Institute (NCI)

National Heart, Lung, and Blood Institute (NHLBI)

National Institute on Alcohol Abuse and Alcoholism (NIAAA)

National Institute of Allergy and Infectious Diseases (NIAID)

Centers for Disease Control and Prevention (CDC) Components:

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

National Center for Environmental Health (NCEH)

National Center for Emerging Zoonotic and Infectious Diseases (NCEZID)

National Center for Immunization and Respiratory Diseases (NCIRD)

3 DEFINITIONS

3.1 General Definitions

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

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

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

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

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

Awardee. The organizational entity receiving an SBIR Phase I, Phase II, or Phase III award.

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

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

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

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

Covered Small Business Concern. A small business concern that:

- (1) Was not majority-owned by multiple venture capital operating companies (VCOs), 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 Phase III award that an awardee delivers to the Government during or upon completion of a Federally-funded project, and to which the Government receives a license.

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

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

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

(a) *Ownership and control.*

(1) An SBIR awardee must:

- (i) Be a concern which is more than 50% directly owned and controlled by one or more individuals (who are citizens or permanent resident aliens of the United States), other small business concerns (each of which is more than 50% directly owned and controlled by individuals who are citizens or permanent resident aliens of the United States), an Indian tribe, ANC (Alaska Native Corporation) or NHO (Native Hawaiian Organization) (or a wholly owned business entity of such tribe, ANC or NHO), 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 contract costs.

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

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

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

4.3 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.

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.

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. If the cost of the proposed technical assistance provider is determined to be appropriate and allowable, this cost will be in addition to the base SBIR award budget established in the appropriate Topic description in [Section 12](#). Please note, if funds are requested to utilize your own technical assistance vendor and an award is made, the awardee is not eligible to apply for the NIH-provided technical assistance program for the phase awarded.

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

To provide small business concerns engaged in SBIR or STTR projects with technical 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 be submitted no more frequently than on a monthly basis unless otherwise authorized by the contracting officer.

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

4.18 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 twenty (20) years. After expiration of the 20- 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 States Department of Agriculture (USDA), the Contractor shall register with the Secretary of Agriculture of the United States in accordance with 7 U.S.C. 2136 and 9 CFR 2.25 through 2.28. The Contractor shall furnish evidence of the registration to the Contracting Officer.
- b. The Contractor shall acquire vertebrate animals used in research from a dealer licensed by the Secretary of Agriculture under 7 U.S.C. 2133 and 9 CFR 2.1 2.11, or from a source that is exempt from licensing under those sections.
- c. The Contractor agrees that the care, use, and intended use of any live vertebrate animals in the performance of this contract shall conform with the Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals (PHS Policy), the current Animal Welfare Assurance (Assurance), the Guide for the Care and Use of Laboratory Animals (National Academy Press, Washington, DC) and the pertinent laws and regulations of the United States Department of Agriculture (see 7 U.S.C. 2131 et seq. and 9 CFR subchapter A, Parts 1-4). In case of conflict between standards, the more stringent standard shall govern.
- d. If at any time during performance of this contract, the Contracting Officer determines, in consultation with the Office of Laboratory Animal Welfare (OLAW), National Institutes of Health (NIH), that the Contractor is not in compliance with any of the requirements and standards stated in paragraphs (a) through (c) above, the Contracting Officer may immediately suspend, in whole or in part, work and further payments under this contract until the Contractor corrects the noncompliance. Notice of the suspension may be communicated by telephone and confirmed in writing. If the Contractor fails to complete corrective action within the period of time designated in the Contracting Officer's written notice of suspension, the Contracting Officer may, in consultation with OLAW, NIH, terminate this contract in whole or in part, and the Contractor's name may be removed from the list of those contractors with Animal Welfare Assurances.

Note: The Contractor may request registration of its facility and a current listing of licensed dealers from the Regional Office of the Animal and Plant Health Inspection Service (APHIS), USDA, for the region in which its research facility is located. The location of the appropriate APHIS Regional Office, as well as information concerning this program may be obtained by contacting the Animal Care Staff, USDA/APHIS, 4700 River Road, Riverdale, Maryland 20737 (Email ace@aphis.usda.gov; Web site: (<http://www.aphis.usda.gov/wps/portal/aphis/ourfocus/animalwelfare>). (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 twenty years from the date of award unless, subject to paragraph (b) (3) of this section, the agency obtains permission to disclose such SBIR technical data from the awardee or SBIR applicant. Agencies are released from obligation to protect SBIR data upon expiration of the protection period except that any such data that is also protected and referenced under a subsequent SBIR award must remain protected through the protection period of that subsequent SBIR award. For example, if a Phase III award is issued within or after the Phase II data rights protection period and the Phase III award refers to and protects data developed and protected under the Phase II award, then that data must continue to be protected through the Phase III protection period. Agencies have discretion to adopt a protection period longer than twenty years. The Government retains a royalty-free license for Government use of any technical data delivered under an SBIR award, whether patented or not. This section does not apply to program evaluation.
- (3) SBIR technical data rights apply to all SBIR awards, including subcontracts to such awards, that fall within the statutory definition of Phase I, II, or III of the SBIR Program, as described in section 4 of the SBIR Policy Directive. The scope and extent of the SBIR technical data rights applicable to Federally-funded Phase III awards is identical to the SBIR data rights applicable to Phases I and II SBIR awards. The data rights protection period lapses only:
 - (i) Upon expiration of the protection period applicable to the SBIR award; or
 - (ii) By agreement between the awardee and the agency.

5.13 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 2019, Executive Schedule, Level II of the Federal Executive Pay Scale is \$192,300.

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.

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/oe_offices/olaw.htm
- Biohazards/Select Agents/Recombinant DNA <http://grants.nih.gov/grants/guide/notice-files/not95-209.html>
- Dual Use Research of Concern: <http://phe.gov/s3/dualuse/Documents/oversight-durc.pdf>

For NIH Awarding Components:

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

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

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

6.2 Award Decisions

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

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

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

6.3 Phase I Technical Evaluation Criteria

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

FACTORS FOR PHASE I PROPOSALS	WEIGHT
1. The soundness and technical merit of the proposed approach. <ul style="list-style-type: none"> a. Identification of clear, measurable goals (<i>i.e.</i>, milestones) that have a reasonable chance of meeting the topic objective in Phase I. b. Demonstration of a Strong Scientific Premise for the Technical Proposal. (<i>I.e.</i>, Sufficiency of proposed strategy to ensure a robust and unbiased approach, as 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 <ul style="list-style-type: none"> a. Identification of clear, measurable goals (<i>i.e.</i>, milestones) that have a reasonable chance of meeting the topic objective in Phase II b. Demonstration of a Strong Scientific Premise for the Technical Proposal. (<i>I.e.</i>, Sufficiency of proposed strategy to ensure a robust and unbiased approach, as appropriate for the work proposed. Adequacy of proposed plan to address relevant biological variables, including sex, for studies in vertebrate animals and/or human subjects.) c. For Direct to Phase II only: Demonstrated feasibility of the methodology or technology equivalent to meeting Phase I-level objectives, providing a solid foundation for the proposed Phase II activity. 	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 III 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 **August 27, 2019**. 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 7, 2019** 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://attendee.gotowebinar.com/register/4384275519409493762>. Following registration, a confirmation e-mail will be sent containing information about joining the webinar.

Presentation material from this webinar shall be posted on FedBizOpps and the NIH [SBIR/STTR webpage](#) following its completion.

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

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

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

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. 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/sbirsttr/home/howto>. Offerors may also reference Frequently Asked Questions regarding online submissions at <https://ecps.nih.gov/sbirsttr/home/faq>.
1. Be advised that registration is required to submit a proposal into eCPS and registration may take several business days to process.
 2. The proposal must be uploaded in 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. For NIH proposals, use of the [NIH Biosketch format](#) is recommended, though not required.
- 9) **Subcontractors/Consultants.** Involvement of a university or other subcontractors or consultants in the project may be appropriate and is permitted. If such involvement is intended, it should be described in detail, identified in the cost proposal, and supported by appropriate letters from each individual confirming his/her role in the project. These letters must be included within the Technical Proposal. Supporting budget documentation may be placed in the Business Proposal; however, at the NIH, nothing in the Business Proposal will be considered during Technical Evaluation.
- 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; or, Summary of the 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. Use of the [NIH Biosketch format](#) is recommended, though not required.
- 5) **Subcontractors/Consultants**. Describe in detail any involvement of subcontractors or consultants, and provide resumes for all key subcontractor staff. For NIH proposals, use of the [NIH Biosketch format](#) is recommended, though not required. Also, include letters of commitment with proposed subcontractors and consultants, confirming his/her role in the project, the extent of involvement and hourly/daily rate. These letters must be included within the Technical Proposal. Supporting budget documentation may be placed in the Business Proposal; however, at the NIH, nothing in the Business Proposal will be considered during Technical Evaluation.
- 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 Phase III and begin the revenue stream. Plans for this financing stage may be demonstrated in one or more of the following ways:
 - i) Letter of commitment of funding.
 - ii) Letter of intent or evidence of negotiations to provide funding, should the Phase II project be successful and the market need still exist.
 - iii) Letter of support for the project and/or some in-kind commitment, e.g., to test or evaluate the innovation.
 - iv) Specific steps you are going to take to secure Phase III funding.
 - f) **Production and Marketing Plan.** Describe how the production of your product/service will occur (e.g., in-house manufacturing, contract manufacturing). Describe the steps you will take to market and sell your product/service. For example, explain plans for licensing, internet sales, etc.
 - g) **Revenue Stream.** Explain how you plan to generate a revenue stream for your company should this project be a success. Examples of revenue stream generation include, but are not limited to, manufacture and direct

sales, sales through value added resellers or other distributors, joint venture, licensing, service. Describe how your staffing will change to meet your revenue expectations.

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

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 seq.) and other Federal statutes and regulations relating to animals. These documents are available from the Office of Laboratory Animal Welfare, National Institutes of Health, Bethesda, MD 20892, (301) 496-7163, e-mail: olaw@mail.nih.gov.

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

8.11 Dual Use Research of Concern

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

- a. Identification of the agents or toxins subject to the DURC policy:
 - Avian influenza virus (highly pathogenic)
 - *Bacillus anthracis*
 - Botulinum neurotoxin
 - *Burkholderia pseudomallei*
 - Ebola virus
 - Foot-and-mouth disease virus
 - *Francisella tularensis*
 - Marburg virus
 - Reconstructed 1918 influenza virus
 - Rinderpest virus
 - Toxin-producing strains of *Clostridium botulinum*
 - Variola major virus
 - Variola minor virus
 - *Yersinia pestis*
- b. A description of the categories of experiments in which the identified agents or toxins produces or aims to produce or can be reasonably anticipated to produce one or more of the effects identified in Section 6 of the DURC policy.
- c. For projects involving any of the agents listed in the DURC policy and that involve or are anticipated to involve any of the categories of experiments listed in the DURC policy, an indication of whether or not the project meets the definition of “dual use research of concern” in Section 4C of the policy.
- d. For projects meeting the definition of “dual use research of concern,” a draft risk mitigation plan.
- e. Certification that the offeror is or will be in compliance with all aspects of the DURC policy prior to use of pertinent agents or toxins.

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

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

8.12 Human Subjects and Clinical Trials Information Form

All proposal submissions must include Appendix H.2 – Human Subjects and Clinical Information Form.

Attachments must also be included if applicable, based on the nature of your project.

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

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

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

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

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

8.12.1 Human Specimens and/or Data

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

8.12.2 Human Subjects Research with an Exemption from Federal Regulations

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

8.12.3 Protection of Human Subjects

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

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

- Offerors may consult with OHRP only for general advice or guidance concerning either regulatory requirements or ethical issues pertaining to research involving human subjects. ONLY the contracting officer may offer information concerning a solicitation.
- The offeror's proposal shall document that it has an approved or active FWA from OHRP, related to the designated IRB reviewing and overseeing the research. When possible the offeror shall also certify the IRB has reviewed and approved the research. If the offeror cannot make this certification at the time of proposal submission, its proposal must include an explanation. Never conduct research covered by 45 CFR part 46 prior to receiving certification of the research's review and approval by the IRB. If the offeror does not have an active FWA from OHRP, the offeror shall take all necessary steps to obtain an FWA prior to the deadline for proposal submission. If the offeror cannot obtain an FWA before the proposal submission date, the proposal shall indicate the steps/actions the offeror will take to obtain OHRP approval prior to human subjects work beginning. Upon obtaining FWA approval, submit the approval notice to the Contracting Officer. (End of provision)

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

B. Instructions to Offerors Regarding Protection of Human Subjects

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

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

- a. Risks to the subjects
 - Human Subjects Involvement, Characteristics, and Design
 - Briefly describe the overall study design in response to the solicitation.
 - Describe the subject population(s) to be included in the study; the procedures for assignment to a study group, if relevant; and the anticipated numbers of subjects for each study group.
 - List any collaborating sites where human subjects research will be performed, and describe the role of those sites and collaborating investigators in performing the proposed research.
 - Study Procedures, Materials, and Potential Risks
 - Describe all planned research procedures (interventions and interactions) involving study subjects; how research material, including biospecimens, data, and/or records, will be obtained; and whether any private identifiable information will be collected in the proposed research project.
 - For studies that will include the use of previously collected biospecimens, data or records, describe the source of these materials, whether these can be linked with living individuals, and who will be able to link the materials.
 - Describe all the potential risks to subjects associated with each study intervention, procedure or interaction, including physical, psychological, social, cultural, financial, and legal risks; risks to privacy and/or confidentiality; or other risks. Discuss the risk level and the likely impact to subjects.
 - Where appropriate, describe alternative treatments and procedures, including their risks and potential benefits. When alternative treatments or procedures are possible, make the rationale for the proposed approach clear.
- b. Adequacy of Protection Against Risks
 - Recruitment and Informed Consent:
 - Describe plans for the recruitment of subjects and the procedures for obtaining informed consent. Include a description of the circumstances under which consent will be sought and obtained, who will seek it, the nature of the information to be provided to prospective subjects, and the method of documenting consent. When appropriate, describe how potential adult subjects' capacity to consent will be determined and the plans for obtaining consent from a legally authorized representative for adult subjects not able to consent. The informed consent document

for the Contractor and any collaborating sites should be submitted only if requested elsewhere in the solicitation. Be aware that an IRB-approved informed consent document for the Contractor and any participating collaborative sites must be provided to the Government prior to patient accrual or participant enrollment.

- For research involving children: If the proposed studies will include children, describe the process for meeting HHS regulatory requirements for parental permission and child assent (45 CFR 46.408). See the HHS page on Research with Children FAQs and the NIH page on Requirements for Child Assent and Parent/Guardian Permission.
- If a waiver of some or all of the elements of informed consent will be sought, provide justification for the waiver.
- Protection Against Risk:
 - Describe the procedures for protecting against or minimizing potential risks, including risks to confidentiality, and assess their likely effectiveness.
 - Discuss provisions for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects where appropriate.
 - In studies that involve interventions, describe the provisions for data and safety monitoring of the research to ensure the safety of subjects.
- **Vulnerable Subjects, if relevant to your study** – Explain the rationale for the involvement of special vulnerable populations, such as fetuses, neonates, pregnant women, children, prisoners, institutionalized individuals, or others who may be considered vulnerable populations. 'Prisoners' includes all subjects involuntarily incarcerated (for example, in detention centers).
 - Pregnant Women, Fetuses, and Neonates or Children - If the study involves vulnerable subjects subject to additional protections under Subparts B and D (pregnant women, fetuses, and neonates or children), provide a clear description of the risk level and additional protections necessary to meet the HHS regulatory requirements.
 - HHS' Subpart B - Additional Protections for Pregnant Women, Fetuses, and Neonates
 - HHS' Subpart D - Additional Protections for Children
 - OHRP Guidance on Subpart D Special Protections for Children as Research Subjects and the HHS 407 Review Process
- c. Potential Benefits of the Proposed Research to the Subjects and Others
 - Discuss the potential benefits of the research to the subjects and others.
 - Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to subjects and others.
 - Describe treatments and procedures that are alternatives to those provided to the participants by the proposed research, where appropriate.
 - Note: Financial compensation of subjects should not be presented as a benefit of participation in research.
- d. Importance of the Knowledge to be Gained
 - Discuss the importance of the knowledge gained or to be gained as a result of the proposed research.
 - Discuss why the risks to subjects are reasonable in relation to the importance of the knowledge that may reasonably be expected to result.
 - Note: If a test article (investigational new drug, device, or biologic) is involved, name the test article and state whether the 30-day interval between submission of offeror's certification to the Food and Drug Administration (FDA) and its response has elapsed or has been waived and/or whether the FDA has withheld or restricted use of the test article.

Collaborating Site(s)

When research involving human subjects will take place at collaborating site(s) or other performance site(s), the offeror must provide in this section of its proposal a list of the collaborating sites and their assurance numbers. Further, if you are awarded a contract, you must obtain in writing, and keep on file, an assurance from each site that the previous points have been

adequately addressed at a level of attention that is at least as high as that documented at your organization. Site(s) added after an award is made must also adhere to the above requirements.

8.12.4 Required Education in the Protection of Human Research Participants

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

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

- (1) a list of the names of the principal investigator and any other individuals proposed under the contract who are responsible for the design and/or conduct of the research;
- (2) the title of the education program completed (or to be completed prior to the award of the contract) for each named personnel;
- (3) a one sentence description of the program(s) listed in (2) above.

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

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

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

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

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

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

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

Inclusion of Women and Minorities in Research Involving Human Subjects

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

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

Information Required for ALL Clinical Research Proposals

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

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

The proposal must include the following information:

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

NOTE : *For all proposals, complete the Inclusion Enrollment Report, and use ethnic and racial categories, in accordance with the Office of Management and Budget (OMB) Directive No. 15, which may be found at :*
http://www.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 Inclusion Of Individuals Across The Lifespan As Participants In Research Involving Human Subjects

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

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

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

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

8.14 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.

8.15 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)	1-3	Scientific and Technical Merit Review: February-April 2020 Anticipated Award Date: July-September 2020
National Institutes of Health (NIH) National Cancer Institute (NCI)	42-70	Scientific and Technical Merit Review: January-March 2020 Anticipated Award Date: July - August 2020
National Institutes of Health (NIH) National Heart, Lung, and Blood Institute (NHLBI)	4	Scientific and Technical Merit Review: February-April 2020 Anticipated Award Date: July-September 2020
National Institutes of Health (NIH) National Institute on Alcohol Abuse and Alcoholism (NIAAA)	2-5	Scientific and Technical Merit Review: March-May 2020 Anticipated Award Date: September 2020
National Institutes of Health (NIH) National Institute of Allergy and Infectious Diseases (NIAID)	19-34	Scientific and Technical Merit Review: March 2020 Anticipated Award Date: August 2020
Center for Disease Control and Prevention (CDC) National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP)	1	Scientific and Technical Merit Review: May-June 2020 Anticipated Award Date: August 2020
Centers for Disease Control and Prevention (CDC) National Center for Environmental Health (NCEH)	1	Scientific and Technical Merit Review: May-June 2020 Anticipated Award Date: August 2020
Centers for Disease Control and Prevention (CDC) National Center for Emerging Zoonotic and Infectious Diseases (NCEZID)	3-6	Scientific and Technical Merit Review: May-June 2020 Anticipated Award Date: August 2020
Center for Disease Control and Prevention (CDC) National Center for Immunization and Respiratory Diseases (NCIRD)	1-2	Scientific and Technical Merit Review: May-June 2020 Anticipated Award Date: August 2020

10 CONTRACTING OFFICE 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)

Jessica Adams

Contracting Specialist

NIDA Office of Acquisition

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NATIONAL CANCER INSTITUTE (NCI)

Brittany Gibau

Contracts Analyst

Office of Acquisitions, OM, NCI (Contractor)

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NATIONAL HEART, LUNG, AND BLOOD INSTITUTE (NHLBI)

Kristi Cooper

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NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM (NIAAA)

Jeremy White

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NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES (NIAID)

Charles H. Jackson, Jr.

Contracting Officer

Office of Acquisitions, DEA, NIAID

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Email: Charles.Jackson@nih.gov

CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

For general administrative SBIR program questions, contact:

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

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

NATIONAL CENTER FOR CHRONIC DISEASE AND HEALTH PROMOTION (NCCDPHP)

Jerry Outley
Contracting Officer
Centers for Disease Control and Prevention
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E-mail: Jmo4@cdc.gov

NATIONAL CENTER FOR EMERGING ZOOBOTIC AND INFECTIOUS DISEASES (NCEZID)

Priscilla Turner
Contracting Officer
Centers for Disease Control and Prevention
Office of Financial Resources
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Fax: (770) 488-2024
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NATIONAL CENTER FOR ENVIRONMENTAL HEALTH (NCEH)

Dale Bish
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E-mail: uwo8@cdc.gov

NATIONAL CENTER FOR IMMUNIZATION AND RESPIRATORY DISEASES (NCIRD)

Pellumbeshe Hoxhaj
Contracting Officer
Centers for Disease Control and Prevention

Office of Financial Resources
Office of Acquisition Services
Phone: (770) 488-2805
Fax: (770) 488-2847
E-mail: KFX2@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://nmlm.gov/> or contact the Office of Communication and Public Liaison at publicinfo@nlm.nih.gov, (301) 496-6308.

Other sources that provide technology search and/or document services include the organizations listed below. They should be contacted directly for service and cost information.

National Technical Information Service

1-800-553-6847

<http://www.ntis.gov>

National Technology Transfer Center

12 COMPONENT INSTRUCTIONS AND TECHNICAL TOPIC DESCRIPTIONS

NATIONAL INSTITUTES OF HEALTH

NATIONAL 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:

019 Alternatives to commercially available cell culture insert membranes and manufacturing techniques

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

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

Number of anticipated awards: 1-3

Budget (total costs, per award): Phase I: \$225,000 for 9 months; Phase II: \$1,500,000 for 2 years

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

Phase II information is provided only for informational purposes to assist Phase I offerors with their long-term strategic planning.

Summary

There has been an increased focus in the life sciences industry on the use of more complex 3D cellular and tissue models to help provide physiologically relevant platforms to be used in in-vitro drug testing. Nearly all high throughput in-vitro drug testing experiments utilize multi-well microtiter plates to act as a vessel where individual reactions between the biological model and the sample under test occur. The use of these more complex 3D cellular models has driven the use of more complex microtiter plates, namely cell culture insert-plates (CCIP) with permeable membranes.

There are several factors that make these CCIPs suitable for use in the creation of complex cellular models, including the ability to co-culture cells with or without cell-to-cell contact, allowing for either apical or basolateral feeding to promote cellular metabolic activities, and provide an anchorage point which is typically required for most mammalian cells to remain viable. All these factors are needed to support cell proliferation and function, as well as formation of complex tissues, making the choice of membrane available for use in CCIPs a critical one towards the production of a physiologically relevant tissue model. The current membranes used in CCIPs are made using a variety of materials with options in pore size, coatings and surface treatments that can be selected depending upon the type of cell model to be produced.

Most of these models incorporate the use of biomaterials to be used as scaffolds for the cells to be functional and create a new tissue. Many of the biomaterials used are naturally occurring and readily available such as collagen, alginate, chitosan and others. In many cases, these biomaterials are present in the extracellular matrix (ECM) produced by cells, so their use helps to provide a natural environment for the cells until they are healthy and producing ECM of their own.

Aside from the biocompatibility of these scaffolding biomaterials, another factor is controlled biodegradability. This rate of biodegradation is a key factor for certain tissue model types where an initial scaffold is necessary to promote structural

integrity, cellular anchorage, viability and proliferation but where over time the desire is for the scaffold to degrade and be replaced by naturally produced ECM and promote cell to cell interaction in co-culture models.

The need for biodegradation of certain tissue models presents an inherent challenge to commercially available CCIPs that for all their advantages have one key limitation: there are none available on the market that have a biodegradable membrane. To overcome this limitation researchers at NIH have developed a technique that utilizes a biocompatible adhesive to attach an electrospun biodegradable poly(lactic-co-glycolic acid) (PLGA) membrane to the bottom of a cell culture insert. The production of these parts has become a standard practice to develop several tissue types, but it has limitations in that the process is laborious, time consuming and not scalable beyond a 24-well plate density.

Topic Goals

The goal of this project is to identify potential new biodegradable membranes that can be used to create CCIPs. Equally important is to identify manufacturing techniques that allow for the attachment of these custom membranes to CCIPs in a reproducible and cost-effective fashion without toxic adhesives or other contaminants in scalable well density formats (6, 12, 24, 96+).

The optimal outcome would be a commercially available off-the-shelf 96 well CCIP that utilizes a biodegradable membrane. The availability of such a plate would increase the capabilities of groups conducting research that use CCIPs by potentially increasing the overall quantity, quality and viability of complex cellular constructs. Increasing the well density up to 96 wells would also push closer to true high throughput screening for groups using advanced cell models for in-vitro drug discovery.

Phase I Activities and Expected Deliverables

Phase I proposals must specify clear, appropriate, measurable goals (milestones) to be achieved. Phase I activities and deliverables may include the following:

- Develop a prototype CCIP that has the following features:
 - Adheres as closely as possible to current ANSI/SLAS Microplate Standards
 - ANSI/SLAS 1-2004 (R2012) Microplates – Footprint Dimensions (formerly ANSI/SBS 1-2004)
 - ANSI/SLAS 2-2004 (R2012) Microplates – Height Dimensions (formerly ANSI/SBS 2-2004)
 - ANSI/SLAS 3-2004 (R2012) Microplates – Bottom Outside Flange Dimensions (formerly ANSI/SBS 3-2004)
 - ANSI/SLAS 4-2004 (R2012) Microplates – Well Positions (formerly ANSI/SBS 4-2004)
 - Utilizes membranes that have the following properties:
 - Biocompatibility with tissue culture environments
 - Biodegradability within a time period between 2-6 weeks
 - Suitable for cellular health and function for long term experiments (1+ month)
 - Have a thickness of <10 μm
 - Have a pore size <1 μm
 - Ability to increase cell attachment without the need for additional coatings
 - Incorporates a ridge or a cap on the underside of the insert such that it extends below the bottom of the membrane and ideally matches the inner diameter of the well wall. This in effect creates an additional well on the underside of the insert that provides greater structural integrity for three-dimensional tissues added to that portion of the insert.
 - This ridge or cap should extend no greater than 1mm from the bottom of the membrane layer.

- This ridge or cap should match the inner diameter of the well wall as closely as possible to maximize the membrane surface area available for cell placement on the underside of the plate.
 - Utilizes manufacturing techniques and materials that do not introduce artifacts when undergoing standard high throughput screening measurements such as fluorescent microscopy.
- Has at a minimum a 6 well density as a proof of concept.
- Identify a tissue model to use as a standard to validate the functionality of the produced part.
 - This model should incorporate standard fluorescent labels such as DAPI, GFP, mCherry or others to determine if any of the materials used introduce a measurement artifact.
 - We have encountered certain adhesives that are biocompatible, although when introduced to a measurement system such as fluorescent microscopy the adhesive itself auto-fluoresces at the same emission wavelength as a cellular label such as GFP. This introduces a high degree of background signal that makes quantification of cellular features difficult if not impossible. This should be taken into consideration with regards to the identification of a tissue model to act as a means of validation.
- Cost estimates to manufacture a device 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 plate that meets the Phase I specifications with a 96 well density as a minimum.
 - This requires all of the necessary tooling and infrastructure necessary to manufacture the plate.
- Provide a test plan to evaluate the Phase I validated tissue model in the 96 well density plate.
 - Provide NCATS with all data from each executed test to properly evaluate the model.
- Develop a robust manufacturing plan for the plate, using off the shelf OEM components where possible to minimize expense.
- 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-19-047.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.

397 Manufacturing Innovation for the Production of Cell-Based Cancer Immunotherapies

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

Cancer immunotherapy is a therapeutic approach that directs a patient's own immune system to eradicate their tumor cells. Past and current NCI investments in adoptive T cells, CAR-T cells, NK cells, and other cell-based cancer immunotherapies

have resulted in the translation of many lab-specific approaches into early clinical trials. Importantly, reproducible and robust production methods are critical to ensure that advances in basic research result in successful translation of cell-based therapies. Clinical development of such therapies requires multi-center, randomized clinical trials that must be supported with high quality, consistent, and reproducible cell-based products. Patient-specific autologous or allogeneic lots must be adequately characterized to ensure that similar products are given to all patients. For non-patient specific cell-based therapies, large-scale and reproducible manufacturing technologies are needed to produce high-quality products with uniform identity and potency. Current limitations in cell manufacturing can increase both the cost and time required to bring a therapy to market and can result in missed opportunities to evaluate promising new cell-based therapies. Product failures can be attributed to poor product design and characterization, as well as inadequate scale-up and manufacturing processes; therefore, further investments are needed to develop state-of-the art manufacturing technologies and processes to advance cell-based cancer immunotherapies at the commercial-scale. Effective use of science and engineering principles during the early development phase of a cell-based therapy can improve both the efficiency and reliability of the manufacturing process and the quality of the final product. Moreover, it is anticipated that standardized approaches to manufacturing, process analytics, release testing, and product characterization will result in more rapid, cost-effective product development and a higher level of regulatory success. Achieving the desired level of standardization for current and future cell-based cancer immunotherapy products will require both pragmatic research to establish consistent manufacturing processes, as well as the development of new innovations and technologies.

Project Goals

The overall goal of this contract topic is to facilitate the development of innovative methods and technologies capable of improving and modernizing product manufacturing processes for cell-based cancer immunotherapies. This includes the use of autologous, allogeneic, or pluripotent cells. Offerors submitting proposals under this solicitation are strongly encouraged to establish collaborative relationships with clinical product development companies focused on the development of specific cell-based products. In all cases, it is expected that offerors will demonstrate the utility of their innovation(s) in the context of at least one cell-based product, which is representative of a particular class of cell-based cancer immunotherapies.

Examples of manufacturing innovations/advancements might include, but are not limited to:

- Automated closed systems for cell separation, genetic modification, differentiation, and/or expansion;
- Low-cost, high-efficiency methods for genetic modification to support cell engineering;
- Standardized assays and/or surrogates to evaluate cell attributes that ensure lot-to-lot consistency in terms of phenotype, functionality, quality, and potency;
- Real-time, non-destructive test methods with sensors and/or imaging technologies to assess critical quality attributes (e.g., contamination); and/or
- Process analytics capable of feedback control in response to real-time changes in critical attributes of the cell product.

It is expected that Phase I proposals will focus on novel inventions related to innovations or improvements in cell manufacturing processes, including in-line or on-line (i.e., continuous) process analytics to support product consistency and safety, as well as GMP production of a particular class of cell therapies. Phase II proposals should demonstrate the scalability and validation of the production platform or process improvements developed in Phase I. Engineering and process solutions must be capable of regulatory compliance with FDA Guidelines. The long-term goal of this initiative is to provide the tools necessary for efficient, high-quality manufacturing of novel products in the emerging field of cell-based cancer immunotherapies.

Phase I Activities and Deliverables

- Develop a device/technology/process to support commercially-relevant manufacturing advancements or improvements for the production of a specific class of cell-based cancer immunotherapies (e.g., CAR-T cells, adoptive T-cells, NK cells)
- Establish defined specifications, assays and/or metrics to interpret scientific data supporting the feasibility of the device/technology/process, with respect to reproducible product manufacturing, process analytics, and/or process controls

- Demonstrate the suitability of the device/technology/process to improve relevant manufacturing metrics (e.g., product uniformity, quality, efficiency, cost-effectiveness) for at least one cell-based product, which is representative of a particular class of cell-based cancer immunotherapies
- Provide proof of collaboration or partnership with an entity that is developing a representative cell-based therapeutic agent OR otherwise demonstrate access to a representative cell-based therapeutic agent through other means (e.g., internal drug development program), that can be used for validation of the device/technology/process
- Demonstrate pilot-scale beta-testing of the production process to demonstrate reproducible performance within appropriate specifications for identity, purity, potency, and/or other relevant metric for the chosen cell-based immunotherapy product

Phase II Activities and Deliverables

- Generate scientific data demonstrating the proposed scalability (e.g. scale-up, scale-out, point-of-use) of the production platform, process analytics and/or process controls
- Develop an at-scale prototype of the device/technology/process with detailed specifications for hardware/software that supports the production platform or process analytics/process controls improvements
- Validate the production innovation and/or process improvements, including standards for calibrating any novel process analytics or process controls that monitor production

398 Development of Senolytic Agents for Cancer Treatment

Fast track proposals **will** be accepted.

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

Number of anticipated awards: 3-4

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

Age is a well-recognized risk factor for cancer development, and older patients pose a growing healthcare challenge since they are prone to developing more aggressive and therapy-resistant tumors. A key biological contributor to aging and age-related diseases is cellular senescence - a complex state characterized by not only its role in wound healing and tumor suppressive function via stress-induced replicative arrest, but also in driving neoplastic transformation and tumor aggressiveness downstream of its anti-apoptotic effect and expression/secretion of wide-ranging pro-tumorigenic cytokines, growth factors, and matrix-degrading enzymes. Aging tissues accumulate senescent cells, and the *in vivo* selective elimination of spontaneously emerging, age-associated senescent cells has been documented to delay tumor formation and deterioration of cardiac, renal, and adipose tissue function. Furthermore, senescence is induced by a range of cancer therapies, including radiation, chemotherapy, and several targeted therapies. In certain cancer types, this therapy-induced senescence (TIS) promotes invasive and metastatic phenotypes. Eliminating TIS cells has been reported to reduce many side effects of cancer drugs, including bone marrow suppression, cardiac dysfunction, fatigue, and also to reduce cancer recurrence. For research purposes, several genetically encoded methods to eliminate senescent cells have been developed and have proved critical in understanding the biology of senescence. More recently, attention has turned to the development of pharmacologic agents that selectively kill senescent cells (i.e., senolytic agents). A variety of agents have been reported to have senolytic activity and have demonstrated promising results in animal models.

Project Goals

The purpose of this contract topic is to support the pre-clinical development of senolytic agents for use in neoadjuvant and/or adjuvant/combination cancer therapy. Projects supported under this contract topic should further the pre-clinical development of senolytic agent(s). To apply for this topic, offerors should:

- Identify a molecular target(s) and provide a clear rationale for how the proposed senolytic agent, or combination, will induce selective elimination of either spontaneously emerging or therapy-induced senescent cells, which are induced by relevant anti-cancer treatments (e.g., chemotherapy, radiation, etc.). Offerors should use clearly defined parameters and accepted markers of senescence to define the population of senescent cells being targeted by their agent.
- Provide preliminary data or cite literature to support the proposed mechanism of action.

- Demonstrate ownership of, or license for, at least one lead agent (e.g., compound or antibody) with preliminary *in vitro* data demonstrating senolytic activity.
- Select and provide clear rationale for a specific indication that the senolytic agent will address (cancer type and context of treatment induced senescence).
- Identify and provide justification for the choice of human cancer-relevant *in vitro* assays and *in vivo* models.

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

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

Phase I Activities and Deliverables

- Demonstrate *in vitro* efficacy for the agent(s) in human cancer-appropriate models.
- Conduct structure-activity relationship (SAR) studies, medicinal chemistry, and/or lead biologic optimization (as appropriate).
- Optimize formulation of senolytic agent(s) (as appropriate).
- Perform animal efficacy studies in an appropriate, and well justified animal model, for cancer therapy-induced senescence, or aged mouse models that have accumulated senescent cells through aging, and conduct experiments to determine whether senolytic agent(s) confer benefits with respect to side effects and/or cancer therapy efficacy.

Phase II Activities and Deliverables

- Conduct structure-activity relationship (SAR) studies, medicinal chemistry, and/or lead biologic optimization (as appropriate).
- Perform animal toxicology and/or pharmacology studies as appropriate for the agent(s) selected for development.
- Expand upon initial animal efficacy studies in an appropriate model for cancer therapy-induced senescence and conduct experiments to determine whether senolytic agent(s) confer benefits with respect to side effects and/or cancer therapy efficacy.
- Other research and development activities necessary to submit an IND application.

399 Combinatory Treatment Utilizing Radiation to Locally Activate Systemically Delivered Therapeutics

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

Systemic administration of therapeutic agents for cancer treatment is common practice; however, drug exposure in normal tissues often leads to adverse toxicities thereby limiting the administered dose and treatment efficacy. The use of heat or ultrasound to achieve local activation or release of therapeutic agents has been an active area of research for many years, and approaches involving thermal release of drugs from liposomes has been used in clinical practice. In addition to these approaches, toxicity in off-target tissues might also be avoided if the agent remained encapsulated or inactive until exposed to external radiation within a well-defined target volume. Using external radiation for local drug activation or release may provide unique opportunities and benefits compared to previous strategies. For example, X-rays could be used with nanoscintillators to generate visible photons *in vivo*, which could then activate photosensitizers for photodynamic therapy (PDT). Such a strategy could extend the range of PDT to deep-seated tumors that are currently intractable with existing PDT. Using external radiation to remotely trigger therapeutic agents could also be used to carefully control the timing of drug

release to achieve the appropriate therapeutic drug concentrations within a specific target volume at the right time. Successful treatment using this approach would require delivering safe doses of external radiation to quantitatively control the localized activation or release of the therapeutic agent. Toward achieving these goals, this solicitation is intended to develop combinatory treatment modalities utilizing external ionizing radiation to locally activate or release systemically or intratumorally delivered therapeutics, including high-atomic number elements that emit auger electrons. Remote release triggering mechanisms could include X rays or particle (e.g. proton) beams currently used for radiation therapy of cancer. The goal of this topic is to leverage existing radiation therapy infrastructure that is readily available in many clinical centers. In the future, such therapeutic approaches could be implemented as an addition to the current standard of care involving radiation therapy to achieve improved clinical outcomes.

Project Goals

This contract solicitation seeks to stimulate research, development, and commercialization of innovative techniques that could synergistically improve the effectiveness of radiation therapy and therapeutic agents or auger emitters to reduce toxicity to normal tissues. Proposals addressing the following technology areas are encouraged:

- New treatment strategies
- Design, synthesis, and evaluation of innovative therapeutic agents
- Development of new drug formulations (e.g., nanoformulations)

The short-term goal of the project is to perform feasibility studies for the development and use of combinatory treatment modalities for the treatment of cancer. The long-term goal of the project is to enable small businesses to advance fully developed combinatory treatment modalities to the clinic and eventually to the market.

To apply for this topic, offerors should:

- Identify or develop an appropriate therapeutic agent that could be activated *in vivo* by radiation
- Develop a drug formulation that could be triggered to release a therapeutic agent by radiation *in vivo*
- Define the mechanism(s) of action for the proposed therapeutic agent
- Identify the patient population(s) likely to be impacted by this technology

While modification of the radiation delivery device for eventual use with the therapeutic agent in the clinic is acceptable, it must not be the focus of the proposal.

Please note that the following are NOT considered appropriate for development under this solicitation:

- Development of agents that act as radiation sensitizers
- New instrumentation for triggering the release of the therapeutic agent
- Combinatory treatment strategies that do not involve the delivery of external radiation

Phase I Activities and Deliverables

- Demonstrate that the expected release/activation action with a proper amplitude can be induced *in vitro* and *in vivo* by safe doses of radiation
- Demonstrate (if appropriate) tumor-specific targeting and localization of the therapeutic agent and activation of the therapeutic agent only after exposure to radiation
- Carry out a pilot animal pharmacokinetic/pharmacodynamic studies utilizing an appropriate animal model
- Significantly characterize the chemistry and purity of the therapeutic agent and chemistry of the reaction

Phase II Activities and Deliverables

- Demonstrate an improved therapeutic efficacy and improved therapeutic index, assessment of toxicity to normal tissues *in vivo*
- Development of the manufacturing and scale-up scheme
- IND-enabling studies carried out in a suitable pre-clinical environment for PK/PD, preclinical efficacy, and safety assessment
- When appropriate, demonstration of similar or higher efficacy of the proposed strategy when compared to current therapies

400 Sensing Tools to Measure Biological Response to Radiotherapy

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

Treatment planning for radiation therapy is becoming increasingly complex with the advent of image-guided radiation therapy (IGRT) and charged particle therapy (CPT). Fundamental to treatment planning is dose. The goal of any treatment plan is optimization of dose distribution. In the vast majority of planning this is the physical dose – energy delivery in Joules per kilogram of body mass, or units of Gray (Gy). Simply stated, we engage in creating a complex plan using advanced technology so that we can deliver dose to areas of tumor and avoid delivering dose to areas of normal tissue.

To this end, a large portion of the treatment team's time and effort is allocated to reproducibly positioning, locating, and contouring key tumor and normal tissue structures, to optimize physical dose distribution. Even upon successful efforts to optimize physical dose delivery, tumor control and toxicity vary. Variation in biologic dose (biologic response to a given physical dose) may make even perfect physical dose delivery systems unable to properly deliver expected therapeutic dose to tumor in the patient. Biologic response and therefore optimal dose prescription may vary in the same patient across time and across location even at the same time. Tools are needed to measure biologic response to delivered physical dose in host systems, ideally that are volumetric – hence our focus on miniature and integrated sensors.

Contemporary engineering and device miniaturization (including nanotechnology) offer many compelling approaches that could enable a new generation of measurement tools to measure biological response directly and/or indirectly. Examples include: nanoparticle systems that self-assemble upon interaction with endogenous biomolecules, nanoparticles that target and allow direct imaging assessment of the tumor and its microenvironment, sensor systems that respond to local cues of biological damage and are excreted for ex vivo assessment, among many others. Standard dosimeters, even implantable dosimeters, cannot address biology in this context. Implantable dosimeters are much larger in scale. For this reason, integrated sensor solutions for measurement of biological response will be the focus of this contract solicitation. These systems can be used alone or in combination and can be utilized both in the body (*in vivo*) to allow volumetric assessment and extracorporeally (*in vitro*) to allow rapid, lab-test style measurements.

Project Goals

The purpose of this solicitation is to develop *in vivo* or *in vitro* sensor tools to measure biologic response to radiation, specifically, to help to redefine dose from solely the traditional physical dose to include the additional dimension of biological response. The resulting new, multidimensional definition of dose may allow more refined treatment planning and clinical trial development, avoidance of toxicity from overdosing, avoidance of tumor escape from biological underdosing, and hopefully allow truly personalized medicine to be performed in the combined modality space where chemotherapy, surgery, immunotherapy, and radiation are used in combination to treat patients.

The overarching goal of this solicitation is to produce a toolbox of sensor tools that will be used to improve the outcome for patients with cancer. By developing biologic response measurement tools, it will ultimately be possible to design and interpret biologically optimized treatment. These newly developed sensors are to allow study of the biological effects of radiation and combination therapies. These sensors should facilitate the development and study of precision radiation oncology. The sensors can be used alone, in combination, in the body, or outside of the body. A sensor would report temporal and spatial information about, for example, one biologic pathway, molecule's activity, or a complex's formation/function. Ideally, these sensors should be able to generate response via CT or MRI to allow non-invasive dynamic and real-time data collection. As such, the development and evaluation of sensor systems that can measure in a validated fashion biologic response to physical dose from radiation therapy will be preferred. Nanotechnology-based sensors are encouraged.

Overall scope:

Such systems are diverse (e.g. surface chemistries, material properties) as noted in the above examples, and thus this request does not limit the scope of the technical methodologies allowed. The work requested in this announcement includes any type of systems (including but not limited to nanotechnology) that can convey biological information and that can be correlated

with radiation therapy physical dose delivery in treated and untreated human tissue. Thus, sensors should measure biological status in collected liquid or solid samples and/or should evaluate biologic signals *in situ* that are correlated with tumor control, tumor survival, and toxicity. Mechanisms that involve conjugation and / or chemistry to monitor property changes to nanoparticles (e.g., self-assembly, emission changes, reporter release, etc.) are other examples of methods that fall into the scope of this solicitation. Furthermore, it is desired that sensors be able to be used serially and in combinations in patients before, during, and after treatment. Such biologic response sensors should function with combination therapy (radiation with chemotherapy or other biologic therapy). Sensors that can be imaged via 4D techniques already utilized in radiation therapy are also of particular interest so that spatial biological data can be collected over time to measure spatial changes correlated to treatment. As noted above, mixtures of these agents that can be differentiated via signal characteristics would be of a high priority as well because it may be true that a combination of markers offers unique biologic insights such as toxicity fingerprints or treatment failure fingerprints. Robust combinatorial analysis capabilities of new agents will be a key goal of this project and should be addressed in applications.

Prior to the start of the project a multidisciplinary team must be constructed. This needs to be outlined in submissions for this award. Creation of a multidisciplinary team to design and evaluate the sensor's design parameters and goals in terms of biology, chemistry, human toxicity, and reporting capabilities is critical. Examples of desired team members will be radiobiologists, imaging scientists, radiation oncologists, chemists, small animal model specialists, and molecular biologists. Failure to outline such a team in the proposal will be considered non-responsive to the FOA.

Projects that may be supported:

Devices/agents that can measure tumor biological change caused by radiation therapy that are injectable or otherwise distributed into *in vitro* or *in vivo* models of cancer and normal tissue. Work toward use in humans is of particular interest. The Phase I application must provide a detailed experimental strategy to develop and deliver the biologic response sensor and identify an appropriate cancer biologic signal for the sensor.

Activities not responsive to announcement:

Systems or tools that measure physical dose delivery only. Devices meant to interact with radiation and either potentiate its effects or mitigate its effects. Software solutions to model these effects without actual particle development would also be considered non-responsive.

Phase I Activities and Deliverables

- Development of the sensor to measure biologic response to radiation
- Demonstrate sensor stability *in vitro*
- Perform *in vitro* efficacy studies in the relevant cancer cell line(s) and in normal tissue(s); measurement of the target gene/enzyme/other signal
- Establish specificity of the construct and conduct validation studies
- Perform a small *in vivo* efficacy study in animal model systems to evaluate appropriate correlative endpoints

Activities and deliverables that will be used to evaluate whether the project should continue to be funded for Phase II include:

- Successful measurement of a biologic signal with the construct designed and produced.
- Concordance between known tissue signaling and sensor response (testing for false positive and false negatives).
- Establishment of partnerships for potential validation.

Phase II Activities and Deliverables

- Consultation with FDA regarding development of a regulatory strategy and timeline for an IND submission
- Refinement process development of construction and purification process to allow GMP production
- Demonstrations of sensor use serially in samples at a minimum that are relevant in a pathology/diagnostic capacity but preferably *in vivo* (properly powered studies)
- Evaluation of tissue with testing in the context of causing toxicity and evaluation of sensor use to predict and/or measure the degree of this toxicity with a goal to taking these agents to clinical use in humans, *in vitro* and *in vivo*
- 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
- By the end of Phase II, submit an IND to FDA

401 Quantitative Biomimetic Phantoms for Cancer Imaging

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 patient care for many types of cancer. Therefore, there is a constant need to develop, optimize, and validate new quantitative imaging 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 data in a tissue-equivalent context can be compared to data obtained by imaging these agents in the patient.

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 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 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 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
- 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 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

402 Artificial Intelligence-Aided Imaging for Cancer Prevention, Diagnosis, and Monitoring

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

Tremendous progress has been made in cancer imaging in the last decade, and much of this is due to computers that have revolutionized imaging protocols and image analysis. Magnetic resonance imaging (MRI), positron emission tomography (PET), computed tomography (CT), ultrasound, optical imaging, and other modalities have become fundamental tools for cancer research and clinical applications. While these medical imaging modalities are the workhorses of cancer prevention, diagnosis, and monitoring, there is increasing evidence that the accuracy of pattern recognition, predictions, and clinical decision making can be improved by the use of machine learning (artificial intelligence; AI) in image analysis. For example, retrospective review of false negative cases indicates that missed cancer diagnosis is often due to misinterpretation of perceived abnormality. In addition, the amount of imaging data has increased tremendously. Rich data have empowered physicians but also challenged them with computational complexity.

As imaging data are continually growing and readily available, they offer an incredibly abundant resource for scientific and medical discovery, particularly in the application of AI for medical imaging. AI, which is defined as an area of computer science that mimics cognitive functions, such as learning and problem solving, has been progressing rapidly over the past decade. More and more physicians have started to recognize that AI-aided imaging tools (e.g. machine learning, or deep

learning based on learning data) could help them with clinical decision making and improve imaging efficiency that would otherwise not be possible.

Project Goals

The goal of this solicitation is to call for development of AI-aided imaging software for cancer prevention, diagnostics, prognostics, and/or response to therapy. The system that will be developed can be used either as a stand-alone package for clinical applications or a tool for facilitating clinical decision making. The AI-based system may also be used to provide a better mechanistic understanding of tumor development and progress with the idea that this knowledge may lead to better therapeutic targets and improve patient outcome. The data sources for cancer imaging can be from conventional X-ray, MRI, PET, CT, ultrasound, optical imaging, and/or other imaging modalities or imaging devices. Since a single imaging modality may not be sufficient to quantitatively process, reconstruct, and analyze specific cancer imaging, integration of images from multi-imaging modalities or imaging devices that could make the system more robust for their technology development is permitted. The sensitivity and specificity for the cancer prevention, diagnosis, and/or monitoring will depend on the clinical question and unmet need that the tool is attempting to answer. Products addressing cancers of the brain, cervix, colon, head and neck, lung, prostate, and rare cancers as well as childhood cancers are particularly encouraged for this topic. However, proposals may be focused on any single cancer type. Cloud-based AI-aided imaging systems are also encouraged.

To apply for this topic, offerors must outline and indicate the clinical question and unmet clinical need in the areas of cancer prevention, diagnosis, and/or monitoring that their AI-aided imaging system will address. Proposals focused on sharing and archiving imaging information, radiation therapy treatment planning, or mammography will not be considered responsive to this solicitation.

Phase I Activities and Deliverables

- Select one modality, or a set of imaging modalities (e.g., MRI, PET, CT, ultrasound and/or optical imaging, etc.), and data sources that are associated with the modalities for the AI-aided imaging software that will be developed for cancer prevention, diagnosis, and/or monitoring
- Perform a software usability study for the prototype software with at least 25 users
- Demonstrate in a small-scale, proof-of-concept study with animal or human medical image data the feasibility of an algorithm and software package for an AI-aided imaging system for cancer prevention, diagnosis, and/or monitoring. This study should be designed to assess the sensitivity and cancer specificity of the prototype software
- Deliver to NCI the SOPs of the system for cancer prevention, diagnosis, and/or monitoring
- Develop a regulatory strategy/plan and timeline for seeking approval from FDA to market the AI-aided imaging software

Phase II Activities and Deliverables

- Engage with FDA to refine the regulatory strategy
- Refine and modify the software based on usability and feasibility data from Phase I
- Perform a large-scale usability study with at least 100 users
- Perform a large-scale validation study with human medical image data. The study should be designed to show a statistically significant improvement in the performance of the AI-aided image software
- 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
- By the end of Phase II, submit a regulatory application to FDA to obtain marketing approval for the AI-aided software for cancer prevention, diagnosis, and/or monitoring

403 Spatial Sequencing Technologies with Single Cell Resolution for Cancer Research

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

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 micro environment, 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 its local environment; therefore, this information could 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 tools to improve cancer early detection, diagnosis, and prognosis for precision medicine. Such tools could be used to identify the 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 versus 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 DNA or RNA within fresh frozen or fixed normal and tumor cells without destroying their spatial context, and 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 information without losing 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 within it.

Activities outside the scope of this Topic:

Technologies that are solely based in computational development are not appropriate 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, such as single cell fluorescence *in situ* hybridization (FISH) based technologies. Projects that propose to integrate image modalities with orthogonal -omics measurement other than sequencing information should respond to Topic for “Subcellular Microscopy and -Omics in Cancer Cell Biology”.

Phase I Activities and Deliverables

- Demonstrate sensitivity, resolution, reliability, robustness, and usability in basic and/or clinical cancer research.
- If the technology 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, the proposal 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.
- 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 benchmarks, alternative assays) or absolute metrics (e.g. minimum level of detection in a clinically meaningful indication).
- Demonstrate utility with benchmark experiments obtained across a range of generally accepted cancer indications.
- Show feasibility to be scaled up at a price point that is compatible with market success and widespread adoption by the basic and/or clinical research community.

404 Subcellular Microscopy and -Omics in Cancer Cell Biology

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

Advances in microscopy have improved the ability to resolve, describe, and quantify subcellular anatomic structures, organization, and dynamics. Concurrently, single-cell molecular ‘omics technologies have revolutionized our understanding of intracellular processes and intercellular communication. Our understanding of basic cancer mechanisms is informed by multiple orthogonal perspectives, including employment of technologies such as high-resolution microscopy and multiscale ‘omics. However, experimental or computational methods that facilitate true integration of advanced high-resolution cellular and subcellular microscopy and multi-scale molecular ‘omics technologies are not readily available to the broader research community. Technologies that offer such integration will facilitate multidimensional and spatially preserved mapping of the tumor ecosystem, leading to a broader understanding of tumor heterogeneity, and the role of cell-cell and/or cell-matrix interactions in response to cancer therapy, and will provide data for building predictive computational models of cancer initiation, progression, metastasis, and response to treatment.

Recommendations of the Cancer Moonshot Blue Ribbon Panel call for enabling technologies that combine approaches from disparate fields, such as imaging at the cellular to subcellular scales with single cell “-omics” approaches. It is anticipated that the innovation in the small business sector can provide instrumentation and enabling technologies to serve the basic cancer biology research needs, in particular, technologies that directly link cellular phenotypes measured through high-resolution cellular and sub-cellular imaging in combination with multi-scale ‘omics measurements.

Project Goals

The main objective of this contract topic is to support the broader goal of developing an infrastructure to accelerate the microscopy-omics community and enable transformative research in cancer cell biology, diagnostics, or monitoring strategies. The short-term goal of this contract topic will be to stimulate innovation that integrates cellular imaging modalities with technologies that provide single cell -omic level data (e.g. proteomic, transcriptomic, etc.) that are relevant to cellular processes and are disabled or exploited in cancer. Projects supported by this contract topic should enable multidimensional interrogation of cancer cell biology in a manner that combines the spatial-temporal strengths of imaging modalities with complementary orthogonal measurements achieved through -omics and physicochemical approaches.

This solicitation seeks to encourage the development of new imaging platforms, probes, or a unique combination of platforms with image-based approaches that leverage a multidimensional perspective of cancer cell biology. It is anticipated that that projects may include the development of new algorithms or software that facilitates image analysis or multimodal data analysis to render an understanding of cancer cell biology from a multidimensional perspective; however, proposals that are solely software based will not be responsive. The focus of this topic is on non-sequencing based -omic technologies. Proposals to integrate single cell sequencing technologies with imaging should respond to the contract solicitation for the “Spatial Sequencing Technologies with Single Cell Resolution for Cancer Research”.

Phase I Activities and Deliverables

Phase I activities should generate data to confirm the feasibility and potential of the technology(ies) to combine microscopy at the subcellular scale with orthogonal cell “-omics” and physicochemical measurement approaches.

Activities and deliverables include:

- Define the cancer biology application the device(s) or combined device-computational approaches addresses.
- Generate proof-of-concept data in a generally accepted cancer cell model system that demonstrates the ability to sense, interrogate, detect or resolve and map spatial cellular anatomy and/or dynamics using microscopy or other imaging modalities with nano- to micro-scale resolution.
- Demonstrate feasibility of combining the imaging modality(ies) in Phase I Deliverable #2 with orthogonal assessments at the molecular scale (such as genomic, proteomic, metabolomic, or epigenomic analyses), physicochemical scale (such as redox, pH, force/stiffness), and/or functional scale (such as proliferation, transformation, motility, invasion, resistance, or cell death) to generate multidimensional data.
- 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 absolute metrics (e.g. minimum level of detection).

Phase II Activities and Deliverables

Phase II activities should support the commercialization of the proposed technology and include the following activities:

- Demonstrate reliability, robustness and usability in basic and/or clinical cancer research.
- 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 benchmarks, alternative assays) or absolute metrics (e.g. minimum level of detection).
- Demonstrate utility with benchmark experiments obtained across a range of generally accepted cancer cell model systems.
- Show feasibility to be scaled up at a price point that is compatible with market success and widespread adoption by the basic research community.

405 Intra-Tumor Sensing Technologies for Tumor Pharmacotyping

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

Determining the best treatment for each individual cancer patient can be a difficult task. To make that decision, clinicians rely on information such as the tumor type and stage, the presence of certain prognostic markers, and specific genetic characteristics of the tumor. Nevertheless, it is not always possible to determine whether a patient will respond to a specific therapeutic agent; and in some cases, several rounds of varied treatments are required to find one that is effective in a given patient. An emerging possibility identified by the Cancer Moonshot Blue Ribbon Panel (BRP) is to use the patient’s own tumor to safely and simultaneously test sub-therapeutic doses of multiple candidate drugs to more efficiently determine the most effective therapeutic agent(s). A major advantage of this strategy is that it can be personalized to each individual patient, thus allowing clinicians to more rapidly determine whether a patient will respond to a specific agent or drug combination. This capability would allow clinicians to optimize treatment decisions not only at the early stages of treatment, but also during later stages of treatment to address acquired resistance to initial therapies. In the future, such technologies might be used to generate pharmacotyping data that would accompany genotyping data in databases from large numbers of patients, which could be further mined to predict sensitivity to certain drugs and drug combinations. The BRP identified several

emerging technologies that might contribute to such a “pharmaco-typing” capability; however, further development and validation of these technologies is needed before they are ready to be deployed in a clinical setting.

Project Goals

The primary goal of this topic is to expand the capabilities that can enable these emerging pharmaco-typing approaches by developing intra-tumoral sensing technologies. Proposals under this topic must involve the *in vivo* measurement of specific intra-tumoral markers of anti-cancer activity that are triggered in response to the delivery of sub-therapeutic doses of candidate therapeutic agents. Responsive proposals must offer approaches that can eventually report on patient-specific efficacy from a variety of potential treatment options while maintaining patient safety. To demonstrate the sensing capabilities of their technologies, offerors may utilize any route of administration to deliver candidate therapeutic agents (e.g., intratumoral administration, multiple/sequential rounds of systemic dosing, or other delivery strategies). However, the proposed sensing technology and/or process must enable sufficient throughput to evaluate an appropriate number of therapeutic agents that would be needed to inform clinical decision-making within a relevant timeframe.

For Phase I projects, offerors must demonstrate intra-tumoral sensing capabilities using at least one solid tumor animal model; however, technologies that are capable of intra-tumoral sensing in multiple solid tumors are preferred. In all cases, offerors must provide a scientific justification for the methods, assays, and metrics that will be used to identify the optimal therapeutic agent or combinations that will be tested in their chosen tumor model(s). For Phase II projects, offerors will be expected to further develop the technology and/or process for use in human patients. Small businesses developing more mature technologies may advance far enough during Phase I to propose clinical trials during their Phase II projects; therefore, clinical trials will be allowed for Phase II SBIR contracts but will not be required.

Phase I Activities and Deliverables

- Demonstrate intra-tumoral sensing capabilities using at least one solid tumor animal model
- Conduct proof-of-concept experiments using an appropriate number of anti-cancer agents, combinations, and/or doses (at least four) to demonstrate throughput capability that would eventually support clinical decision-making for the chosen tumor(s)
- Conduct preliminary safety studies in the chosen animal model (animal safety studies may be limited in scope, but they should provide early evidence that the technology is likely to support human testing without compromising patient safety or interfering with standard of care)

Phase II Activities and Deliverables

- Perform testing in multiple solid tumor models and/or PDX models to advance the technology for clinical testing in specific solid tumors
- Conduct preclinical studies as required for regulatory approval of the device and/or a specific clinical test
- Conduct clinical trials in animals (as appropriate)
- Conduct human clinical trials (as appropriate)
- Complete other activities required for regulatory approval and/or marketing of the technology or test

406 Software for Patient Navigation Through the Cancer Care Continuum

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

Cancer care delivery systems are complex and difficult to navigate. Patient navigators (PNs) help patients navigate these systems. PNs facilitate timely cancer screening, diagnosis and treatment by decreasing barriers to care. Navigation programs have successfully [reduced time from detection](#) to diagnosis, and from diagnosis to start of treatment, in cervical, breast, and colorectal cancers, and have reduced disparities in cancer outcomes due to differences in income or employment.

Nurses, social workers, and lay persons may serve as PNs. PNs work with patients to overcome health system barriers, provide health education, and psychosocial support. Common tasks of PNs include patient education and communication, scheduling and coordinating appointments, communication with clinicians, connecting patients and caregivers with community resources, and assistance with medical paperwork.

Patient navigation services are [mandated](#) by the Commission on Cancer. There is an increasing demand for expanding the use of PNs in all phases of the cancer care continuum. A National Academy of Medicine (NAM) [report](#) has identified several challenges faced by PNs, including: care coordination, tracking patients through their trajectory of care with different clinicians and facilities, supporting patients throughout the cancer care continuum, and addressing communication, transportation, and financial barriers. It takes significant time for PNs to collate information across different information systems, from patients and their caregivers, and from the relevant clinicians. It can be cognitively burdensome for navigators to synthesize this information, triage key tasks, and address patient needs in a timely manner. Projected [increases in cancer survivors](#) will further strain the capacity of the existing professional PN workforce, accelerating the need for new approaches to support and extend the work of both professional and lay PNs.

Information technology (IT) has the potential to increase the reach and effectiveness of patient navigation programs by supporting the day-to-day work of PNs. IT-based tools can provide education, support communication and coordination, curate information, assist decision-making, reduce cognitive burden by improving information synthesis or decision support, and adaptively meet patients' needs. However, the lack of user-centered design and [sub-optimal integration](#) of navigation related IT tools into existing IT systems are significant barriers. User-friendly IT tools are needed to reduce the cognitive and time burden of performing navigation tasks. User-friendly IT tools that are integrated in the workflow of PNs can improve cancer care delivery and patient outcomes.

Project Goals

The long-term goal is to provide timely cancer care and improve patient outcomes by developing new software tools that support patient navigation. The short-term goals are to develop, deploy and evaluate IT tools that: 1) reduce the cognitive or time burden (or both) of navigation-related tasks performed by either PNs or patients; 2) are well-integrated in the work flow of PNs and existing IT architecture; 3) securely transmit information across a variety of IT systems.

The technical scope includes the development, deployment and evaluation of IT tools that support patient navigation. The tool design approach must account for integration within existing IT systems, interoperability, cyber-security and protecting patient's privacy.

Activities outside the scope of this Topic:

Not using a human-centered design process to understand and meet the users' needs; development of tools that do not use current best practices for inter-operability, cybersecurity and patient privacy; development of tools that are either not integrated in the work flow or in the existing IT architecture; merely increasing access to patient data (e.g. increasing access to data within a patient portal) without synthesis and presentation of data in a manner that reduces the user's cognitive burden.

Phase I Activities and Deliverables

- Project team: Establish a project team with expertise in: cancer patient navigation; software development and evaluation; user-centered design; health services research; and the design, deployment and use of health IT in a healthcare delivery organization. Knowledge and design of systems architecture, health IT interoperability, cybersecurity, and HIPAA and other laws and regulations to protect privacy and confidentiality of patient information will be required.
- Perform a targeted literature review to inform the needs assessment of PNs and the approach to be used to design, develop and evaluate the IT tool(s).
- Conduct a needs assessment of PNs and cancer patients in at least one cancer care delivery site.
- Develop prototype software tool(s) to support two or more patient navigation tasks. Tasks include, but are not limited to, providing education to patients, scheduling or coordinating appointments, communicating with clinicians, coordination care planning, referring patients to appropriate resources to meet their financial or transportation needs.
- Conduct at least one usability study of the IT tool(s) with the participation of a minimum of 25 users.
- Submit a report specifying approach taken to design and evaluate the IT tool(s), usability study findings and the plans and approach to be taken to improve the tool(s) usability.

- Submit a report detailing plans for implementation of IT tool(s), including technical assistance and a review of technical specifications for systems interoperability, within existing EHR and other health IT systems, cybersecurity and patient privacy.
- Present Phase I findings and demonstrate the functional prototype system to an NCI evaluation panel via webinar.

Phase II Activities and Deliverables

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

- Deploy the IT tool(s) in at least one cancer care delivery site.
- Conduct a study to evaluate the usability and effectiveness of the deployed IT tool(s) in supporting two or more patient navigation tasks. The specific aims, approach, outcomes and analysis plan of the evaluation study should be explicitly stated. A minimum of 100 users should participate in this evaluation study, and the human subjects protection plan (including IRB review and patient consent) should be in place before the start of the study.
- Refine the IT tool(s) based on the evaluation of the usability and effectiveness.
- Evaluate the interoperability of the IT tool(s), the effectiveness of the cybersecurity design and the protection of patient privacy.
- Submit a report that details the aims, approach, data analysis, and conclusions of the evaluation of usability, effectiveness, interoperability, cybersecurity and protection of patient privacy.
- Submit a report that details the future approach to modify the tool(s) to support additional PN tasks and to support patients across the cancer care continuum. This report should include a plan to commercialize the IT tool(s).
- Present Phase II findings and demonstrate the system via a webinar at a time convenient to the contractor and NCI Program and Contracting staff.
- In the first year of the contract, provide the Program and Contract officers with a letter(s) of commercial interest.
- In the second year of the contract, provide the Program and Contract officers with a letter(s) of commercial commitment.

407 Cloud-Based 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 \$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

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), Therapeutically Applicable Research to Generate Effective Treatment (TARGET), and Clinical Proteomic Tumor Atlas Consortium (CPTAC) to generate a wealth of 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, population, and clinical data, by challenges in integration across disparate datasets. To address these challenges, NCI has created the Cancer Research Data Commons (CRDC) as part of the National Cancer Data Ecosystem recommended by the Cancer Moonshot 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 analytic tools that can be disseminated and sustained within the cancer research community. The SBIR contract funding mechanism will offer small businesses the opportunity to contribute solutions to address unmet challenges of big data analysis that are not currently provided by the 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 by offering enhanced data analysis capabilities, visualization tools, and data access and sharing

platforms. This topic is relevant to the BRP recommendation to develop a national cancer data ecosystem for sharing and analysis.

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 that operate across the CRDC and other data commons such as Gabriella Miller's Kids First for multi-domain 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 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 datasets stored in CRDC such as TCGA 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 outside the scope of this Topic:

Proposals for the development of big data analysis tools without consideration for integration with the CRDC will not be considered for award under this Topic.

Phase I Activities and Deliverables

The proposed Phase I research is expected to clearly demonstrate at minimum a 'proof of concept' feasibility of adaption of the offeror's informatics tool(s) to the CRDC through the Data Commons Framework. The proposal should 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, project management, team communication, and user-centered design.
- Design the specifications for the development/extension of cloud-based informatics tools to operate in the Cancer Research Data Commons.
- Develop an early software prototype.
- Demonstrate the feasibility of CRDC integration through the DCF. Examples of feasibility qualification include, but are not limited to, user authentication using [Fence](#) to access datasets stored in at least one CRDC node such as the [Genomic Data Commons](#) (which exists now) and providing authorization to datasets the user has access to. More nodes, such as the Proteomic Data Commons, are expected to be available for feasibility testing by the end of 2019.
- Conduct a pilot software usability study with the participation of 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 a 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 detailed 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 data analysis using the offeror's tools or resources. Examples of large-scale data analysis include, but are not limited to, demonstration of integration of user-provided data with available datasets such as TCGA from CRDC to perform comparative analyses.
- Conduct usability testing with the participation of at least 100 users.
- Provide a report that synthesizes feedback from all relevant categories of end-users (minimum of 100 users and end users include biomedical researchers and computational scientists) and summarizes the modifications made to the platform after each round of usability testing.
- Develop systems documentation and user guides to facilitate commercialization.
- Develop and implement a business process for broader adoption of their tools and resources by actively engaging with the user communities.
- Develop business process that includes business plans for marketing and long-term sustainability, such as sustained hosting of tools, training and associated resources.
- Conduct outreach and training activities.
- Present Phase II findings and demonstrate the system to NCI program staff.
- In the first year of the contract, provide the Program and Contracting 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.

408 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: 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

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:

- Establish Web-based or containerized visualization tools that allow seamless traversal across scales of heterogeneous 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 heterogeneous 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)
- 3) Cellular (e.g., cell-state, cell-type)
- 4) Tissue (e.g., tissue morphology, metabolic state)
- 5) Individual patient (e.g., clinical data, exposure, microbiome)
- 6) Population (e.g., epidemiological)

Activities outside the scope of this Topic:

Work that would not fall under this Topic includes: (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 usability 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.

409 Software for Automated Analysis of 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 the 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. This work builds on developments in 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 is required. 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 environment, and automated measurement of human performance in sport and animation domains along with growing capacity of computers to identify and count objects 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.

Activities outside the scope of this Topic:

Proposals addressing medical images such as MRI scans, microscopy, or DEXA scans will not be considered for award under this Topic.

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 software 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.
- 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. Phase II usability testing should include the participation of at least 100 users.
- 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.

410 Cancer Clinical Trials Recruitment and Retention Tools for Participant Engagement

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

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

Number of anticipated awards: 3-4

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

A large number of NCI funded clinical trials fail to meet their accrual goals which leads to delays, early termination, or inability to draw conclusions at trial completion due to loss of statistical power. A study in 2014 reported that 1 in 4 cancer clinical trials were terminated early with 1 in 10 being terminated for poor accrual. There are no easy solutions to solving accrual challenges. Retention of subjects enrolled in trials can also be a challenge. NCI provides various educational resources and tools to support and enhance participant accrual through portals like AccrualNet. However, most of these resources are limited to educating the study team on good practices to enhance accrual. Tools that could be either clinic-facing or participant-facing or both and that are based on empirical evidence and have been shown to increase participant accrual and retention are mostly lacking.

This solicitation has the potential to enhance clinical trials recruitment and retention by developing tools that could be used across NCI clinical trials networks and beyond. The goal of these tools is to enhance communication between participants and study staff and reduce the participant burden of traveling to the clinic when virtual communication is sufficient.

Project Goals

The goal is to solicit proposals to advance the development of tools for clinical trials recruitment, retention, or both. The tool could be clinic-facing or participant-facing or both. If clinic-facing for recruitment, it should help identify protocol barriers to recruitment and present options for addressing the challenge(s), effective recruitment strategies, potentially integrate with electronic medical records, and allow for tracking of screening efforts. If clinic-facing for retention, it should enhance patient engagement, potentially integrate with electronic medical records, and allow for tracking of retention efforts. If participant-facing for recruitment, it should be designed to engage potential participants, help them understand details of a given trial, and be easily adaptable for different trials. If participant-facing for retention, it should be designed to engage enrolled participants, help them adhere to protocol requirements and communicate with clinic staff in an effective and efficient manner, and be easily adaptable for different trials. Preference will be given to projects that are easily adaptable between trials.

The best practices for recruitment and retention that are relevant to tool development include [Denicoff AM et al. (2013) J Oncol Pract. 9(6): 267-76]:

- 1) Consider the patient point of view of potential research, including potential barriers, when reviewing and implementing trials. Patient advocates could support this effort.
- 2) Identify and address reasons why eligible patients decline trial participation.
- 3) Simplify informed consent documents and enhance personal communication during the informed consent process, including clarifying possible financial liability the patient may incur by participating in the trial.
- 4) Educate patients and the community, including community providers, about clinical trials, using culturally appropriate material.
- 5) Use smart devices, social media, patient registries, and electronic databases to identify potential participants, notify providers, and enhance recruitment and retention to prevention, treatment, quality-of-life, survivorship, and rare-cancer studies.
- 6) Provide access to peer mentors (other patients who have participated in a clinical trial) and patient navigators for those patients identified as in need of additional support.
- 7) Increase awareness and provide easy access to information on all ongoing clinical trials.

The tools should incorporate these best practices and should

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

Phase I Activities and Deliverables

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

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

- Present Phase I findings and demonstrate the functional prototype system to an NCI evaluation panel via webinar.

Phase II Activities and Deliverables

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

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

411 De-Identification Software Tools for Cancer Imaging Research

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

Imaging data are a core component in the development of the National Cancer Data Ecosystem and are important in areas from basic research to diagnostics and surveillance. Sharing of any data collected from patients, however, requires that information that can connect that data to the individual from which the data were collected must be removed, or anonymized to the extent possible. Removal of Protected Health Information (PHI) from imaging data files is a twofold problem. 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, this information is often found in fields not intended to contain such information. In the image field itself, PHI can be found in different forms, inserted into the image by the imaging system, or by the presence of identifying jewelry in the image (in the case of radiological images). 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. This need for human participation in the de-identification process is a significant bottleneck; it impedes the generation of 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 proposed Imaging Data Commons of the Cancer Research Data Commons. For example, on a TCIA data curation team, one person manually reviews files for PHI. Improved tools would shift a large portion of the de-identification burden to software, improving data throughput and increasing data accessibility. Currently, tools do not exist to properly remove PHI from proprietary file formats (e.g. digital pathology images) while retaining other data that maybe be useful to researchers.

Project Goals

The goal of this contract solicitation is to support development and sustainment of software tools and pipelines for image de-identification, especially for but not exclusive to CT patient data sets and images produced by whole slide imagers (WSI) for digital pathology applications. These tools will selectively remove PHI while retaining other metadata fields that help provide interoperability with other image formats and other data types, such as genomic data and proteomic data.

The following tasks/objectives should be met by the software tool:

- 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 (e.g., comment fields that may contain PHI)
- 3) Scanning of images for PHI, identification, labeling, and subsequent resolution
- 4) Production of processed images that meet a threshold level of de-identification
- 5) Validation algorithm to confirm images within the processed dataset are de-identified
- 6) Identification (e.g., flagging) of processed data files that may require manual resolution to remove PHI

Brute force methods for de-identification (e.g., erasing of all header information) are not acceptable. Retention of data and metadata necessary for downstream applications (population studies, segmentation training) is required. Solutions should not compromise the biomedical use of data files. To build upon previous work for field retention, removal, and alteration, the TCIA de-identification knowledge base (<https://wiki.cancerimagingarchive.net/display/Public/De-identification+Knowledge+Base>) may serve as a foundation for determining and prioritizing similar attributes in digital pathology images.

Phase I Activities and Deliverables

- In addressing WSI datasets, identify different WSI vendor file types and the fields that contain PHI (i.e., conduct landscape analysis)
- Ability to recognize and open multiple WSI file formats
- Provide data set(s) for Phase I activities
- Display PHI field variable values
- Remove or alter PHI field values from fields labeled with PHI
- Identify the data sets and file types required to demonstrate software capability in Phase II
 - WSI data sets should include at least 1000 differentiated case files (i.e., one image per patient case) from across various imager systems as identified from the performed landscape analysis
 - CT data sets should include at least 1000 difference case files (e.g., 100 images per patient case) from across at least 5 distinct research institutions
 - Requests to use NCI data sets from the TCIA database or similar may be directed to the NCI Contracting contact person listed for this solicitation. Requests will be granted at the discretion of NCI.

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 fields
- Detection of PHI within image
- Masking of PHI within image
- Generation of de-identified images with provenance of process
- Validation with a test data set should demonstrate successful PHI removal from image and image file meta data for $\geq 95\%$ test files
- Statistical analysis of validation testing will be provided to NCI
- The software tool should identify and flag any cases that are less than fully verified for PHI removal
- For any dataset where 5% or less of files are not fully verified with successful PHI removal, such files should be flagged for manual correction
- 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

412 Software Enabling Data Integration from Wearable Sensors for Cancer Patients

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 \$1,680,879 for up to 2 years

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

Summary

The rapid adoption of wearable, cyber-physical, and ambient sensing platforms since 2015 by the consumer health market have begun to pave the way for similar platforms to act as objective measures for continuous, out-of-clinic cancer research and patient assessment. They collectively will be a key component of the perceived future for Smart and Connected communities via a continually linked internet of health sensors. The passive, continuously measured data streams generated by current or future physical and chemical/biological sensors will allow direct/indirect measures of cancer progression and its symptoms. Increased out-of-clinic patient and clinician engagement via these tools will allow more precise delivery of cancer care after as well as during cancer remission. Ultimately, these passive sensing platforms' data for digital biomarkers will afford clinicians: 1) more objective metrics of response to therapeutics; 2) control and auto-reporting of symptoms and their fluctuations; 3) monitoring of side-effects of experimental or standard of care therapies; and 4) more ecologically valid clinical endpoints, all decreasing assessment burden via increased continuity of physiological measurement sampling and patient context in the ambulatory setting.

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

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

There is a considerable need for scalable informatics tools that allow automated data aggregation, integration and machine learning/artificial intelligence (AI)/predictive analytics that can pull from disparate data sets across device vendors and have the flexibility to add new measures as they are developed. Furthermore, a central software platform that could obtain wearable, implantable, or external device data and uniformly compare/contrast/couple data streams to understand physiology versus patient context with respect to time will advance this unique approach to aid cancer patients, clinician assessment and clinical trial design.

Project Goals

The goal is in development, and subsequent commercialization, of scalable informatics tools and resources for their broad adoption across the burgeoning clinical cancer research applications that continuous, passive monitoring of multiple biological parameters via wearable platform technologies are beginning to be used. A limitation to their current use in cancer research, to more objectively understand cancer patient progression or cancer-specific symptoms, is that device manufacturers and platform technology developers do not utilize identical data sets / standards and no resources are available to easily assess large multiparameter data sets via traditional bioinformatics methods. As such, the primary focus of this contract topic is on data agnostic informatics tools and resources that can be easily adopted in the cancer research communities for cohort studies involving their monitoring platform(s) of choice to understand their specific research problem / patient cohort of choice. Informatics *tools* include mobile apps for sensor data retrieval; computer software tools and platforms to aggregate, integrate and organize data streams from multiple devices; and machine/deep learning or predictive analytic informatics 'AI' platforms for subsequent interpretation of integrated data streams derived from a myriad of continuous passive monitoring devices that could be used by cancer researchers. The informatics *resources* include sensor and patient data repositories and platforms that provide data, workflow, and a workspace for online research collaboration, evaluation as well as dissemination of informatics tools and resources, and support for population-based research.

The overall scope of proposed funding approach includes the entire spectrum of passive continuous monitoring devices being commercialized or developed, extending from wearable sensor platforms and implantable devices to external monitoring devices for all phases of cancer clinical research. Offerors will be expected to formulate and execute well-

designed project plans with clearly defined milestones that will eventually lead to commercially viable solutions for: 1) sustained development and evolution of passive continuous monitoring platform informatics tools and resources; and 2) their broad adoption in clinical cancer research.

Activities outside the scope of this Topic:

Tools that do not allow the integration and subsequent interpretation of a myriad of current wearable sensor platforms simultaneously, or that use only data from inertial sensing wearables; tools that are not scalable to future wearable, implantable or external out of clinic monitoring; tools that do not incorporate safeguards to protect privacy and confidentiality of information; design approaches that don't account for scalability, interoperability or user-centered design; approaches that don't plan for using tools in diverse sites and IT systems.

Phase I Activities and Deliverables

- Establish a project team including proven expertise in: sensor technology for physiological monitoring, wireless sensor integration with mobile devices, secure wireless transport of health data using standards based protocols, secure cloud computing models, bioanalytical technologies, epidemiology, biostatistics/bioinformatics, and systems architecture
- Provide a report including a detailed description and/or technical documentation of the proposed:
 - Development of bioinformatic methods or algorithms (e.g., machine/deep learning, etc.) for wearable sensor data integration across data inputs from diverse wearable bio-/sensor platforms, including harmonization of data of the same biometric from different vendor device platforms
 - Evaluation of a wide range of wearable, implantable, and external sensor platforms that would be of legitimate use for out of clinic patient monitoring and / or understanding disease / symptom progression (e.g., therapy-induced fatigue, patient performance status, cachexia, experimental therapeutic side effects, toxicity, etc.) vs. the myriad of potential physical and / or physiological factors
 - Development of the database structure for the proposed system's chem-/bio-/physical sensor-based data inputs and metadata requirements
 - Database formats that support the import and export of individual datasets and coalesced datasets, store structured data from different sources of wearable sensor data, and are readily used for data integration and Quality Control (QC) protocols
 - Specific approach to QC
 - Technology compatibility matrix for Phase I and Phase II wearable sensor data sources by platform, sensor type, sensor technology, and differing device data streams as well as and back-end server systems to be developed
 - Data visualization, feedback, and reporting systems for population or clinical monitoring and research applications
 - Data integration approaches to leverage multiple data input streams
 - Data types for exchange of physiological-metrics between mobile platforms and secure servers
 - Data standards for transfer and importation of individual wearable sensor data and storage of individual and coalesced wearable sensor data
 - Transparent, documented, and non-proprietary bio-/informatic methods
 - Description of additional software and hardware required for use of the tool.
- Provide wireframes and user workflows for proposed Graphical User Interface (GUI) and software functions that:
 - Support the import and export of individual datasets and coalesced datasets
 - Implement, script or automate all features and functions of the data integration tool(s)
 - Conduct QC of coalesced datasets
- Develop a functional prototype system from the planned Phase I compatibility matrix that includes:
 - Front-end mobile applications to facilitate and control the collection and transport of multiple wearable chem-/bio-/physical sensor data inputs and any associated metadata used within the system
 - Integration with several wearable chem-/bio-/physical sensor
 - Automated data screening algorithms and importation protocols for data transferred from the mobile application to the back-end server systems
 - Software systems GUI (web- or computer-based)
 - Software tools as mobile and web applications
 - Back-end user-interface controls for custom data integration and visualization for individual or group-level data

- Finalize database formats and structure, data collection, transport, and importation methods for targeted data inputs
- Include funds in the budget to present Phase I findings in a detailed report and demonstrate the final prototype to an NCI evaluation panel.

Phase II Activities and Deliverables

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

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:

109 Transcatheter trileaflet tricuspid suture repair system

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

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

Number of anticipated awards: 2

Budget (total costs): Phase I: \$400,000 for up to 12 months; Phase II: \$3,000,000 for 36 months

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

Summary

Primary and secondary tricuspid valve regurgitation can cause disabling right heart failure, hepatic dysfunction, cardiorenal syndrome, and death. Primary surgical repair or replacement is highly morbid especially at the advanced stage of typical clinical presentation. Transcatheter repair using marketed and investigational clip-type devices is poorly suited for the trileaflet tricuspid valve. There is substantial unmet need.

This solicitation aims to support the development of an Transcatheter trileaflet tricuspid suture repair system for commercial clinical application.

Project Goals

The goal of this project is to develop a catheter system to achieve a non-surgical off-pump tricuspid valve LEAFLET repair that allows 3 or more sutures to reappose 3 or more tricuspid valve leaflets to repair secondary or primary tricuspid valve regurgitation, sometimes described as “clover-leaf repair.”

This project should generate an Early Feasibility Study (EFS) IDE for clinical evaluation in the United States, towards commercialization through a mechanism such as Phase IIb bridge-to-commercialization.

Phase I Activities and Expected Deliverables

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

The offeror should provide a complete transcatheter solution to effect suture apposition repair of three or more tricuspid leaflets. Elements of a complete system would typically include

- Low profile transvenous access
- Multi-axial deflectable guiding sheaths
- Leaflet traversal tools such as radiofrequency or mechanical energy transmission

- Retrieval tools to use in tandem with traversal tools
- Radiopaque tension elements such as sutures
- Force-redistribution elements that are radiopaque, such as pledgets, to prevent tension-induced leaflet injury
- Features to accomplish real-time image guidance including visibility under ultrasound and visibility under X-ray fluoroscopy
- Biocompatibility required of permanent endovascular clinical implants
- Capabilities to accomplish three or more points of apposition

Proposals that include novel image guidance and catheter navigation assistance in 3-dimensional space are welcomed.

A phase I award would develop and test functioning prototype system, including accessories, in vivo. At the conclusion of the Phase I award, the contractor should provide a detailed report of pre-IDE interactions with the Food and Drug Administration to identify clear requirements for human testing, including the summary of mutual understanding.

The contracting NHLBI DIR lab is willing to provide feedback about design at all stages of development. The contracting NHLBI DIR lab will test the final deliverable device for success in vivo in swine.

Phase II Activities and Expected Deliverables

In addition to meeting all requirements for Phase I, a phase II award would support testing and regulatory development for the device to be used in human investigation in the United States, under Investigational Device Exemption or other mutually agreed pathway. All FDA communications regarding the device should be shared with NHLBI.

The contracting DIR lab offers to perform an IDE clinical trial at no cost to the awardee. A complete Early Feasibility Study IDE application short of device verification and validation testing would constitute the deliverable.

A plan for separate Bridge-to-Commercialization funding support is invited to complete the Early Feasibility IDE licensed clinical study.

Offers are encouraged to supply a detailed milestone plan.

The offeror should have a proven track record of safe and compliant early-phase clinical testing of structural heart cardiovascular implants in the United States.

110 MRI myocardial biopsy system

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

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

Number of anticipated awards: 2

Budget (total costs): Phase I: \$400,000 for up to 12 months; Phase II: \$3,000,000 for 24-36 months

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

Summary

Endomyocardial biopsies are performed approximately 10,000 times each year worldwide. The procedure suffers large anatomic sampling error because of no current appropriate image guidance. Endomyocardial biopsy is currently performed without targeting, whether under X-ray or ultrasound guidance. This may account for the known low diagnostic yield and high sampling error.

MRI operation affords exquisite imaging and delineation of soft tissue beyond what is afforded by X-ray fluoroscopy, CT, and ultrasound guidance. Image-guided myocardial biopsy using MRI might enhance the diagnostic utility and safety of myocardial biopsy in inflammatory or infiltrative cardiomyopathies. This solution would be especially attractive in pediatrics, where the risk of and need for biopsy is higher than in adults, yet the need more frequent.

This solicitation aims to support the development of an MRI myocardial biopsy forceps and accessories for commercial clinical availability.

Project Goals

The goal of the project is to develop a myocardial biopsy catheter of materials safe for MRI operation yet sufficiently sharp to extract myocardial tissue effectively. First a prototype would be developed and tested in animals, and ultimately a clinical-grade device would undergo regulatory development for clinical testing.

This project should generate an Early Feasibility Study (EFS) IDE for clinical evaluation at NIH or another suitable medical center, towards commercialization through a mechanism such as Phase IIb bridge-to-commercialization. Alternatively it is possible that 510(k) market clearance can be achieved depending on the selected technologies.

Phase I Activities and Expected Deliverables

A phase I award would develop and test a biptome prototype along with necessary accessories. The awardee deliverable would be tested *in vivo* at NHLBI DIR.

The specific deliverable would be:

- Myocardial biopsy forceps catheter with an outer diameter 6-7 French
- Biptome sharpness equivalent or superior to commercially available stainless steel myocardial biopsy forceps catheters
- Able successfully to cut endomyocardial biopsy specimens 1-2mm x 2-3mm each
- Deflectable curve or shapable to impart a curve analogous to Stanford-style endomyocardial biptome
- Suitable for transjugular or transfemoral venous biopsy of the right ventricle or transfemoral arterial retrograde aortic biopsy of the left ventricle
- Free from clinically-important heating (2°C at 1W/kg SAR) during MRI at 0.55T-1.5T
- Visibility during MRI. If visible using magnetic susceptibility phenomena, the tip should be distinctly visible, and at least the distal 40cm of the shaft should also be visible. In general, susceptibility markers should be > 3mm in diameter using commonly used steady state free precession or fast gradient echo MRI techniques.
- There should be a characteristic imaging signature that distinguishes the “open” from the “closed” position of the biopsy forceps, using MRI
- The deliverable includes all accessories necessary to perform right and left ventricular biopsy under real-time MRI guidance via a pre-positioned vascular introducer sheath. This specifically includes MRI-conspicuous guiding catheters or sheaths, whether pre-shaped or deflectable.
- Proposals for alternative visualization strategies, such as “active” or “inductively-coupled” receiver coils, are welcomed.

A phase I award would develop and test functioning MRI myocardial biopsy forceps system, including accessories, *in vivo*. The contractor should provide a detailed report of pre-IDE interactions with the Food and Drug Administration to identify requirements for premarket notification [510(K)] under Phase II, including the summary of mutual understanding.

The contracting DIR lab is willing to provide feedback about design at all stages of development. The contracting DIR lab will test the final deliverable device for success *in vivo* in swine. This may require tailored hardware compatibility with the NIH investigational MRI system, or the test can be performed by NHLBI DIR staff at an outside facility.

Phase II Activities and Expected Deliverables

A phase II award would allow mechanical and safety testing and regulatory development for the device to be used in human investigation, whether under Investigational Device Exemption or under 510(k) marketing clearance. The contracting DIR lab offers to perform a IDE clinical trial at no cost to the awardee.

All FDA communications regarding the device should be shared with NHLBI.

Proposals should include key milestone for contract review including FDA presubmission meeting(s), design lock, DFEA creation and completion, GLP experiments, etc.

IDE license or 510(k) clearance and 10 functioning clinical devices would constitute the deliverable.

NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM (NIAAA)

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) conducts and supports research to expand and disseminate fundamental knowledge about the effects of alcohol on health and well-being, and apply that knowledge to improve diagnosis, prevention, and treatment of alcohol-related problems, including alcohol use disorder, across the lifespan. To learn more about the NIAAA, please visit our web page at <https://www.niaaa.nih.gov>.

NIAAA Topics

This solicitation invites proposals in the following areas:

018 Alcohol Biosensor Development for Continuous Alcohol Consumption Monitoring

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

Number of anticipated awards: 1-3

Budget (total costs, per award): Phase I: up to \$500,000 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.

Background

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) seeks a wearable or otherwise discreet device capable of measuring, recording and storing blood alcohol levels in real time. Alcohol biosensors that are unnoticeable by the user and provide continuous alcohol use monitoring will advance the mission of NIAAA in the arenas of research, treatment, rehabilitation, and recovery.

For example, research that seeks to understand the progression of medical conditions exacerbated by alcohol to discover treatments depends on the ability to accurately measure and record alcohol consumption continuously over time. Alcohol biosensors will simplify the process of determining close to real time alcohol consumption for both the scientists and the participants by providing an objective, biomedical measure of alcohol consumption; allowing participants to avoid the inconvenience and discomfort of having blood drawn at regular intervals. Likewise, during treatment of individuals with alcohol use disorder (AUD), and especially in clinical trials designed to identify the most effective treatments for AUD, it is essential to know accurately the extent of alcohol consumption of trial participants to determine the effectiveness of the intervention being studied. The current method of determining alcohol consumption (Time-Line Followback (TLFB)) is cumbersome, time-consuming, relies on retrospective recall and can be highly variable from one interviewer to another. Alcohol biosensors in contact with the human body will decrease the assessment variability experienced with the TLFB and increase the rigor and reproducibility of measuring alcohol consumption in clinical trials. Current technological developments in electronics, miniaturization, wireless technology, and biophysical techniques of alcohol detection in humans increase the likelihood of successful development of a useful alcohol biosensor in the short term.

Objectives

NIAAA seeks the design and production of a discreet device to measure, record, and store blood alcohol levels in real time (or close to real-time). The device should be inconspicuous, low profile, and appealing to the wearer. The design can take the form of jewelry, clothing, or any other format located in contact with the human body. The detection of alcohol should be passive, close to real time, and accurate.

Alcohol biosensors that detect consumed alcohol in sweat or sweat vapor have been used in criminal justice settings for a decade or more. More recently, advances in more discreet wearable alcohol sensing devices has been made; however, these still depend on detection of alcohol in the sweat, rather than in blood. It is important to note that there is a forty-minute to two-hour lag in detection of alcohol in sweat relative to actual blood alcohol levels. Under certain circumstances, this can have significant consequences. For this reason, this solicitation seeks the development of techniques that are not sweat-based. Only advances in alcohol detection that depart from measuring alcohol in sweat or sweat vapor will be responsive to this solicitation. Offerors are encouraged to pursue any technology - including but not limited to- biophysical, optical, wave, or other novel approaches that passively quantify blood alcohol in human subjects... NIAAA recognizes that there are other technologies that also offer promise; so innovative, original approaches to alcohol quantification as well as the adaptation and miniaturization of existing technologies are welcome.

The device should be able to quantitate blood alcohol level, interpret, and store the data or transmit it to a smartphone or other device by wireless transmission. The device should have the ability to verify standardization at regular intervals and to

indicate loss of functionality. The power source should be dependable and rechargeable. Data storage and transmission must be completely secure for the protection of the privacy of the individual. A form of subject identification would be an added benefit. If the device is removable by the user, the ability to record the exact time the device is removed is preferred. Ideally, the device will be stable, with expectation of long-term function. The design should be acceptable to the wearer from comfort, privacy, financial, and convenience standpoints.

It is envisioned that subject alcohol monitoring will serve useful purposes in research, clinical, and treatment settings, may play a role in public safety, and will be of interest in the consumer market to individuals interested in tracking personal health parameters. Designs may emphasize any of these potential market subsets or may seek to be broadly marketable.

While achievable lower limits of detection remain to be demonstrated, devices capable of detecting 0.02% BAC would be of value to NIAAA.

To apply for this topic, offerors should:

Include a description of the technology by which the device will quantitate blood alcohol level. Provide preliminary data or cite literature to support the rationale for the underlying approach. If modifying an existing technology to wearable scale, describe the potential for success of the miniaturization process. Explanations of data handling should discuss how the device will collect, interpret, store and protect the data or transmit it to a smartphone or other device by wireless transmission and address data security measures. The approach should address the ability to verify standardization at regular intervals and to alert a loss of functionality. The power source, charging duration, and battery life (if applicable) should be addressed.

Since alcohol biosensors may be of great benefit to treatment professionals, clinicians, researchers, and individuals, designs may emphasize any of these potential market subsets or may seek to be broadly marketable. Proposals should identify the intended target audience(s) and provide the rationale for their design decisions regarding both technology and form factor.

This SBIR will not support:

Development or improvement of biosensors that detect alcohol exuded through the skin in sweat or vapor.

Phase I activities and expected deliverables

- Demonstration of the ability of the technology to detect alcohol.
- Demonstration that the detection signal is proportional to amount or concentration of alcohol.
- Demonstration of the specificity of alcohol detection in blood or a solution approximating the physiological mixture.
- Demonstration of the limit of detection (sensitivity).

While not required, if validation of new or existing technology in human subjects is proposed in the Phase II portion, evidence of the availability of existing clinical infrastructure and knowledge and familiarity with NIH and FDA regulations on human protections must be provided before progression to the Phase II.

As the development of a wearable alcohol biosensor is a priority for NIAAA (https://www.niaaa.nih.gov/sites/default/files/StrategicPlan_NIAAA_optimized_2017-2020.pdf) and NIH (<https://www.nih.gov/sites/default/files/about-nih/strategic-plan-fy2016-2020-508.pdf>), NIAAA envisions that the Phase I milestones will be quickly met, leading to rapid advancement to the Phase II period.

Phase II activities and expected deliverables

- Incorporation the alcohol sensor into a discreet device in a form factor in contact with the human body.
- Refinements of functionality, accuracy, security, and integration of data collection, data transmission and data storage.
- Further refinement of accuracy of quantitation of blood alcohol concentration. Development of an algorithm that accurately converts the detection signal to blood alcohol concentration.
- Demonstration that the detection of alcohol is passive, not requiring action on the part of the wearer.
- Demonstration of frequency of measurement.
- Demonstration that the device shows the time of detection and that the BAC value corresponds to the time of measurement.

- Summary of human testing completed.
- Plans for process of manufacture.
- Evidence of a functional, marketable, alcohol biosensor is the specific deliverable of the Phase II portion of the contract.

019 Data Science Tools for Accelerating Alcohol Research

Fast-Track proposals will not be accepted.

Number of anticipated awards: 1-2 Budget (total costs, per award): Phase I: up to \$225,000 for 6-12 months.

Summary

NIAAA supported studies in genomics, imaging, electrophysiology and optogenetics, electronic health records, and personal wearable devices presents new challenges in analyses and interpretations and opportunities for discovery. The NIAAA data sharing policy (NOT-AA-18-101), effective January 25, 2019, expects that investigators and their institutions will submit their grant-related human subjects data to an NIAAA-sponsored data repository. The future data sources will be combined with significant current data repositories and archives, including: database of Genotypes and Phenotype, dbGaP, <https://www.ncbi.nlm.nih.gov/gap>, Collaborative Studies on Genetics of Alcoholism (COGA), <https://niaaagenetics.org/>, National Epidemiologic Survey on Alcohol and Related Conditions-III (NESARC-III), and the NIMH Data Archive, NDA, <https://data-archive.nimh.nih.gov/> to form a large and rich source for analysis of alcohol use, suitable for analysis by data science methods. Examples of electronic health records (EHRs) include: (NIH-funded) Health Care Systems Research Collaboratory, <https://commonfund.nih.gov/hcscollaboratory>, (NIH-funded) Clinical and Translational Science Awards (CTSA) Program, <https://ncats.nih.gov/ctsa/about/hubs>, Health Care Systems Research Network, <http://www.hcsrn.org/en/>.

Data science includes and extends beyond bioinformatics and computational neuroscience to discover new relationships and pathways for complex systems of normal human function and during adaptations due to disorders or disease. However, many of the tools needed to answer questions in alcohol research require specific applications, algorithms or toolkits that are not currently available. User-friendly methods and applications program interfaces (APIs) for retrieving metadata and data from the repositories for secondary analyses are not currently available. Alcohol researchers require assistance from data scientists to appreciate the power of tools such as machine learning, deep learning and artificial intelligence and the skills for programmers to implement analysis methods to answer key questions about alcohol use.

NIAAA is interested in analytical approaches and tools that can integrate data (i.e. genetic, social, economic, EHR, treatment approaches) to predict the development of alcohol use disorder, or the effectiveness of interventions that reduce or delay the onset or progression of alcohol use disorder, or guide effective treatment and management strategies for alcohol use disorder, including recovery and relapse. One possible example is a tool that assists researchers in developing a risk algorithm for alcohol use disorder when researchers combine multiple existing data sets. The tool could parse out age, sex, race/ethnicity, with alcohol use measures (quantity/frequency/binge episodes), consequences and other risk factors.

Project Goal

The goal is to develop data science analysis algorithms, mathematical models, and software tools for use in alcohol research, integrating data across disciplines and clinical and basic sciences realms.

Phase I Activities and Deliverables

Specific deliverables may include any of the following:

- New algorithms for integrative analysis of current NIAAA and public ‘big data’ sets, including machine learning, deep learning, artificial intelligence, data mining and other model based and model-free approaches.
- Software applications for data interfaces for aggregation, imputation, harmonization, or visualization of data from multiple sources, including current and future NIH data systems (i.e. NCBI (National Center for Biotechnology Information), dbGaP (database of Genotypes and Phenotypes), National Institute of Mental Health Data Archive), or other studies of alcohol research.

- Algorithms and/or software tools for improving data collection, i.e. smart phone apps, extraction of specific alcohol research parameters from existing large databases and established public health studies, biological sensors or wearable devices, natural language processing for analysis of survey data.
- Generation and validation of computational and/or systems biology models of alcohol exposure and use on cellular, organ, network, or organism scales. Multiscale models are appropriate, along with models that include data from clinical and basic science research.

Activities and deliverables are expected to use currently available data sets and databases. Offerors should discuss potential deliverables with NIAAA-supported researchers to determine research needs and goals. All funded NIAAA studies can be found in the public database, NIH RePORTER, <https://projectreporter.nih.gov/reporter.cfm>. The generation of new primary data is not supported by this topic.

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:

076 Co-delivery and Formulation of Adjuvants for HIV Vaccine Development

Fast Track proposals will be accepted.

Direct to Phase II will not be accepted.

Number of anticipated awards: 1

Budget (total costs):

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

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

Background

The RV144 Phase III Thai trial, which tested the heterologous prime-boost combination of two vaccines: ALVAC® HIV vaccine (prime) and AIDSVAX® B/E vaccine adjuvanted with Alum (boost), showed limited 31% protective efficacy and revealed the need for novel and more potent vaccine formulations. Co-delivery of adjuvant/immunomodulators with HIV antigens has the potential to modulate the type, quality, and durability of antigen-specific immune responses through a variety of mechanisms that include the induction of regulatory T cells or by altering the profile of the pathogenic lymphocyte response (e.g., Th1 to Th2 or vice versa). Significantly, induction of protective and long-lasting durable immune responses, activation of germline B cells along with enhanced magnitude and breadth of antibodies that can be harnessed by optimal HIV antigen-adjuvant/immunomodulators/Toll-like receptor agonists (TLR) formulations would aid in the rational design of a safe and effective preventive HIV vaccine. More recent efforts have focused on testing adjuvant formulations that can boost the immune response and generate broadly neutralizing antibodies to HIV-1 Env. Despite these efforts, significant challenges remain towards achieving optimal and effective immunogen/adjuvant formulations for an efficacious HIV vaccine.

While ongoing new strategies and efforts for developing an effective HIV vaccine have predominantly focused on design of new HIV immunogens and targets, an understudied area of investigation are studies involving co-delivery and formulation of HIV immunogens with adjuvants. As such, several challenges remain, including poorly understood and variable humoral and cellular immune responses in preclinical and clinical setting, lack of consistent tier 2 broadly neutralizing antibodies (nAbs), maintenance of Env immunogenicity, selection of optimal inoculation sites and trafficking to lymphatics, stability of the incorporated and/or co-delivered antigens and Env neutralizing epitopes in select adjuvant formulations, and induction of mucosal immunity and long-term maintenance/durability of the immune response.

Moreover, access to promising new/proprietary adjuvant systems developed by commercial organizations, development of effective combinations of adjuvant formulations and public-private partnerships are highly desirable and warranted for HIV vaccine development. While alum-based adjuvants and variations of oil-in-water approaches have been tested with other non-HIV recombinant protein immunogens, the results obtained from other immunogens, which are generally more stable and less glycosylated than Env protein, have been difficult to extrapolate to HIV vaccines. Finally, the empirical basis of studies and the large inter-laboratory variations in antigen/adjuvant mixture formulations and protein stability assays used to characterize these mixtures further limits the usefulness of these data for HIV vaccine research.

Project Goal

Co-delivery of adjuvants with HIV antigens combined with HIV immunogen design is not mutually exclusive and should converge to accelerate the development of safe and effective adjuvanted HIV vaccine candidates that are capable of effective B/T-cell activation, enhanced antibody avidity or broadening of effector immune responses while minimizing reactogenicity

and preserving the protective immune responses against HIV. The primary goal of this SBIR solicitation is to support, accelerate and advance early stage and/or pre-clinical development and optimization of a promising HIV antigen-adjuvant formulation or select combination-adjuvant(s) for co-delivery/co-administration for a preventative HIV vaccine.

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

- Developing optimal parameters/conditions for HIV protein antigen(s) and adjuvant co-formulations; developing conjugating technologies to attach immunogens to adjuvants.
- Developing and evaluating particulate adjuvant systems 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, biosimilars and/or novel adjuvants/TLR agonists.
- Evaluating formulations with immunomodulatory agents such as mineral salts, microbial products, emulsions, cytokines, chemokines, polymers, liposomes, lipid nanoparticles, saponins, carbohydrate adjuvants, TLR agonists, etc.
- Developing and harmonizing all relevant analytical assays and testing methods for physicochemical, biophysical and functional/potency characterization of antigen-adjuvant formulations and its individual components, as applicable.
- Evaluating and screening compatibility of excipients, buffers, pH on adjuvanted antigen formulations and its performance.
- Measuring the effects of these interactions using critical *in vitro* performance metrics and quality attributes related to vaccine adsorption, desorption, potency, antigen integrity, and stability.
- Developing and optimizing novel adjuvant combinations by admixing previously known individual adjuvants, including characterization of adjuvant combinations previously shown to enhance immune responses synergistically and/or additively.
- Evaluating conditions for vaccine presentation as a two-vial system with bedside mixing and/or one vial co-formulation of adjuvanted antigen.
- As appropriate, evaluating and comparing different adjuvanted formulations in small animal models, assess the influence of route of administration, delivery and dose-sparing capacity of HIV antigen-adjuvanted vaccines on the kinetics of immune response.
- Conducting short term stability studies on antigen-adjuvant formulations.
- Testing for batch-to-batch reproducibility and consistency of adjuvanted formulations for manufacturing.

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

- Developing lead antigen-adjuvant formulation into an efficient, stable and reproducible formulation 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).
- cGMP manufacturing processes for developing adjuvanted formulations.
- Evaluating the performance, effectiveness, and toxicity of adjuvanted HIV vaccine candidates vs. soluble antigen in small animal models.
- Evaluating adjuvants in NHP studies.
- Establishing quality assurance and quality control, methodology and development protocols for generation of HIV antigen-adjuvanted formulations for co-delivery.

As appropriate, collaborating and/or partnering with different labs to harmonize inter-laboratory variations in antigen/adjuvant mixture formulations and for characterization and protein stability assays.

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

Fast Track Proposals will be accepted.

Direct to Phase II will not be accepted.

Number of anticipated awards: 2-4

Budget (total costs):

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

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

Background

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 codelivery.

078 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.

079 Small Molecule Targeting of HIV RNA

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 one year;

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

Background

Therapeutic targeting of RNA may be a strategy which could inhibit the translation of one or more disease-associated proteins. Antisense technologies have been highly effective; however, these technologies rely on derivatized oligonucleotide structures which have poor cell permeability and biodistribution which limits their effectiveness as a therapeutic. The identification of detailed RNA structures now allows the design of small molecules which are capable of binding to RNA with high selectivity and specificity. This strategy has the potential to expand the use of small molecules beyond inhibiting functional activity, by preventing the translation of mRNAs, so that the targeted protein is never expressed.

Small molecule drugs have been developed that successfully inhibit several HIV intracellular proteins. However, a number of HIV proteins have not been successfully inhibited since they lack a reactive site that can bind a small molecule. By developing small molecules to selectively bind to key sites on transcribed HIV RNA the translation of RNA to protein may be inhibited for any HIV intracellular protein. Targeting one or more HIV RNA sequences with small molecules may be an effective way of shutting down viral replication, preventing cellular transmission and ultimately leading to sustained viral remission.

Project Goal

The goal of this SBIR solicitation is to support the discovery and design of RNA-targeted small molecules which specifically bind to HIV RNA transcripts to prevent RNA processing and translation into protein.

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

- Designing, optimizing and testing strategies for the targeting of small molecules to key sites on HIV RNA.
- Performing proof-of-concept studies to demonstrate that small molecule binding to HIV RNA can prevent processing and translation into proteins in relevant cell lines and primary cells.
- Evaluating off-target effects.
- Performing proof-of-concept studies in an HIV animal model.

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

- 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.

080 Adjuvant Discovery for Vaccines against Infectious or Immune-mediated Diseases

Fast-Track proposals will be accepted.

Direct-to-phase II proposals will be accepted.

Number of anticipated awards: 1-3

Budget (total costs):

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

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

Background

The goal of this program is to support the screening for new vaccine adjuvant candidates against infectious diseases or for tolerogenic adjuvants for immune-mediated 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.

The field of tolerogenic adjuvants is still in its infancy. No compounds have been licensed yet in the U.S. and immune-mediated diseases continue to be treated mostly with broadly immunosuppressive drugs or long-term single or multi-allergen immunotherapy. In contrast to drugs, tolerogenic or immunomodulatory adjuvants would interfere with immune responses to specific antigens through a variety of mechanisms including the induction of regulatory T cells, or by changing the profile of the pathogenic lymphocyte response (e.g., Th1/Th2/Th17, etc).

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 for 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., 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). Examples of applications of tolerogenic adjuvants include: combination with allergen immunotherapy to accelerate tolerance induction, increase the magnitude of tolerance and decrease treatment duration; and combination with self- or donor-derived antigens to induce tolerance in the recipient.

Project Goal

The objective of this program is to support the screening for new adjuvant candidates for vaccines against infectious diseases or for immune-mediated diseases (autoimmune and allergic diseases or transplant tolerance); adjuvant 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 testing of newly identified immunomodulatory compounds or formulations as stand-alone immunotherapeutics (i.e., without a specific antigen)
- The testing of newly identified immunomodulatory compounds or formulations in cancer models
- The further development of previously identified adjuvants, if being used for the original indication (i.e., in vaccines against infectious diseases or as a tolerogenic 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)

081 Adjuvant Development for Vaccines against Infectious or Immune-mediated Diseases

Fast-Track proposals will be accepted.

Direct-to-phase II proposals will be accepted.

Number of anticipated awards: 1-3

Budget (total costs):

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

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

Background

The goal of this program is to support the preclinical development of novel vaccine adjuvant candidates against infectious diseases or of tolerogenic adjuvants for immune-mediated diseases (i.e., autoimmunity, organ/tissue transplant rejection, allergic diseases and asthma). 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, donor-specific-antigens in transplant rejection, 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).

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, or for autoimmune or allergic diseases, or organ/tissue transplantation tolerance. The adjuvant products supported by this program must be studied and further developed toward human licensure with currently licensed or new investigational vaccines and cannot be developed as stand-alone agents.

Phase I Activities

Depending on the developmental stage at which an adjuvant is entered 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

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 used 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
- Discovery of the vaccine's antigen component, though further development as part of adjuvant/antigen formulation is acceptable

- The development of immunostimulatory compounds or formulations as stand-alone immunotherapeutics (i.e., without a specific antigen/pathogen-specific vaccine component)

082 Production of Adjuvants

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 adjuvants with those used in licensed vaccines or at late stages of clinical development is hampered by limited access to such reagents. NIAID supports the discovery and development of novel adjuvants through different mechanisms; and this topic is intended to address the limited availability of adjuvants that mimic the functionality of those with a favorable clinical track record. This topic also supports the development of formulations with immunostimulatory components that are functionally, but not necessarily chemically, similar to those used in licensed vaccines or at late stages of development

Project Goal

Development, validation and production of adjuvants that are based on, or similar to, compounds or formulations successfully used (i.e., efficacious) in clinical trials or part of licensed vaccines, 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 are 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
- 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)
- **Intellectual Property:** The awardee is solely responsible for the timely acquisition of all appropriate proprietary rights, including intellectual property rights, and all materials needed for the awardee to perform the project. Before, during, and subsequent to the award, the U.S. Government is not required to obtain for the awardee any proprietary rights, including intellectual property rights, or any materials needed by the awardee to perform the project. .

083 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 specific 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- κ B 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 specific non-mammalian models or underrepresented mammalian models. Justification should be provided for the selection of proposed targets which may include immune cell markers, receptors with immune function and or other molecules important for immune function. 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:

- Development of antibodies or other reagents against these targets
 - If polyclonal antibodies are being developed, the plan also must include the development of monoclonal antibodies
- Characterization of antibodies or reagents developed (e.g. confirmation of binding to intended antigen/immunogen)

Phase II Activities MAY include, but are not limited to:

- Comprehensive evaluation of specificity and functional utility of the reagent(s), such as evaluation of non-specific binding to cells or unrelated molecules and utility of antibodies/reagents for specific indications (e.g., Western blotting, immunoprecipitation, immunohistochemistry, flow cytometry)
- Screening for cross-reactivity with related molecules on other non-mammalian species or mammalian immune cells
- Optimization (e.g., secondary modifications/conjugations) of the antibodies/reagents for use in different assays and platforms
- Scale-up production of the reagents

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

084 Antiviral drugs to cure chronic hepatitis B virus infection

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

Chronic infection with hepatitis B virus (HBV) leads to serious and often fatal liver diseases like cirrhosis and hepatocellular carcinoma. Current therapy uses potent antiviral drugs that significantly lower viral replication in patients. However, all the currently used small molecule drugs - nucleoside/nucleotide analogs - target the function of a single HBV protein, the polymerase (reverse transcriptase), and none achieves complete and permanent cure. Thus, these drugs are used for many years, even lifelong, at the risk of inducing toxicity and drug resistance. With the elucidation of new viral and cellular targets and pathways involved in HBV infection and replication, novel antiviral drugs may be within reach. Novel drugs may potentially be used as monotherapies or in combination with existing therapies. It is imperative that the pace of development of new drugs be measurably accelerated to lower the very substantial global burden of HBV.

Project Goal

The purpose of this solicitation is to invite research on candidate drugs and mechanisms of action different from that of existing licensed drugs, and pre-clinical development of such candidates, with the express purpose of advancing them commercially. The objective is to obtain functional cure of HBV - defined as loss of virus, loss of hepatitis B surface antigen (HBsAg) and seroconversion, which rarely occurs with current regimens. As the intent of this project is to obtain potentially curative drugs, it may be necessary to develop, in parallel, additional determinants of post-treatment efficacy (both short- and intermediate-term).

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

- Selection of lead compounds that efficiently target viral or cellular products or pathways with potent anti-HBV effects and low cell toxicities.
- Studies on mechanisms of action of potent inhibitors of HBV and/or host cellular pathways that support HBV infection, replication, and persistence.

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

- Developing promising selected lead compounds characterized in phase I studies, including investigating structure activity relationships (SARs) for optimization of lead compounds.
- Studying efficacy parameters of new anti-HBV drug candidates in an animal model of HBV replication, as envisioned in the project goals.
- Optimizing absorption, distribution, metabolism, and excretion (ADME); pharmacokinetics (PK); and minimizing cytotoxicity.
- Examining potential synergistic activity of candidate drug with currently used standard of care HBV drug(s).

This SBIR will not support:

The design and conduct of clinical trials (see <http://www.niaid.nih.gov/researchfunding/glossary/pages/c.aspx#clintrial>) for the NIH definition of a clinical trial). For SBIR phase II clinical trial support, see the [NIAID SBIR Phase II Clinical Trial Implementation Cooperative Agreement program announcement](#).

085 Broad spectrum antibody against human enteroviruses

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

Human enterovirus (HEV) infections can cause a variety of conditions including conjunctivitis, hand-foot-mouth disease (HFMD), viral meningitis, viral encephalitis, pericarditis, acute flaccid paralysis (AFP), myocarditis, and possibly type 1 diabetes. While HEV infections are common and generally mild, in some patients HEV infections can cause severe symptoms, including sepsis in neonates, aseptic meningitis in children, and meningitis in adults. EV-D68, EV-71, and coxsackie viruses have been implicated in causing acute flaccid myelitis (AFM) in recent years. Currently, there are no therapeutics available to treat enterovirus infections. There are seven HEV species, each of which includes multiple members, and many of them are known to cause disease. Non-pathogenic strains can evolve to acquire pathogenic potential as well, which can cause difficulty for therapeutic development. One way to address this problem is to focus on broad-spectrum therapeutics, specifically monoclonal antibodies.

Project Goal

The goal of this topic is to develop broad spectrum prophylactic and therapeutic monoclonal antibody therapeutics against human enteroviruses. The final product can be monoclonal antibodies specific to multiple enteroviruses, a combination of multiple monoclonal antibodies with a narrow specificity, or both. The final product should target different strains of a single family, for example, multiple EV-D68 strains, multiple members in one species (for example Enterovirus A species), or members in multiple species (for example, coxsackie viruses in A and B species). The choice of strains should be medically relevant.

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

- Develop multi-spectrum monoclonal antibodies.
- Demonstrate neutralizing activity in vitro against target enteroviruses.
- Humanize antibodies if applicable.

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

- Further improve multi-spectrum humanized monoclonal antibodies including but not limited to humanizing monoclonal antibodies and improve potency.
- Demonstrate therapeutic potential in animal models.
- Develop an efficient delivery system.

This SBIR will not support:

- Products primarily focused on poliovirus.

The design and conduct of clinical trials (see <http://www.niaid.nih.gov/researchfunding/glossary/pages/c.aspx#clintrial>) for the NIH definition of a clinical trial). For SBIR phase II clinical trial support, see the [NIAID SBIR Phase II Clinical Trial Implementation Cooperative Agreement program announcement](#).

086 Development of rapid fungal diagnostics for select endemic dimorphic fungi

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

Timely recognition and treatment of invasive fungal diseases (IFDs) is necessary to reduce the morbidity, mortality and inappropriate antibiotic usage commonly associated with IFDs. Recent medical advances in the management of cancer patients and hematopoietic stem cell and organ transplantation, in addition to immunocompromising diseases, such as AIDS, have created an expanding population at risk for IFDs. Unfortunately, the management of patients with suspected IFDs often involves empiric, prophylactic antifungal therapy until the results of time-consuming, culture-based and/or highly technical assays are made available. The prophylactic use of antifungal agents is associated with an increase in resistance to the available antifungal therapies and a rise in fatal IFDs by previously rare fungal organisms such as the Mucorales and *Fusarium* spp. Assays that rapidly diagnose fungal infections will preserve the utility of the available antifungal therapies and reduce the inappropriate use of antibiotics.

Project Goal

The purpose of this project is to support the development of rapid, sensitive, specific, simple, and cost-effective diagnostics for primary health-care settings (hospitals and point-of-care (POC)) to detect IFDs.

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

- Identification of appropriate biomarkers for a prototype POC diagnostic for invasive fungal diseases.
- Development of the prototype POC diagnostic product for detection of invasive fungal diseases.
- Determination of the sensitivity, specificity and other performance characteristics (e.g. time to result, limit of detection, test stability) of the prototype POC diagnostic.

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

- Further characterization of appropriate biomarkers for a prototype POC diagnostic for invasive fungal diseases.
- Further development of the prototype POC diagnostic product for detection of invasive fungal diseases.
- Further determination of the sensitivity, specificity and other performance characteristics (e.g. time to result, limit of detection, test stability) of the product.
- 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). For clinical trial support, please refer to the [NIAID SBIR Phase II Clinical Trial Implementation Cooperative Agreement program announcement](#) or the NIAID Investigator-Initiated Clinical Trial Resources [webpage](#).
- Proposals that do not include the identification of at least one of the following dimorphic fungi: *Coccidioides* spp, *Histoplasma* spp, *Blastomyces* spp, *Paracoccidioides* spp, *Talaromyces* spp, and *Sporothrix* spp.

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.

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

The CDC's National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP) carries out a variety of activities that improve the nation's health by preventing a range of chronic diseases such as arthritis, cancer, diabetes, heart disease, obesity and stroke, while promoting health and wellness in the areas of reproductive health, oral health, nutrition and physical activity. The Center's activities include supporting states' implementation of public health programs; public health surveillance; translation research; and developing tools and resources for stakeholders at the national, state, and community levels.

NCCDPHP's Web site: <http://www.cdc.gov/chronicdisease/index.htm>

NCCDPHP Topics

For this solicitation, NCCDPHP invites Phase I proposals in the following areas:

043 Objective Measurement of Opioid Withdrawal in Newborns

Phase I SBIR proposals **will** be accepted.

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

Phase I clinical trials will be accepted.

Number of anticipated awards: 1

Budget (total costs): Phase I: up to \$150,000 for up to 6 months

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

Background

Reflective of the larger opioid epidemic, the number of newborns dependent on opioids has increased dramatically, from 2,920 in 2000 to 31,904 in 2014, the latest year of published data. These newborns experience withdrawal symptoms after birth, which can include: high-pitched and excessive crying, increased muscle tone, uncontrollable shaking (tremors), sweating or fever, rapid breathing rate, frequent yawning, and poor feeding and growth. Newborns born dependent to opioids have longer birth hospitalizations (17 days versus 2 days mean length of stay for a healthy newborn) and higher hospitalization costs (\$19,340 versus \$3,700 for a healthy newborn). Assessment of withdrawal symptoms depends on the judgement and

experience of clinical staff, which may vary and can result in inadequate treatment. For example, assessment of a high-pitch and excessive cry can vary between nurses. Different observations can result in incorrect treatment. Additionally, it may be difficult for staff to distinguish whether observed symptoms are due to withdrawal or simply waking a sleeping newborn at set times. Using technology to standardize symptom measurement would reduce variation in diagnosis and quality of care; however, no such device exists. Creating a device that objectively measures withdrawal symptoms in a continuous manner could greatly improve the care of these newborns.

Project Goals

The goal of this project is to create a wearable device that objectively measures a newborn's withdrawal symptoms, including:

1. tremors (frequency and duration, start and stop time);
2. muscle tone (degree of rigidity);
3. crying (frequency, duration, pitch);
4. body temperature (fluctuations); and,
5. sleep (duration, frequency of sleep cycles).

The device will have the following characteristics:

1. small and unnoticeable for newborn wear;
2. humidity-resistant;
3. bacteria-resistant (infection-controlled);
4. single use;
5. wireless;
6. able to capture data for 12-hours without interruption; and,
7. user-friendly interface for clinicians to view symptoms.

Phase I Activities and Expected Deliverables

The expected deliverable for Phase I is a functional prototype with the above mentioned specifications. Wearable technology is capable of capturing body temperature, movement, and sleep cycles for adults. It is anticipated that this technology could be adapted or developed for newborns. Activities for Phase I include:

1. Build upon existing technology to create a device that not only captures body temperature, movement, and sleep, but also sound (crying frequency, duration, pitch) and muscle tone (degree of rigidity);
2. Ensure the device is small enough and safe for newborn wear;
3. Create a user-friendly interface to view symptoms and guide diagnosis, treatment, and management of opioid withdrawal in newborns.

Impact

The number of newborns with opioid withdrawal has increased dramatically from only 2,920 newborns in 2000 to 31,904 newborns in 2014. In 2011-2014, newborns with opioid withdrawal cost Medicaid \$462 million. A device that assists clinicians in accurate assessment of withdrawal symptoms in newborns could lead to improved diagnosis and management along with shorter lengths of stay (and lower costs).

Exposure to medication-assisted treatment can also lead to newborns with opioid withdrawal. Initiatives to improve the care of these newborns, supplemented by devices that can objectively monitor symptoms, is key to improving quality and standards of care.

To be successful, the awardee will have to demonstrate ability to design a safe, functional device (as described above) and navigate Institutional Review Board approval for any potential clinical research or requirements necessary for FDA approval. Compliance requirements for FDA approval may vary depending on how the device is developed.

Commercialization Potential

This technology could greatly improve the diagnosis and management of newborns with opioid withdrawal in hospitals and neonatal intensive care units. In 2014, over 31,904 U.S. newborns had opioid withdrawal and stayed an average of 15 days in

the hospital longer than newborns without withdrawal. Estimates of newborns with opioid withdrawal are expected to increase with the ongoing opioid epidemic. This technology could be used across the U.S. in all hospitals and neonatal intensive care units that care for newborns with withdrawal.

NATIONAL CENTER FOR ENVIRONMENTAL HEALTH (NCEH)

The environment is everything around us: the air we breathe, the water we drink and use, and the food we eat. At the National Center for Environmental Health (NCEH) we work to prevent illness, disability, and death from contacts between people and the environment. We are especially committed to protecting the health of vulnerable populations — children, the elderly, and people with disabilities – from certain environmental hazards. NCEH will prioritize funding meritorious applications that address the NCEH program topics listed in this program announcement. NCEH may also consider meritorious applications that address current NCEH research priorities. To learn more about NCEH research priorities, please visit our web site at: https://www.cdc.gov/nceh/information/mission_vision_goals.htm

NCEH's Web site: <https://www.cdc.gov/nceh/information/about.htm>

NCEH Topic

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

002 Web-Based Platform for Flooding Vulnerability and Healthcare Access

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

Number of anticipated awards: 1
Budget (total costs): Phase I: up to \$150,000 for up to 6 months

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

Background

The number of extreme flooding events that have been declared as “Billion Dollar Disasters” by federal agencies have increased in the last decade. Projections are that such events will become more widespread, as well as increase in frequency and intensity in the years to come. The direct impact of these flooding events cause disruptions in the provision of healthcare by affecting the operations of critical health infrastructure (such as hospitals) as well as impede access to care when roads become flooded. The lack of robust information on potential risk of flooding for healthcare facilities (e.g., hospitals, urgent care centers, and pharmacies) and real-time information on flooding that impedes patients’ access to care affects preparedness planning before and during flooding events. There are no existing online platforms or websites that link flooding and hospital data to aid healthcare resiliency and protect public health during floods.

Project Goals

The goals of this project are to (i) prepare a national database that assesses the risk of flooding to health facilities (e.g., hospitals, urgent care centers, and pharmacies); and (ii) disseminate information via a web-based platform or app on baseline risk and real-time information on inundation zones through mobile technology to stakeholders (e.g., facility managers, patients, emergency responders) that would facilitate preparedness planning. The ultimate goal of this project is the launch of an online data portal or platform, providing high-resolution spatial information on baseline flood risk and real-time inundation information. The proposed data platform, intended to receive updated data feeds from federal agencies and private partners, can protect human health during flooding disasters by facilitating access to healthcare and emergency care.

Phase I Activities and Expected Deliverables

The expected deliverables are the:

1. Collection and synthesis of publicly available baseline flood risk information from sources such as the Environmental Protection Agency (EPA) and the Federal Emergency Management Association (FEMA).
2. Creation of a national dataset of critical healthcare facilities using data from sources such as the American Hospital Association, Urgent Care Association, and "Healthcare Ready." Software developers must attend to privacy concerns associated with these data systems (e.g., protected health and law enforcement data).

3. Merging of two datasets into a single pilot web-based platform that overlays flooding maps with healthcare facilities, demonstrating potential facilities at risk from flooding. Software must be user-friendly, and accompanied by guidance for effective utilizations of the platform.

Impact

This project will provide scientifically robust risk information that will facilitate healthcare agencies development of preparedness plans to improve resiliency to extreme weather events. Individual patients seeking emergency and/or regular healthcare services can use the mobile app to seek alternatives, if normal services are disrupted due to an extreme weather event. This can improve the resiliency of the healthcare system and access to care.

Commercialization Potential

The resulting platform or app could be seen as a unique innovation and beneficial to hospitals, long-term care facilities, other healthcare facility managers, healthcare transportation-related companies (e.g. ambulance contractors and others that may travel roads to healthcare facilities that could be impeded by flood waters), and other relevant users.

NATIONAL CENTER FOR EMERGING ZOO NOTIC 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:

021 Assay to Detect and Quantify *E. Coli* O157 in Water Samples

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

Number of anticipated awards: 1-2

Budget (total costs): Phase I: up to \$150,000 for up to 6 months

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

Background

Current methods for detecting and quantifying *E. coli* in water samples do not detect *E. coli* O157 or other related Shiga toxin-producing *E. coli* (STEC) strains. There are several commercially available assays to quantify *E. coli* in water samples; however, they rely on detection of the beta-glucuronidase enzyme, which is not present in STEC strains. Food Safety and Modernization Act (FSMA) regulations now require food producers to ensure that all water used for irrigation meet the standards for recreational water, which sets a maximum value at 126 cfu/100 ml. Despite this regulation, a multistate outbreak of *E. coli* O157 was linked to contaminated irrigation water used for romaine lettuce production. The outbreak strain was isolated from three irrigation water samples. Importantly, all three of these samples were below the FSMA-required *E. coli* levels, suggesting that even water that passes standard water quality metrics can harbor dangerous levels of *E. coli* O157.

Project Goals

The goal of the proposed research is to develop an assay that can detect and quantify *E. coli* O157 in water samples. This assay must be amenable to on-site use by stakeholders, such as farm managers, environmental health consultants, water managers, and packing shed managers. The assay can use molecular or non-molecular methods to detect and quantify *E. coli*, but must not require an advanced molecular laboratory. The assay will provide a quantitative measure of *E. coli* O157 present in the sample and must be able to detect 1 cfu/100 ml.

Phase I Activities and Expected Deliverables

The expected deliverables are:

1. Develop or adapt a method to detect and quantify *E. coli* O157 in water samples; the assay must be able to detect 1 cfu/100 ml.
2. Determine the sensitivity and specificity of the test against *E. coli* O157, other STEC serotypes, and non-STEC *E. coli*.
3. Conduct matrix evaluation to understand the assay performance using different water types (e.g., varied mineral or chemical composition, pH, etc. of the water source being tested).

Impact

The product of this proposed research will allow food producers to monitor their water supplies for *E. coli* O157, which is currently not possible. Once monitoring is available, control processes can be implemented to protect food products and ultimately reduce the burden of *E. coli* O157 infections.

Commercialization Potential

This research will lead to the development of a new water quality test method that can be implemented by stakeholders at every point in the supply chain from the farm to the packing shed operators. Potential products include assay kits, assay reagents, and water sampling devices. These products could be used by farm managers, water managers, and packing shed operators, as well as federal, state, and local public and environmental health agencies.

022 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** be accepted.

Number of anticipated awards: 1-2

Budget (total costs): Phase I: up to \$150,000 for up to 6 months

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

Background

Sampling surfaces to investigate disease transmission is a common practice. Surfaces touched by patients and healthcare workers, such as bedrails, tables, and 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; 4in²) and wipes or sponges (for larger surfaces; 100 – 200 in²), 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 metagenomics 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 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 bio threat 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 is able to 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 in² to 200 in² 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.

The criteria for a successful device are:

- 1) Easy to use.
- 2) Packaged as sterile and pre-moistened OR be easily pre-moistened aseptically at the sampling site.
- 3) Sterile gloves are not required by the person using the device to collect organisms from a surface.
- 4) After sampling, the device can be sealed aseptically to prevent contamination.
- 5) 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.
- 6) The 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.
- 7) Effective at collecting and eluting organisms, recovering the same log₁₀ level of organisms known to be present on a surface.
- 8) Low cost (<\$15 for each device).

Phase I Activities and Expected Deliverables

The expected deliverables are:

- 1) Develop prototype sampling, elution and concentration device.
- 2) 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, and 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 bio threat 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.

023 Diagnostic Testing Platform to Assess Antibiotic Activity on Microbial Communities of Cystic Fibrosis Patients

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

Number of anticipated awards: 1-2

Budget (total costs): Phase I: up to \$150,000 for up to 6 months

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

Background

Each year approximately 1,000 new cases of cystic fibrosis (CF) are diagnosed, with over 30,000 living with CF in the United States. Over half of the CF patient population is now over the age of 18; these patients are living longer and, consequently, are exposed to more and more antibiotics over time, often as part of the daily care regimen. Critically important for their care, these chronic and repeated antibiotic treatments can have unintended consequences, such as the development and spread of antibiotic resistance and multidrug-resistant organisms, including *Pseudomonas aeruginosa*. More than other patients, those with CF have suffered longest under the threat of untreatable pan-resistant infections

Antimicrobial susceptibility testing (AST) relies on standardized microbiological techniques assessing growth of pure cultures using either solid or liquid media and various concentrations of antibiotics. The inhibition of growth is predictive of treatment success and is 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). Lung infections in cystic fibrosis patients is one example of such infections; traditional antibiotic susceptibility testing fails to account for the impact of an antibiotic on the 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 goal of this project is to support the development of a standardized diagnostic platform for use in a clinical laboratory to determine the microbial community susceptibility/antibiogram of an infection using primary cystic fibrosis (CF) clinical specimens (i.e., sputum). This test should produce data useful for informing clinical treatment decisions. The proposal should incorporate appropriate methods for specimen management and processing, medium composition, including potential host factors that affect microbial growth or antibiotic activity *in vivo*, standard methodologies to arrive at a quantitative measurement of minimum inhibitory concentration, and back end detection/verification of target pathogen activity. Such work may involve laboratory-developed test methodologies/models or significantly adapted commercial platforms for use in parallel and in comparative assessments with standard clinical isolate-level 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 diagnostic test development will require dedicated and highly refined approaches specific to primary specimen and pathogen combination. The technical merit or feasibility of the proposed methodology should be assessed through initial bench-top (*in vitro*) studies of sputum, with the focus on a single pathogen and associated/community and matrix attributes. For these efforts, an existing set or bank of clinical sputum specimens from CF patients, collected longitudinally before, during, and after antibiotic treatment, and with complete data available (antibiotic treatment, single pathogen antimicrobial susceptibility testing results, clinical indicators and outcomes) is needed. These studies should be designed to provide a proof-of-concept.

Expected deliverables would include:

1. Establish a laboratory-developed *in vitro* test methodology/model, or significantly adapt an existing commercial platform, that can test clinical sputum specimens for microbial community-susceptibilities or yield a microbial community-antibiogram.
2. Apply the method/model from deliverable #1 to sputum from an existing set or bank of clinical specimens (described above), to track sequential sputum community composition (or changes in sputum community) following treatment with one or more antibiotics (same antibiotics as the patient received). Microbial community composition would be defined using next generation sequencing.
3. Proof of concept: Compare these *in vitro* community changes to microbial community changes observed in clinical sputum specimens from the same patient during/following antibiotic treatment. Demonstrate whether the *in vitro* microbial communities are or are not significantly different from the sequential clinical

sputum specimens from the same patient. Microbial community composition would be defined using next generation sequencing.

Impact

This project has the potential to impact antibiotic stewardship and therapeutic practice using available primary sputum 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. The results of this project have the potential to impact other settings involving intellectual property rights extended to preserving microbial community strata formulations for modeling biological interactions.

NATIONAL CENTER FOR IMMUNIZATION AND RESPIRATORY DISEASES (NCIRD)

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

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

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

034 Accelerating Time to Detection of *Legionella* in Environmental Samples

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

Number of anticipated awards: 1

Budget (total costs): Phase I: up to \$150,000 for up to 6 months

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

Background

Legionnaires' disease is a severe pneumonia typically caused by inhalation of aerosolized water containing *Legionella* bacteria. In the United States, more than 8,000 illnesses are reported annually, though this likely underestimates the true burden of disease. This represents an increase of more than 500% since 2000. When complex building water systems are not well maintained, *Legionella* bacteria can grow and spread, creating a risk for infection. Common sources of exposure to *Legionella* include showers, hot tubs, water misters, and large air conditioning devices known as cooling towers. During outbreak investigations, public health professionals often collect environmental samples from these and other devices to identify potential sources of exposure. Testing for *Legionella* bacteria is time-consuming, requires specific expertise, and typical takes between 7-14 days before results are available. Recently, PCR-based technologies have been introduced that have the potential speed up the testing process. Unfortunately, current tests that rely solely on detecting *Legionella* genetic material cannot distinguish between live and dead bacteria, limiting their usefulness. A test that could rapidly identify viable *Legionella* in environmental water samples has the potential to accelerate detection of exposure sources. This would significantly improve the ability of public health professionals to halt outbreaks of Legionnaires' disease when they occur.

Project Goals

The goal of this research is to develop a test that can rapidly detect viable *Legionella* bacteria in water samples collected from environmental sources. Ideally, this test would be simple to perform, have the ability to detect and identify all species of *Legionella* in a sample, and require minimal processing of the sample. The true innovation of this research would be shortening the time to detection and quantification of *Legionella* bacteria. A true breakthrough would require this time to be shortened considerably from the current 7-14 day requirement for traditional *Legionella* culture. A successful test would not need to be purely culture-independent if other project goals were met. This test would also not need to generate *Legionella* isolates.

Phase I Activities and Expected Deliverables

The expected deliverables are:

1. Develop a laboratory assay that detects viable *Legionella* bacteria in environmental (water) samples. The approach may use molecular, serological, or chemical procedures singly or in combination. Minimum performance criteria are:
 - Time to result less than 72 hours
 - Discrimination of strains of clinical interest (i.e., *Legionella pneumophila* serogroup 1.)

- Detailed typing information is not necessary, but at minimum, the procedure must be able to differentiate between *Legionella pneumophila* and all other *Legionella* spp.
2. Demonstrate proof of principle by comparing results with traditional *Legionella* culture methods. This could be accomplished using laboratory-generated, *Legionella*-containing water samples using multiple water sample sources (e.g. potable water, cooling tower basin water, utility distribution system water, etc.).
 3. Determine ranges of sensitivity and specificity for all water sample sources tested. If the procedure provides quantification of viable *Legionella*, the limit of detection and precision should also be determined.
 4. Develop a protocol to validate the assay in the field.

Impact

The development of a rapid assay would significantly advance public health response. The current 7-14 day wait time associated with *Legionella* culture testing can lead to additional cases of disease, limits the ability of public health to identify the exposure source, and delay recommendations that could protect the public. Shortening this time can speed up the response to cases and outbreaks of Legionnaires' disease. It could also lead to more widespread testing to identify risky exposure sources before they cause disease. The wait for testing results can delay the time before action can be taken to eliminate any risk that might be present. A more rapid test with actionable results could solve this problem. Finally, successful completion of this project could expand environmental *Legionella* testing to more public health, academic, hospital, and private labs. Currently *Legionella* culture testing is difficult to perform and requires significant expertise. A simpler test could lead to adoption of *Legionella* testing in more labs, increasing the ability for healthcare facilities, hotel owners, cooling tower operators, and state and local public health jurisdictions to obtain results during outbreak investigations or for routine testing purposes.

Commercialization Potential

A test developed as part of this research proposal has significant commercialization potential. Cases and outbreaks of Legionnaires' disease have increased significantly over the past 10 years. This has resulted in more investigations, which typically require testing of environmental samples. A product that simplified and sped up this process would be useful to both public health labs and private consulting companies. Recently, the Centers for Medicare & Medicaid Services (CMS) released a memorandum stating that all acute care facilities must implement a water management program to prevent the growth and spread of *Legionella* bacteria. While not required, many of these facilities may choose to begin routinely testing their water systems for presence of *Legionella*. A rapid, easy to administer, reliable test to detect *Legionella* could prove very useful for these facilities. Recent reports have estimated that the market for *Legionella* testing eclipsed \$180 million in 2016. This number is expected to increase to nearly \$400 million by 2025. The advent of a *Legionella* test that solves many of the problems associated with the current technologies could prove extremely lucrative from a commercial standpoint.

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. ***

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