

**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 2019-1**

**Closing Date: October 22, 2018, 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 22, 2018, 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\\_pd\\_with\\_1-8-14\\_amendments\\_2-24-14.pdf](https://www.sbir.gov/sites/default/files/sbir_pd_with_1-8-14_amendments_2-24-14.pdf) to read the SBIR/STTR Policy Directive issued by the Small Business Administration for further information.

# Table of Contents

<b>1</b>	<b>INTRODUCTION .....</b>	<b>1</b>
<b>2</b>	<b>PROGRAM DESCRIPTION .....</b>	<b>4</b>
2.1	Objectives.....	4
2.2	Three Phase Program .....	4
2.3	Fast Track Proposals (NIH Only).....	5
2.4	Direct to Phase II Proposals .....	5
2.5	I-Corps™ at NIH.....	5
2.6	Grant Opportunity - Phase IIB Competing Renewal Awards (INFORMATION ONLY) .....	7
2.7	Awarding Components.....	8
<b>3</b>	<b>DEFINITIONS.....</b>	<b>9</b>
3.1	General Definitions .....	9
3.2	Definitions (Relating to R&D).....	12
<b>4</b>	<b>PROPOSAL FUNDAMENTALS.....</b>	<b>17</b>
4.1	Introduction .....	17
4.2	Offeror Eligibility and Performance Requirements.....	17
4.3	SBIR/STTR Performance Benchmarks for Progress towards Commercialization.....	17
4.4	Multiple Principal Investigators .....	18
4.5	Joint Ventures and Limited Partnerships.....	18
4.6	Majority Ownership in Part by Multiple Venture Capital, Hedge Fund, and Private Equity Firms.....	18
4.7	Conflicts of Interest.....	18
4.8	Market Research.....	18
4.9	Debriefing .....	19
4.10	Phase I Award Information .....	19
4.11	Phase II Award Information .....	19
4.12	Registrations and Certifications .....	19
4.13	Promotional Materials .....	20
4.14	Prior, Current, or Pending Support of Similar Proposals or Awards.....	20
4.15	Reporting Matters Involving Fraud, Waste, and Abuse .....	21
4.16	State Assistance and Technical Assistance .....	21
4.17	Payment.....	22
4.18	Proprietary Information.....	22
4.19	Identification and Marking of SBIR Technical Data in Contract Reports and Deliverables.....	22
<b>5</b>	<b>CONTRACT REQUIREMENTS.....</b>	<b>23</b>
5.1	NIH Policy on Enhancing Reproducibility Through Rigor and Transparency.....	23
5.2	CARE OF LIVE VERTEBRATE ANIMALS, HHSAR 352.270-5(b) (December 2015).....	23
5.3	Animal Welfare .....	24
5.4	PROTECTION OF HUMAN SUBJECTS, HHSAR 352.270-4(b) (December 2015).....	24
5.5	Required Education in the Protection of Human Research Participants .....	24
5.6	Inclusion of Women and Minorities in Research Involving Human Subjects .....	25
5.7	Good Clinical Practice Training for NIH Awardees Involved in NIH-Funded Clinical Trials .....	25
5.8	Clinical Trial Registration and Results Information Submission .....	26
5.9	Single Institutional Review Board (sIRB).....	27
5.10	Research Involving Recombinant or Synthetic Nucleic Acid (Including Human Gene Transfer Research) .....	27
5.11	Copyrights.....	28

5.12	Technical Data Rights .....	28
5.13	Patents and Invention Reporting .....	29
5.14	Salary Rate Limitation .....	29
5.15	Other Contract Requirements.....	29
<b>6</b>	<b>METHOD OF EVALUATION .....</b>	<b>32</b>
6.1	Evaluation Process .....	32
6.2	Award Decisions .....	33
6.3	Phase I Technical Evaluation Criteria .....	33
6.4	Phase II Technical Evaluation Criteria.....	34
<b>7</b>	<b>PROPOSAL SUBMISSION .....</b>	<b>35</b>
7.1	Questions.....	35
7.2	Pre-Proposal Conference.....	35
7.3	Limitation on the Length of the Technical Proposal (Item 1) .....	35
7.4	Submission, Modifications, Revision, and Withdrawal of Proposals .....	35
<b>8</b>	<b>PROPOSAL PREPARATION AND INSTRUCTIONS .....</b>	<b>38</b>
8.1	Introduction .....	38
8.2	Fast Track Proposal Instructions (NIH Only) .....	38
8.3	Phase I Proposal Instructions .....	38
8.4	Phase II Proposal Instructions (NIH Only – For Fast Track Submissions).....	39
8.5	Technical Proposal Cover Sheet (Item 1).....	39
8.6	Table of Contents (Item 1) .....	40
8.7	Abstract of Research Plan (Item 1) .....	40
8.8	Content of Technical Element (Item 1) .....	40
8.9	Enhancing Reproducibility through Rigor and Transparency .....	45
8.10	Research Involving Vertebrate Animals .....	45
8.11	Dual Use Research of Concern .....	46
8.12	Human Subjects and Clinical Trials Information Form .....	47
8.12.1	Human Specimens and/or Data.....	47
8.12.2	Human Subjects Research with an Exemption from Federal Regulations.....	48
8.12.3	Protection of Human Subjects.....	48
8.12.4	Required Education in the Protection of Human Research Participants .....	50
8.12.5	Inclusion of Women and Minorities in Research Involving Human Subjects and Inclusion of Children in Research Involving Human Subjects .....	51
8.12.6	Data and Safety Monitoring in Clinical Trials .....	54
8.12.7	Plan for the Dissemination of Information of NIH-Funded Clinical Trial (ClinicalTrials.gov) .....	55
8.12.8	Plan for Single Institutional Review Board (sIRB).....	56
8.12.9	Research Involving Recombinant or Synthetic Nucleic Acid Molecules (Including Human Gene Transfer Research).....	57
8.12.10	Human Stem Cell Research .....	58
8.13	Content of the Pricing Proposal (Item Two). .....	59
8.14	Reminders .....	60
<b>9</b>	<b>SUMMARY OF HHS COMPONENTS ANTICIPATED NUMBER OF AWARDS .....</b>	<b>61</b>
<b>10</b>	<b>CONTRACTING OFFICER POINTS OF CONTACT FOR QUESTIONS RELATED TO SPECIFIC TOPICS .....</b>	<b>62</b>
<b>11</b>	<b>SCIENTIFIC AND TECHNICAL INFORMATION SOURCES .....</b>	<b>66</b>

<b>12 COMPONENT INSTRUCTIONS AND TECHNICAL TOPIC DESCRIPTIONS.....</b>	<b>67</b>
National Institutes of Health.....	67
National Center for Advancing Translational Sciences (NCATS).....	67
National Cancer Institute (NCI) .....	73
National Heart, Lung, and Blood Institute (NHLBI).....	102
National Institute on Alcohol Abuse and Alcoholism (NIAAA) .....	107
National Institute of Allergy and Infectious Diseases (NIAID) .....	110
National Institute on Drug Abuse (NIDA) .....	126
Centers for Disease Control and Prevention (CDC).....	132
Center for Global Health (CGH).....	132
National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP) .....	135
National Center for Emerging Zoonotic and Infectious Diseases (NCEZID) .....	139
National Center for Environmental health (NCEH) .....	141
Office of Public Health Preparedness and Response (OPHPR) .....	143
<b>13 APPENDICES.....</b>	<b>145</b>

## 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. Other Topics allow for ‘Fast Track’ submissions, which include both a complete Phase I proposal and a complete Phase II proposal. For more information on the three-phase program and the Fast Track process, refer to Section 2.**

TOPIC NUMBER	PHASE I PROPOSAL ALLOWED?	FAST TRACK ALLOWED? (A Phase I proposal and a Phase II proposal submitted simultaneously)	TOPIC TITLE
NIH/NCATS 016	Yes	No	Synthetic Technologies for Advancement of Research and Therapeutics (START)
NIH/NCATS 017	Yes	No	Universal Medium/Blood Mimetic for Use in Integrated Organs-on-Chips
NIH/NCATS 018	Yes	No	Non-PDMS Biocompatible Alternatives for Organs-On-Chips
NIH/NCI 382	Yes	Yes	Integrated Subcellular Microscopy and ‘Omics in Cancer Cell
NIH/NCI 383	Yes	Yes	Smart, Multi-Core Biopsy Needle
NIH/NCI 384	Yes	Yes	Digital Healthcare Platform to Reduce Financial Hardship for Cancer Patients
NIH/NCI 385	Yes	Yes	Leveraging Connected Health Technologies to Address and Improve Health Outcomes of Long-Term Cancer Survivors
NIH/NCI 386	Yes	Yes	Novel Approaches for Local Delivery of Chemopreventive Agents
NIH/NCI 387	Yes	Yes	Multiplexed Preclinical Tools for Longitudinal Characterization of Immunological Status in Tumor and its Microenvironment
NIH/NCI 388	Yes	Yes	<i>In vitro</i> Diagnostic for the Liver Flukes <i>Opisthorchis viverrini</i> and <i>Clonorchis sinensis</i>
NIH/NCI 389	Yes	No	Development of Artificial Intelligence (AI) Tools to Understand and Duplicate Experts’ Radiation Therapy Planning for Prostate Cancer
NIH/NCI 390	Yes	Yes	Clonogenic High-Throughput Assay for Screening Anti-Cancer Agents and Radiation Modulators
NIH/NCI 391	Yes	Yes	Drugs or Devices to Exploit the Immune Response Generated by Radiation Therapy
NIH/NCI 392	No	Yes	Clinical Trials of Systemic Targeted Radionuclide Therapies
NIH/NCI 393	Yes	Yes	Sensing Tools to Measure Biological Response to Radiotherapy

<b>TOPIC NUMBER</b>	<b>PHASE I PROPOSAL ALLOWED?</b>	<b>FAST TRACK ALLOWED?</b> (A Phase I proposal and a Phase II proposal submitted simultaneously)	<b>TOPIC TITLE</b>
NIH/NCI 394	Yes	Yes	Combinatory Treatment Modalities Utilizing Radiation to Locally Activate or Release Systemically Delivered Therapeutics
NIH/NCI 395	Yes	Yes	Targeted Therapy for Cancer- and Cancer Therapy-Related Cachexia
NIH/NCI 396	Yes	Yes	Imaging for Cancer Immunotherapies
NIH/NHLBI 106	Yes	Yes	Active MRI Needle
NIH/NHLBI 107	Yes	Yes	Transcatheter Potts Shunt
NIH/NHLBI 108	Yes	Yes	Device System for Transcatheter Repair of Postinfarction Ventricular Septal Defect
NIH/NIAAA 016	No	Yes	A Wearable Alcohol Biosensor that Quantifies Blood Alcohol Concentration in Real Time
NIH/NIAAA 017	Yes	No	Data Science Tools for Alcohol Research
NIH/NIAID 063	Yes	Yes	<i>In Vivo</i> Targeted Degradation of HIV Proteins
NIH/NIAID 064	Yes	Yes	Particle-Based Delivery of HIV Env Immunogens
NIH/NIAID 065	Yes	Yes	Co-Delivery and Formulation of Adjuvants for HIV Vaccines
NIH/NIAID 066	Yes	Yes	Effective Targeted Delivery of RNA-based Vaccines and Therapeutics
NIH/NIAID 067	Yes	Yes	Methods Improving HIV Protein Expression: Cell Substrate and Protein Purification
NIH/NIAID 068	Yes	Yes	Reagents for Immunologic Analysis of Non-mammalian and Underrepresented Mammalian Models
NIH/NIAID 069	Yes	No	B Cell Receptor and T Cell Receptor Repertoire Computational Tools
NIH/NIAID 070	Yes	No	Development of Sample Sparing Assay
NIH/NIAID 071	Yes	Yes	Adjuvant Discovery for Vaccines and for Autoimmune and Allergic Diseases
NIH/NIAID 072	Yes	Yes	Adjuvant Development for Vaccines and for Autoimmune and Allergic Diseases
NIH/NIAID 073	Yes	Yes	Mobile Health Point-of-Care Diagnostics
NIH/NIAID 074	Yes	Yes	Development of POC Assays to Quantify anti-Tuberculosis Antibiotics in Blood
NIH/NIAID 075	Yes	Yes	POC Diagnostic for Gonorrhea and Determination of Antimicrobial Susceptibility

<b>TOPIC NUMBER</b>	<b>PHASE I PROPOSAL ALLOWED?</b>	<b>FAST TRACK ALLOWED?</b> (A Phase I proposal and a Phase II proposal submitted simultaneously)	<b>TOPIC TITLE</b>
NIH/NIDA 165	Yes	Yes	DEA-Compliant Drug Detection and Deactivation Technology to Deter Opioid Theft in Hospitals for Next Generation Controlled Substance Diversion Prevention Program (CSDPP)
NIH/NIDA 166	Yes	Yes	Leveraging Health IT Solutions to Combat Opioid Misuse
CDC/CGH 010	Yes	No	Multiplex Detection of Recent and Prior Exposure to Pathogens
CDC/CGH 011	Yes	No	Preservation of Supply Quality During Unmanned Aerial Vehicle (UAV) Transport
CDC/NCCDPHP 041	Yes	No	Community Based Worksite Wellness App Linking Employees to Wellness Resources
CDC/NCCDPHP 042	Yes	No	Objective Measurement of Opioid Withdrawal in Newborns
CDC/NCEZID 020	Yes	No	Novel Coatings/Surfaces on Indwelling Medical Devices to Prevent Biofilms
CDC/NCEH 01	Yes	No	Rapid Field Test to Improve Swimming Pool Water/Air Quality
CDC/OPHPR 03	Yes	No	Rapid Test for Simultaneous Detection of Influenza (types A and B) and Streptococcus (Group A)

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 February 24, 2014. 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

**This solicitation will not accept Direct Phase II proposals. The congressional authority for Direct to Phase II proposals has expired.**

### 2.5 I-Corps™ at NIH

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

- **All NIH awarding components** (NCATS, NCI, NHLBI, NIAAA, NIAID, and NIDA), as well as **CDC/NCEZID**.

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

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

The I-Corps™ at NIH program is selective, with each NIH/CDC cohort consisting of up to 24 companies, split amongst current grant and contract SBIR Phase I award recipients throughout the NIH and CDC. For a firm fixed price option amount not to exceed \$50,000 (in addition to the price for performing the base research project), companies selected to participate in this program will perform additional requirements and develop additional deliverables which will ultimately provide the resources to submit a refined Commercialization Plan within the Final Report for an SBIR Phase I award, meaning that I-Corps™ at NIH participation runs concurrently with the performance of the SBIR Phase I research.

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

- Chief-Level Corporate Officer  
(CEO of the SBIR awardee company strongly preferred)
- Industry Expert  
(internal, such as a Business Development Manager or Board Member, or external, such as a consultant or mentor with the [National Innovation Network](#))

- Program Director/Principal Investigator (PD/PI)  
(or, in the case that PD/PI is also the CEO, an additional technical/scientific expert)

To successfully complete the I-Corps™ at NIH Program, the entire I-Corps™ team must be deeply committed and dedicated to the time-intensive curriculum. Each team member should plan to spend at least 20 hours per week on I-Corps™ activities for the full duration of the 8-week program. In-person attendance of all 3 team members is mandatory for a 3-day immersion ‘kickoff’ workshop and a 2-day closing workshop, location to be determined (within the United States), where team members will give presentations as well as participate in lectures and training sessions. There will also be weekly webinar sessions and requirements to get “out of the lab” and gather information by conducting at least 100 discovery interviews with potential customers, strategic partners, and other third-party stakeholders.

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

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

### *Application Process*

The first step in the I-Corps™ at NIH application process is submitting an additional, separate “Appendix C – Contract Pricing Proposal,” in your Business Proposal. Specify “I-Corps” in the “Title of Proposal” field. This separate budget must not exceed \$50,000 in total direct costs – indirect costs may not be included. Of that amount, \$20,000 must go towards covering workshop registration fees, which should be listed in field 4.e. OTHER of Appendix C. Remaining budget should be allocated as appropriate to cover personnel time for the I-Corps™ team members – at least 20 hours per week for 8 weeks for the 3 team member roles discussed above – as well as travel costs to participate in the in-person workshops and conduct on-site customer development interviews within the U.S.

Dates, times, and locations for NIH/CDC 8-week cohorts in 2020 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 6, 2020 to May 29, 2020 with travel to Los Angeles, California for a workshop April 6-9, 2020 and travel to Bethesda, Maryland for a workshop May 28-29, 2020.

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

The second step in the I-Corps™ application process will take place several months into Phase I project performance, when the Government will notify companies with the I-Corps™ contractual option and allow them the opportunity to prepare a brief application to be considered for I-Corps™ selection, subject to availability of funds. The estimated deadline for this application is early January 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/CDC reviews written I-Corps™ applications, it will conduct phone interviews to determine which companies will be invited to join the I-Corps™ cohort. The NIH/CDC awarding component selection committee will consider the ability of the proposed I-Corps™ effort to increase the overall success of the Phase I research project. (Specific criteria will be discussed in the notification provided by the Government containing finalized application due dates and cohort participation dates.)

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

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

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

## 2.6 Grant Opportunity - Phase IIB Competing Renewal Awards (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](mailto: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 Gary Robinson, Ph.D., at [gary.robinson@nih.gov](mailto:gary.robinson@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](mailto: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)

National Institute on Drug Abuse (NIDA)

Centers for Disease Control and Prevention (CDC) Components:

Center for Global Health (CGH)

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

National Center for Emerging Zoonotic and Infectious Diseases (NCEZID)

National Center for Environmental Health (NCEH)

Office of Public Health Preparedness and Response (OPHPR)

### 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](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](http://www.SBIR.gov) and [www.SBA.gov/size](http://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), 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 4.20 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 Award

Before a contract award can be made, 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](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](https://www.sbir.gov/state_services) for further information.

##### Technical 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 \$5,000 for assistance. 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 assistance services, such as access to a network of scientists and engineers engaged in a wide range of technologies, 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) before the award of a contract.

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 four (4) years. After expiration of the 4- year period, the Government has a royalty-free license to use, and to authorize others to use on its behalf, these data for Government purposes, and is relieved of all disclosure prohibitions and assumes no liability for unauthorized use of these data by third parties, except that any such data that is also protected and referenced under a subsequent SBIR award shall remain protected through the protection period of that subsequent SBIR award. Reproductions of these data or software must include this legend.”

## 5 CONTRACT REQUIREMENTS

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

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

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

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

- a. Before undertaking performance of any contract involving animal-related activities where the species is regulated by the United 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](mailto: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](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](http://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](http://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](http://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](http://www.clinicaltrials.gov). The responsibilities of the Contractor will fall within one of the following three categories:

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

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

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

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

## 5.9 Single Institutional Review Board (sIRB)

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

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

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

### Exceptions to the NIH Single IRB Policy

The Contractor may request an exception in the following instances:

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

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

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

- a. Offerors should request an exception in the sIRB plan attachment within the contract proposal, by uploading an attachment to Field 3.2 in the **Appendix H.3 Study Record**, which is itself an attachment to the **Appendix H.2 Human Subjects and Clinical Trials Information form**.
- b. Offerors must include the name of the site(s) for which an IRB other than the sIRB of record is proposed to review the study for the sites(s).
- c. Offerors must substantiate their exception request with sufficient information that demonstrates a compelling justification for *other exceptions* to the sIRB policy. The rationale should include why the sIRB of record cannot serve as the reviewing IRB for the site(s), and why the local IRB is uniquely qualified to be the reviewing IRB for the specific site(s).
  - For instance, the justification may consider ethical or human subjects protections issues, population needs, or other compelling reasons that IRB review for the site(s) cannot be provided by the single IRB of record.
- d. Note that the proposed budget in the proposal must reflect all necessary sIRB costs without an approved *other exception*. The Offerors should not assume that an *other exception* will be granted when considering what sIRB costs to include in the budget.

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

All research projects (both NIH-funded and non-NIH-funded) involving recombinant or synthetic nucleic acid molecules that are conducted at or sponsored by an entity in the U.S. that receives any support for recombinant or synthetic nucleic acid research from NIH shall be conducted in accordance with the *NIH Guidelines for Research Involving Recombinant or*

*Synthetic Nucleic Acid Molecules ( NIH Guidelines )* available at: <http://osp.od.nih.gov/biotechnology/nih-guidelines> ). All NIH-funded projects abroad that include recombinant or synthetic nucleic acid molecules must also comply with the *NIH Guidelines* .

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

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

## 5.11 Copyrights

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

## 5.12 Technical Data Rights

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

- (1) Each agency must refrain from disclosing SBIR technical data to outside the Government (except reviewers) and especially to competitors of the SBC, or from using the information to produce future technical procurement specifications that could harm the SBC that discovered and developed the innovation.
- (2) SBIR agencies must protect from disclosure and non-governmental use all SBIR technical data developed from work performed under an SBIR funding agreement for a period of not less than four years from delivery of the last deliverable under that agreement (either Phase I, Phase II, or Federally-funded SBIR Phase III) 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 four years. The Government retains a royalty-free license for Government use of any technical data delivered under an SBIR award, whether patented or not. This section does not apply to program evaluation.
- (3) SBIR technical data rights apply to all SBIR awards, including subcontracts to such awards, that fall within the statutory definition of Phase I, 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](mailto: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 2018, Executive Schedule, Level II of the Federal Executive Pay Scale is \$189,600.

### 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](https://grants.nih.gov/grants/peer/guidelines_general/Resource_sharing_plans.pdf)
  - Data Sharing Plan [http://grants.nih.gov/grants/policy/data\\_sharing](http://grants.nih.gov/grants/policy/data_sharing)
  - Model Organism Sharing Plan [http://grants.nih.gov/grants/policy/model\\_organism/](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](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](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"> <li>a. Identification of clear, measurable goals (<i>i.e.</i>, milestones) that have a reasonable chance of meeting the topic objective in Phase I.</li> <li>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.)</li> </ul>	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"> <li>a. Identification of clear, measurable goals (<i>i.e.</i>, milestones) that have a reasonable chance of meeting the topic objective in Phase II</li> <li>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.)</li> </ul>	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 31, 2018**. 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 16, 2018** at 2:00 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 (NIH Only – For Fast Track Submissions)

A complete Phase II proposal (as part of a Fast Track submission) 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. Refer to the table in [Section 1](#) to see which Topics are allowing Fast Track 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, complete the form identified as Appendix D and use it as the first page of the proposal. No other cover sheet should be used.** For the

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

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

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

## 8.6 Table of Contents (Item 1)

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

## 8.7 Abstract of Research Plan (Item 1)

Complete the form identified as Appendix B

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

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

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

## 8.8 Content of Technical Element (Item 1)

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

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

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

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

Discuss the following elements in the order indicated:

- 1) **Identification and Significance of the Problem or Opportunity.** Provide a clear statement of the specific technical problem or opportunity addressed.
- 2) **Technical Objectives.** State the specific objectives of the Phase I effort, including the technical questions it will try to answer to determine the feasibility of the proposed approach.
- 3) **Detailed Approach and Methodology.** Provide an explicit, detailed plan for the Phase I R&D to be carried out, including the experimental design, procedures, and protocols to be used. Address how the objectives will be met and the questions stated in Item b above. Discuss in detail the methods to be used to achieve each objective or task. The plan should indicate what is planned, how, when, and where the work will be carried out, a schedule of major events, the final product to be delivered, and the completion date of the effort. The Phase I effort should determine the technical feasibility of the proposed concept.
  - Address the points discussed in the Section 8.9 Enhancing Reproducibility through Rigor and Transparency.
  - If a project involves vertebrate animals, include a Vertebrate Animals Section, as discussed in Section 8.10 Research Involving Vertebrate Animals.
  - If Section 8.11 Dual Use Research of Concern is applicable to your project, address it here.
- 4) **Related Research or R&D.** Describe significant research activities directly related to the proposed effort, including any conducted by the Project Director/Principal Investigator (PD/PI), the proposing firm, consultants, or others. Describe how these activities interface with the proposed project and discuss any planned coordination

with outside sources. The PD/PI must persuade reviewers of his or her awareness of recent significant research or R&D conducted by others in the same scientific field.

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

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

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

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

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

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

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

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

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

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

12) **Resource Sharing Plan(s).** NIH considers the sharing of unique research resources developed through NIH-sponsored research an important means to enhance the value and further the advancement of the research. When resources have been developed with NIH funds and the associated research findings published or provided to NIH, it is important that they be made readily available for research purposes to qualified individuals within the

scientific community. If the final data/resources are not amenable to sharing (for example, human subject concerns, the Small Business Act provisions ([15 U.S.C. 631](#), et seq., as amended), etc.), this must be explained in the proposal.

- a) **Sharing Model Organisms:** Regardless of the amount requested, all proposals where the development of model organisms is anticipated are expected to include a description of a specific plan for sharing and distributing unique model organisms or state appropriate reasons why such sharing is restricted or not possible. See [Sharing Model Organisms Policy](#), and [NIH Guide NOT-OD-04-042](#).
- b) **Genome Wide Association Studies (GWAS):** Regardless of the amount requested, offerors seeking funding for a genome-wide association study are expected to provide a plan for submission of GWAS data to the NIH-designated GWAS data repository, or an appropriate explanation why submission to the repository is not possible. GWAS is defined as any study of genetic variation across the entire genome that is designed to identify genetic associations with observable traits (such as blood pressure or weight) or the presence or absence of a disease or condition. For further information, see Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies, [NIH Guide NOT-OD-07-088](#), and [Genome-Wide Association Studies](#).

**(B) Research Plan for Phase II proposals (including 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 -** 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.
- 2) **Detailed Approach and Methodology -** Provide an explicit detailed description of the Phase II approach. This section should be the major portion of the proposal and must clearly show advancement in the project appropriate for Phase II. Indicate not only what is planned, but also how and where the work will be carried out. List all tasks in a logical sequence to precisely describe what is expected of the contractor in performance of the work. Tasks should contain detail to (1) establish parameters for the project; (2) keep the effort focused on meeting the objectives; (3) describe end products and deliverables; and (4) describe periodic/final reports required to monitor work progress under the contract.
  - Address the points discussed in the Section 8.9 Enhancing Reproducibility through Rigor and Transparency.
  - If a project involves vertebrate animals, include a Vertebrate Animals Section, as discussed in Section 8.10 Research Involving Vertebrate Animals.
  - If Section 8.11 Dual Use Research of Concern is applicable to your project, address it here.
- 3) **Innovation -** Discuss how the end product or technology being developed would offer significant advantages over existing approaches, methodologies, instrumentation, or interventions on the market currently being utilized in research or clinical practice, such as meaningful improvements in quality, capability, cost, speed, efficiency, etc.
- 4) **Personnel -** List by name, title, department and organization, the extent of commitment to this Phase II effort, and detail each person's qualifications and role in the project. Provide resumes for all key staff members, describing directly related education, experience, and relevant publications. Describe in detail any involvement of subcontractors or consultants, and provide resumes for all key subcontractor staff. Also, include letters of commitment with proposed consultants confirming the extent of involvement and hourly/daily rate.
- 5) **Subcontractors/Consultants.** Involvement of a university or other subcontractors or consultants in the project may be appropriate and is permitted. If such involvement is intended, it should be described in detail and identified in the cost proposal. In addition, supported by appropriate letters form each individual confirming his/her role in the project must be included.

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

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

- 7) **Resources** - List/describe all equipment, facilities and other resources available for this project, including the offeror's clinical, computer and office facilities/equipment at any other performance site that will be involved in this project. Briefly state their capacities, relative proximity and extent of availability to this effort. (Any equipment specifically proposed as a cost to the contract must be justified in this section as well as detailed in the budget. Equipment and products purchased with Government funds shall be American-made, to the extent possible. Title to the equipment will vest in the Government.)
- 8) **Resource Sharing Plan(s).** NIH considers the sharing of unique research resources developed through NIH-sponsored research an important means to enhance the value and further the advancement of the research. When resources have been developed with NIH funds and the associated research findings published or provided to NIH, it is important that they be made readily available for research purposes to qualified individuals within the scientific community. If the final data/resources are not amenable to sharing (for example, human subject concerns, the Small Business Act provisions ([15 U.S.C. 631](#), et seq., as amended), etc.), this must be explained in the proposal. See [http://grants.nih.gov/grants/policy/data\\_sharing/data\\_sharing\\_faqs.htm](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.** 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.

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



## 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](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](mailto: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](mailto: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](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](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](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](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](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](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](http://hescregapp.od.nih.gov/NIH_Form_2890_Login.htm).

### 8.13 Content of the Pricing Proposal (Item Two).

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

- List all key personnel by name as well as by number of hours dedicated to the project as direct labor.
- While special tooling and test equipment and material cost may be included under Phase I, the inclusion of equipment and material will be carefully reviewed relative to need and appropriateness for the work proposed. The purchase of special tooling and test equipment must, in the opinion of the Contracting Officer, be advantageous to the Government and should be related directly to the specific topic. These may include such items as innovative instrumentation or automatic test equipment. Title to property furnished by the Government or acquired with Government funds will be vested with the HHS Component; unless it is determined that transfer of title to the contractor would be more cost effective than recovery of the equipment by the HHS Component.
- Cost for travel funds must be justified and related to the needs of the project. Describe reason for travel, location of travel, number of travelers, and number of nights of lodging in the Description fields in Appendix C.
- Cost sharing is permitted for proposals under this solicitation; however, cost sharing is not required nor will it be an evaluation factor in the consideration of a Phase I proposal.
- All subcontractor costs and consultant costs must be detailed at the same level as prime contractor costs in regards to labor, travel, equipment, etc. Provide detailed substantiation of subcontractor costs in your cost proposal. Enter this information in the Explanatory Material section of the on-line cost proposal form.
- **NIH Policy on Threshold for Negotiation of General and Administrative (G&A)/Indirect Costs (IDC) Rates for SBIR proposals** – SBIR offerors who propose a G&A/IDC rate of 40 percent of total direct costs or less will not be required to negotiate Final Indirect Rates with the NIH Division of Financial Advisory Services (DFAS), or other cognizant auditing agency. However, awarding Contracting Officers may require offerors to document how they calculated their IDC rate(s) in order to determine that these costs are fair and reasonable. Furthermore, the Division of Financial Advisory Services (DFAS) will retain the authority to require well-documented proposals for G&A/IDC rates on an *ad hoc* basis. If the SBC has a currently effective negotiated indirect cost rate(s) with a Federal agency, such rate(s) shall be used when calculating proposed G&A/IDC costs for an NIH proposal. (However, the rate(s) must be adjusted for IR&D expenses, which are not allowable under HHS awards.)

SBCs are reminded that only actual G&A/IDC costs may be charged to projects. If awarded at a rate of 40 percent or less of total direct costs, the rate used to charge actual G&A/IDC 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 \$5,000 for technical assistance as discussed and outlined in Section 4.21 of the solicitation.
- **Prior, Current, or Pending Support of Similar Proposals or Awards.**

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

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

#### **8.14 Reminders**

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

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

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

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

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

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



**9 SUMMARY OF HHS COMPONENTS ANTICIPATED NUMBER OF AWARDS**

<b>HHS COMPONENTS</b>	<b>ANTICIPATED NO. OF AWARDS</b>	<b>ANTICIPATED TIME OF AWARD</b>
National Institutes of Health (NIH) National Center for Advancing Translational Sciences (NCATS)	1-6	Scientific and Technical Merit Review: February-April 2019 Anticipated Award Date: July-September 2019
National Institutes of Health (NIH) National Cancer Institute (NCI)	34-52	Scientific and Technical Merit Review: March-May 2019 Anticipated Award Date: August-September 2019
National Institutes of Health (NIH) National Heart, Lung, and Blood Institute (NHLBI)	4-5	Scientific and Technical Merit Review: February-April 2019 Anticipated Award Date: July-September 2019
National Institutes of Health (NIH) National Institute on Alcohol Abuse and Alcoholism (NIAAA)	3-5	Scientific and Technical Merit Review: March-May 2019 Anticipated Award Date: September 2019
National Institutes of Health (NIH) National Institute of Allergy and Infectious Diseases (NIAID)	21-39	Scientific and Technical Merit Review: March 2019 Anticipated Award Date: August 2019
National Institutes of Health (NIH) National Institute on Drug Abuse (NIDA)	7-10	Scientific and Technical Merit Review: May-June 2019 Anticipated Award Date: August 2019
Center for Disease Control and Prevention (CDC) Center for Global Health (CGH)	2-3	Scientific and Technical Merit Review: May-June 2019 Anticipated Award Date: August 2019
Centers for Disease Control and Prevention (CDC) National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP)	2	Scientific and Technical Merit Review: May-June 2019 Anticipated Award Date: August 2019
Centers for Disease Control and Prevention (CDC) National Center for Emerging Zoonotic and Infectious Diseases (NCEZID)	2	Scientific and Technical Merit Review: May-June 2019 Anticipated Award Date: August 2019
Center for Disease Control and Prevention (CDC) National Center for Environmental Health (NCEH)	1	Scientific and Technical Merit Review: May-June 2019 Anticipated Award Date: August 2019
Centers for Disease Control and Prevention (CDC) Office of Public Health Preparedness and Response (OPHPR)	1	Scientific and Technical Merit Review: May-June 2019 Anticipated Award Date: August 2019

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

General Questions about the NIH SBIR Program

Email: [sbir@od.nih.gov](mailto: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)

Jeffrey Schmidt  
Contracting Officer  
NIDA Office of Acquisition  
Phone: (301) 402-1488  
Email: [schmidtjr@mail.nih.gov](mailto:schmidtjr@mail.nih.gov)

#### NATIONAL CANCER INSTITUTE (NCI)

Tiffany Chadwick  
Procurement Analyst & Contract Officer  
Office of Acquisitions, OM, NCI  
Phone: (240) 276-7293  
E-mail: [ncioasbir@mail.nih.gov](mailto:ncioasbir@mail.nih.gov)

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

Joanna Magginas  
Deputy Director  
Office of Acquisitions, OM, NHLBI  
Phone: (301) 827-7740  
E-mail: [magginaj@nhlbi.nih.gov](mailto:magginaj@nhlbi.nih.gov)

#### NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM (NIAAA)

Jeremy White  
Contracting Officer  
Branch Chief, NIAAA Branch  
NICHD Office of Acquisitions  
National Institutes of Health, DHHS  
Phone: (301) 402-4572  
Email: [jeremy.white@nih.gov](mailto:jeremy.white@nih.gov)

#### NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES (NIAID)

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

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

Kenneth Janosko  
Contracting Officer  
Office of Acquisition, NIDA  
Phone: (301) 443-6677  
Fax: (301) 443-7595  
E-mail: [kenneth.janosko@nih.gov](mailto:kenneth.janosko@nih.gov)

---

**CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)**

For general administrative SBIR program questions, contact:

**Office of the Director, Office of the Associate Director for Science**

Sean David Griffiths, M.P.H.  
SBIR Program Manager  
Office of Technology and Innovation  
Office of the Associate Director for Science  
Phone: 404-639-4641  
Fax: 404-639-4903  
E-mail: [SBIR@cdc.gov](mailto:SBIR@cdc.gov)

Gwen Barnett, M.P.H.  
Deputy Director  
Office of Technology and Innovation  
Office of the Associate Director for Science  
Phone: 404-639-4791  
Fax: 404-639-4903  
Email: [SBIR@cdc.gov](mailto:SBIR@cdc.gov)

**CENTER FOR GLOBAL HEALTH (CGH)**

Theresa Routh-Murphy  
Contracting Officer  
Centers for Disease Control and Prevention  
Office of Financial Resources  
Phone: (770) 488-2713  
Fax: (770) 488-2778  
Email: [TRouthMurphy@cdc.gov](mailto:TRouthMurphy@cdc.gov)

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

Julio Lopez  
Contracting Officer  
Centers for Disease Control and Prevention  
Office of Financial Resources  
Phone: (770) 488-2892  
Fax: (770) 488-2044  
E-mail: [JLopez3@cdc.gov](mailto:JLopez3@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  
Phone: (770) 488-2821  
Fax: (770) 488-2024  
E-mail: [PBTurner@cdc.gov](mailto:PBTurner@cdc.gov)

**NATIONAL CENTER FOR ENVIRONMENTAL HEALTH (NCEH)**

Vallerie Redd  
Contracting Officer  
Centers for Disease Control and Prevention  
Office of Financial Resources  
Phone: (770) 488-2845  
Fax: (770) 488-2847  
E-mail: [GFJ3@cdc.gov](mailto:GFJ3@cdc.gov)

**OFFICE OF PUBLIC HEALTH PREPAREDNESS AND RESPONSE (OPHPR)**

Christine Godfrey  
Contracting Officer  
Centers for Disease Control and Prevention  
Office of Financial Resources  
Phone: (770) 488-2519  
Fax: (770) 488-2024  
E-mail: [CNP9@cdc.gov](mailto:CNP9@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](mailto: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:

#### **016 Synthetic Technologies for Advancement of Research and Therapeutics (START)**

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

Number of anticipated awards: 1-2

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:*

Traditional drug development pipelines are largely inefficient, with greater than 80% attrition of new drugs that move into Phase 2 clinical trials. Currently, it takes more than \$1 billion and up to 14 years to bring a drug to market. One of the main contributors to this is our inefficiency to access unexplored biologically-relevant chemical space. About 40% of the chemical scaffolds found in natural products are absent in today's medicinal chemistry repertoire. Natural compounds harbor chemical and structural diversity that can be utilized to develop novel treatments. Most importantly, natural compounds are evolutionarily optimized as drug-like molecules. Challenges of natural products in drug discovery and development include (i) extremely low yields and limited supply, (ii) complex structures that preclude practical synthesis, and (iii) complex structures posing enormous difficulty for structural modifications. Synthetic biology is making promising strides in reshaping and streamlining drug discovery thanks to the recent advances in gene editing, gene synthesis, metabolomics and analysis techniques.

#### *Topic Goals:*

Current developments in synthetic biology have offered tools to design or modify organisms that can be used for a specific function, allowing for natural biological systems to be tailored as machines that produce desired compounds. Further, synthetic biology has a broad application and can be used to synthesize biologically relevant compounds and therapeutics that are not easily and/or not cost-effectively produced in a traditional laboratory setting. There is also an immense capability to scale-up production of said compounds using bioreactors and other platforms specific for growing microorganisms. Synthetic biology has the potential to accelerate the field of drug development by introducing tools and resources that can readily and efficiently produce desired compounds that are more cost effective.

The primary goal of this topic is to apply synthetic biology to produce and fully characterize both known and novel analogs of naturally occurring compounds to increase the diversity of compounds in drug libraries.

We are primarily interested in proposals focused on discovery, isolation and characterization of non-addictive natural compounds to treat pain, opioid abuse disorders and overdose. Other critical areas for therapeutic drug development will be considered pending strong scientific justification.

***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:

- Formulate naturally occurring and biologically relevant pathways into a set of design rules that can then be used to engineer **new candidate therapeutic molecules:**
  - Develop novel tools and technologies that would allow engineering of pathways into a host organism
  - Develop genetic switches to control of gene expression
  - Develop synthetic control systems for the production of bioactive molecules with therapeutic potential
- Expand the current catalog of naturally occurring compounds and their analogs to enhance the diversity of chemical libraries:
  - Identify and create biosynthetic gene clusters or pathways for the biosynthesis of natural products
  - Apply synthetic biology tools to improve production of natural products from their native sources
  - Utilize synthetic biology tools to assemble biosynthetic machinery and optimize yield for natural product production in heterologous hosts
  - Synthesize, isolate and fully characterize novel bioactive compounds and demonstrate bioactivity of compounds following isolation
- Provide NCATS with all data and resources (i.e.: molecules created, producer organisms, etc.) resulting from Phase II Activities and Deliverables for independent validation of yield and bioactivity.

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

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

- Continue the development of tools and technologies and prepare them for dissemination to the scientific community through, for example, licensing or servicing
- Develop a robust manufacturing process to scale-up production of novel compounds
  - Demonstrate bioactivity of compounds following scaled-up isolation
- Develop platforms that would allow large-scale applications of the developed tools and technologies as relevant to synthesis, isolation, characterization and modification of natural compounds
- Provide NCATS with all data and resources (i.e.: molecules created, producer organisms, etc.) resulting from Phase II Activities and Deliverables for independent validation of yield and bioactivity.
- In the first year of the Phase II contract, provide the program and contract officers with a letter(s) of commercial interest.
- In the second year of the Phase II contract, provide the program and contract officers with a letter(s) of commercial commitment.
- Present Phase II findings and final deliverables to NCATS Programs Staff via webinar.

**017 Universal Medium/Blood Mimetic for Use in Integrated Organs-on-Chips**

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

Number of anticipated awards: 1-2

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:**

The objective of this topic is to develop a universal medium, or blood mimetic, that can be used to perfuse and support multiple tissue constructs or organ types within multiple integrated microphysiological systems (MPS), or organs-on-chips.

Organs-on-chips are bioengineered micro devices that model the function of human organ tissues *in vivo*. The development of these platforms has provided tools that can be used to investigate the effects of drugs, compounds and therapeutics on human tissues *in vitro*, providing information on safety and efficacy of promising compounds. They are also used to model a wide variety of disease states and investigate pathophysiology and disease mechanisms in novel ways. However, their full utility can be realized when tissue systems are linked and cellular constructs from multiple organs can interact in a physiologically relevant way, moving towards a “human-on-a-chip”. Linking multiple tissue constructs is challenging to achieve as linked organs-on-chips need support in the culture medium for many different tissue construct types, yet the ability to link them is limited because each tissue construct requires specific nutrients and growth factors which may not be optimal for other tissue types. Currently, researchers do not have a fluid that can adequately support multiple human tissues in integrated systems. This means that tissue combinations cannot survive adequately for meaningful studies to be conducted and therefore limits the current utility of integrated organ-on-chip systems.

NCATS has previously issued supplemental funding to investigators funded under the Tissue Chips for Disease Modeling program, and some solutions to the problem have been developed, as in the inclusion of endothelial barriers to create organ-specific niches and the mixing of culture media for linked organ systems by number of systems e.g. 50:50 for two systems; 33:33:33 for three systems. However, these solutions are not tenable for broader adoption of tissue chip technology as they are technically and biologically challenging, cannot fulfil appropriate cellular support, or are not scalable to more than two or three tissue constructs. This SBIR topic will allow experts with experience in extended cell culture to address the issue.

**Topic Goals:**

This topic aims to address a pressing need in the field of microphysiological systems (MPS), or organs-on-chips, to develop a universal cell culture medium/blood mimetic that can be used to support multi-cellular tissues from multiple organ systems in linked, integrated organ-on-chip platforms. The goal of this project is to create a universal medium/blood mimetic that can be used with multiple tissue types to maintain cells in a healthy and functional state for extended cell culture (>1 month) and can supply the basic universal requirements of cells e.g. appropriate pH, oxygen and carbon dioxide levels, and certain growth factors.

This task will be achieved by addressing the following aspects:

- (1) Culture and maintenance of multiple (at least 3) cellularly heterogeneous and discrete induced pluripotent stem cell (iPSC)-derived tissue constructs by perfusion of tissues with a universal medium/blood mimetic on a single or linked cell culture platform(s) e.g. heart, liver and lung through linked microfluidic channels or across permeable membranes;
- (2) Creation of a cell medium that will address all basic universal cellular requirements e.g. pH; oxygenation; nutrients and growth factors of multiple interconnected tissue types;
- (3) Creation of a cell medium that can retain cells in a viable and/or functional state for at least one month, according to standard metrics of cell health or functionality assays e.g. cell viability and growth; pH buffering; stable gene transcription; and other functional readouts.

**Phase I Activities and Expected Deliverables:**

- Creation and maintenance of **at least** three separate mature iPSC-derived cellularly heterogeneous and discrete tissue constructs (e.g. heart, liver and lung) in independent tissue-specific culture media.
  - Tissues must remain differentiated and in a stable and mature phenotype (as shown by widely accepted cellular and genetic markers) for at least 28 days.
  - Tissues must express appropriate functional markers at the end of the >28-day culture period (e.g. albumin production by hepatocytes; calcium transients by neurons; expression of glucose transporter proteins in kidney tubule cells; appropriate RNA expression profiles).

- Linkage of **at least** two separate iPSC-derived tissue constructs perfused by a single culture medium that adequately supports all constructs for at least 7 days.
  - Tissues must remain differentiated and in a stable and mature phenotype at the end of this >7-day period (as shown by widely accepted cellular and genetic markers).
  - Tissues must express appropriate functional markers at the end of this >7-day period.
- Monitoring and/or proven absence of cellular distress/death markers or unexpected decreased production of functional markers in tissues in linked systems perfused by single culture medium at the end of the >7-day culture period.
- Provide NCATS with all data resulting and resources from Phase I Activities and Deliverables

**Phase II Activities and Expected Deliverables:**

- Creation of **at least** three iPSC-derived tissue constructs containing heterogeneous cellular types e.g. hepatocytes, liver-specific endothelial cells, liver-specific immune cells.
  - Tissues must remain differentiated and in a stable and mature phenotype (as shown by widely accepted cellular and genetic markers) for at least 28 days.
  - Tissues must express appropriate functional markers at the end of the >28-day culture period.
- Linkage of **at least** three separate cellularly heterogeneous iPSC-derived tissue constructs perfused by a single culture medium that adequately supports all constructs for at least 28 days.
  - Tissues must remain differentiated and in a stable and mature phenotype at the end of this >28-day period (as shown by widely accepted cellular and genetic markers).
  - Tissues must express appropriate functional markers at the end of this >28-day period.
- Proven compatibility with current iterations of microfluidic technology materials and organ-on-chip platforms.
- Development of reliable manufacturing protocols that ensure <5% batch variation of the universal medium.
- Provide NCATS with all data and resources resulting from Phase II Activities and Deliverables.
- In the first year of the Phase II contract, provide the Program and contract officers with (a) letter(s) of commercial interest.
- In the second year of the Phase II contract, provide the Program and contract officers with (a) letter(s) of commercial commitment.
- Present Phase II findings and demonstrate final deliverables to the NCATS Program staff via webinar.

**018 Non-PDMS Biocompatible Alternatives for Organs-on-Chips**

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

Number of anticipated awards: 1-2

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:**

The development of organs-on-chips, also known as microphysiological systems (MPS), has provided tools that can be used to investigate the effects of drugs, compounds and therapeutics on human tissues in vitro, providing information on safety and efficacy of promising compounds. They are also used to model a wide variety of disease states and investigate pathophysiology and disease mechanisms in novel ways. Organs-on-chips are often fabricated in part or wholly from polydimethylsiloxane (PDMS), an oxygen-permeable, optically-clear, non-flammable, non-toxic silicon-based organic polymer. However, PDMS absorbs or binds compounds or proteins under certain conditions, leading to loss of drugs or compounds that are introduced into the system. This is undesirable in the context of organs-on-chips as it reduces the ability

to accurately assess protein binding or calculate dosage ranges and responses of small molecules. Additionally, it can lead to cross-contamination of surrounding areas or tissues, reducing the reliability and predictivity of these systems for producing human-relevant drug responses.

Currently, researchers employ a variety of techniques to account for these shortcomings but these are expensive, time-consuming or not feasible to recreate due to the need for specialized equipment. Previously, NCATS has awarded supplemental funding for researchers funded under the Tissue Chips for Drug Screening program to address this issue, leading to development of some surface coating techniques and mathematical modeling to account for various adsorption properties of PDMS. An alternative material is desired for fabrication of organ chips for studies involving small molecule drugs/compounds and therapeutics. Replacement of PDMS will enable a broader range of experiments to be performed on tissue chip platforms and increase the utility of these systems to a wider community.

### ***Topic Goals:***

This topic aims to address a pressing need in the field of microphysiological systems (MPS), or organs-on-chips, to develop and produce a biocompatible alternative material that can be used in place of PDMS, which is a silicon-based material currently widely used in the fabrication of organ-on-chip platforms.

This goal will be achieved through the following:

- (1) Fabrication of a biocompatible, non-toxic material that could feasibly provide an alternative to PDMS;
- (2) Fabrication of a material that mimics the MPS-appropriate properties of PDMS such as gas permeability, optical clarity, non-toxicity, easy fabrication or availability, and predictable molecular binding;
- (3) Demonstration of appropriate material properties and a lack of undesirable properties such as drug/compound absorption, channel cross-contamination, or high variability in binding of different compounds.

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

- Development and production of an alternative material to PDMS that displays **at least** three of the following nine properties:
  - Optical clarity – proven ability of material to allow penetration of light at wavelengths of ~400-700nm.
  - Gas permeability of oxygen and carbon dioxide.
  - Non-toxic and biocompatible to a wide variety of iPSC-derived cells and tissues (5-10 cell/tissue types tested).
  - Widely available/accessible, either whole or by material components.
  - Proven reliable and reproducible manufacturing properties.
  - Easily manipulated without the need for extensive specialist equipment (above what PDMS requires).
  - Proven ability for manufacture of microfluidic components e.g. channels, ports, etc.
  - Proven lack of microfluidic channel cross-contamination at distances of <20µm for a variety of substances e.g. cell culture media, drugs, compounds, small molecules etc.
  - Reliable and predictable (variability <5%) molecular binding properties e.g. Log P, surface binding of plasma proteins etc.
  - Non-reactive with other standard materials used in MPS production e.g. glass, PDMS, poly(methyl methacrylate) (PMMA) etc.
- Provide NCATS Program staff with all data and resources resulting from Phase I Activities and Deliverables.

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

- Development of an alternative material to PDMS that displays **an additional** 4-6 of the following nine properties:
  - Optical clarity – proven ability of material to allow penetration of light at wavelengths of ~400-700nm.
  - Gas permeability of oxygen and carbon dioxide.
  - Non-toxic and biocompatible to a wide variety of iPSC-derived cells and tissues (5-10 cell/tissue types tested).
  - Widely available/accessible, either whole or by material components.
  - Proven reliable and reproducible manufacturing properties.
  - Easily manipulated without the need for extensive specialist equipment (above what PDMS requires).
  - Proven ability for manufacture of microfluidic components e.g. channels, ports, etc.

- Proven lack of microfluidic channel cross-contamination at distances of <math><20\mu\text{m}</math> for a variety of substances e.g. cell culture media, drugs, compounds, small molecules etc.
- Reliable and predictable (variability <math><5\%</math>) molecular binding properties e.g. Log P, surface binding of plasma proteins etc.
- Non-reactive with other standard materials used in MPS production e.g. glass, PDMS, PMMA etc.
- Proven success in culturing **at least** 5 types of viable, mature and functional iPSC-derived cell types and/or tissues;
  - Viability as shown by standard tissue-appropriate markers of cell health and survival e.g. lack of apoptotic markers;
  - Maturity as shown by presence of standard tissue-appropriate markers of mature phenotype or lack of dedifferentiation markers;
  - Functionality as shown by presence of standard tissue-appropriate markers of cell functionality e.g. albumin secretion in hepatocytes; contractility in cardiomyocytes etc.
- Employment of Quality Assurance manufacture standards to ensure the validity of analytical and quantitative measurements.
- Proven success in fabrication and employment of the alternative material in a microfluidic setting.
- Proven success in replacement of PDMS in a microphysiological systems setting e.g. adaptation of existing MPS platforms with PDMS components replaced by the alternative material.
- Provide NCATS Program staff with all data and resources resulting from Phase II Activities and Deliverables.
- In the first year of the Phase II contract, provide the Program and contract officers with (a) letter(s) of commercial interest.
- In the second year of the Phase II contract, provide the Program and contract officers with (a) letter(s) of commercial commitment.
- Present Phase II findings and demonstrate final deliverables to the NCATS Program staff via webinar.

## 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-18-011.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.

#### **382 Integrated Subcellular Microscopy and 'Omics in Cancer Cell**

Fast track proposals **will** be accepted.

Number of anticipated awards: 2-3

Budget (total costs, per award): Phase I: up to \$300,000 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. Recent NIH/NCI programs, such as the Physical Sciences-

Oncology Network, the 4-D Nucleome Program, and the Human Tumor Atlas Network, aim to understand cancer from 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 research community. Technologies that offer such integration will facilitate multidimensional spatially preserved mapping of the tumor ecosystem, leading to a broader understanding of tumor heterogeneity, the role of cell-cell and/or cell-matrix interactions in the response to cancer therapy, and will provide data for building predictive computational models of cancer initiation, progression, metastasis, and response to treatment.

Importantly, recommendations of the [Cancer Moonshot Blue Ribbon Panel](#) call for technology-based deliverables 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. NCI currently supports grants within the IMAT portfolio that are poised to respond to such a solicitation. While there are current efforts to promote small business activity within the single-cell analysis community, this proposal offers a complimentary, but distinct, opportunity through its focus on directly linking cellular phenotypes measured through high-resolution cellular and sub-cellular microscopy with multi-scale ‘omics measurements.

These needs include (but are not limited to) technologies that enable:

- multidimensional coupling of subcellular-to-cellular imaging modalities with orthogonal -omics and physicochemical measurement approaches;
- combination of spatial and temporal imaging at the super-resolution scale with phenotypic processes at the cellular scale;
- subcellular mapping and molecular characterization of individual cells in tumor tissue sections that informs on clonal evolution dynamics and heterogeneity;
- determination of subcellular dynamics coupled with computational methods to examine drug response and cancer cell resistance;
- analysis of subcellular processes in cancer that inform on cell phenotypes within the microenvironment or in the context of tissue relevant niches;

Advances in pre-clinical research in these areas have the potential to be translated into new methods to aid the detection and diagnosis of cancer, and to guide clinical decisions. Commercialization of the research tools supported by this contract solicitation will enable a broader community of researchers to engage in these studies, and thus increase the rate of scientific progress in this field.

### ***Project Goals***

Projects to be supported under this FOA will 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 FOA will be to stimulate innovation that integrates cellular imaging modalities with technologies that provide single cell -omics level data (e.g. genomic, transcriptomic, proteomic, etc.) that are relevant to cellular processes that are disabled or exploited in cancer. Projects supported by this contract solicitation 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, applications that are solely software based would not be responsive.

### ***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.

Offerors will need to:

1. Define the cancer biology application the platform(s), device(s) or combined device-computational approaches addresses.
2. Generate proof-of-concept data in a generally accepted cancer cell model system with the means to sense, interrogate, detect or resolve and map spatial cellular anatomy and/or dynamics using microscopy or other imaging modalities with micro- to nano-scale resolution.
3. Demonstrate feasibility of integrating 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:

1. Demonstrate reliability, robustness and usability in basic and/or clinical cancer research.
2. 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)
3. Demonstrate utility with benchmark experiments obtained across a range of generally accepted cancer cell model systems.
4. Show feasibility to be scaled up at a price point that is compatible with market success and widespread adoption by the basic research community.

### **383 Smart, Multi-Core Biopsy Needle**

Fast track proposals **will** be accepted.

Number of anticipated awards: 2-3

Budget (total costs, per award): Phase I: up to \$300,000 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***

Tumor recurrence or resistance to treatment often arises due to the underlying genomic or phenotypic heterogeneity of cancer cells and the microenvironment. Tissue cores taken by needle biopsies are used to provide diagnostic and prognostic information about solid tumors. Currently, if multiple cores are needed from a solid tumor, additional needles must be inserted at different locations in the tumor. Problems with this approach include the need for multiple injections, lack of data on positioning and physical parameters (e.g. pH and rigidity) within the tumor, and absence of retaining the layout of the tissue when the tissue is extracted from the needle. The current method lacks capability for measuring physical and biological characteristics like pH, oxygenation, rigidity, and tissue integrity. The goal of this contract solicitation is to support the development and engineering of a smart, multi-core biopsy needle that will allow for simultaneous sampling of a tumor while maintaining and elucidating geographical and physical information, ultimately to gain a better understanding of intra-tumor heterogeneity. The dimensions of the biopsy needles need to be comparable with current methods of aspiration or surgical incision biopsies for specific tumor types, and these new smart devices need to incorporate components to: 1) collect biopsies from multiple tumor cores in a biologically and clinically feasible manner, 2) identify specific locations of the biopsies

relative to the tumor and one another, 3) maintain physical and positioning characteristics of tumor on the extracted tissue, and 4) be adaptable for use under current image-guided biopsy or needle tracking practices.

### ***Project Goals***

The development and engineering of a smart, multi-core biopsy needle would allow for simultaneous extraction of tumor core biopsies with 3D positioning [similar to global positioning system technologies (GPS)] and physical parameter data and maintenance of tumor tissue integrity. The biopsy needle must be adaptable for use with image-guidance approaches that are currently used in clinical practice. In the short-term, the project will help provide additional information that can be utilized to elucidate the biological complexity of intra-tumor heterogeneity. In the long-term, it is envisioned that the pH and other physical parameter data (e.g. stiffness) of a tumor across multiple regions could be probed and mapped to the spatial positioning of cancer cells and these data integrated with genotypic and phenotypic data of cancer and stromal cells. Ultimately, the project will have an impact on our understanding of tumor heterogeneity and help guide clinical decisions in designing the course of cancer therapy by obtaining live, intact tumor tissue simultaneously from multiple regions of a solid tumor.

Issues with existing approaches of aspiration and incision biopsies are the need for multiple injections, lack of data on positioning and physical parameters (e.g. pH or rigidity) within the tumor, and absence of retaining the layout of the tissue when the tissue is extracted from the needle. These issues lead to the unmet need addressed with this project, which is the ability to obtain positioning and pH data while maintaining the layout of a tumor from a single biopsy. Activities designed to address this unmet need will be supported, including development of a biopsy needle that has simultaneous multiple core sampling capability. All needles will be required to have positioning and pH sensing capabilities and material coating to allow for maintaining the layout of the tumor once deposited onto a slide or similar platform. The smart, multi-core biopsy needle will also have the capability to be used with current image-guided mechanisms, such as CT, MR, or ultrasound that are often used for obtaining biopsies. The GPS capable smart needle will allow for 3D spatial mapping of the tumor after the tumor is extracted, whereas the image-guided mechanisms are used to guide the needle location during biopsy. This project will be focused on supporting development and engineering of the biopsy needle, and it will not support development of image-guidance technologies alone.

### ***Phase I Activities and Deliverables***

- Design and manufacture a smart, multi-core needle device with the following features:
  - Multiple needles that extract radially from a single, traditional biopsy needle once positioned in a tumor (or other innovative methods to collect multiple cores in a clinically and biologically feasible manner);
  - Global positioning system along each of the needles within the tumor to allow for 3D spatial mapping of the tumor;
  - Sensors to monitor pH along each of the needles within the tumor (and other physical parameters where possible such as tissue stiffness or rigidity);
  - Material coating of the needles (or other innovative methods) to allow for maintaining the layout of the tumor once deposited onto a slide or similar platform;
  - Does not significantly damage, change tissue biology, or cause excessive bleeding in regions surrounding the needle placement site;
  - Adaptability for use with existing image-guided needle placement methods and needle biopsy procedures.
- Identify the tumor type for which the needle will be developed with adequate justification.
- Specify biopsy needle gauges, spacing and other characteristics for the multi-core biopsy needle that will be developed with adequate justification.
- Show preliminary proof-of-concept of the sensor-guided biopsy in a tumor model (engineered phantom or appropriate animal model) to demonstrate the required design and manufacturing features have been achieved.
- Produce written methodology for the sensor manufacturing with quality assurance and control measures using the Standard Operating Procedure (SOP) template.

### ***Phase II Activities and Deliverables***

- Optimize the smart, multi-core biopsy needle design and performance for a clinical setting and refine the manufacturing process.
- Show the feasibility of this novel technique to complement current biopsy procedures.



- Demonstrate the performance of the device as designed and intended in fit-for-purpose studies in relevant large animal models.
- Obtain sufficient animal safety data in preparation for 510(K) or IDE application with the FDA.

### **384 Digital Healthcare Platform to Reduce Financial Hardship for Cancer Patients**

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

Number of Anticipated Awards: 2-3

Budget (total costs, per award): Phase I: up to \$300,000 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 cost of cancer care has risen exponentially over the last 20 years, with new cancer drugs routinely priced over \$120K per year. Concurrently, commercial insurers have been shifting healthcare costs to patients through higher co-pays and deductibles. On average, cancer patients pay about \$5K/year in out-of-pocket costs, however, prices higher than \$10K a month for individual drugs and biologic agents are common. A growing number of patients experience financial hardship during cancer treatment, which negatively affects their quality of life. When compared to individuals without a cancer history, cancer survivors report higher out-of-pocket costs, lasting years after diagnosis. Further, cancer and its treatment can limit survivors' ability to work, which further exacerbates the financial burden of cancer. There is growing concern that the exorbitant cost of cancer therapies will limit patients' access to their potential benefits, leading to poorer treatment response and worse prognosis.

The National Academy of Medicine has cited patient-physician communication as a key strategy for helping patients understand and anticipate the costs of their cancer treatment. However, conversations about cost rarely occur. An important barrier to discussing costs as part of treatment decision making is that oncologists, nurses and other members of the healthcare team seldom know how much patients will have to pay for their care. Estimating a patient's costs for a course of treatment is time consuming and expensive. It requires someone within the healthcare system to aggregate information about pricing, patient's insurance coverage, available rebates, and other related information, all of which are stored in different places. Although some systems have dedicated financial counselors or financial navigators who can collate this information and help patients minimize financial burden, even practices willing to devote substantial resources to financial navigation are not equipped to do this for everyone. As a result, many patients begin a course of treatment, only to be blind-sided by expensive medical bills.

#### ***Project Goals***

The goal of this contract solicitation is to develop an IT-based platform to streamline the calculation of patient's out-of-pocket costs for cancer treatment. Depending upon clinic workflow, information about costs could be provided by the oncologist or nurse during the clinical encounter or soon after the clinical encounter by a financial navigator. When cost information is readily available, providers can inform patients about the expense of different treatment options; patients can make more informed treatment decisions; and providers, financial navigators or other staff can proactively explore strategies to minimize patients' financial hardship.

Offerors are required to incorporate a cost calculation function into their proposed platform, which will be used by healthcare providers to estimate a patient's out-of-pocket costs for cancer therapy. Out-of-pocket cost calculations can be based on the treatment plan for primary and adjuvant therapy, patient's insurance coverage, or negotiated health system and pharmacy pricing. Additional modules that could also be included as part of the platform are tools to facilitate prescription and other financial assistance and visualization tools to support side-by-side comparisons of alternative treatment options. To be considered responsive, applicants should partner with at least one provider system (hospital, clinic), or insurer. The platforms should be developed for medical oncology providers who treat adult cancer patients. Offerors should design approaches that can be scaled up for the treatment of several cancers, although the platform can initially be developed in the context of a single cancer.

*Activities not responsive to this announcement:*

Development of applications that are only patient-facing will not be considered responsive.

### ***Phase I Activities and Deliverables:***

- Establish a project team with expertise in the areas of software development, computer programming, user-centered design, health communication, oncology, oncology nursing, health services research, and cyber security, as appropriate for the proposed project. Provide a report outlining team member credentials, specific project roles, and timelines for performance.
- Conduct an environmental scan of currently available technological platforms for financial hardship to identify gaps, existing capabilities and resources.
- Identify a partner hospital, clinic or insurer and conduct key informant interviews with anticipated end-users to understand user needs and clinical workflows.
- Provide a report including detailed description and/or technical documentation of the proposed system capabilities and specifications, including:
  - specific data systems that will support each module of the platform;
  - how the platform will interoperate with these systems to extract the necessary data;
  - how data will be visualized for the end-users; and
  - protections to ensure the confidentiality of patient information.
- Develop a prototype that includes:
  - the database structure for the proposed platform, user-interfaces, and metadata requirements;
  - data and security standards for collection, transport, and storage of data inputs that ensure patient privacy following standard NIH policies;
  - data visualization, data query functions, feedback and reporting systems for clinical monitoring and research applications; and
  - data adaptation for mobile application(s) if applicable.
- Conduct a pilot usability testing.
- Present Phase I findings and demonstrate prototype to an NCI evaluation Panel.

### ***Phase II Activities and Deliverables:***

Phase II deliverables will focus on specifying technical requirements, testing usability of the prototype and evaluate its implementation in a cancer delivery system.

- Evaluate specific IT customization requirements to support hardware, software, or communications system integration of the technology into the target software environment in preparation for validation. Provide a report documenting the specific IT customization requirements and timelines for implementation.
- Evaluate (and enhance as necessary) and document that the technology and communications systems maintain compliance with HIPAA, data security, privacy, and consent management protocols as required for the proposed project.
- Enhance systems interoperability for deployment in diverse software environments and provider networks. Provide a report detailing communication systems architecture and capability for data reporting to healthcare providers, researchers, electronic health records, and health surveillance systems as appropriate for the proposed project.
- Refine prototype and conduct usability testing
- Test the integration of the technology in the information system of the cancer delivery system. Provide a report documenting the results of system testing and timelines for trouble-shooting.
- Design and conduct a validation study, including:
  - specify study aims, participant characteristics, recruiting plans, inclusion and exclusion criteria, measures, primary and secondary endpoints, design and comparison conditions (if appropriate), power analyses and sample size, and data analysis plan;
  - develop appropriate human subjects protection / IRB submission packages and documentation of approval for the research plan; and
  - provide study progress reports quarterly, documenting recruitment and enrollment, retention, data quality assurance and control measures, and relevant study specific milestones.

- Prepare a tutorial session for presentation at NCI and/or via webinars describing and illustrating the technology, its intended use and results from the validation study.
- In the first year of the contract, provide the program and contract officers with a letter(s) of commercial interest.
- Provide the program and contract officers with a letter(s) of commercial commitment.

### **385 Leveraging Connected Health Technologies to Address and Improve Health Outcomes of Long- Term Cancer Survivors**

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

Number of Anticipated Awards: 2-3

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

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

#### ***Summary***

One of the consequences of living longer is the symptom burden of cancer survivorship, which is having a substantial impact on quality of life for many survivors. Persistent and late effects of cancer treatment include physical limitations, cognitive sequelae, depression, anxiety, sleep problems, fatigue, sexual dysfunction, and, in some patients, a great deal of pain.

Similarly, when cancer survivors transition from oncology-based to primary care, they still need coordinated monitoring for cancer recurrence, screening, and early detection of second primary cancers, assessment and management of potential physical and psychosocial effects of cancer and its treatment, counseling on health promotion strategies for nutrition, physical activity, tobacco cessation, and alcohol consumption.

Individuals increasingly are using wearable devices and smartphone apps to collect health-related data and help them reach personal health goals. These person-generated health data provide valuable insights into people’s everyday lives and have potential to help individuals more accurately track symptoms and healthcare providers deliver more patient-centered care. Among other things, personal devices can be used to gather patient-reported outcomes (e.g., symptom self-reporting), which can enhance quality of care.

Through this contract topic, NCI is seeking to capitalize on its rich portfolio of research to develop and link data from connected devices and patient reports in meaningful ways to enhance symptom management, timely patient-centered clinical care, and improve health outcomes for cancer survivors --- particularly those who are managing the late and long-term effects of cancer treatment and transitioning to primary and community-based care.

By integrating person-generated health data -- readily collected by connected devices --- with robust symptom lifestyle reporting and management systems, this contract topic encourages novel and essential approaches to improve the quality of life for long-term cancer survivors. This concept helps address the compelling need not just to improve symptom care and ensure adherence to long-term treatment and health promotion strategies, but expand evidence-based self-management strategies, identify recurrence and secondary cancers, and extend survival.

#### ***Project Goals***

The overall goal is for small businesses to develop “connected health” (software, database systems and/or mobile application) tools which will readily allow for the efficient and comprehensive monitoring, managing, and reporting of patient-reported symptoms by long-term cancer survivors. The result will enhance care quality and effectiveness, provide real-time feedback to cancer survivors, and allow care delivered beyond clinic walls into the home setting, ultimately aiming to improve patient outcomes.

This goal will be accomplished by:

- Building a system/tool/app/device capable of remotely collecting individual health behavior data to support and reinforce efficacious self-management and disease prevention, remote monitoring, behavior modification and personalized intervention patient-reported outcomes.
- A system that follows best behavioral and disease prevention guidelines for adherence to care recommendations while keeping track of psychological needs.

- A system that allows for bi-directionality of symptom data: to bring poorly controlled symptoms to the attention of the cancer care team and use the patient-reported outcome (PRO) data to guide symptom control efforts.
- Prompts to monitor for psychosocial quality of life effects (e.g., sexual dysfunction, marital discord, depression) should be included.
- Integrating accountability tools, checklists, and reminders into the system to ensure safe and timely delivery of services as well as reinforcing positive health behaviors.

### ***Expected Activities and Deliverables***

#### *Scope of activities to be supported:*

- A review of currently available technological platforms for cancer survivors to identify gaps, existing capabilities, and resources.
- Interviews/focus groups with cancer survivors and healthcare providers, and survivorship researchers to further identify areas of unmet needs.
- The development of a software system with mobile application to connect cancer survivors with healthcare provider teams to extend clinical interactions and provide further information resources and service referral.
- Key task domains should include organization-level (hospital or clinic), provider-level, and individual (survivor)-level dashboards that allow for assessment of adherence to treatment and post-treatment clinical practice guidelines, capability to identify high-risk patients, ability to identify care gaps and enable clinical data query functions.
- The development of secure bi-directional communication system to allow healthcare providers and individual cancer survivors to push messages directly through the system.
- The development and testing of a prototype of a platform and applications to be tested with cancer survivors and their healthcare providers, and survivorship researchers.
- Further enhancement and refinement of the software system and mobile application.

### ***Phase I Activities and Deliverables:***

- Establish a project team with expertise in the areas of software development, patient-centered design, health communication, oncology, oncology nursing, behavioral science, health services, and computer programming
- Perform an environmental scan of available and relevant software systems designed to support symptom management, health maintenance behaviors and to identify major gaps
- Conduct a small number of key informant interviews with longer-term cancer survivors and primary care providers to further refine and prioritize areas of unmet needs
- Provide a report including detailed description and/or technical documentation of the proposed system capabilities and specifications, including:
  - Database structure for the proposed modules and user-interfaces (survivors, healthcare provider) and metadata requirements
  - Architecture that includes the following components:
    - a personal health dashboard to track key symptom indicators, and prompt survivor to share critical information with their primary care provider.
    - A psycho-social health dashboard to track key factors associated with Quality of Life (QOL) outcomes in cancer survivors
  - The dashboard would be needed to be able to communicate with the survivor as well as primary care provider and download and upload information
- Data and security standards for collection, transport, and storage of data inputs that ensure patient and caregiver privacy following standard NIH policies.
- Data visualization, feedback and reporting systems for clinical monitoring and research applications
- Data adaptation for mobile application(s)

Develop a functional prototype of the software system that includes:

- Front-end mobile application(s) to facilitate tracking and monitoring of care, communications, and survivor support.
- Healthcare provider systems to facilitate remote patient care monitoring, communications, and resource provisions (e.g. content management for tailored caregiver support).
- Required server systems architecture to facilitate interaction with necessary provider Health IT systems or patient facing portals and personal health records.
- Present Phase I findings and demonstrate functional prototype to an NCI Evaluation Panel.
- Develop a prototype into a pilot system for usability testing.
- Conduct usability testing mobile applications and user interface features including system management, analyses, and reporting applications.

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

- Establish a project team for Phase II activities and outcomes. This team should include personnel with training and research experience in chronic disease patient clinical trial or intervention design, implementation, and statistical methods for validation/evaluation as appropriate for the proposed project. Provide a report outlining team member credentials, specific project roles, and timelines for performance.
- Evaluate specific IT customization requirements to support hardware, software, or communications system integration of the technology into the target clinical, health system or service, or other relevant software environment in preparation for validation. Provide a report documenting the specific IT customization requirements and timelines for implementation.
- Evaluate, enhance as necessary and provide documentation that the technology and communications systems maintain compliance with HIPAA, data security, privacy, and consent management protocols as required for the proposed project.
- Enhance systems interoperability for deployment in diverse software environments and provider networks. Provide a report detailing communication systems architecture and capability for data reporting as appropriate for the proposed project.
- Conduct beta-testing of the software system and corresponding portals and mobile applications.
- Test the integration of the technology into the target clinical, health system or service, or other relevant software environment in preparation for validation. Provide a report documenting the results of system testing and timelines for trouble-shooting.
- Develop user support documentation to support all applicable potential users of the technology. Provide a report documenting user support resources, including but not limited to, links to online resources and copies of electronic or paper user support resources as appropriate.
- Present finding and demonstrate functional product to NCI evaluation panel via webinar.
- Provide the program and contract officers with a letter(s) of commercial commitment.

**386 Novel Approaches for Local Delivery of Chemopreventive Agents**

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

Number of Anticipated Awards: 2-4

Budget (total costs, per award): Phase I: up to \$300,000 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 clinical value of an agent is reflected by both its efficacy and its toxicity. In the chemoprevention space, the intention to minimize toxicity is even greater, since agents are administered to a relatively healthy (albeit high-risk) population, and most chemopreventive agents require administration over long periods of time. This limit on toxicity presents a major challenge in the development of chemopreventive agents with acceptable benefit risk ratios.

Our ability to identify populations at higher risk of developing cancer has significantly improved over the past decade. For example, women with Hereditary Breast and Ovarian Cancer syndrome (HBOC) are at increased risk of developing breast and ovarian cancer, and potentially other cancers (*e.g.*, pancreatic); individuals with Lynch syndrome are at increased risk of developing multiple cancer types including colorectal, endometrial, and gastric cancer. We are also able to detect cancer at earlier stages and often as precancerous lesions. Multiple studies have shown that these individuals at high risk for cancer or with precancerous lesions could benefit from chemoprevention approaches. A small number of chemopreventive agents have found some degree of success in the clinic, including tamoxifen and raloxifene for breast cancer prevention, and aspirin and celecoxib for colorectal cancer prevention. However, the systemic toxicities of these agents have limited their widespread use and acceptability.

Local agent delivery is an important strategy to reduce toxicity of chemopreventive agents, while maintaining clinical benefit. Local delivery of an agent can be performed by a physician or self-administered by an individual, which overcomes some of the access barriers that exist in healthcare. A localized chemoprevention approach is ideal in high risk individuals or individuals with premalignant diseases, as the agent can be applied locally to provide high drug concentrations at specific locations from where early disease would originate, while limiting systemic toxicity.

### ***Project Goals***

The goal of this concept is to solicit proposals to advance the development and/or application of local delivery devices or formulations for chemoprevention. The technology should be designed for effective delivery of agent to a specific organ while minimizing systemic toxicities. Acceptable toxicities will depend on the agent and target population. Toxicity should not exceed minimal grade 2 local toxicities, while short term local grade 3 toxicity may be acceptable in some populations. The proposed local delivery device/formulation may utilize any technology or agent capable of meeting the goals of this topic. Examples of local administration include topical (for oral, breast, skin or cervical cancers), inhalant or aerosolized (for lung or esophageal cancers), or digestive (for esophageal, stomach, or colorectal cancers). Proposals for development of local delivery devices or formulations via other administration routes or for other cancer types are also encouraged. Potential chemoprevention agents include but are not limited to active metabolites of tamoxifen, aromatase inhibitors, anti-progestin agents, rexinoids, Cox2 inhibitors, PARP inhibitors, Imiquimod, Polyphenon® E, Stat inhibitors, Tyrosine kinase inhibitors, etc.

The activities that fall within the scope of this contract solicitation include development and application of local delivery formulations or devices. Examples of appropriate activities include pre-clinical toxicity and efficacy studies in appropriate animal models, acceptability studies, and initial first-in-human testing. The offerors may develop a local delivery approach for FDA approved chemoprevention agents or for novel chemoprevention agents. For novel chemoprevention agents, the offerors should demonstrate significant reduction in cancer incidence in suitable cancer prevention animal models. Phase II clinical trials and beyond are not appropriate for this mechanism; investigators are encouraged to seek support for these studies from alternative NCI programs.

#### Notes:

- Novel agents and/or technologies to locally deliver chemoprevention agents to lungs are especially encouraged.
- Local approaches for treatment of invasive cancers will not be accepted.
- Adequate justification for the appropriateness of an agent for chemoprevention is critical.

### ***Phase I Activities and Deliverables:***

- Select cancer type(s), organ site(s), chemoprevention agent(s), and method(s) of local delivery with adequate justification.
- Demonstrate that the chemoprevention agent is:
  - Stable in local formulation and/or when incorporated with the local delivery device/technology
  - Released at the organ(s) of interest when incorporated into a local delivery device/technology
- Perform preliminary proof-of-concept of the local delivery approach in a suitable animal model and demonstrate:
  - Accumulation/presence of the agent at the organ/tissue of interest at greater concentration than in the circulation (exact metric will depend on the toxicity of the agent under study)
  - Reduction in agent concentration in the blood compared to systemic delivery/administration (exact metric will depend on the toxicity of the agent under study)
  - Efficacy of the agent with relevant standard tests based on MOA of the agent (*e.g.*, proliferation assay, apoptosis assay)
  - Significant reduction in toxicity with the local approach compared to systemic administration; relevant organ observed toxicity could be used with appropriate justification.

## *Phase II Activities and Deliverables*

- For agent(s) (or their metabolites) with known chemoprevention effect when administered systemically (FDA approved):
  - Demonstrate efficacy in suitable animal model(s)
    - Perform ADME, bioavailability and efficacy studies of the local delivery approach in suitable animal model(s) and demonstrate:
      - at least same level of agent concentration at the organ/tissue of interest compared to systemic delivery/administration
      - at least 90% higher concentration of the agent in the organ of interest than in the circulation
      - at least 90% reduction in agent concentration in the blood compared to systemic delivery/administration
      - at least same level of efficacy demonstrated with appropriate standard tests reflecting the MOA of the agent (e.g., proliferation assay, apoptosis assay) compared to systemic delivery/administration
  - Perform maximum tolerated dose (MTD) and/or biological active dose study and demonstrate superior therapeutic index using local approach compared to systemic administration with adequate justification.
    - Toxicity should not exceed minimal grade 2 systemic toxicities while short term local grade 3 toxicity may be acceptable in some populations.
  - IND Submission
    - Develop and execute an appropriate regulatory strategy; schedule pre-IND meeting with the FDA.
    - Perform IND-enabling GLP safety toxicology studies in relevant animal model(s) following FDA guidelines.
- For novel (non-FDA approved) chemoprevention agent(s):
  - Demonstrate efficacy in suitable animal model(s)
    - Perform ADME and bioavailability and efficacy studies of the local delivery approach in suitable animal model(s) and demonstrate:
      - reduction of oncogenic molecular/cellular characteristics reflecting the MOA of the agent (e.g., proliferation assay, apoptosis assay)
      - at least 50% reduction in cancer incidence following local administration of the chemoprevention agent in suitable cancer prevention animal model(s)
      - Accumulation/presence of the agent at the organ/tissue of interest at greater concentration than in the circulation (exact metric will depend on the toxicity of the agent under study)
      - Reduction in agent concentration in the blood compared to systemic delivery/administration (exact metric will depend on the toxicity of the agent under study)
  - Perform maximum tolerated dose (MTD) and/or biological active dose study and demonstrate superior therapeutic index using local approach compared to systemic administration with adequate justification
    - Toxicity should not exceed minimal grade 2 systemic toxicities while short term local grade 3 toxicity may be acceptable in some populations.
  - Perform IND-enabling safety toxicology studies in relevant animal model(s) to warrant a type B or type C meeting with the FDA.
- For offerors that have completed advanced pre-clinical work, NCI may support pilot human trials.

### **387 Multiplexed Preclinical Tools for Longitudinal Characterization of Immunological Status in Tumor and Its Microenvironment**

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

Number of Anticipated Awards: 3-4

Budget (total costs, per award): Phase I: up to \$300,000 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

Evolution of cancer is complex: from the early lesion to the development of primary tumor to widespread metastasis, numerous and complex interactions occur among normal and malignant cells, as well as their microenvironment. Within the last decade, researchers have found that the tumor environment (TME) is consisted of a multitude of cell types and a host of mediators, whose dynamic interplay contributes to complex tumor behaviors and pose significant therapeutic challenges.

Consisting of non-cancerous cells, TME has an abnormal vasculature, stromal components, immune and non-immune cells embedded in an extracellular matrix (ECM), and plays a critical role in tumor initiation, malignant progression, metastasis and treatment response - barriers to drug delivery and resistance to therapy. There is substantial evidence of a dynamic tripartite interaction between cancer cells, immune cells, and tumor stroma, which contributes to a chronically inflamed TME with pro-tumorigenic immune phenotypes and facilitated tumor metastasis. Both cancer cells and cells in the TME release bioactive molecules (e.g., chemokines, metabolites, and lipid mediators) which can influence cancer progression. Although discovered many years ago via cellular energetics studies (i.e. the Warburg effect) that the metabolic programming and reprogramming of immune cells in TME affects the tumor initiation, the importance of the interconnection of metabolic components and immune signaling pathways for determining the phenotype of tumor-associated macrophage (TAM) was recently noted. In sum, the complex interactions of different cell types (including the immune and non-immune cells), as well as the associated bioactive molecules contribute to the immune-metabolic characteristics of the tumor and its TME.

There are emerging cancer treatment strategies via modulating the immune or metabolic conditions of tumor and its TMEs in recent years with limitations. As an immune-suppressive TME is a barrier to the antitumor function of immune cells, immune priming of TME by radiation has been suggested to promote cancer treatment efficacy. On the other hand, as a sustained inflammation is a common feature of many cancers, novel cancer treatment strategies have been proposed which tackle the inflammation in tumor and TME through the modulation of lipid metabolism and the production of specialized pro-resolving mediators (SPMs). Immunotherapies utilizing checkpoint inhibitors to modulate the immune components of tumor cells and TME have shown efficacy in treating multiple cancer types, and more are currently undergoing clinical trials; however, immunotherapies only work in a restricted group of patient populations. The less than optimal outcome can be attributed to limited knowledge in individual's immunological profile encompassing inflammatory cells, immuno-suppressor cells and immunomodulatory factors within the tumor and TME. For this reason, tracking the dynamic evolution of heterogeneous cell populations, molecular characteristics, and metabolic signatures to characterize the immunological status within the tumor and its TME would add significant knowledge in cancer progression and could lead to the development of novel therapeutics and more efficacious treatment strategies.

Studies of immune or metabolic signatures of tissues are usually based on histopathological analysis of the tissue biopsies. However, these methods are destructive and lack temporal information; thus, the ability to use tumor and TME-associated molecular, cellular and metabolic signatures for tumor prediction, diagnosis, prognosis, and therapy response are somewhat limited. The use of techniques capable of *in vivo* molecular characterization and cell mapping of the tumor and its TME, in its physical location and over time, augmented by the assessment of metabolic signatures, can advance research efforts in this increasingly important topic and could accelerate lead compound identification. Clinical applications of responsive technologies could assist in patient stratification, monitor therapeutic response and modulate therapy accordingly.

Recent advances in imaging techniques are enabling assessment of tumor and TME with improved accuracy due to higher monitoring speed, sensitivity, and resolution. For example, magnetic resonance imaging techniques, with both excellent image resolution and depth penetration, are widely used to detect abnormal pre-malignant, tumor and TME structures and conditions: blood oxygenation level dependent (BOLD)-MRI for hypoxic conditions; Chemical Exchange Saturation Transfer (CEST)-MRI for reduced pH; MR angiography for vascular structure and diffusion MRI for structural integrity; and, MR spectroscopy Imaging (MRSI) for interrogating the concentration of various metabolites. Positron Emission Tomography (PET) of radio-nuclei-labeled tumor or TME-associated molecular and immunological targets has been used in pre-clinical and clinical settings. All these *in vivo* methods are valuable tools to spatiotemporally examine the targeting efficiency, associated molecular events and provide insight into the normalization of tumor and TME, and its effect on anticancer drug delivery. In parallel, although not applicable *in vivo*, high throughput analytical tools such as liquid chromatography-mass spectroscopy (LC-MS) and other advanced mass spectrometer techniques allow lipidomic and metabolic analyses in TME's interstitial fluid and provide functional insights into the activities of tumor and its TME.

Longitudinal evaluation of the immunological status, based on multiple immune or metabolic signatures in the tumor and its TME, within the same subject is a comprehensive strategy for early detection of cancer, the prognosis of tumor progression as well as prediction of treatment outcome. To accelerate research and potentially translational efforts focused on dynamic profiling of the immunological status in tumor and TME, the National Cancer Institute (NCI) requests proposals for the development of tools that can dynamically measure multiple immune or metabolic signatures of the tumor and its TME.



### ***Project Goals***

Tumor diagnosis at an early stage is critical to improving survival of patients with the tumor. Similarly, being able to predict tumor response to treatment is essential to eliminate the use of ineffective treatment options and allow alternative treatment options. As such, the ability to characterize the dynamic changes in the immune or metabolic signatures of tumor and TME at the molecular, cellular and metabolic levels in an individual patient for early diagnosis and during treatment is critical. The **goal** of this solicitation is to develop minimally-invasive, imaging and analytical platforms that can repeatedly evaluate immunological status of the tumor and its TME to facilitate pre-clinical research in the immunological space for better cancer diagnosis and treatment prediction. To be considered for this topic, the proposed technology should be focused on interrogating **at least two** of the following tumor and TME immunological parameters across time via *in vivo* imaging techniques which can be augmented by additional *in vitro* analytical measurements. These parameters should allow comprehensive evaluation of an immunology status, based either on signatures from multiple immune pathways, from both etiological and consequential events, or of both immunogenetic and immunosuppressive natures. **Proposals to perform *in vivo* measurements not meeting the above criteria or to solely develop software tools to analyze multiplexed image data are not responsive to this topic.**

Potential molecular, cellular, metabolic and physiological parameters to be measured for characterizing immune or metabolic signatures may include but are not limited to the following:

- Gene expression profiles of cells associated with immunological activities;
- Protein expression profiles associated with immunological activities;
- Tissue metabolic profiles associated with immunological activities;
- Tissue integrity and/or pH associated with immunological activities;
- Maps of chemokine receptors associated with immunological activities;
- Maps of enzymatic activities associated with immunological activities;
- Profiles of lipid mediators associated with immunological activities;
- Markers or surrogate markers of inflammation associated with immunological activities;
- Immune and non-immune cell trafficking associated with immunological activities.

Novel or currently existing *in vivo* imaging agents or probes (targeting specific molecular or cellular signatures) may be developed and optimized to enable molecular, cellular and physiological measurements. *In vitro* assessment of immunosuppressive and immunomodulatory factors and cells, their individual genomic and proteomic profiles, and complex networks promoting tumor growth can be included as a part of the proposal to enhance the specificity of the *in vivo* tools. Developing software algorithms or tools specifically for the interpretation of multiplexed measurement from the proposal can be included.

### ***Phase I Activities and Deliverables***

Phase I activities should generate scientific data to demonstrate proof of concept that the technology can quantitatively characterize immune and/or metabolic signatures with sufficient signal sensitivity and resolution. Expected activities and deliverables should include but not limited to:

- Optimize detection scheme to demonstrate *in vitro* signal specificity and correlate signals to cell, molecular target or bioactive mediator concentrations measured using conventional assays;
- Establish calibration curves correlating *in vivo* signal changes to concentration of cells, molecular targets or bioactive mediators measured via conventional biological assays;
- Demonstrate robust signal changes in response to *in vivo* perturbation;
- Demonstrate feasibility in generating maps of measurable parameters as a function of time;
- If new molecular targets are proposed, demonstrate specific binding/targeting capabilities of the agent/probe to the molecular target (tumor and/or TME target);
- If new imaging (or detection) agents are proposed, determine optimal dose and detection window through proof-of-concept small animal studies with evidence of systemic stability and minimal toxicity;
- Benchmark experiments against currently state-of-the-art methodologies;
- Present Phase I results to NCI staff.

For successful completion of benchmarking experiments, demonstrate a minimum of 5x improvement against comparable or gold-standard methodologies.

## **Phase II Activities and Deliverables**

Phase II activities should support commercialization of the proposed technology. Expected activities and deliverables may include:

- Demonstrate *in vivo* clearance, tumor accumulation, *in vivo* stability, bioavailability, and the immunogenicity/toxicity of imaging (or detection) agents or probes;
- Demonstrate high reproducibility and accuracy of the imaging agents or probes in multiple relevant animal models;
- Demonstrate superiority over currently available imaging or detection tools in spatial and/or temporal resolution;
- Demonstrate that sensitivity of proposed imaging agents or probes is sufficient to detect *in vivo* perturbation;
- Demonstrate sensitive maps of measurable parameters as a function of time;
- Perform toxicological studies;
- Demonstrate utility:
  - for diagnosis, demonstrate that the probes can detect tumors at early stages and demonstrate superiority to current diagnosis methods;
  - for predictive/decision, validate the predictive capability of the marker by performing prospective pre-clinical animal trials: stratify the animals into treatment groups and demonstrate that the imaging agent accurately predicts appropriate therapy to use;
  - for therapy response, demonstrate that the imaging tool can accurately visualize changes in response to therapy and validate characteristics of response and non-response.

### **388 *In vitro* Diagnostic for the Liver Flukes *Opisthorchis viverrini* and *Clonorchis sinensis***

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

Number of Anticipated Awards: 2-3

Budget (total costs, per award): Phase I: up to \$300,000 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 liver flukes, *Opisthorchis viverrini* and *Clonorchis sinensis*, are known to cause cholangiocarcinoma (CCA), a type of liver cancer that develops within the bile duct. These species of flukes are classified as Group I carcinogens by the International Agency for Research on Cancer (IARC). They are primarily transmitted to humans by eating raw or undercooked fish, and it is estimated that approximately 45 million people worldwide are infected. Although CCA is generally considered a rare disease with a worldwide incidence of 2-3 cases per 100,000 people, the incidence in areas where liver fluke infections are prevalent (e.g., Southeast Asia and China) is up to 85 cases per 100,000 people. US veterans who served in Vietnam have shown an increasing incidence of CCA, and a pilot study conducted by the Veterans Administration (VA) suggests that 25% of Vietnam veterans were infected with *C. sinensis* during their military service. This statistic might not be entirely accurate since the VA test was not designed to detect *O. viverrini*, the more prevalent fluke in South Vietnam. The VA test, as well as other tests developed in academic laboratories, suffers from low sensitivity and specificity. Detecting fluke infections is the rate-limiting step in intervention as effective treatment is available for fluke infections; therefore, the lack of a reliable test represents an unmet need worldwide and is potentially very important for screening the millions of US veterans who served in southeast Asia. Additionally, the CDC estimates that 10-15% of US immigrants from Asian countries may have been infected. To address this need, this SBIR solicitation will support the development of diagnostic tests or kits to detect chronic and early/mild acute liver fluke infections.

#### **Project Goals**

The primary goal of this contract solicitation is to facilitate the commercial development of a diagnostic test(s) to detect chronic and early/mild acute liver fluke infections caused by *O. viverrini* and *C. sinensis* and thereby decrease the incidence of CCA and possibly also hepatocellular carcinoma (HCC). For each of the other infectious Group I carcinogens associated with human cancers (i.e., hepatitis B and C, Helicobacter pylori, HPV, EBV), FDA-approved diagnostics are available. Currently, the standard diagnostic tool for liver fluke infection is a fecal smear and either direct examination or variations using concentration to increase the number of eggs within the sample. The sensitivity of these tests is low and requires repeated testing over several days to detect true positives and is not routinely performed in the US. Egg production of the flukes can vary widely (from zero to thousands), depending on adult fluke load as well as the length of the infection. Thus, the limit of detection of these

techniques precludes reliable diagnosis of early, mild, chronic and resolved (please see discussion below) infections. The specificity of these tests is also low since the eggs of many helminths look similar.

The average lifespan of *C. sinensis* within the human host is reported at 30 years and that of *O. viverrini* is estimated to be on the same order. Consequently, Vietnam veterans could theoretically fall into one of two categories: (1) those with low level chronic infections, and (2) those with infections that eventually resolved without drug treatment. Diagnostic approaches for Vietnam veterans may be different than for patients with early or mild acute disease.

This solicitation is intended to result in a diagnostic test for *O. viverrini* and *C. sinensis* without any preconceived biases regarding the best approach. Therefore, the proposed platform/approach may utilize any technology capable of meeting the stated goals of this contract solicitation. Diagnostic tests that are useful in developed countries where lab equipment is not limited are welcomed, as are simple point-of-care diagnostics that can be utilized in the absence of such equipment.

The short-term goal of this topic is to develop a CLIA diagnostic test or kit to detect chronic and early/mild acute liver fluke infections. The long-term goal is to develop an FDA-approved diagnostic test.

Acceptable technologies/approaches under this contract topic may include, but are not necessarily limited to:

- Antibody based assays
- Point of care diagnostics using synthetic biology
- Biosensors
- Paper or micro-fluidic devices, lab on a chip, dynamic biomaterials

Please note that the following are **NOT** considered appropriate for development under this contract topic:

- Studies focusing solely on measuring liver fluke infections in animal models
- Development of assays and/or technologies for research use only
- Developing diagnostics to other species of liver flukes, such as *Fasciola hepatica*
- General studies to identify biomarkers associated with *O. viverrini* and *C. sinensis* infection

#### ***Phase I Activities and Deliverables***

- Develop a working diagnostic assay and/or prototype point-of-care diagnostic device that can identify the target pathogens (*O. viverrini* and *C. sinensis*) in low biomass infections.
- Determine the sensitivity, specificity and other performance characteristics (e.g. limit of detection, cross reactivity with other helminth infections, reproducibility, feasibility for newly infected, chronically infected, and resolved infected clinical samples, test stability) of the diagnostic test.
- Conduct initial testing using samples from animal models and/or preferably on patient isolates to demonstrate feasibility.
- Offerors may need to establish a collaboration or partnership with a medical facility or research group in the US or overseas that can provide relevant positive control and patient samples; offerors must provide a letter of support from the partnering organization(s) in the proposal.

#### ***Phase II Activities and Deliverables***

Activities leading to the ultimate development of an FDA approved diagnostic test, including but not limited to:

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

### **389 Development of Artificial Intelligence (AI) Tools to Understand and Duplicate Experts' Radiation Therapy Planning for Prostate Cancer**

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

Number of Anticipated Awards: 2-3

Budget (total costs, per award): Phase I: up to \$300,000 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 goal of this topic is to stimulate Artificial Intelligence (AI) technology to improve treatment planning for prostate cancer by training algorithms to “read” standard Computerized Tomography (CT) and/or MRI images and recommend suitable treatment plan approaches. The resulting AI software may be a tool to aid radiation oncologists in reaching consensus treatment planning, reducing professional costs, and improving quality assurance in clinical trials and patient care. Also, by understanding the AI processes used to achieve an optimal solution, the software may have application in training junior radiation oncologists and updating practitioners.

Treatment planning for radiation therapy is becoming increasingly complex with the advent of image-guided radiation therapy (IGRT) and charged particle therapy (CPT). A substantial amount of physician time and effort is allocated to locating and contouring key tumor and normal tissue structures. Prostate cancer is chosen as it is a common disease worldwide, has well-defined risk groups and patient data-bases including outcomes. The treatment decision process involves assessing the patient’s risk status for disease progression based on tumor size, grade and biomarkers (e.g., prostate specific antigen or other tests); and assigning one of three risk groups: low, intermediate and high. Imaging includes CT and often MRI. Based on the images obtained, the physician and medical physicists plan the target volume to be treated and normal tissue to be avoided. In practice, treatment guidelines are established by consensus papers. However, even between world-renowned experts, treatment plans can exhibit significant differences.

It may be possible to go beyond verbal consensus texts as a basis for defining treatments using an approach similar to AI-based contextual image analysis that does not rely on an understanding of the rationale behind expert “preferences” in treatment plans. Such an AI-based approach would provide an agnostic initial plan, based on computerized image interpretation, upon which the physician and physicist could build a treatment plan. In addition, by studying the AI processes used to achieve an optimal solution, the processes for clinician decisions could be further optimized. The AI software delivered through this contract solicitation could reduce the time burden of image segmentation 75%, from four hours to one hour or less freeing up time for patient care. (<https://www.technologyreview.com/s/602277/deepmind-will-use-ai-to-streamline-targeted-cancer-treatment>). It may result in a substantial reduction in time for physicists and physicians and may improve quality control by having AI assist in initial plan. For smaller facilities with limited funds for staffing, this could improve quality by defining an initial plan developed by AI that could then be reviewed and modified by the physician without starting from unannotated images.

#### ***Project Goals***

The goal of this contract solicitation is to develop and evaluate AI’s capacity to duplicate expert radiation therapy planning. The purpose is to develop radiation therapy treatment plans through AI interpretation of radiomic data from diagnostic images with the intent of fully or at least largely automating treatment planning to eliminate subjective biases, improve treatment quality and reduce cost. The objective of this FOA is not to achieve a breakthrough in Artificial Intelligence, but rather benefit from the recent advances in the development of treatment planning systems and machine learning to improve radiation therapy by eliminating repetitive, time-consuming and subjective biases in treatment delivery, which can result in sub-optimal plans and inadvertent normal tissue injury.

The initial goal is to improve the outcome for patients with prostate cancer. By developing knowledge-based planning solutions it may be possible to provide a more standardized treatment, which would facilitate quality assurance, possibly extending it to facilities with limited expert personnel, and facilitate the conduct of research by reducing the variability and apparent arbitrariness and/or preference that individuals incorporate in their treatment design. The long-term goal will be to apply this technology to other tumor sites.

#### **Technical scope:**

There are many considerations that go into the selection of a target volume for treatment. Nowadays prostate cancer radiation therapy is based on “risk” stratification groups (low, medium and high), which generally determine the tumor dose, volume and other ancillary treatments such as hormonal therapy. Thus, the target volumes include the prostate, varying amounts of

the seminal vesicles and the local lymph nodes for the more advanced risk group. The normal tissues are the rectum, particularly the anterior rectal wall, base of the bladder, femoral heads and occasionally additional abdominal content for lymph node fields.

There are emerging algorithms being developed to outline the normal tissues and the prostate. The scope of the activities here would be having three world renowned experts outline the same set of cases of the varying risk group with the process being “watched” by AI. The expert would dictate the thinking of why the chosen treatment volume and dose are being selected and this would be transcribed. Enough training cases would be used (the estimate of training cases needed is part of the proposal) for the AI to then take a second “test” batch of patients being planned and compared how the AI does in comparison to each of the experts. One question would be how many training cases it takes for the AI to reliably anticipate what the expert will do and to understand the discrepancies between the expert and AI.

Next, using the results from the second “test” batch, the plans for the three experts will be compared, as in consensus panels, and the plans by the AI system for each of the experts will be compared to see if the AI “understood” the differences and how AI would reach a consensus. Should this be effective, one could begin to use the AI to do the initial plan. Some of the cases could be chosen that had grade 2 bowel or bladder side effects to see how the AI and expert plans approach this.

#### Projects That May Be Supported:

Algorithms for AI are now rapidly emerging. This proposal would allow small businesses and start-ups, often comprising the most creative new people in a field, to test their creativity solving a clinical problem that has some degree routine and repetition. The support would be used for assembling and anonymizing the treatment planning, supporting some of the time and facilities of the experts and for bringing them together for consensus discussions. The AI group would receive support for time and resources. AI platforms such as Google TensorFlow, IBM Watson or Definiens’ Image Intelligence suites are likely to be used to emulate human cognitive process of treatment planning and then extract information and develop AI algorithms.

#### Projects That Will NOT Be Supported:

Proposals from the large manufacturers. AI that only outlines tumor and normal tissues but does not select a treatment plan for the three risk groups.

#### ***Phase I Activities and Deliverables:***

Design and deliver an AI approach to develop radiation therapy planning for prostate cancer.

- Choose three expert radiation therapy planning teams comprised of a physician and planners (i.e., a person who is knowledgeable in treatment planning with good understanding of the treatment planning system) and evaluate expert cognition process in developing treatment planning for all three strata of patient risk groups (i.e., low, intermediate, and high).
- Teams including experts must be identified prior to submission of the proposal.
- Companies must already have a dataset including patients in the 3 risk groups, including radiation data and outcome (at least one year post treatment to assess toxicity) in hand before Phase I starts. Additional resource datasets that they can use to test the performance of their auto-segmentation tools can be the annotated prostate database from TCIA (The Cancer Imaging Archive) : <https://wiki.cancerimagingarchive.net/display/DOI/NCI-ISBI+2013+Challenge%3A+Automated+Segmentation+of+Prostate+Structures> as well as the non-annotated dataset: <https://wiki.cancerimagingarchive.net/display/Public/SPIE-AAPM-NCI+PROSTATEx+Challenges>.
- Identify criteria by which an expert planner develops each treatment plan and plan for each risk group
- Describe plan on harmonizing imaging for tumor and normal tissue identification
- Present a justification for the number of training and validation sets that would be needed for each of the risk groups so that the AI results can provide a starting point for the planning team to refine the initial plan and determine the final course of treatment. (If this had been underestimated, it is expected that a suitable number of additional cases will be obtained).
- Design and develop computational methods aimed at developing treatment planning for prostate cancer patients.
- Propose plan to develop, incorporate, compare AI planning system with expert treatment planning system and validate AI based treatment planning system
- Present AI concept to develop knowledge-based radiotherapy treatment planning to SBIR Development Center and the Radiation Research Program

- At a minimum, this technology should be applied to standard 3D CT datasets. Use of additional imaging is at the preference of the planning team, which could include MR fusion into the planning CT to define size/shape of the gland rather than using CT alone.
- Describe and demonstrate cross validation of image delineation, reproducibility of the Planning Target Volume (PTV) and treatment plans.

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

- Creation of an algorithm.
- Demonstration of the ability for the AI to provide a treatment plan (or 3 options of plans).
- Estimation of the number of cases needed to compare the verbal consensus by the three planning teams and the consensus by the AI from each of the teams.
- Concordance between expert treatment plans and AI plans.
- Use of datasets for training, testing, and validation.
- Execution and validation of computational tool, method, or model.
- Establishment of partnerships for potential empirical validation.

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

- Refinement of algorithm.
- Demonstration of utility of AI plan as the initial step to then be reviewed and modified by the planning team.
- Apply AI to data sets and determine how many sets are required before physician and AI are largely in agreement.
- Expand types of data sets to include MRI or PET or other sources of information that would improve AI's performance.
- Establish external partnership(s) for empirical validation of method, as demonstrated with letters of intent from strategic partners.

**390 Clonogenic High-Throughput Assay for Screening Anti-Cancer Agents and Radiation Modulators**

Fast-Track proposals will be accepted.

Number of Anticipated Awards: 3-4

Budget (total costs, per award): Phase I: up to \$300,000 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 goal of anti-cancer treatment modalities is to eradicate cancer cells via several killing mechanisms that include metabolic death, apoptotic cell death (apoptosis) and reproductive death (clonogenic death). Apoptosis is programmed cell death leading to nuclear DNA fragmentation, mostly assessed by flow cytometry, enzymatic activity or membrane staining (annexin 5). Loss of key metabolic activity such as loss of NAD(P)H-dependent cellular oxidoreductase enzymatic activity can result in non-viable cells. This is mostly assessed by colorimetric methods. Clonogenic death is defined as the loss of ability of a cancer cell to proliferate indefinitely, which can only be assessed accurately by clonogenic assays and considered the gold standard assay to determine efficacy of a given radiation combined therapeutic modality. Colorimetric assay for viability and apoptotic assays measure short-term effects, while clonogenic assays measure long-term effects and integrate all forms of cell death, but these assays are costly and labor-intensive. While high-throughput screening (HTS) systems are available for apoptosis and colorimetric cell viability assessments, there is no HTS technology available for clonogenic assays. Colorimetric / apoptotic assays are more often used in screening than clonogenic assays, but do not directly measure residual cell clonogenic potential. Therefore, there exists an opportunity for using HTS in radiation oncology for screening vast number of drugs or drug combinations to improve the efficacy of radiation treatment, by integrating already developed robotics components, such as automated liquid handlers, centrifuges, incubators, imaging and statistical software as well as an irradiator to assess the effect of radiation in a laboratory. It is well known that cancer recurrence is a common event after treatment and often-attributed to

re-population of surviving clones. Thus, evaluating surviving clones becomes a vital test *in-vitro* to assess treatment efficacy, making colony-forming assays the gold standard. Further, designing an HTS for clonogenic assays will increase its utility to screen for drugs, radiation sensitizers and protectors *in vitro*.

Chemotherapy is used for both solid and hematologic malignancies. In addition, more than half of US cancer patients undergo radiotherapy alone or in combination with drugs; percentage of which is expected to only increase. Screening that allows for more accurate testing of chemotherapeutic and combinatorial treatments will better focus development to more promising agents and accelerate development of drug and drug-radiotherapy combinations. With expanded global access to radiotherapy and increased utilization rate, pharma and academics will be further incentivized to discover agents with anti-cancer and radiation sensitizing properties. Assays that are adaptable to the incorporation of molecular targeting, imaging, and evaluation of genetically defined cell panels for drug screening and discovery will be required with ongoing precision medicine initiatives. Companies can utilize clonogenic HTS assays to screen for new agents and to test newly identified agents in combination for radiation. Results from this type of screen should improve success in subsequent *in vivo* model testing and will accelerate clinical translation.

### ***Program Goals***

The purpose of this contract solicitation is to: (i) promote stronger academic industry partnerships in radiobiology to develop clonogenic survival-based HTS systems (ii) to exploit recent advances in the technical maturity of HTS technologies and combine them with advances in clonogenic assays, (iii) encourage small businesses to specifically develop HTS systems for screening potential anti-cancer agents based on a clonogenic endpoint, and (iv) integrate relevant technologies. Colony-forming assay survival experiments currently involve the use of several drug and/or drug + radiation doses as well as several plated cell numbers for each cell line and hence the assays are labor and material intensive. Further, developing an HTS system with a clonogenic endpoint will enhance screening/cross validating chemotherapeutic agents as well as radiation effect modulators and combinatorial treatments, while reducing labor and costs.

To apply for this topic, offerors need to design integration of robotic instrumentation, micro-fluidics, thermal and gas control, colony counting microscopic imaging and image analysis. An integrated system may also require the development of “bridging” components and graphic user interfaces. Offerors are required to develop standard operating procedures matched to validated cell lines for use with the integrated system. Offerors must include an integration of microfluidics/culture system with radiation exposure under conditions allowing precise dosimetry, which is critical. Offerors are also required to integrate and adopt software to capture and calculate survival. This solicitation is not intended for development of systems with non-clonogenic endpoints.

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

- Prototype of integrated/customized robotic or automated platform for cell plating, maintaining the temperature and CO<sub>2</sub>.
- Develop integrated HTS system that couples plating micro-fluidics, irradiation system, microscopy, imaging software and statistical software for estimating cell survival (inactivation radiobiologic estimates) and dose enhancement and modification factors to demonstrate improved efficacy of radiation treatment.
- Integration of localized radiation exposure with precise real-time dosimetry into HTS platform.

### ***Phase II Activities and Expected Deliverables***

- Delivery of a prototype system with validated SOPs that are translatable to other laboratories.
- Imaging of colonies and software to capture and calculate the survival.
- Cross-check validation of HTS data with conventional clonogenic assays.
- Defined cell line panels that have been shown to be appropriate for use with the system and the clonogenic endpoint. Validation of representative “hits” using conventional clonogenic assay.
- Software to calculate radiation-inactivation estimates and graphing cell survival curves and calculate dose enhancement factor if done in combination with agents.
- Licensing of individual components for use in the system as needed.

## 391 Drugs or Devices to Exploit the Immune Response Generated by Radiation Therapy

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

Number of Anticipated Awards: 2-3

Budget (total costs, per award): Phase I: up to \$300,000 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*

Tumor irradiation promotes recruitment of immune activating cells into the tumor microenvironment, including antigen presenting cells that activate cytotoxic T-cell function. However, tumor irradiation can also recruit immunosuppressive cells into the tumor microenvironment. Local irradiation can also impact tumor growth at a distance from the irradiated tumor site, known as the abscopal effect. This effect is potentially important for tumor control and is mediated through ceramide, cytokines, and the immune system.

Ionizing radiation can induce the following changes in the tumor micro-environment and such changes can be important targets to develop agents that can augment or negate radiation-induced immune activation or suppression respectively. Tumor-associated antigens (TAAs) are released by irradiated dying cancer cells. TAAs and cell debris are engulfed in the tumor microenvironment by phagocytes such as macrophages, neutrophils, and dendritic cells for antigen processing and presentation.

- RT-induced cell death releases danger signals including heat-shock protein (Hsp), HMGB1, and calreticulin (eat-me signal for phagocytes).
- RT induces increased expression of tumor antigens and MHC class I molecules on tumor cells.
- RT-induced T cell activation increases expression of negative stimulatory molecules such as CTLA-4.
- Certain radiation doses may increase tumor production/secretion of immunosuppressive cytokines such as IL-10 and TGF $\beta$ .
- Activated APCs migrate to the draining lymph node, further mature upon encountering T helper cells, release interferons (IFNs) and IL-12/18 to stimulate Th<sub>1</sub> responses that support the differentiation and proliferation of antigen-specific CTLs. Activated antigen-specific CTLs traffic systematically from the draining lymph node to infiltrate and lyse primary and distal tumors.

Several factors can influence the ability of radiation to enhance immunotherapy, including a) the dose of radiation (IR) per fraction and the number of fractions, b) the total dose of IR, and c) the volume of the irradiated tumor tissue. However, the impact of these variables is not well understood. Inducing anti-tumor cellular-mediated immune responses has been the subject of some pre-clinical tumor regression studies and is being applied in immune-modulatory clinical trials using antibodies against molecules that suppress immune responses such as PD1, PDL1 and CTLA4 or immune agonists such as OX40, CD27, GITR, 4-1BB, TNFR receptors, ICOS, and VISTA. Overall, discovery of checkpoint protein functional control of T-cells in tumor microenvironment led to the development of checkpoint blockade therapy and many checkpoint inhibitors including Nivolumab, Pembrolizumab, and Atezolizumab have been approved by the FDA for several indications. Several clinical trials testing combination of radiation with check point inhibitors are underway and have resulted in mixed results. Further, many of these combination trials lack robust pre-clinical scientific rationale raising queries if such checkpoint agents augment the immune modulating effects of radiation. Hence, more agents and/or devices that can augment immune activation or inhibit immune suppression induced by standard conventional 2 Gy fractions, (3-8 Gy) hypofractionation and high-dose hypofractionated (>10 Gy) radiotherapy are warranted.

### *Project Goals*

Augmentation of radiation induced immune activation and/or inhibition of radiation induced immune suppression could enhance anti-tumor effects. The goal of this solicitation is to develop agents or devices (engineered cellular therapies, antibodies, small molecules, siRNA/CRISPR-CAS9 or in-vivo physical/chemical modulating instrumentation-based approaches) that can augment (immune stimulation) or negate (immune suppression) one or more of the immune modulation events induced by radiation therapy. Radiation therapy can include conventional clinically relevant radiation, hypofractionated radiation, and high-dose hypofractionated radiation.

It is critical that the proposed agent or device **must specifically exploit the radiation induced immune response.**



### Projects That Will NOT Be Supported:

Immune modulating agents that are already being tested in combination with radiation in clinical trials will not be supported. Testing of immune modulating agents **in the absence of radiation** will not be supported.

### **Phase I Activities and Deliverables:**

- Selection of cancer type(s), organ site(s), immune modulation agent(s), and radiation dose & fractions, with adequate justification.
- Proof of concept animal (mice or rat) studies demonstrating augmentation or inhibition of radiation-induced immune activation or suppression respectively with the combination of the agent or device.
  - Demonstrate augmentation of immune activation in irradiated environment with appropriate standard markers showing an increased influx of positive effector immune cells (such T-cells, macrophages, dendritic cells etc.) in the tumor micro environment.
  - Demonstrate negation of immune suppression in irradiated environment with standard appropriate markers showing reduction in the influx of negative effector immune cells (such neutrophil, T-reg and MDSCs) in the tumor micro environment.
- Proof of concept animal (mice or rat) studies demonstrating tumor regression in a syngeneic contra-lateral tumor model whereby regression is observed in both the irradiated primary tumor as well as distal non-irradiated tumor when the agent is combined with radiation.

### **Phase II Activities and Deliverables:**

- Perform absorption, distribution, metabolism and excretion (ADME) of agents with bioavailability and efficacy studies in appropriate animal models with adequate justification (the models chosen could be syngeneic rodent models, humanized rodent models or canine models) and demonstrate:
  - Improved efficacy (both immune modulation and tumor regression) compared to radiation or agent alone
  - Radiation sensitizing effects on tumors using standardized in vivo radiation regrowth delayed assays
  - Comparative (similar or lower) toxicity compared to the agent or radiation alone
- Perform IND-enabling GLP safety toxicology studies in relevant animal model(s) following FDA guidelines.
- For offerors that have completed advanced pre-clinical work, NCI will support pilot human trials.

## **392 Clinical Trials of Systemic Targeted Radionuclide Therapies**

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

Number of Anticipated Awards: 2-4

Budget (total costs, per award): Phase I: up to \$300,000 for up to 9 months; Phase II: up to \$2,000,000 for up to 2 years

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

### **Summary**

This topic calls for “first in human” studies and Phase I/II clinical trials of targeted radionuclide therapy (TRT) for cancer using novel radiopharmaceuticals or TRT treatment strategies as described in the project goals below.

TRT enables personalized cancer treatment by combining the therapeutic effect of radiation therapy with the targeting capability of molecularly targeted agents, such as antibodies used for biologically targeted therapy or immunotherapy. In TRT, a cytotoxic dose of a radioactive isotope is attached to a tumor-targeting agent that binds to malignant tumor cells selectively. For instance, the ability of the antibody to bind only to a tumor-associated antigen ensures that the tumor gets a lethal dose of radiation, while normal tissue gets only a minimal dose. This minimizes toxicity to normal tissues and can increase therapeutic efficacy (therapeutic index).

The first clinical application of TRT was the treatment of thyroid cancer with radioactive iodine, and the field of TRT has since expanded with clinically approved indications for non-Hodgkin lymphoma, bone metastases, and neuroendocrine tumors including neuroblastoma. Two radioimmunotherapy agents involving <sup>90</sup>Y- and <sup>131</sup>I-labeled CD20 (Bexxar and Zevalin) were approved for the treatment of non-Hodgkin lymphoma, but their clinical use has been limited due to lack of coordination between nuclear medicine physicians and oncologists, concerns about radiation safety, and issues surrounding reimbursement. Building on the prior success of <sup>89</sup>Sr and <sup>153</sup>Sm, <sup>223</sup>RaCl<sub>2</sub> (Xofigo) was shown to improve survival for men with bone metastases

from castration-resistant prostate cancer and has reinvigorated interest in the development of novel TRT agents. Most recently, <sup>177</sup>Lu-dotatate (Lutathera) has been approved by FDA for treatment of neuroendocrine tumors.

As this class of treatments shows tremendous clinical potential, the NCI SBIR program issued TRT-focused contract solicitation for preclinical research in three consecutive years and awarded 16 contracts in this field. In addition, more than 30 TRT-related grants (14 of them funded by NCI SBIR program) have been awarded by different NCI funding mechanisms. Some of those projects are mature enough to enter the clinical testing phase within the next two years. To facilitate the translation of this investment in pre-clinical studies, there is a need for funding of first-in-human studies (Phase I/II clinical trials) to assess the feasibility, safety, and efficacy of novel TRT compounds (radiopharmaceuticals) or treatment strategies.

### ***Project Goals***

This contract solicitation seeks to stimulate research, development, and commercialization of innovative TRT techniques that could potentially improve the treatment efficacy and reduce toxicity to normal tissues. Proposals addressing clinical applications of the following technology areas are encouraged: clinical evaluation of innovative ligands and radiotracers for TRT; novel dosimetry techniques; new patient selection and treatment planning strategies taking into consideration the pharmacokinetics of the radiopharmaceutical and the resulting radiation dose delivered to the tumor and normal tissues in individual patients; and for mature projects, the combination of a TRT with conventional therapies.

To apply for this topic, offerors must have met IND requirements for their product or provide convincing data indicating that an IND will be accepted by the end of the Phase I period of performance.

The short-term goal of the project is to perform clinical studies testing the use of new TRT compounds or strategies for the treatment of cancer as described above. The long-term goal of the project is to enable a small business to bring a fully developed TRT compound or novel TRT treatment strategy to the clinic and eventually to the market.

### ***Phase I Activities and Deliverables***

- For offerors who do not expect to have an IND accepted by September 2019, it is expected that specific plans for a pre-IND meeting with FDA will be described in the SBIR proposal. Pre-IND Phase I work may include:
  - Scale up and manufacturing of the new tested radiopharmaceutical
  - Completion of any activities required for IND submission
  - Finalized Clinical Trial Protocol for submission to FDA
- Examples of other Phase I activities include:
  - Clinical trial initiation activities such as protocol development, site selection and initiation
  - Development of methods and establishment of procedures for radiation dosimetry
  - Completion of regulatory approvals

IND acceptance is critical at the end of Phase I. Offerors that do not have IND acceptance and Phase I deliverables met will not be allowed to move to Phase II.

### ***Phase II Activities and Deliverables***

Clinical trials. Depending on how advanced the development of a new therapeutic strategy is to be tested, the clinical trial might be: (i) feasibility, first-in-human, testing the biodistribution of the radiopharmaceuticals and assessment of therapeutic ratio based on radiation dosimetry; (ii) Phase 1, assessing the safety of the treatment and maximum tolerated dose of the tested compound; or (iii) Phase 2 assessing the optimal treatment strategy and its efficacy, preferably by comparing it in a randomized trial with that of the current standard of care.

- Implementation of appropriate dosimetry methods
- Quantitative assessment of radiation doses delivered to tumor and normal tissues
- Patient recruitment plan
- Data safety management plan
- Registration of clinical trial in ClinicalTrials.gov
- Data collection
- Completion of primary endpoint and secondary endpoint data analyses
- Completion of final report of the primary outcome
- Reporting of results in ClinicalTrials.gov

## 393 Sensing Tools to Measure Biological Response to Radiotherapy

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

Number of Anticipated Awards: 3-4

Budget (total costs, per award): Phase I: up to \$300,000 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 dose to areas of normal tissue in order to increase the therapeutic ratio.

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. While defining the geometry remains critical, currently employed dose models consider the patient to be a volume of water and, at most, apply a fixed corrective ratio of the x-ray dose in the context of CPT. 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 dose to tumor in the patient. For example, a physical dose on day one of treatment has a very different biological effect than on the tenth day of treatment across tumor cells and normal tissue. Patients have varying states of baseline health, varying states of genetic capacity to repair radiation related damage, and tumors have varying capacities to survive a given physical dose. To truly optimize dose prescription, what is needed is the ability to specify the temporal, local biologic dose that is delivered via physical dose. The capacity to measure the biologic changes in a host system over time could even lead to rational optimization of physical dose modification of both the forms of radiation being used as well as other agents during the course of therapy. This technology could ultimately allow adaptive combined modality therapy in a spatially individualized fashion. 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.

Contemporary engineering and device miniaturization (including nanotechnology offers many compelling properties 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. Even if they could, implantable dosimeters are much larger in scale and can require physical insertion that can have significant morbidity. 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 to allow volumetric assessment and extracorporeally to allow rapid, lab-test style measurements. Two examples of current physical dose measuring nanoparticle sensor systems include luminescent nanoparticles that provide *in vivo* bioimaging as a response to soft X-ray use (DOI: 10.1039/c6nr09553d) and a colorimetric plasmonic nanosensor capable of measuring physical dose delivered by ionizing radiotherapy (DOI: 10.1021/acsnano.5b05113). The goal of this solicitation is to expand these sorts of nanoparticles to allow the measurement of biologic changes.

### *Project Goals*

The purpose of this solicitation is to develop *in vivo* or *in vitro* sensor tools to measure biologic response to radiation. These will ultimately be used in optimizing the definition and use of radiation dose; 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 under-dosing, 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. Ultimately, development of these tools could enable an expanded definition of prescribed dose from the physical to the biologic as well as eliminating subjective biases, improving treatment quality and reducing overall cost.

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 “biologic response sensors or dosimeters are to allow study of the biological effects of radiation therapy and potentially that can be correlated with physical dose and other parameters. These biologic dosimeters or 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. As an example, a specific nanoparticle would report temporal and spatial information about, for example, one biologic pathway, molecule’s activity, or a complex’s formation/function. Ideally, these biologic response sensors should be able to be imaged via CT or MRI to allow non-invasive dynamic and real-time data collection. As such, the development and evaluation of systems that can measure in a validated fashion biologic response to physical dose from radiation therapy when used alone and in combination with other agents, will be preferred.

#### Overall scope:

Such systems are diverse as noted in the above examples (e.g., surface chemistries, material properties, etc.), as such 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* and *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.

#### Projects That Will NOT Be Supported:

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***

- 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*
- Consultation with FDA regarding development of an IND.

### **394 Combinatory Treatment Modalities Utilizing Radiation to Locally Activate or Release Systemically Delivered Therapeutics**

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

Number of Anticipated Awards: 2-4

Budget (total costs, per award): Phase I: up to \$300,000 for up to 9 months; Phase II: up to \$2,000,000 for up to 2 years

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

#### ***Summary***

This solicitation calls for the development of combinatory treatment modalities utilizing external ionizing radiation to locally activate or release systemically or intratumorally delivered therapeutics. The goal is to leverage an existing radiation therapy infrastructure to provide this radiation.

Systemic administration of therapeutic agents (TA) for cancer treatment is a common practice. However, their presence in normal tissues leads to adverse toxicities limiting the administered dose and the resulting treatment efficacy. The undue toxicity might be avoided if the TA remained encapsulated or inactive until exposed to an extremal radiation within a well-defined volume. In addition, the time of release/activation could be adjusted, so that the concentration of the TA at the target volume reaches levels necessary for an effective treatment. The key criteria towards achieving an effective and safe treatment include safe doses of the external radiation and quantitative control of localized TA release or activation. Remote triggering mechanisms may include X-rays or particle, e.g. proton, beam currently used for radiation therapy (RT) of cancer.

Use of heat or ultrasound to activate or release therapeutic agents has been an active research front in many academic centers with fruitful results. Thermal release of drugs from liposomes has been in clinical practice for years. An example is ThermoDox (Celsion Corporation: <http://celsion.com/thermodox/>), which uses LTSL (lysolipid thermally sensitive liposome) technology to encapsulate doxorubicin, a proven and commonly used cancer drug. The heat-sensitive liposome rapidly changes structure when heated to 40°C-45°C, creating openings in the liposome that release doxorubicin directly into and around the targeted tumor.

This solicitation focuses on systems that might release drugs or induce a toxic effect in response to external ionizing radiation that is currently used for cancer treatment. Such approach promises unique clinical benefits over conventional systems that release their cargo passively or are activated internally. For instance, X-ray might be used to stimulate local release of drugs from nanoparticles, or combination of X-rays with nanoscintillators emitting light that activates photosensitizers in photodynamic therapy (PDT) would allow extension of PDT to deep seated tumors. This approach could be implemented as an addition to the current standard of care involving RT. It will allow to utilize already existing radiation infrastructure. Patients undergoing RT will be given an opportunity to combine it with novel TAs or potent tumoricidal agents that could not be delivered by conventional systemic administration methods. Well defined spatial and temporal control of the TA release or activation will limit the toxicity while maximizing the efficacy of the combinatory treatment leading to an improvement of the quality of life and overall survival of cancer patients. Therefore, there is a need to encourage the development of such technologies.

### ***Project Goals***

This contract solicitation seeks to stimulate research, development, and commercialization of innovative techniques that could synergistically improve the effectiveness of RT and TA and reduce toxicity to normal tissues. Proposals addressing the following technology areas are encouraged: new treatment strategies, design, synthesis, and evaluation of innovative TA and formulations.

The short-term goal of the project is to perform feasibility studies for development and use of the combinatory treatment modalities for the treatment of cancer. The long-term goal of the project is to enable a small business to bring a 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 TA that could be activated by radiation or TA formulations that could be triggered to release the TA by radiation *in vivo*.
- Define the mechanisms of the proposed TA tumoricidal activity *in vivo*.
- Identify the set of patients that are likely to be impacted by this technology.

Approaches using systemic administration of agents that act as radiation sensitizers are not appropriate for this solicitation. This solicitation is not intended for the development of the instrumentation for triggering the release of the TA. While modification of the device for eventual use with the TA in the clinic is acceptable, it must not be the focus of the proposal.

### ***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 TA and activation of the TA 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 TA 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.

## **395 Targeted Therapy for Cancer- and Cancer Therapy-Related Cachexia**

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

Number of Anticipated Awards: 2-3

Budget (total costs, per award): Phase I: up to \$300,000 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***

Cachexia is characterized by a dramatic loss of skeletal muscle and adipose tissue mass, which cannot be reversed by nutritional intervention. More than half of all cancer patients experience cachexia, and it is estimated that nearly one-third of cancer deaths can be attributed to cachexia. Patients suffering from cachexia are often so frail and weak that walking can be extremely difficult. Cachexia occurs in many cancers, usually at the advanced stages of disease. Cancer cachexia is most prevalent in gastric, pancreatic, and esophageal cancer (80%), followed by head and neck cancer (70%), and lung, colorectal,

and prostate cancer (60%). Despite cachexia's impact on mortality and data strongly suggesting that it hinders treatment responses and patients' abilities to tolerate treatment, no effective therapies have been developed to prevent or hamper its progression. Even for patients able to eat—appetite suppression or anorexia is a common cachexia symptom—improved nutrition often offers no respite. Overall, cachexia is characterized into three prominent stages, namely pre-cachexia, cachexia, and refractory cachexia. Pre-cachexia is characterized by some metabolic and endocrine changes, but weight loss is minimal. In cachexia, the patient undergoes more prominent weight loss, anorexia, muscle mass depletion, and reduced muscle strength. At this point, weight loss can be somewhat countered by health supplements and corticosteroids, but improved muscle function has not been achieved. In refractory cachexia, there is severe body weight, muscle, and fat loss; the reversal of weight loss is negligible even with the dietary supplements.

Over the last few years, researchers have begun to better understand the underlying biology of cancer- and cancer therapy-related cachexia. Findings from several studies point to potential therapeutic approaches, and a number of clinical trials of investigational drugs and drugs approved for other uses have been conducted or are under way. For recent research on the biological pathways involved in cachexia, please refer to Abstracts from the 3<sup>rd</sup> Cancer Cachexia Conference published in [J Cachexia Sarcopenia Muscle](#). 2017 Feb; 8(1): 145–160. Published online 2017 Feb 27. doi: [10.1002/jcsm.12186](https://doi.org/10.1002/jcsm.12186).

### ***Project Goals***

The goal of this SBIR contract solicitation is to provide support for the development of targeted agents, including small molecules and biologics, to prevent or treat cachexia related to cancer and/or cancer therapy, including chemotherapy and/or radiotherapy. Proposals submitted in response to this topic must focus on cancer indications with the highest prevalence of cancer- and cancer therapy-related cachexia. Any route of administration is acceptable, but it must be kept in mind that once cachexia has developed, absorption in patients may be impaired.

To apply for this Topic, offerors should:

- Identify a therapeutic target and explain in detail the mechanism by which their drug will exhibit efficacy in preventing or treating cancer- or cancer therapy-related cachexia.
- Provide preliminary data or cite literature to support the role of the target in the development of cancer- or cancer treatment-related cachexia.
- Demonstrate ownership of, or license for, at least one lead agent (e.g., compound or antibody) with preliminary data showing that the agent hits the identified target.
- Possess experience with well-validated *in vitro* assays and *in vivo* models. Preliminary animal studies establishing proof-of-concept efficacy must be completed in Phase I. Common animal models used in cachexia research include: Lewis Lung Carcinoma (LLC), C-26 colon adenocarcinoma and Apc<sup>Min/+</sup> mice. More recently, orthotopic patient-derived pancreatic xenograft models have been employed to more closely recapitulate the muscle wasting seen in human disease.
- The scope of work proposed may include structure activity relationships (SAR); medicinal chemistry for small molecules, antibody, and protein engineering for biologics; formulation; animal efficacy testing; pharmacokinetic, pharmacodynamic, and toxicological studies; as well as production of GMP bulk drug and clinical product. These data will establish the rationale for continued development of the experimental agent to the point of filing an investigational new drug application (IND).
- Offerors must also have the appropriate team members including expertise in: cachexia, drug development, and regulatory strategy.

### ***Activities not supported by this Topic:***

Proposals involving supplements and food products will not be considered.  
Projects proposing to develop anti-tumor agents will not be considered.

### ***Phase I Activities and Deliverables***

- Demonstrate *in vitro* efficacy for the agent(s) in appropriate models.
- Conduct structure-activity relationship (SAR) studies, medicinal chemistry, and/or lead biologic optimization (as appropriate).
- Perform animal toxicology and pharmacology studies as appropriate for the agent(s) selected for development.

- Perform animal efficacy studies in an appropriate model of cancer- or cancer treatment-related cachexia (see examples above). Include controls to preclude drug-drug interactions (e.g., the drug for cachexia should not decrease efficacy or increase toxicity for standard-of-care cancer drug).
- Develop a detailed experimental plan necessary for filing an IND or an exploratory IND (for potential SBIR phase II award).

### ***Phase II Activities and Deliverables***

- Complete IND-enabling experiments and assessments according to the plan developed in Phase I (e.g., demonstration of desired function and favorable biochemical and biophysical properties, PK/PD studies, safety assessment, additional preclinical efficacy as warranted, GMP manufacturing, and commercial assessment). The plan will be re-evaluated and refined as appropriate.
- Develop and execute an appropriate regulatory strategy. If warranted, provide sufficient data to file an IND or an exploratory IND for the candidate therapeutic agent.
- Demonstrate the ability to produce a sufficient amount of clinical grade material suitable for an early clinical trial.

## **396 Imaging for Cancer Immunotherapies**

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

Number of Anticipated Awards: 3-4

Budget (total costs, per award): Phase I: up to \$300,000 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***

Immunotherapies have emerged as one of the promising approaches for cancer treatment by exploiting patients' own immune systems to specifically target tumor cells. However, it has been recognized that responses often occur in only a subset of patients in any given immunotherapy. This treatment is also associated with drug toxicity (e.g., cytokine storm), potential development of autoimmune diseases, in addition to the high cost. As this treatment modality continues to evolve, a significant clinical question that needs to be addressed is to determine which patients would benefit from immunotherapies. In addition, there is increasing need for newer methods to evaluate the efficacy and potential toxicities of the treatment, monitor cancer patients' prognosis, and implement early interventional steps to minimize adverse effects upon completion of immunotherapies.

Cancer imaging is routinely used to: 1) stratify patients for cancer treatment; and, 2) monitor and provide reliable predictive and/or prognostic information for a specific treatment. With the rapid advancement of imaging technologies, particularly molecular imaging technology, this technique provides detailed visualizations and measurements of biologic processes taking place inside the body at molecular, cellular, anatomical, and functional levels. As such, imaging capability offers capability to assess early changes in molecular expression, cellular activity, and functional perturbation in response to therapies. Furthermore, cancer imaging provides nearly real-time information about tumor target expression levels, potentially allowing physicians to predict which patients may respond to therapies. In addition to patient stratification, cancer imaging of therapeutic targets may provide insight into predicting efficacy and reducing toxicity of the cancer treatment and overall disease progression.

The purpose of this initiative is to provide much needed support for the development of cancer imaging technologies or approaches to identify patients who are likely to respond to cancer immunotherapies, evaluate the efficacy and potential toxicities of the treatment, and/or monitor cancer patients' treatment prognosis. This solicitation is intended specifically to address cancer immunotherapies that depend upon eliciting an immune response. Projects that do not meet this requirement will not be funded. For example, a monoclonal antibody-based therapy that exerts a direct antitumoral effect either by neutralizing the antigen or by activating signaling pathways within the target tumor cells but does not elicit an immune response for its clinical application, is not considered an immunotherapy and would not be funded.

### ***Project Goals***

The goals of the solicitation are to develop a cancer imaging technology to identify patients who are likely to respond to cancer immunotherapies, evaluate the efficacy and potential toxicities of the treatment, and/or monitor cancer patients' prognosis. The imaging modality could be one of the following, but is not limited to: ultrasound imaging, optical imaging,



photoacoustic imaging, PET, SPECT, MRI or combination of multiple modalities. Molecular markers of interest could include but are not limited to: cell surface receptors, immune or associated non-immune cells, cellular infiltrates, enzymes, metabolites or metabolic states, DNAs, RNAs, or epigenetic modifications. The technology development should be platform driven. For example, the procedure for the cancer imaging that targets immunotherapy for breast cancer or its subtype should be easily applied for other cancer types/subtypes, such as colon cancer or prostate cancer. To apply for this topic, offerors need to outline and indicate the clinical question and unmet clinical need that their cancer imaging will address. Offerors are also required to use novel or validated imaging targets. This solicitation will not support efforts for imaging biomarker discovery

The long-term goal of this solicitation is to enable small businesses to bring novel or improved imaging modalities of fully developed imaging technologies for cancer immunotherapies to the clinic and the market.

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

Phase I activities should generate scientific data confirming the clinical potential of the proposed imaging for cancer immunotherapies. The Phase I research plan must contain specific, quantifiable, and testable feasibility milestones.

Expected activities may include:

- Demonstrate proof-of-concept for the development of a novel, modification of an existing imaging technology or approach to identify patients who are likely to respond to immunotherapies, and/or evaluate efficacy and toxicities of immunotherapy, and/or monitor tumor prognosis under immunotherapy using the imaging technology.
- Quantify sensitivity and specificity of such imaging technology or approach.
- Conduct preliminary biosafety study for the imaging technology or approach.
- Benchmark experiments against current state-of-the-art methodologies.
- Present Phase I results and future development plan to NCI staff.

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

Phase II should follow the development plan laid out in the Phase I and should further support commercialization of proposed imaging technology for cancer immunotherapies. The Phase II research plan must contain specific, quantifiable, and testable milestones.

Expected activities may include:

- Complete all experiments according to the development plan.
- Demonstrate capability of imaging technology to: 1) identify whether cancer animal models and/or human patients respond to cancer immunotherapies; and/or, 2) evaluate efficacy and toxicities of cancer immunotherapies in animal models and/or human patients; and/or, 3) monitor tumor prognosis in animal models and/or human patients under cancer immunotherapies.
- Demonstrate high sensitivity and specificity of the imaging technology in animal models and/or human patients.
- Demonstrate high reproducibility and accuracy of the imaging technology in animal models and/or human patients.
- Determine biosafety of the imaging technology with animal or human toxicology studies.
- If warranted, initiate FDA approval process for the candidate imaging technology.

## **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:

#### **106 Active MRI Needle**

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

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

Budget (total costs, per contract): Phase I: up to \$300,000 for up to 12 months; Phase II: up to \$2,500,000 for up to 2 years

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

### ***Summary***

Needle access to deep organs is common to numerous catheter, radiological, and surgical procedures, both diagnostic and therapeutic, including access to blood vessels, pericardial and cardiac chambers, viscera, etc. MRI operation affords exquisite imaging and delineation of soft tissue beyond what is afforded by X-ray fluoroscopy, CT, and ultrasound guidance. “Passive” needles visualized solely by their materials properties, afford inadequate tracking and visualization into and around precise or precious structures. “Active” MRI catheter devices contain electronic elements to accomplish MRI visibility. This solicitation aims to support the development of an active MRI needle tools for commercial clinical availability.

### ***Project Goals***

The goals of this project are to develop and obtain market clearance for an active MRI needle to be used in patients.

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

The deliverable is a market-cleared system including active MRI needle and all necessary accessories for MRI-guided active needle access in patients. “Active” refers to visualization by virtue of serving as one or more resonant antennae connected or coupled to the MRI hardware system.

The deliverable must have the following characteristics

- a. Available in a range of sizes as small as 21G and as large as 18G
- b. Available in a range of lengths as short as 5cm and as long as 20cm
- c. Accommodates guidewires from 0.014” to 0.035” outer diameter for the 21G to 18G embodiments, respectively
- d. Luer-type hub connection for syringes
- e. Conical hub inside Luer to simplify guidewire insertion
- f. Electrical isolation type “CF” for patient safety
- g. Free from clinically-important heating during continuous MRI at base magnetic fields up to 1.5T.
- h. Visualized using continuous (“active profiled”) or interrupted (“active marker”) antenna or resonator designs
- i. Provides confident certain visualization of the needle tip under the full range of operating conditions.

- j. Ergonomic signal transmission system that does not impede mechanical operation of needle (such as a heavy connector cable to the scanner).
- k. Accessory capabilities, such as connectors, transmission lines, and/or coil configuration files, as required for operation with MRI systems, at least including the MRI system manufacturer allowing testing by NHLBI DIR (Siemens). This requires evidence of a collaboration agreement with a system manufacturer.
- l. Proposals that include novel strategies to mitigate heating of the needle or of transmission lines (connectors to MRI scanner hardware) are encouraged
- m. Proposals for novel visualization strategies are welcomed

A Phase I award would develop and test an actively visualized needle system *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 requires specific hardware compatibility with the NIH Siemens Aera 1.5T MRI system.

### ***Phase II Activities and Expected Deliverables***

A phase II award would allow testing and regulatory development for the device (described under phase I) suitable for marketing in the United States, whether under premarket notification [510(k)] marketing clearance. 510(k) clearance would constitute the deliverable.

## **107 Transcatheter Potts Shunt**

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

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

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

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

### ***Summary***

Pulmonary hypertension of diverse etiologies causes severe symptoms and high mortality rate. Symptoms include inability to exercise, shortness of breath, right-sided congestive heart failure, and sudden death. New pharmacologic options have significantly prolonged survival in adults with severe pulmonary hypertension. These therapeutic options have led to nationwide centers of excellence for the care of pulmonary hypertension. Despite successful pharmacotherapy, the disease progresses in the majority causing progressive right ventricular failure and declining functional status. Heart-lung transplantation may not be an option.

Potts Shunt (between the left pulmonary artery and the descending thoracic aorta) is a surgical procedure that can divert blood flow to relieve right heart failure in patients with end-stage pulmonary hypertension {J Blanc, N Engl J Med, 2004;350:6, PMID [14762197](#) }. It can be offered as a bridge to transplantation or as a destination therapy. Surgical Potts shunt is morbid and complex. A catheter-based Potts shunt has been described using commercial off-the-shelf devices, but shortcomings of these devices have caused fatal complications and limited adoption of the technique.

A simplified catheter system for Potts shunt would enable a new therapeutic option for severe or otherwise end-stage patients with severe pulmonary artery hypertension who are refractory to pharmacologic therapy.

The commercial market is small enough to discourage the early development costs of a transcatheter Potts shunt. There is a considerable unmet need for a purpose-built non-surgical aorto-pulmonary anastomosis system.

### ***Project Goals***

The goals of this project are to develop and test a transcatheter Potts Shunt prototype system *in vivo* in Phase I, and in Phase II to develop a clinical device and obtain an FDA Investigational Device Exemption for first human testing in the United States.

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

The deliverable is a catheter system to establish a non-surgical Potts shunt (transcatheter pulmonary-to-aortic anastomosis) to treat refractory pulmonary artery hypertension.

The system includes:

- a. Catheter system to allow traversal from donor to recipient blood vessel (typically left pulmonary artery and descending aorta).
- b. Catheter traversal system between donor and recipient blood vessel (most likely using transcatheter electrosurgery techniques)
- c. A system to establish donor and recipient side-to-side anastomoses, secure from extravasation, in a range of expected anatomies in adults requiring Potts shunt for severe pulmonary artery hypertension. Proposed solutions should accommodate both adjacent and non-adjacent donor/recipient pairs.
- d. Delivery systems are ideally 12 French or smaller
- e. Solutions should be sufficiently resistive to allow patient-tailored shunt that balance decompressive flow against excessive shunt causing lower extremity hypoxemia
- f. Solutions should not cause hemodynamically significant obstruction in either donor or recipient vessel
- g. Solutions must resist inadvertent operator “pull-through” from both donor and recipient vessel
- h. Considerable detail should be supplied about the intended mechanical and biological performance of the anastomoses, including resistance to inadvertent separation and pull-through, hemorrhage, thrombosis, neointimal overgrowth, angulation, distortion or failure by patient and cardiovascular motion, and anticipated flow characteristics
- i. The implant and the delivery system should be conspicuous under the intended image-guidance modality; MRI compatibility is considered important
- j. Solutions must address mural recoil, kinking, and motion throughout the cardiac and respiratory cycles.
- k. Preferred solutions could also accommodate growing children by allowing late post-dilatation to adult vessel dimensions (ultimately dilatable to adult size vessels).

Phase I should focus on mechanical and biological performance of the proposed endograft, taking into account mechanical strength required for the application; geometry of the access vessels and geometry and morphology of target vessels; features to accommodate late post-dilatation achieve larger size in growing children, implantation, and visualization strategies.

At the conclusion of phase I, a candidate device design should be selected for clinical development based on in vivo performance of a mature prototype resembling a final design. The contractor should provide a detailed report of pre-IDE interactions with the Food and Drug Administration to identify requirements for IDE development under Phase II, including the summary of mutual understanding.

The sponsoring NHLBI laboratory may offer to perform a limited number in vivo proof-of-principal experiments in swine (by mutual agreement) to confirm mechanical performance.

### ***Phase II Activities and Expected Deliverables***

The specific Phase II deliverables are as described under Phase I. At the conclusion of phase II, the offeror should submit an investigational device exemption (IDE) for a USA first-in-human research protocol, involving at least 15 subjects. If the exemption is not granted during Phase II, the offeror must provide an FDA response that indicates the specific deficiencies are limited to Current Good Manufacturing Design Verification and Validation, and that offeror proposed plan would be considered acceptable. Furthermore, such a deficient application must be accompanied by a plan for Phase IIb funding and matching funding.

The sponsoring NHLBI laboratory may perform a limited number of in vivo proof-of-principal experiments in swine (by mutual agreement).

NHLBI offers but does not require to perform the clinical trial at no expense to the offeror, to participate in the development of the clinical protocol, and to provide clinical research services. The vendor is expected to perform or obtain safety-related in vivo experiments and data to support the IDE.

## 108 Device System for Transcatheter Repair of Postinfarction Ventricular Septal Defect

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

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

Budget (total costs, per award): Phase I: up to \$400,000 for 12-18 months; Phase II: up to \$3,000,000 for up to 36 months

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

### *Summary*

Postinfarction ventricular septal defect (VSD) is an uncommon but devastating mechanical complication of acute myocardial infarction with extremely high mortality. Patients already suffering myocardial dysfunction usually die from acute volume overload superimposed on cardiogenic shock. Surgical repair confers an unacceptably high mortality, and the sole nitinol occluder device currently available under Humanitarian Device Exemption (St Jude Amplatzer Muscular VSD occluder) is highly unsatisfactory (too small, too rigid, too permeable, wrong geometry) and usually unsuccessful.

There is a clear need for a purpose-built device to achieve early occlusion of postinfarction VSD, which could be lifesaving in approximately 2-4000 patients annually. This market size is too small for the large medical device manufacturers to address, but fortunately is suitable for Humanitarian Device Exemption regulatory pathway.

### *Project Goals*

The goal of the project is to develop a device for percutaneous closure of postinfarction VSD in adults. First a prototype would be developed and tested in animals, and ultimately a clinical-grade device would undergo regulatory development for clinical testing, which NIH DIR offers to assist in performing.

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

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

### *Phase I Activities and Expected Deliverables*

A phase I award would develop and test a postinfarction VSD occluder prototype. The NHLBI Division of Intramural Research laboratory may be willing to test the final prototype in vivo, at no expense to the offeror. The offeror is expected independently to perform animal testing as needed to meet phase I requirements.

Device requirements include:

- a. Delivery profile of 12-14 Fr or smaller
- b. Suitable for antegrade (transvenous) or retrograde (transarterial) transcatheter delivery
- c. Designs must address a range of defect diameters from 20-40mm. Because these defects are variable and non-uniform, designs are invited that specifically address this heterogeneity, including with non-circular profiles.
- d. Designs are invited that are able to accommodate a range of ventricular septal wall thicknesses
- e. Designs are invited to accommodate specific anatomic variations, including postinfarction VSDs at or near the ventricular apex and bordering on the anterior or posterior free wall
- f. Designs are invited that are self-centering so that the central portion of the device fills the entire space created by the VSD
- g. Devices must be completely repositionable and recapturable without exacerbating myocardial injury
- h. Devices must contain a central guidewire port to allow position to be maintained despite retrieval or repositioning
- i. Designs are invited that have small, little or no right ventricular disc to avoid interference from right ventricular trabeculation
- j. Designs that balance the forces required to assure permanent fixation without tearing necrotic margins, even if retrieved or repositioned
- k. Devices must achieve nearly complete hemostasis (obliteration of shunt flow) within two hours or fewer, although immediate hemostasis is preferred. Most designs will require low-profile hemostatic material within the "left

ventricular” and “septal neck” elements of the device. Because of the risk of hemolysis the designs that impose a “barrier” are preferred over permeable “meshes.”

- l. Implants must be MRI compatible so that cardiac function and flow can be measured unimpeded after implantation using MRI, and MRI conspicuity is desirable
- m. Designs having absorbable components are welcomed
- n. The implant should have mechanisms or a range of morphologies to avoid heart valve entrapment or distortion
- o. Proposals should include specific plans, and device features, to allow operator recovery of the device if it embolizes after release
- p. The delivery system and implant must be conspicuous under the proposed image-guidance modality whether ultrasound or X-ray, and must be conspicuous under X-ray after release. The delivery system must be kink-resistant under the intended use conditions.
- q. The device should accomplish acute or subacute occlusion without early or late thromboembolism, and proposals should specifically address these considerations
- r. The system should be accompanied by a proposed robust methodology or device to select the appropriate device size
- s. The results of a pre-IDE meeting with FDA CDRH, which indicates a sufficiently mature device and which will guide Phase II.

Final payment is contingent on meeting all of the above requirements.

### ***Phase II Activities and Expected Deliverables***

In addition to meeting all requirements specified for Phase I, the phase II award would allow mechanical and safety testing and regulatory development for the device to be used in human investigation. The NHLBI Division of Intramural Research laboratory offers but does not require to perform an IDE clinical trial at no cost to the awardee. Complete Investigational Device Exemption documentation and license and a suitable supply of clinical materials would constitute the final deliverable. The offeror will provide a complete report of prior investigation along with all other elements of the IDE application and accompanying regulatory correspondence. For all purposes, a Humanitarian Device exemption or an expedited Premarket Approval would be considered responsive in place of IDE.

The offeror should provide clear project milestones that trigger review and payment, along with detailed research and development plans, risk analysis, and contingency plans. Representative project milestones include, not necessarily sequentially:

- a. a device build and short-term survival study to identify additional failure modes
- b. elements of a quality system including product specification, design and failure mode analysis, design verification and validation and test plan, biocompatibility and sterility assessment and plan, design review, design freeze, design transfer to manufacturing
- c. manufacturing plan
- d. iterative ex vivo testing such as animal explants
- e. iteration for unexpected design or device failure
- f. FDA pre-IDE meeting #1 and #2
- g. modeling and fatigue study for chronic implant
- h. chronic GLP animal studies
- i. design of clinical protocol including informed consent, risk analysis for early feasibility, and case report form, whether or not conducted in collaboration with NHLBI Division of Intramural Research laboratory
- j. preparation of IDE
- k. submission and resubmission of IDE
- l. manufacturing of test articles.

The offeror is expected to conduct animal experiments and provide care as required to obtain the IDE. The offeror is advised to propose how to proceed in case of hold from FDA.

## 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:

#### **016 A Wearable Alcohol Biosensor that Quantifies Blood Alcohol Concentration in Real Time**

**Only** Fast-Track 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 can be worn discreetly and used by individuals during their daily lives 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 over time. Wearable alcohol biosensors will simplify the process of determining real time (and thus retrospective) 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 how much alcohol trial participants have consumed 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. Wearable alcohol biosensors 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 wearable device to measure, record, and store blood alcohol levels in 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. A non-invasive technology is preferred. The detection of alcohol should be passive, 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 to quantitate alcohol in blood or interstitial fluid and their incorporation into a wearable device. 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 works in a non-invasive way and can be incorporated into a wearable. 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. The device can be removable with the ability record the exact time the device is removed. Ideally, the device will be stable, with expectation of long term function. The design must be acceptable to the wearer from comfort, privacy, financial, and convenience standpoints.

It is envisioned that wearable alcohol monitors 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 wearable 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](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, attractive, wearable 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.
- A functional, marketable, wearable alcohol biosensor is the specific deliverable of the Phase II portion of the contract.

## 017 Data Science Tools for 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.

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

### *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. 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. The volumes of data produced by NIAAA-supported research, along with publicly available databases and future results, can be analyzed using data science approaches. However, many of the tools needed to answer questions in alcohol research require specific applications, algorithms or toolkits that are not currently available.

### *Project Goal*

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

### *Phase I Activities and Deliverables*

Specific deliverables are:

- 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.
- 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. 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:

#### **063 In Vivo Targeted Degradation of HIV Proteins**

Fast Track proposals **will** be accepted

Number of anticipated awards: 1-2

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

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

#### *Background*

Antiretroviral drugs are effective in controlling an HIV infected person's viral load by inhibiting the fusion of the virus to a CD4 T-cell or inhibiting HIV enzymes such as reverse transcriptase, integrase and protease. The success of these drugs is dependent on their ability to bind to a reactive site on their target. Attempts to generate small molecule inhibitors to other HIV proteins have been difficult since they lack a reactive site that can bind a small molecule. This leaves multiple HIV expressed proteins in an infected cell as "undruggable". Targeting therapeutics to one or more HIV proteins may be an effective way of shutting down viral replication, preventing cellular transmission and ultimately lead to a sustained viral remission.

Newly developed methods have demonstrated the ability of specially prepared reagents to harness the ubiquitin proteasome system for the degradation of targeted proteins. Reagents can be prepared to bind specifically to proteins without the need of a reactive site. This technology can be expanded to HIV expressed proteins in an infected cell and ultimately target them for degradation in the proteasome. Current strategies which target HIV proteins with a small molecule are limited to the inhibition of a single function. However, the total elimination of an HIV protein from an infected cell would remove all of its biological functions and provide a more thorough consideration of its importance in HIV infectivity.

#### *Project Goals*

The goal of this contract solicitation is to support the development of reagents that specifically bind to HIV expressed proteins in an infected cell and deliver them to the proteasome for degradation.

#### *Phase I activities may include:*

- Designing, optimizing and testing strategies for both targeting HIV proteins and degrading HIV proteins through the ubiquitin proteasome system
- Performing proof-of-concept of HIV protein degradation in cell lines
- Evaluating off-target effects
- Performing proof-of-concept studies in an HIV animal model

#### *Phase II activities may include:*

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

## 064 Particle-Based Delivery of HIV Env Immunogens

Fast Track proposals **will** be accepted

Number of anticipated awards: 3-4

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

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

### **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 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 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 Goals**

Tailored immunogens (such as Envs, monomers, native and/or native-like trimers, nucleic acids/RNA) combined with 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.

### **Phase I activities may include:**

- Engineering, fabricating nanoparticle platforms/systems and approaches (such as synthetic and/or self-assembling and/or covalent chemical attachment of an antigen to a nanoparticle) for delivering existing and/or novel HIV immunogens (such as Envs, monomers, native and/or native-like trimers, nucleic acids/RNA) that can augment HIV vaccine development by way of enhanced presentation, trafficking and targeting the antigen presentation pathway(s) for the induction of broad humoral and cellular immune responses
- Evaluating particulate systems (such as synthetic and/or self-assembling and/or covalent chemical attachment of an antigen to a nanoparticle) 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 licensed or 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 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 short term stability studies (generate baseline data) on particulated HIV antigen 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 to evaluate the sterile filterability of particulated formulations and assess the composition of components post sterilization
- Developing an efficient process for early stage/pre-clinical studies, which could be adapted to scale-up studies 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 germline 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:***

- 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

**065 Co-Delivery and Formulation of Adjuvants for HIV Vaccines**

Fast Track proposals **will** be accepted

Number of anticipated awards: 3-4

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

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

***Background***

The RV144 Phase III Thai trial, which tested the heterologous prime-boost combination of two vaccines: ALVAC<sup>®</sup> HIV vaccine (prime) and AIDSVAX<sup>®</sup> 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 have 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 effective HIV vaccine have predominantly focused on design of new HIV immunogens and targets, an understudied area of investigation is with 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; 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 combination of adjuvant formulations and public-private partnership is 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 goals***

Co-delivery of adjuvants with antigens coupled with immunogen design are 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 contract 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:***

- Developing optimal parameters/conditions for HIV protein antigen(s) and adjuvant co-formulations
- Evaluating formulations with immunomodulatory agents such as mineral salts, microbial products, emulsions, cytokines, chemokines, polymers, liposomes, saponins, carbohydrate adjuvants, TLR agonists etc.
- Developing, 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 to generate baseline data on antigen-adjuvant formulations
- Testing for batch-to-batch reproducibility and consistency of adjuvanted formulations for manufacturing

### ***Phase II activities may include:***

- 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
- Evaluation of 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, collaborate and/or partner with different labs to harmonize inter-laboratory variations in antigen/adjuvant mixture formulations and for characterization and protein stability assays

## **066 Effective Targeted Delivery of RNA-based Vaccines and Therapeutics**

Fast Track proposals **will** be accepted

Number of anticipated awards: 1-2

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

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

### ***Background***

RNA-based vaccines and therapeutics have emerged as great promise for HIV prevention and treatment, respectively. However, many obstacles still need to be overcome, in particular RNA instability, manufacturing problems, and clinically relevant delivery mechanisms of RNA into target cells. RNA vaccine approaches have some advantages in relation to other vaccine technologies; they can be delivered directly into the cytoplasm and do not require nuclear localization to generate expression. Improvements of methods for mRNA synthesis and stabilization and development of improved self-amplifying RNAs have recently yielded promising results. RNA approaches also stimulate the host's innate defense system, in part through activation of the TLR pathways that recognize single and double stranded RNAs. Furthermore, RNA-based therapeutics have shown the potential to silence HIV effectively upon direct transfection in vitro, but delivery into cells in vivo is still unsatisfactory. Vector-based (lentivirus, adeno-associated virus) delivery to quiescent cells has proven inefficient, and the vectors themselves pose a risk to the host. To enhance stability and to confer vehicle-free delivery, RNA-based drugs have been chemically modified to improve their properties. Progress was also made in chemical-based delivery strategies, e.g., liposomes, molecular-sized chemical conjugates, and supramolecular nanocarriers. An additional advantage is that RNA can be produced in vitro in a cell-free manner, avoiding safety and manufacturing issues associated with cell culture. Despite these advances, nucleic acids per se are relatively large, negatively charged polymers, and significant clinical challenges from the standpoint of delivery to cells still persist.

### ***Project Goals***

The primary goal of this contract solicitation is to encourage small businesses to develop improved platform technologies for the delivery of RNA into specific cells and tissues to improve the efficacy of HIV vaccines or therapeutics. Examples of HIV RNA vaccines include, but are not limited to mRNA and self-amplifying RNAs. Examples of RNA therapeutics include small interfering RNA (siRNA), microRNA (miRNA), microRNA antagonists, aptamers, messenger RNA (mRNA), splice-switching oligonucleotides, antisense oligonucleotides, and plasmid or other circular DNAs encoding messenger RNAs and transcription regulatory sequences. To enhance the efficacy of traditional HIV vaccines and therapeutics, combinations of cytokines, adjuvants, broadly neutralizing monoclonal antibodies, immune checkpoint inhibitors, etc. can also be co-delivered in mRNA form. The short-term goal of this project is to perform feasibility studies for the development and use of delivery mechanisms for RNA-based HIV vaccines and therapies. The long-term goal of this project is to enable a small business to bring fully developed delivery systems for RNA-based HIV vaccines and therapies to the clinic and eventually to the market.

### ***Phase I activities may include:***

- Design and test in vitro small-scale delivery strategies for RNA-based HIV vaccines or therapeutics, including exosomes, nanoparticles, liposomes, viral vectors, condensates, carriers, or delivery devices
- Assess potency and stability of RNA-based HIV vaccines or therapeutics.
- Improve RNA stability through chemical modifications

- Perform proof-of-concept HIV animal model studies for assessment of organ toxicity, HIV immune responses, innate immune responses (e.g., Toll-like receptor activation), and pharmacokinetic/pharmacodynamic studies, if applicable
- For RNA-based therapeutics:
  - Evaluate off-target effects in cell lines and primary PBMC.
  - Develop strategies for eliminating off-target effects, including software tools for re-designing RNAs.

***Phase II activities may include:***

- Scale-up manufacturing of RNA-based vaccines or therapeutics
- IND-enabling studies, preferably in consultation with the FDA
- For RNA-based vaccines:
  - Test improved delivery mechanism for efficacy and mechanism of action in animal models of HIV
- For RNA-based therapeutics:
  - Demonstrate that the RNA delivery approach is effective and non-toxic in animal models for HIV
- When appropriate, demonstration of superiority of developed technology compared to other delivery mechanisms

Where cooperation of other vendors or collaborators is critical for implementation of proposed technology, the offeror should provide evidence of such cooperation (through written partnering agreements, or letters of intent to enter into such agreements) as part of the Phase II proposal.

**067 Methods Improving HIV Protein Expression: Cell Substrate and Protein Purification**

Fast Track proposals **will** be accepted

Number of anticipated awards: 3-4

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

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

***Background***

There is an urgent need to have multiple HIV envelope immunogen components for use in HIV vaccine clinical studies. Results of the RV144 vaccine clinical trial indicated that antibody responses to the gp120 Env proteins were the major components of the vaccine that contributed to the efficacy signal. In addition, the discovery of both broad and potent neutralizing antibodies against the HIV envelope in HIV infected individuals, provides additional evidence that the human immune system can respond effectively to the HIV envelope and so envelope could be the major component of an effective HIV vaccine.

Results of contract manufacturing organizations (CMOs) efforts to produce envelope proteins using pre-existing platforms developed for Chinese hamster ovary (CHO)-based monoclonal antibody production have been disappointing. Despite the widespread use of GMP-established pharma cell substrates (e.g., CHOs, 293 etc.) in development of monoclonal antibodies and recombinant protein antigens, critical bottlenecks still exist in their use for large-scale, high-yield GMP manufacturing of HIV protein antigens. For example, the use of CHO-based protein expressions systems previously used for the generation of monoclonal antibodies (mAbs) have resulted in significantly lower yields of HIV envelope proteins (100-1000x fold lower) compared to mAb expression (mgs/l of envelope product compared to the typical g/l yield of mAb). Additional limitations relate to their intrinsic incapacities to metabolically express high levels of stable, properly folded and glycosylated recombinant HIV Env protein; often times requiring extensive clonal screening to identify the rare high-level producer clone.

Beyond issues of primary yield of the expression system, traditional downstream purification processes for HIV Env purification are equally plagued with inefficiencies due to multi-step purification cycles resulting in low yields. As a result, subsequent purification schemes for mAbs are not readily transferrable to HIV envelope purification and often result in 80-90% losses of envelope material. Moreover, purification schemes developed for one HIV envelope are not necessarily suitable for another HIV envelope due to the potentially large differences in post-translational modifications. While, monoclonal antibodies may be able to withstand harsh viral clearance procedures, whereas HIV envelopes which are more sensitive glycoproteins may not be able to sustain the harsh viral clearance procedures.

These constraints have a cascading effect in increasing the overall cost and time for production of HIV vaccine antigens from millions of dollars and years of upstream and downstream process development. These problems demonstrate the need for new approaches to enhance and expedite the screening, production and purification of HIV envelope protein candidates. As such, there is an urgency to evaluate alternative strategies and technologies capable for developing highly productive cellular substrates suitable for high yield GMP manufacturing of HIV antigens and reduced product development lead times.

### ***Project Goals***

The goal of this contract solicitation is to support research to improve the expression yield in a specific cell culture system (i.e. CHO), and the purification yield using specific purification regimens designed for HIV envelope protein suitable for use as clinical immunogens. Projects may focus on any step of envelope expression and yield, improvement of substrates (i.e. CRISPR/Cas9 editing, siRNA delivery and gene silencing) by evaluating and modulating the molecular pathways involved in regulating and enhancing HIV envelope/antigen expression in mammalian cell lines. The projects may also focus on development of purification platforms.

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

- Improving HIV Env protein expression in existing cell substrates or development of novel cell substrates should be explored through the following approaches: improving existing cell substrates
  - altering codon usage
  - targeting host cells genes that increase expression
  - improved expression cassettes for the recombinant protein and novel selection marker genes
  - identifying auxiliary proteins essential for protein production, modifying components of secretory and processing pathways, enhancement of cellular processes (e.g. chaperonins)
  - functional phenotypic screening
  - enhancement of transcription or of evaluating mRNA sequence and structure
  - alteration of epigenetic targets
  - methodologies to alter post-translational modifications including glycosylation or disulfide composition, and secreted protein
  - the production of intracellular, membrane-associated, or secreted protein.
- Improving existing cell substrates
  - by removal of deleterious proteases,
  - addition of enzymes involved in glycosylation
  - removal of deleterious proteases
  - alteration in epigenetic targets
- Using of functional genomics to identify gene function and editing. Focusing on siRNA technologies and delivery methods into cell substrates coupled with high throughput screening and analytics, modulation of gene function, expression, regulation and mutation of target cell. Evaluating newer technologies such as CRISPR/Cas9 targeted gene editing stimulating genetic modifications to prepare productive stable cell lines will also be evaluated.
- Evaluating transient transfection/gene expression technologies to support and accelerate phase appropriate manufacturing
- Developing and improving HIV envelope protein purification methodologies including (but not limited to), affinity purification approaches and/or other highly novel strategies;
- Developing analytical assays and testing methods for characterization, identification, quantitation of expressed product during cell line development
- Establishing conditions for removal of host cell protein clearance, endogenous retroviruses (viral inactivation and clearance).
- Developing research cell bank
- Testing and characterizing cell lines and evaluating quality attributes/metrics prior to advancing the cell substrate and processes to GMP scale
- Establishing conditions for removal of host cell protein clearance, viral inactivation and clearance.



**Phase 2 activities may include:**

- GMP development and manufacturing lead cell substrates (e.g., Master Cell bank generation)
- Translating and scaling-up of process development activities including downstream purification unit operations to GMP setting

**068 Reagents for Immunologic Analysis of Non-mammalian and Underrepresented Mammalian Models**

Fast-Track proposals **will** be accepted

Number of anticipated awards: 3-5

Budget (total costs, per award): Phase I: up to \$300,000/year for up to 2 years;

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

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

**Background:**

This goal of this program is to address the limited availability of reagents (e.g., antibodies, proteins, ligands) for the identification and discrimination of immune cells and the characterization of immune responses in non-mammalian models (e.g., arthropods, amphibians, fish, nematodes, marine echinoids) and mammalian models for which immunologic reagents are limited (e.g. guinea pig, ferret, cotton rat).

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 helped to launch 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- $\kappa$ 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.

There are certain mammalian models that 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 and/or the analysis of immune function/responses (e.g. cytokines, chemokines, intracellular signaling) in non-mammalian models and underrepresented mammalian models.

**Phase I Activities must include at least the following 2 activities:**

- Identification of immune cell markers, receptors with immune function, and other molecules important for immune function; and
- Development of antibodies and/or other reagents against these targets.

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

- Validation of antibodies/reagents.
- Screening for cross-reactivity with related molecules on other non-mammalian species and/or mammalian immune cells.
- Scale-up production.

***This SBIR Topic will not support:***

- Identification of immune target molecules and development of antibodies/reagents against immune markers or molecules specifically for mice, rats, dogs, non-human primates or humans.
- Development of antibodies/reagents not involved in immune responses.
- Development of novel or refined animal models

**069 B Cell Receptor and T Cell Receptor Repertoire Computational Tools**

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

Number of anticipated awards: 1-3

Budget (total costs, per award): Phase I: up to \$450,000 for up to 2 years;

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

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

***Background:***

Antigen specificity is a fundamental feature of adaptive immunity, underlying immune homeostasis and control of infection by pathogens in higher vertebrates. B cells and T cells form the two arms of the adaptive immune system, each expressing antigen-specific receptors, B cell receptors (BCR) and T cell receptors (TCR), respectively. Previously, the characterization of receptor sequence repertoires relied on low-resolution approaches, but with the advent of high-throughput sequencing, it has become possible to characterize the receptor repertoires at unprecedented depth. Subsequently, receptor repertoire sequences profiling has become an important part of basic and clinical immunology research, including vaccine design and monitoring responses to therapy.

***Project Goal:***

The goal of this program is to support the development of computational tools to accelerate the analysis of B cell receptor and T cell receptor repertoire sequence data. These tools should improve the ability to collect, compile and compare receptor sequence data for analysis and comparison across cell-types and infectious and immune-mediated diseases. A secondary goal is to facilitate the connection between receptor repertoire patterns and antigen or epitope prediction. Tools generated should have demonstrated utility to compile and interrogate data available to the public, such as NCBI's Single Read Archive, but may also demonstrate use for other publicly available sources of data.

***Phase I Activities include, but are not limited to:***

- Development of computational tools to organize and interrogate receptor sequence data available in existing public databases.
- Development of computational tools to correlate receptor sequence to antigen identity.

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

- Validation of computational tools to correlate receptor sequence to antigen identity.
- Validation of computational tools to interrogate receptor sequence data in public databases.

***This SBIR will not support:***

- Any phase clinical trial.
- Proposals focused exclusively on animal studies and animal disease models.
- Studies that do not fall within NIAID mission.

## **070 Development of Sample Sparing Assays**

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

Number of anticipated awards: 1-3

Budget (total costs, per award): Phase I: up to \$150,000 for up to 6 months; Phase II: up to \$1,000,000 for up to 2 years

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

### ***Background***

The NIAID's Division of Allergy, Immunology and Transplantation (DAIT) supports a wide range of research programs spanning basic immunology, translational and clinical research on protective immunity and immune-mediated diseases, including autoimmune and primary immunodeficiency diseases, allergic diseases, graft-versus host disease (GVHD) and allograft rejection in organ, tissue and cell transplantation. Major constraints encountered in designing mechanism of action studies are related to limited quantity of biological specimens available for study and the paucity of robust, validated, miniaturized assays that can reliably and reproducibly assess immune function, disease state or effects of therapy. The restricted amounts of tissue, cells and fluids that can be collected from adult, pediatric or immunocompromised patients are often inadequate for the application of conventional assays that interrogate immune function. Novel, multi-parameter, sample sparing assays are needed to obtain maximal biologic information from limited amounts of biological materials.

### ***Project Goal***

The goal of this proposal is to accelerate commercial development of novel, standardized sample sparing assays that improve monitoring of the immune system using limited amounts of biological sample. Sample sparing immune assays of interest may include, but are not limited to monitoring or assessments of the following:

- Antigen-specific immune responses
- Distinct immune cell populations
- T-cell and B-cell regulatory networks
- Innate immune responses
- Markers of T-cell turnover and homing to lymphoid tissue
- Cytokine and signaling networks
- Gene and protein expression and regulation
- Mucosal inflammatory and innate immune response

Technologies that address novel sample preparation or cell isolation processes are also included in the areas of interest for this announcement.

The sample sparing assays developed through this funding opportunity must address challenges, gaps or unmet needs in the study of human immune responses and provide clear advantages over existing assays.

### ***Phase I Activities***

Depending on the developmental stage of the sample sparing assay the offeror may choose to perform one or more of the following:

- Preliminary studies performed in a suitable animal model or in human samples to evaluate the assay feasibility (scientific and technical)
- Establish assay's quality of performance, assay reproducibility and validation
- Define process controls
- Establish potential for commercialization

### ***Phase II Activities***

- Further technology developments and assay improvements
- Development and validation of prototype platforms
- Development of quality control program to enable longitudinal measurements in compliance with Good Clinical Laboratory Practice

***This SBIR Topic will not support:***

- Any phase clinical trial
- Identification of new biomarkers
- Validation of biomarker candidates
- Proposals focused exclusively on animal studies and animal disease models. Animals may be used in assay development phase but all assays must be validated using primary human samples
- Development of assays using established cell lines without validation in primary human samples
- Virus-induced cancers
- Studies that do not fall within NIAID mission

**071 Adjuvant Discovery for Vaccines and for Autoimmune and Allergic Diseases**

Fast-Track proposals **will** be accepted

Number of anticipated awards: 1-3

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

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

***Background:***

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

Currently, only four adjuvants have been licensed as components of vaccines in the United States - aluminum hydroxide/aluminum phosphate (alum); 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; and the oil-in-water emulsion MF59 as part of the FLUAD influenza vaccine for people age 65 years and older. The gaps that need to be addressed by new adjuvants include improvements to existing efficacious vaccines (e.g., the acellular pertussis vaccine), and development of vaccines: for emerging threats (e.g., Ebola outbreaks); for special populations that respond poorly to existing vaccines (i.e., elderly, newborns/infants, immunosuppressed patients); or to treat/prevent immune-mediated diseases (e.g., allergic rhinitis, asthma, food allergy, autoimmunity, transplant rejection). Recent advances in understanding innate immunity have led to new putative targets for vaccine adjuvants and for allergen immunotherapy. Simultaneously, progress is slowly being made in the identification of *in vitro* correlates of clinical adjuvanticity which allows the design of *in vitro* screening assays to discover novel adjuvant candidates in a systematic manner.

The field of tolerogenic adjuvants is still in its infancy. No compounds have been licensed yet in the US 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 which include the induction of regulatory T cells, or by changing the profile of the pathogenic lymphocyte response (e.g., Th1/Th2/Th17, etc). The combination of tolerogenic adjuvants with allergen immunotherapy should aim at accelerating tolerance induction, increasing the magnitude of tolerance and decreasing the duration of treatment.

***Project Goal:***

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

***Phase I Activities include, but are not limited to:***

- Optimize and scale-up screening assays to identify new potential vaccine- or tolerogenic adjuvant candidates
- Create targeted libraries of putative ligands of innate immune receptors
- Pilot screening assays to validate HTS approaches for identifying adjuvant candidates
- Develop *in silico* screening approaches to pre-select adjuvant candidates

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

- High-throughput screening 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 and/or formulation
- Screening of adjuvant candidates for their usefulness in special populations, such as the use of cells from cord blood or infants and/or elderly/frail humans or animal models representing human special populations

**072 Adjuvant Development for Vaccines and for Autoimmune and Allergic Diseases**

Fast-Track proposals **will** be accepted

Number of anticipated awards: 1-3

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

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

***Background:***

Adjuvants stimulate innate and/or adaptive immune responses. For the purpose of this SBIR, vaccine adjuvants are defined according to the U.S. Food and Drug Administration (FDA) as “agents added to, or used in conjunction with, vaccine antigens to augment or potentiate (and possibly target) the specific immune response to the antigen”. Tolerogenic adjuvants are defined as compounds that promote immunoregulatory or immunosuppressive signals to induce non-responsiveness to self-antigens in autoimmune diseases, or environmental antigens in allergic diseases. Currently, only four adjuvants have been licensed as components of vaccines in the United States - aluminum hydroxide/aluminum phosphate (alum); 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; and the oil-in-water emulsion MF59 as part of the FLUAD influenza vaccine for people age 65 years and older. Additional efforts are needed to more fully develop the potential capabilities of promising adjuvants, particularly for special populations such as the young, elderly and immune-compromised. In addition, adjuvants may facilitate the development of immunotherapeutics for immune-mediated diseases, such as allergen immunotherapy to treat/prevent 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 US 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 which include the induction of regulatory T cells, or by changing the profile of the pathogenic lymphocyte response (e.g., Th1 to Th2 or vice versa). The combination of tolerogenic adjuvants with allergen immunotherapy should aim at accelerating tolerance induction, increasing the magnitude of tolerance, and decreasing the duration of treatment.

***Project Goal:***

The goal of each project is to accelerate 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. 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. The adjuvant products supported by this program must be studied and further developed toward human licensure with currently licensed or new investigational vaccines, and may not be developed as stand-alone agents.

### ***Phase I Activities:***

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

- Optimization of one candidate compound for enhanced safety and efficacy. Studies may include:
  - Structural alterations of the adjuvant or modifications to formulation; or
  - Optimization of heterologous prime-boost-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.
- Establishment of an immunological profile of activity and immunotoxicity that can be used to evaluate the capability of the adjuvant to advance to human testing.
- Preliminary studies in a suitable animal model to evaluate the protective or tolerizing efficacy of a lead adjuvant:vaccine.
- Analysis of vaccine efficacy through the use of a combination adjuvant and studies to evaluate the safety profile of the combination adjuvant:vaccine-formulation.

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

### ***This SBIR Topic will not support:***

- The further development of an adjuvant that has been previously licensed for use with any vaccine.
- The conduct of clinical trials (see Appendix H.1 for the NIH definition of a clinical trial).
- The discovery and initial characterization of adjuvant candidates.
- The development of adjuvants or vaccines to prevent or treat cancer.
- Development of platforms, such as vehicles, or delivery systems that have no immunostimulatory or tolerogenic activity themselves.
- The development and/or optimization of a pathogen-specific vaccine component.

## **073 Mobile Health Point-of-Care Diagnostics**

Fast-Track proposals **will** be accepted

Number of anticipated awards: 1-2

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

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

**Background:**

The capabilities inherent in smartphones represent a largely untapped opportunity to improve point-of-care (POC) diagnostics for infectious diseases in low resource settings (LRS), where laboratory equipment is scarce and infrastructure is often unreliable. Smartphone features that could be adapted to enhance POC diagnostics include fast computing power, internet connectivity, geo-positioning, a high-quality camera, and long-lasting power/batteries. Smartphones have the potential to increase POC diagnostic sensitivity and specificity through machine-interpreted results; reduce operator error by ensuring accurate collection of data and relevant metadata; and improve analysis and stewardship of results through remote analysis and data storage. Further development of novel technologies, computational tools, and algorithms is needed to transform smartphones into platforms capable of improving POC diagnostic performance, interpretation of results, and data transmission.

**Project Goals:**

The goal of this solicitation is to develop both i) a low cost, rapid, easy-to-use, smartphone-compatible, infectious disease POC diagnostic for use in LRS; and ii) computational tools and algorithms necessary to effectively link the diagnostic test to the smartphone and achieve enhanced performance. The final products should be independent of smartphone manufacturer and operating system, and a physical connection between the test and the smartphone is not required. Algorithms should at a minimum capture all information needed to use, read, and interpret the test (for example in a 2D barcode), as well as provide verification that the test was run correctly. Ideally, the diagnostic test time from sample to answer should be one hour or less including sample processing. Stability of assay reagents at room temperature is preferred.

The development of a smartphone-compatible POC diagnostic and all associated technologies, computational tools and algorithms that address the following research areas are of particular interest:

- Improved sensitivity and reduced time to diagnosis for tuberculosis
- Improved sensitivity for malaria diagnosis
- Ability to accurately distinguish between influenza and other respiratory pathogens
- Ability to accurately distinguish between bacterial and viral pneumonia
- Detection of onchocerciasis (river blindness) adult worms

**Phase I activities may include:**

- Development of a smartphone-compatible, low cost, field-portable, rapid POC diagnostic
- Development of a functional software prototype to enhance the performance of the POC diagnostic
- Integration of the diagnostic assay and the smartphone without requiring high cost adapters, and independent of the smartphone manufacturer
- Determination of sensitivity, specificity and other performance characteristics (e.g. time to result, limit of detection, test stability) of the diagnostic
- Confirmation that accuracy is sufficient to allow clinically relevant results
- Demonstration of software capabilities to ensure accurate data collection, identify failure modes, interpret and share results in a secure environment
- Performance of initial testing on laboratory isolates

**Phase II activities may include:**

- Further optimization of the smartphone-linked assay platform technology and validation of assay reproducibility
- Testing of de-identified clinical samples from diverse cohorts with varying levels of infection
- Evaluation, revision, and enhancement of the software prototype
- Performance of software beta testing with relevant end users

**This SBIR Topic will not support:**

- The development of a prototype POC diagnostic alone without the associated technologies, computational tools and algorithms required to integrate with a smartphone
- The design and conduct of clinical trials (see Appendix H.1 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](#).

#### **074 Development of POC Assays to Quantify anti-Tuberculosis Antibiotics in Blood**

Fast-Track proposals **will** be accepted

Number of anticipated awards: 1-2

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

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

##### ***Background:***

Tuberculosis (TB) is currently the leading infectious cause of death worldwide. TB treatment includes multiple different combinations of antibiotics, doses, and long time periods depending on whether TB is classified as drug-sensitive or drug-resistant. Moreover, therapy is often modified due to factors such as identification of antibiotic resistance, drug-induced toxicity, treatment failure, antibiotic availability, etc. Rapid determination of blood antibiotic concentrations in the clinical laboratory using technologies that do not require sophisticated equipment would allow clinicians to monitor antibiotic concentrations during treatment and allow for dose adjustments to increase efficacy. This would prevent or reduce the development of resistance, treatment failure, and antibiotic induced toxicity and could improve patient survival. Currently, TB antibiotic concentrations are measured only in highly specialized laboratories using expensive instruments, making regular monitoring of antibiotic blood concentrations essentially impractical in the global clinical field.

##### ***Project goal:***

The goal of this project is to develop a rapid POC test to quantify TB antibiotic blood concentrations. Desired outcomes include a portable device (e.g. sensors, readers, etc.) requiring a small blood sample (e.g. strips, capillary tubes, etc.) that will provide consistent rapid readouts during the patient's visit (less than 1 hour).

##### ***Phase I activities may include:***

- Development of a prototype POC test to quantify TB antibiotic concentrations.
- Optimization of the POC test to quantify concentrations for multiple antibiotics in one sample simultaneously.
- Evaluation of the POC test to reliably quantify antibiotic concentrations directly from total blood and/or plasma.

##### ***Phase II activities may include:***

- Determination of validity, sensitivity, and specificity of the POC test.
- Optimization of POC test characteristics, such as portability and development of operator manual.
- Evaluation and determination of the stability of the POC test kit (e.g. shelf life, storage conditions, etc.)
- Scale-up manufacturing of POC test kits.

##### ***This SBIR will not support:***

- The design and conduct of clinical trials (see Appendix H.1 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](#).

#### **075 POC Diagnostic for Gonorrhea and Determination of Antimicrobial Susceptibility**

Fast-Track proposals **will** be accepted

Number of anticipated awards: 1-2

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

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



**Background:**

There are over 450,000 cases of gonorrhea reported in the U.S. annually. Of particular concern is that the causative agent, *Neisseria gonorrhoeae*, is naturally competent and easily acquires resistance to antimicrobials. The U.S. Centers for Disease Control and Prevention changes the recommendation for the treatment of gonorrhea when surveillance data indicate  $\geq 5\%$  resistance to the class of antimicrobial being used at the time. Over the last several decades this change has been implemented numerous times, such that the cephalosporins are the last class of antimicrobials left to treat gonorrhea. Cephalosporin resistance is increasing worldwide, and the loss of this antibiotic as a treatment option would make gonorrhea clinically untreatable. However, since treatment recommendations are based on  $\geq 5\%$  resistance, it is clear that the vast majority of circulating isolates are still sensitive to previously-recommended classes of antimicrobials. Re-introduction of these classes of antimicrobials into clinical use would allow for the continued successful treatment of gonorrhea even if cephalosporin resistance becomes widespread. In order to best select the appropriate and most effective therapy, clinicians need real-time antimicrobial sensitivity tests to characterize phenotypes of infecting *N. gonorrhoeae* strains.

**Project goal:**

The goal of this project is to develop a rapid ( $\leq$  one hour) point-of-care diagnostic capable of: i) identifying *N. gonorrhoeae*; and ii) determining the infecting strain's susceptibility to at least three classes of antibiotics (e.g. quinolones, macrolides, etc.) directly from the patient sample (e.g. urine, urethral/vaginal/cervical swab).

**Phase I activities may include:**

- Development of a prototype product that demonstrates the rapid determination of the antimicrobial susceptibility profile of one or more *N. gonorrhoeae* isolates
- Integration of platform to rapidly identify *N. gonorrhoeae* and antimicrobial susceptibility
- Development of sample preparation methods consistent with the product platform

**Phase II activities may include:**

- Integration of platform to rapidly identify *N. gonorrhoeae* and antimicrobial susceptibility
- Development of sample preparation methods consistent with the product platform
- Further development of the prototype product to determine performance characteristics
- Final validation testing and scale-up manufacturing of test kits

**This SBIR Topic will not support:**

- The design and conduct of clinical trials (see Appendix H.1 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](#).

## NATIONAL INSTITUTE ON DRUG ABUSE (NIDA)

NIDA's mission is to advance science on the causes and consequences of drug use and addiction and to apply that knowledge to improve individual and public health.

This involves:

- Strategically supporting and conducting basic and clinical research on drug use (including nicotine), its consequences, and the underlying neurobiological, behavioral, and social mechanisms involved.
- Ensuring the effective translation, implementation, and dissemination of scientific research findings to improve the prevention and treatment of substance use disorders and enhance public awareness of addiction as a brain disorder.

### *NIDA Topics*

This solicitation invites proposals in the following areas:

#### **165 DEA-Compliant Drug Detection and Deactivation Technology to Deter Opioid Theft in Hospitals for Next Generation Controlled Substance Diversion Prevention Program (CSDPP)**

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

Number of Anticipated Awards: 3-4

Budget (total costs, per award): Phase I: up to \$225,000 for up to 6 months; Phase II: up to \$1,500,000 for up to 2 years

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

In addition, NIDA strongly encourages the offerors submitting a proposal to this Topic to include potential participation in the I-Corps™ at NIH program within its Phase I proposal. For details about the I-Corps™ at NIH program see Section 2.5.

#### ***Background:***

With an increasing number of opioid prescriptions and related opioid misuse and abuse, health care facilities have become sites for diversion of controlled substances. Unfortunately, the diversion of opioids in hospitals is common and can lead to serious patient safety issues, harm to the diverter, and significant liability risk to the organization. The lack of efficient security regarding opioid access has led to its increased diversion and/or abuse. It is estimated that 10-15% of healthcare workers (HCWs) have experience addiction at some point in their careers. The likelihood of deliberate misuse of prescription drugs in hospitals, when compared to street drugs, may rise because prescription drugs are often available and can be readily accessed. There also seems to be a misconception that misuse of drugs for stress alleviation by HCWs may be manageable because of their familiarity with the drugs that may help them to "control" its use. However, the diversion of controlled opioid substances and the associated addiction puts both HCWs and patients at high risk of harm. Issues range from inadequate pain relief to longer-term pain sequelae, and also include inaccurate documentation of patient care in the medical record, exposure to infectious diseases from contaminated needles and drugs, and impaired HCW performance.

When offerors develop their proposals, they should use the existing guidelines, for example current guidelines from American Society of Health-System Pharmacists (ASHP), that support a safe patient-care environment, protect co-workers, and discourage controlled the diversion of substances. These guidelines provide a detailed and comprehensive framework to support health care organizations in developing their controlled substances diversion programs (CSDPPs) and to protect patients, employees, the organization, and the community at-large. Ultimately, each health care organization is responsible for developing a CSDPP that complies with applicable federal and state laws and regulations and also incorporates technology and diligent surveillance to review process compliance and effectiveness, strengthen controls, and proactively prevent diversion.

The current guidelines highlight that substances returns and waste streams remain among the key sources of opioid diversion in the hospitals. Thus, there is an urgent need to develop improved technologies / surveillance systems. An improved surveillance system technology are expected to reduce waste-handling practices and to maintain chain of custody to minimize the risk of diversion. Opioid waste may include expired-date medications, medication products appropriately prepared but not administered to the patient, and the product remaining after a partly used medication is removed from its prepared or originally packaged unit. All items should be time stamped as close to the time of preparation and administration as feasible.

Currently, there is little continuity or generally adhere to standard practices for opioid waste disposal across various health facility systems. DEA compliance is partly addressed by having two healthcare providers licensed to dispense drugs and to timely documenting the disposal of the controlled substances. The recommended procedure includes definitions of key issues, including verification of the drug label, and volume or quantity being wasted. This documentation process is time

consuming and not proactive. The limited tools and strategies for effective opioid waste deactivation or disposal is a key issue that may benefit from the development of more efficient and pro-active disposal systems.

There is a need for modern technologies with the integrated systems to monitor medication dispensing and disposal, provide effective diversion prevention efforts, proactively prevent diversion, and effectively confirm compliance regarding opioid waste control.

#### ***Project Goals:***

The primary goal of this funding opportunity is to incentivize small businesses to develop a new commercially viable devices, tools, technologies or integrated systems for drug detection and deactivation to deter opioid theft in hospitals. NIDA envisions that a new technologically advanced system shall combine a device with analytical approaches that 1) accurately measure waste volume and/or quantities, 2) efficiently synchronize waste information with pre-existing data records, 3) deactivate the opioid waste, and 3) continuously monitor disposal of controlled substances, while securing unused portions and simplifying the process. The purpose of deactivation is to render the controlled substances to a non-retrievable state and to prevent diversion of any portion of such substance to illicit purposes.

A new technology could provide a quantitative assurance against opioid waste theft, as well as saving valuable time for auditing substance disposal data. Implementation can reduce liability risks for the hospitals, improve patient safety, and improve HCW performance. Achieving these goals are expected to contribute to the overarching goal of reducing opioid theft by bringing medical facilities into compliance and establishing next generation CSDPPs.

It is highly encouraged that offerors refer to the current guidelines, for example AHSP guidelines, for discouraging controlled substances diversion and to work with potential purchasers in order to establish a clear regulatory and acquisition/commercialization strategies.

The potential features of new device or system may include, but are not limited to:

- Hospital's level of compliance with the current guidelines, for example AHSP guidelines;
- Compliance with DEA regulations and definition of non-retrievable;
- Identification of staff disposing the opioid waste and time of disposing;
- Detection and identification of substance waste;
- Deactivation of substances with lock & key to deter diversion;
- Integration into a hospital's data continuum (electronic medical record, internal inventory system and purchasing systems).

#### ***Phase I Activities and Deliverables***

The goal of Phase I is to develop a proof-of-concept or prototype technology for opioid detection, deactivation and disposal. Offerors must clearly demonstrate the understanding of the key elements of effective CSDPP and needs for the new generation of drug detection and deactivation technologies. It is expected that the technology developed does not interfere in any way with healthcare provision. Activities and deliverables should include:

- Identify and justify the development of a technology for opioids detection, deactivation and disposal in hospitals.
- Identify the key features of a technology to be compatible with existing hospital systems. Design the core structure and process architecture that further optimize the detection and minimize the occurrence of controlled substance diversion.
- Describe the current state of the art technologies and approaches controlled substance detection, deactivation and disposal and outline the advantages that new approaches will provide for CSDPP.
- Describe how a technology is compliant with DEA, EPA, and ASHP regulations and guidelines.
- Specify and justify quantitative milestones that can be used to evaluate the success of a technology being developed.
- Develop an assay or system for testing and benchmarking the specificity and sensitivity of a technology. Develop milestones to compare it to existing approaches.
- Demonstrate utility and technical validity of a technology in a laboratory study.

- Develop a device or system prototype and describe the architecture of its integration to the modeled CSDPP. Provide an example of a proof-of-concept standard operation procedure (SOP) for incorporation of the innovative approach to CSDPP.

### ***Phase II Activities and Deliverables***

The goal of Phase II is to develop and test the technology to deter opioid theft in clinical setting and optimize for CSDPPs in hospitals. These activities should support commercialization of the product with varying complexity.

Decisions for continued product development into Phase II will be based on:

- Successful proof-of-concept data demonstrating adaptively of the product to the key elements of the best practice of CSDPPs.
- Evidence that the technology can be scaled up and compatible with the general hospital's procedures and DEA/ EPA/ ASHP regulations.
- Evidence for commercialization feasibility by providing feedback from potential purchasers and end-users.

Activities and deliverables in Phase II include:

- Demonstrate high accuracy and reliability of the device or technology.
- Demonstrate superiority over currently available tools and procedures.
- Enhance and validate the technology in the pilot study. Demonstrate utility and capability of the technology in clinical setting.
- Provide a report that synthesizes feedback from all relevant categories of end-users (such as physicians, nurses, pharmacists, administration of pharmacy service and hospital) and summarizes the modifications made the technology after usability testing.
- Further enhance and refine the systems for deployment in diverse software environments and provider network. Provide a report detailing the communication systems architecture and capability for data reporting to hospital's administration.
- Refine SOPs to allow friendly implementation of the tool by the target market.
- Provide a report detailing plans for obtaining DEA regulatory approval and implementation to the market.

### ***References:***

ASHP Guidelines on Preventing Diversion of Controlled Substances:

<http://www.ajhp.org/content/ajhp/early/2016/12/22/ajhp160919.full.pdf?sso-checked=true>

Drug Enforcement Administration, 21 CFR Parts 1300, 13001, 1304, 1307, and 1317. Disposal of Controlled Substances. Federal Register, v.79, No174 /Tuesday, September 9, 2014/Rules and Regulations

## **166 Leveraging Health IT Solutions to Combat Opioid Misuse**

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

Number of Anticipated Awards: 4-6

Budget (total costs, per award): Phase I: up to \$225,000 for up to 6 months; Phase II: up to \$1,500,000 for up to 2 years

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

In addition, NIDA strongly encourages the offerors submitting a proposal to this topic to include potential participation in the I-Corps™ at NIH program within its Phase I proposal. For details about the I-Corps™ at NIH program see Section 2.5.

### ***Background:***

The United States is in the midst of an opioid crisis. Over-prescription of opioid analgesic pain relievers contributed to a rapid escalation of use and misuse of these substances across the country. In 2016, more than 2.6 million Americans were diagnosed with opioid use disorder (OUD) and more than 42,000 have died of overdose involving opioids. This death rate is

more than any year on record and has quadrupled since 1999 (1,2). Leveraging the potential of available data bases and health IT technologies may help to combat opioid crisis by targeting various aspects of the problem ranging from the prevention of opioid misuse to OUD treatment.

***Project Goals:***

The purpose of this RFP is to solicit data-driven solutions and services that focus on issues related to opioid use prevention, opioid use, opioid overdose prevention or OUD treatment. Small businesses – offerors are encouraged to use already existing databases and adapt pre-coded Health IT solutions for use in the OUD marketplace. For the proposed purposes the offerors may assume free of charge or minimum cost access to the federal data resources. However, it is encouraged that offerors contact NIDA to ensure resource availability, levels of restrictions, and data release process prior submission of their proposals. It is also highly encouraged that offerors work with potential purchasers in order to establish a clear acquisition/commercialization strategy.

Usage. In order to develop a clearer understating of the opioid crisis, public health data and misuse reporting is expected to be important. Among the expectations are an achievement of learning who is at risk of opioid misuse or abuse and why. Accessible information about at-risk populations seems likely to better inform policymakers, public health officials, first responders, and other stakeholders who are tasked with prevention or intervention efforts by better identifying issues related to more effective prevention and treatment strategies.

Overdose Prevention. A crucial step in combating the opioid epidemic is to intervene prior to an opioid overdose related event. In order to do so, federal, state and local stakeholders need tools to predict and analyze the supply *and movement of legal and illicit opioids*. This includes both physician prescription patterns and the illegal market for opioids that includes prescription opioids, heroin, fentanyl and other synthetic opioids. By analysis of existing databases, information and correlations are likely to be identified that will allow stakeholders to respond prior to major risks in their communities. This includes being able to predict when and where a population is at risk for opioid availability, misuse and overdose so that first responders are better prepared for emergency situations and opioid overdose treatment, for instance by having drugs such as naloxone readily available in trained first responders and clinicians.

Treatment. Understanding of the patters of OUD treatment process and the available resources is an essential part of successful OUD treatment and reduction of the relapse rate. Unfortunately, most patients with OUD report no use or do not complete the OUD treatment. One likely reason for this shortcoming is that access to treatment and recovery services is not always available. Despite various efforts across the country, states, counties and cities to increase treatment access and to promote evidence-based approaches, opioid overdose and overdose-related mortality continue to increase. Accessible technologies for data analysis can help those involved in providing treatment services, better understand treatment options, address gaps in access to treatment, and improve the range of options available in communities.

Examples of the projects may include, but are not limited to:

- Analytical tools that can be used to appropriately monitor and *control the movement of prescription opioids* at pharmacies where unused or unneeded opioids can be returned, and sources of out of circulation opioids can be identified.
- Analytical tools to detect sources and *movement of illicit opioid sales online*.
- *Technologies to improve access to available treatment and recovery services*.
- *Informational technologies to promote evidence-based approaches to reduce opioid use, opioid overdoses, overdose-related mortality, and the prevalence of opioid use disorder*.
- *Products that use innovative technologies to strengthen understanding of the opioid epidemic through better public health data gathering, analysis and reporting*.
- Advanced real-time technologies to track fentanyl overdoses and to enable area hospitals, local health departments and first-responders to allocate resources where they are most needed.
- Analytical approaches to identify vulnerable and high-risk populations for opioid abuse, addiction, or overdose.
- Products to better understand opioid use patterns and how the frequency and quantity of use can be monitored.
- Sophisticated approaches to better identify behavioral indicators, patient characteristics, and environmental conditions for at-risk populations.

- Tools to ensure clinicians have a full, accurate picture of a patient’s medical history when prescribing or dispensing opioids.
- Studies to define new opioid prescribing patterns through predictive models of prescription opioid usage.
- Facilitating tools that transmit information securely and capture the opioid prescription data in real-time from across state lines.

Examples of federal data sources available to the offerors may include, but are not limited to

***Data Sets from Federal Government (excluding HHS):***

- O\*Net Database (Department of Education)
- National Center for Education Statistics 2016 Outcome Measures (Department of Education)
- Bureau of Economic Analysis Input-Output Accounts (Department of Commerce)
- Current Population Survey (CPS) (Department of Labor)
- Local Unemployment Statistics- Labor force data by county annual averages (Department of Labor)
- National EMS Information System (NEMESIS) (Department of Transportation)
- Mortgage Loan Data (Federal Housing Finance Authority)

***Data Sets from HHS:***

- Medical Expenditure Panel Survey (MEPS) (Agency for Healthcare Research and Quality)
- Healthcare Cost and Utilization Project (HCUP) (Agency for Health Care Quality and Research)
- CDC WONDER -- Multiple Causes of Death (Centers for Disease Control and Prevention)
- Medicare Part D Opioid Prescribing Data (Centers for Medicare & Medicaid Services)
- Medicare Part D Prescribing Data (Centers for Medicare and Medicaid Services)
- Uniform Data Service (Health Resources and Service Administration)
- Area Health Resource File (Health Resources and Services Administration)
- Buprenorphine Treatment Practitioner Locator (Substance Abuse and Mental Health Services Administration)
- National Survey on Drug Use and Health (NSDUH) (Substance Abuse and Mental Health Services Administration)
- Treatment Episode Data Set (TEDS) (Substance Abuse and Mental Health Services Administration)

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

The goal of Phase I is to develop a proof-of-concept or prototype of data-driven technology for opioid use prevention, opioid use, opioid overdose prevention or OUD treatment. Activities and deliverables include:

- Identify and justify the development of a health-IT tool or technology;
- Describe the current state of the art technologies, if any, and needs for new solutions;
- Specify and justify quantitative milestones that can be used to evaluate the success of a technology being developed;
- Identify the key features of a health IT tool or technology to be commercially feasible and useful.
- Design a prototype of software structure and process architecture;
- Describe how a health-IT tool or technology is compliant with health IT regulations and guidelines for data security.

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

The goal of Phase II is to develop and beta-test the technology for opioid use prevention, opioid use, opioid overdose prevention or OUD treatment. Offerors should develop an at-scale prototype of the technology with detailed specifications that supports future commercialization of the product with varying complexity. Decisions for continued product development into Phase II will be based on:

- Successful proof-of-concept data demonstrating adaptability of the product to the market needs;
- Description of the value of the product and expected impact to the society;
- Description of the market and/or market segments;
- Evidence for commercialization feasibility by providing feedback from potential purchasers and end-users.

**References:**

1. [The Numbers Behind the Opioid Crisis: https://www.lee.senate.gov/public/\\_cache/files/b54a2abb-978d-4bbb-a868-531cdfaeae7a/the-numbers-behind-the-opioid-crisis-final.pdf](https://www.lee.senate.gov/public/_cache/files/b54a2abb-978d-4bbb-a868-531cdfaeae7a/the-numbers-behind-the-opioid-crisis-final.pdf)
2. <https://www.cdc.gov/drugoverdose/maps/rxrate-maps.html>
3. [HHS Strategic Objective 5.3: https://www.hhs.gov/about/strategic-plan/strategic-goal-5/index.html#obj\\_5\\_3](https://www.hhs.gov/about/strategic-plan/strategic-goal-5/index.html#obj_5_3)
4. This RFP is the initiative complementary to 2017 [HHS Challenge: Opioid Symposium & Code-a-Thon](#) to support development of innovative solutions to combat the opioid epidemic using data and technology. This PRP is aligned with the HHS strategic goals outlined at the HHS Strategic Goal 5 (Strategic Objectives 5.3: [Optimize information technology investments to improve process efficiency and enable innovation to advance program mission goals](#))

---

## CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

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

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

CDC Role:

- Detecting and responding to new and emerging health threats
- Tackling the biggest health problems causing death and disability for Americans
- Putting science and advanced technology into action to prevent disease
- Promoting healthy and safe behaviors, communities and environment
- Developing leaders and training the public health workforce, including disease detectives
- Taking the health pulse of our nation

Those functions are the backbone of CDC's mission. Each of CDC's component organizations undertake these activities in conducting its specific programs. The steps needed to accomplish this mission are also based on scientific excellence, requiring well-trained public health practitioners and leaders dedicated to high standards of quality and ethical practice.

## CENTER FOR GLOBAL HEALTH (CGH)

The Center for Global Health (CGH) leads the execution of the CDC's global strategy; works in partnership to assist Ministries of Health to plan, manage effectively, and evaluate health programs; achieves U.S. Government program and international organization goals to improve health, including disease eradication and elimination targets; expands CDC's global health programs that focus on the leading causes of mortality, morbidity and disability, especially chronic disease and injuries; generates and applies new knowledge to achieve health goals; and strengthens health systems and their impact.

CGH's Web site: <http://www.cdc.gov/globalhealth/index.html>

### *CGH Topics*

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

#### **010 Multiplex Detection of Recent and Prior Exposure to Pathogens**

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

Number of anticipated awards: 1

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

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

### *Background*

Recent advances in high-throughput assay technologies have allowed for simultaneous detection of multiple pathogens, either by direct detection of antigens and genetic materials (DNA/RNA), and/or antibodies and other immune factor responses against those pathogens. Although both of these methods of disease detection provide critical information to clinical and public health professionals, the implication of positive test results are different. Antigens and DNA/RNA detect pathogens directly, and are usually mostly indicative of active disease, thereby providing information relevant for clinical treatment and intervention. Antibody tests indicate immune response to a pathogen, and can indicate either active/recent disease or past exposure to a pathogen. Because of this, antibody detection assays are more useful for disease surveillance, but detection of specific immunoglobulin isotypes (IgG, IgM, IgE, IgA) may also inform the clinical progression of disease, past or present. Likewise, the interplay of immune factors such as chemokines and cytokines determine individual responses to infection, and



can inform clinicians to predict outcomes, and thereby select appropriate interventions. Currently, there are no multiplex assays that exploit both antigen detection and immune response to multiple pathogens.

### ***Project Goals***

The goal of this project is to solicit the innovative development of diagnostic testing platforms that can simultaneously detect antigens of multiple pathogens and different antibody isotypes and/or immune factors against those pathogens in a single multiplex assay. The pathogens of interest include, but are not limited to, those with a high potential for causing global disease outbreaks that affect vulnerable populations (e.g., children, pregnant women, the elderly, etc.), and those targeted for global disease elimination or eradication.

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

During the Phase I period, the project research shall identify a list of relevant pathogens, appropriate antigens and reactive antibody isotypes (e.g., IgG, IgM, IgA, etc.) to these pathogens that will be included in the single multiplex testing platform format. The multiplex assay performance will be optimized for sensitivity and specificity using mock (spiked) and real clinical specimens.

### ***Impact***

By combining antigen and antibody detection to multiple pathogens in a single multiplex assay, both clinical and public health professionals would be empowered to determine the clinical stages of infection and treatment outcomes amongst affected individuals. Additionally, the burden of disease within specific populations could be assessed and monitored so that targeted disease interventions and prevention programs can be monitored for their efficacy.

### ***Commercialization Potential***

A multiplex assay that detects both antigens and immune responses to several pathogens would be of great interest to both the clinical and the public health sectors. Such an assay would be useful in a clinical setting to rule out or confirm potential disease etiologies, and useful in a population setting to determine specific foci for interventions to improve community health and prevent disease outbreaks.

## **011 Preservation of Supply Quality During Unmanned Aerial Vehicle (UAV) Transport**

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

Number of anticipated awards: 1 – 2

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

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

### ***Background***

Unmanned Aerial Vehicles (UAVS), or drones, have proven utility in aerial surveillance and mapping operations and for civil and commercial purposes, including law enforcement, agriculture and aerial photography amongst others. Many long-range flying drones are quite often fixed wing models that are fuel-powered, and require complex navigation controls and runways for take-off and landing. Thus, these drones are both cost-prohibitive and less agile than battery-powered multi-rotor UAVs.

Other limitations of using drones for logistics include current national aviation regulations for weight, altitude, maintaining visual line of sight (VLOS), and their inability to fly long distances without refueling or battery recharge. In the context of emergency public health response, drones could be extremely useful for transporting necessary supplies to remote or inaccessible locations. Supplies might include dry goods, but would certainly include clinical specimens, reagent kits, vaccines and other perishable goods. These materials would have to be transported at appropriate ambient temperature in order to be utilized as intended upon reaching their intended destination.

### ***Project Goals***

The primary goals for this project are to increase the utility of drone transport of perishable materials by engineering a lightweight transport box that is:

- Airtight
- Impervious to outdoor temperature
- Highly secure

In this way, patient specimens, vaccines, test kit reagents and enzymes must securely arrive at their intended destination at ambient temperature. Since battery technology is rapidly improving as evidenced by current patent applications, this is not a specific aim of the proposal.

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

The Phase I activities should include design of a drone transport box that meets the criteria above (i.e., airtight, lightweight, temperature controlled, secure). Ideally, a rotor or hybrid style (e.g., fixed wing with hover capability) drone used as the transport. Initial flight trials should be conducted in a controlled environment, and mimic extreme outdoor temperature and weather conditions while the internal transport box integrity and temperature of its contents is monitored. Transport box security and integrity should be measured against all disruptive conditions (e.g., falling, fire, immersion, etc.).

### ***Impact***

Availability of an agile device that can deliver supplies to and from remote locations during public health emergencies would save lives. Natural disasters such as floods, fires, and earthquakes often block communications and routes of access to victims. Similarly, disease outbreaks often begin in remote locations that are not easily accessed by public roads. Using drones to assist with triage and to carry needed supplies to and from sites of disaster and disease would decrease response time and avert further spread of disease and death, thereby improving recovery of affected populations.

### ***Commercialization Potential***

As drone technology becomes more mainstream, logistic requirements will become more sophisticated. At current, there is a great deal of interest in drone-mediated logistics among first responders and public health agencies, but the availability of a lightweight, temperature-controlled, secure transport box has excellent commercialization potential among private-sector entities as well. Firstly, as global aviation regulations relax to accommodate new drone technologies, hospitals and the healthcare sector will begin to adopt it for transport of materials and supplies, particularly blood and blood products, specimens and vaccines. Even more compelling is the burgeoning online retail business, since products sold may be valuable, requiring security, and temperature sensitive, requiring insulation.

## 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:

#### **041 Community Based Worksite Wellness App Linking Employees to Wellness Resources**

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

Number of anticipated awards: 1

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

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

### *Background*

One-third of Americans spend more than 8 hours per day, five days a week at the workplace. This makes the worksite a critical point to encourage and enable health promoting behaviors, practices, and activities. Effective workplace wellness programs can support and improve the quality of life for American workers. However, of the nearly 28 million businesses in the United States, over 99% are considered small-sized, as defined by the Small Business Administration (SBA). This means they have 500 or fewer employees and are far less likely to offer wellness programs. In fact, less than 7% of small employers offer comprehensive wellness programs. (U.S. Census Bureau, SUSB, CPS; International Trade Administration; Bureau of Labor Statistics, BED; Advocacy-funded research, Small Business GDP: Update 2002-2010, [www.sba.gov/advocacy/7540/42371](http://www.sba.gov/advocacy/7540/42371)).

Smart devices provide opportunities to connect employees (with or without worksite wellness benefits) with wellness and health-supporting products, services, or activities. These services can be provided at no or minimal cost to the employer, minimizing or eliminating one of the key barriers expressed by small employers. Employees benefit from access to potentially discounted products (e.g., meals or sports equipment) or services (e.g., gym membership). Businesses providing these wellness services can also experience economic benefits via increased patronage and improved integration with the community. Improved employee health, in turn, can lead to foreseeable economic and social benefits, such as increased productivity, reduced health care costs, reduced absenteeism, reduced short and long-term disability, and reduced workers compensation claims. In short, employer-sponsored wellness activities can facilitate healthy lifestyle behaviors and reduce employees' health risks and costs.

### *Project Goals*

The goal of this project is a web-based, smart device application enabling small businesses to build a health and wellness-supporting network of local products and services provided by peer small businesses and others. The worksite wellness app should enable businesses to provide the following, but may provide more:

- Bring community wellness services into the worksite, reducing time and access barriers. For example, enabling businesses to connect directly with other businesses providing services such as healthy food service (e.g., vending or catering) or onsite health screenings or wellness classes.
- Access to public non-commercial resources available to employees that facilitate health and wellness (e.g., local parks with walking trails).
- Connect with a network of local businesses providing a variety of health and wellness products/services.

- Negotiate discounted rates for employees for services (e.g., gym memberships)/products (e.g., healthy snacks).
- Offer specific wellness incentives available from their health insurance plan(s) to facilitate greater uptake by employees (e.g., no or low out of pocket cost prescription tobacco cessation medications including nicotine replacement therapy).

Once a business creates a portfolio of services and shares the account with their employees, the proposed application will present opportunities (e.g., incentives, discounts) and locations (via online maps) on a smart device app and a website. Specific commercial opportunities available to employees may include healthy food (e.g., discounts on healthy offerings at local restaurants, food delivery services, and food retailers), physical activity opportunities (e.g., discounts to gyms, classes, local mass transit information to facilitate active transportation), preventive clinical services (e.g., flu vaccinations, wellness screenings), and dental services. Non-commercial opportunities may include physical activity resources (e.g., information about local parks, walking and riding paths), chronic disease prevention and management classes (e.g., community-based diabetes prevention and management programs, free or discounted community-based exercise classes), tobacco-free living (e.g., tobacco cessation telephone quit-lines), and other public health opportunities (e.g., community health fairs, farmer's markets).

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

In Phase 1, a web-tech design business with expertise in both building social networks as well as health and wellness services will become familiar with CDC's worksite wellness program(s), and other large public health or health oriented companies/businesses to develop a web platform and smart device app. This interface needs to enable small and mid-sized businesses interested in designing or enhancing worksite wellness programs to connect with and build a peer network of businesses offering health-related products, services, and resources. Further, the interface will include incentives and other behavioral economic and design strategies, to enhance worksite wellness programs without a significant financial investment by any businesses involved in this venture.

#### **Planning Phase Deliverables:**

1. Initial planning meetings;
2. Proof of concept: examine similar (web-based, smart device applications) to determine the necessary steps to create and launch a viable product, including concept pilot testing with small businesses;
3. A website wireframes; including a skeleton framework of application, website portals, and smart device apps linking services together and how they are linked (in a static format). Wireframes must consider the range of available functions, informational and functional priorities, rules for displaying various types of information, and the effect of different scenarios of use on outputs, while including:
  - a. A Business (owner) interface with the ability to add employees and opportunities. This interface must be able to receive and share opportunities with its employees (i.e., businesses can contact the website to offer resources).
  - b. An employee (user) interface enabling the viewing of resources in various wellness categories and by time-period.
  - c. The ability for business owners and employees, as appropriate, to specify wellness opportunities, geographic radius, and time-period for opportunity (is there a discount on a healthy lunch nearby?).
  - d. Screen-shots of the website framework (depiction of what the screens and layout will look like).
4. Develop partnerships with local, state, and national level government and non-profit organizations that assist in identifying and creating access to worksite wellness resources (e.g., American Heart Association, Chamber of Commerce, city governments, National Alliance of Health Care Purchasers Coalition, local and state health departments, Health Enhancement Research Organization).
5. Develop automated and other methods to identify and recruit relevant local businesses to the wellness network and to extract relevant information about local resources such as parks and mass transit.

### ***Impact***

This web-based and mobile application has direct utility to the over 99% of the 28 million businesses in America that are small-sized that may not currently offer worksite wellness programs. This App has particular relevance in less densely populated areas, where there are limited if any worksite wellness opportunities. This App will potentially increase access to health by promoting and supporting opportunities American workers who work for small or midsized business. Impact and methods for improvement will be assessed via collecting data and information on access and participation, user feedback,

ease of use/feasibility, utility, and cost. There is also the potential for economic impact by increasing patronage of local business and, in turn improving productivity and decreasing illness and thus absenteeism among workers.

### ***Commercialization Potential***

Employers have an incentive to use this application/website as a worksite wellness platform to improve the health and performance of their employees. Businesses participating in wellness resources gain access to new customers. Consumer and business traffic created by this app may also lead to other commercialization opportunities through advertising, insurance benefits or fee for use after it has established itself.

## **042 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 **not** 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 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:

#### **020 Novel Coatings/Surfaces on Indwelling Medical Devices to Prevent Biofilms**

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

Number of anticipated awards: 2

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

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

### *Background*

Microorganisms may colonize indwelling medical devices such as urinary catheters or intravascular catheters to form a biofilm. Biofilms are sessile microbial communities composed of microbial cells and an extracellular matrix termed the “extracellular polymeric substance” matrix or “EPS” that may contain specific polysaccharides, proteins, and extracellular DNA. Microorganisms comprising biofilms on these medical devices are diverse and may be polymicrobial, containing multiple taxa. Use of urinary or intravascular catheters may be associated with increased risk of catheter-associated urinary tract or central line-associated bloodstream infections, respectively. Biomaterials that completely inhibit microbial attachment have not been discovered. Novel, non-traditional technologies are needed that can prevent or substantially reduce biofilm formation, with particular efficacy against antibiotic-resistant, healthcare-associated pathogens.

### *Project Goals*

The goal of this project is to develop coatings or altered surfaces that can be used on indwelling urinary or intravascular catheters to prevent or significantly reduce biofilm formation by organisms known to cause healthcare-associated infections. Examples of these technologies could include, but are not limited to, catheters that release materials to augment the host immune response, catheters containing enzymes designed to disperse attached microbial cells, catheters containing adsorbed biological agents, or catheters with altered chemical/physical properties.

### *Phase I Activities and Expected Deliverables*

The technical merit or feasibility of the proposed technology should be determined using an *in vitro* model that is designed to simulate biofilm formation on the catheter surfaces. The *in vitro* model should use at least two clinically relevant organisms that are known to be responsible for catheter-associated urinary tract or catheter-associated bloodstream infections. Ideally, two approaches providing complementary data on microbial attachment (using multiple healthcare-associated pathogens) and biofilm formation should be used to provide a proof of concept for the proposed technology. Models containing actual catheter materials would be especially useful, but are not required. The goal of these studies is to provide a proof of concept for the technology.

### *Impact*

Infections associated with the use of indwelling medical devices such as intravascular catheters and urinary catheters comprise a measurable component of healthcare-associated infections in U.S. healthcare facilities. A “biofilm-free” urinary

or intravascular catheter would substantially impact healthcare delivery and could reduce antimicrobial resistance, healthcare costs, and length of stay in the hospital.

***Commercialization Potential***

The commercialization potential of catheters with novel surface coatings is high because such approaches could be patentable, could have potentially broad applications to other types of indwelling medical devices (endotracheal tubes, artificial voice prostheses, intrauterine devices, artificial heart valves, prosthetic joints, etc.), or other, semi-critical devices (e.g., endoscopes), and because the market for these devices is substantial.



## NATIONAL CENTER FOR ENVIRONMENTAL HEALTH (NCEH)

The CDC National Center for Environmental Health (NCEH) protects people's health from environmental hazards that can be present in the air we breathe, the water we drink, and the world that sustains us. NCEH supports research that investigates the relationship between environmental factors and health. The goals of NCEH are to implement environmental health programs and interventions to protect and promote health; prepare for and respond to public health emergencies, including chemical, biological, radiological, and nuclear incidents; natural disasters; and extreme weather events; and identify, characterize, and monitor health outcomes and environmental exposures to guide actions that protect and promote health. NCEH will prioritize funding meritorious applications that address the NCEH program topic 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](https://www.cdc.gov/nceh/information/mission_vision_goals.htm).

### *NCEH Topic*

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

#### **001 Rapid Field Test to Improve Swimming Pool Water/Air Quality**

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

Number of anticipated awards: 1

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

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

### *Background*

To protect swimmers' health, chlorine is commonly added to pool water to kill germs and stop them from spreading. However, chlorine also combines with inorganic and organic materials from swimmers to create organic and inorganic chemical by-products called chloramines. While the organic chloramines tend to accumulate in the water, the inorganic chloramines such as di- and tri-chloramine are volatilized and accumulate in the air above the pool. The inorganic chloramines cause ocular and respiratory distress, particularly in indoor pools. The strong chemical smell people experience and think is chlorine is actually the volatile organic chloramines. CDC has investigated several health incidents reporting skin and eye irritation and acute respiratory distress outbreaks that were associated with exposures to inorganic chloramines. More recent data have suggested a linkage with more severe outcomes such as asthma.

In August of 2014, CDC led a national collaborative effort with public health, industry, and academic partners from across the United States to develop a national guidance document called the Model Aquatic Health Code (MAHC): <http://www.cdc.gov/mahc/> The MAHC is a voluntary guidance document based on science and best practices that can help local and state authorities and the aquatics sector make swimming and other water activities healthier and safer. States and localities can use the MAHC to create or update existing pool codes to reduce the risk for outbreaks, drowning, and pool-chemical injuries. The MAHC effort was unable to set a recommended level for the inorganic chloramines that are associated with health effects, due to the lack of a rapid commercially-available, pool side test to differentiate the volatile inorganic chloramines from the organic chloramines in water samples. Current water tests can only measure the value for the "combined chlorine" and cannot separate out the irritant inorganic chloramines from the organic chloramines that make up the "combined chlorine" measure.

Development of tests that can measure the inorganic chloramines separately from the organic chloramines in a water sample is needed, so actionable levels can be set in the MAHC and other pool codes across the country. With such tests, aquatics staff will be able to respond to actionable levels of volatile inorganic chloramines in the water, so that appropriate water and air quality can be maintained.

### *Project Goals*

The goal of this project is to develop a simple, implementable pool-side test method(s) to gather separate measures for organic and inorganic combined chlorines in pool water. Regulators can then expect that pool operators can test for these

compound groups and respond to regulatory level requirements for water quality. Such a test would assist pool operators in improving water quality and associated air quality.

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

Investigate basic chemistry of these reactions and develop plan for test development.

### ***Impact***

At this time there is no rapid commercial test to differentiate organic and inorganic chloramines in pool water samples. Development of such a test would have significant impact on the improved health of swimmers and others using the nation's aquatic facilities. CDC's Model Aquatic Health Code has not set a recommended level on "combined chlorine" due to the absence of a test to differentiate the irritant inorganic chloramines (the actual causes of ocular and respiratory health effects) from the organic chloramine mix. Development of tests that can measure the inorganic chloramines separately from the organic chloramines in a water sample is needed so actionable levels can be set in the MAHC and other pool codes across the country. With such tests, aquatics staff will be able to respond to actionable levels of volatile inorganic chloramines in the water, so that appropriate water and air quality can be maintained.

### ***Commercialization Potential***

With a rapid commercial test available, the MAHC could set a recommended level for compliance and pool operators could reasonably be expected to measure and meet the water quality limits. A rapid commercial test to differentiate organic and inorganic chloramines in pool water samples could be marketed to states/territories and all aquatic facility operators. If the data were available, recommended levels for organic and inorganic chloramines were set by CDC's MAHC. Pool inspectors across the US and the 300,000 public aquatic facilities in the country would be potential customers for such a test as well as residential pool owners.

## **OFFICE OF PUBLIC HEALTH PREPAREDNESS AND RESPONSE (OPHPR)**

The Office of Public Health Preparedness and Response (OPHPR)'s mission is to strengthen and support the nations' health security to save lives and protect against public health threats. OPHPR has primary oversight and responsibility for all programs that comprise CDC's public health preparedness and response portfolio. Through an all-hazards approach to preparedness-focusing on threats from natural, biological, chemical, nuclear, and radiological events-OPHPR helps the nation prepare for and respond to urgent threats to the public's health. OPHPR carries out its mission by emphasizing accountability through performance, progress through public health science, and collaboration through partnerships.

OPHPR Website: <https://www.cdc.gov/phpr/index.htm>.

### ***OPHPR Topic***

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

#### **003 Rapid Test for Simultaneous Detection of Influenza (Types A and B) and Streptococcus (Group A)**

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

Number of anticipated awards: 1

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

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

### ***Background***

The onset of influenza season sees increasing number of patients visiting clinics and hospitals that have symptoms similar to influenza caused by influenza types A and B, and strep throat caused by group A Streptococcus (GAS). There are several FDA-approved tests available, some of which are CLIA- waived, to detect separately influenza viruses and GAS in the patient specimens. These tests can take from less than 15 minutes (nucleic acid or antigen detection) to several days (culture-based assays). There is a need for an easy-to-use test in the field and health care settings for simultaneous detection of influenza types A and B, and GAS in the patient specimen. An early and accurate identification of the etiological agents will enhance surveillance, improve preparedness and response activities to a potential epidemic, inform use of proper prophylactics for responders, and ensure appropriate use of antiviral and/or antibiotics for patients before disease severity increases or further transmission occurs.

The applicant interested in this topic can develop new reagents, or use or modify reagents already available in the market and the research community to support the development of such a rapid point-of-care (POC) test. The offeror should document relevant biosafety experiences and availability of laboratory space at a biosafety level sufficient to work with influenza types A and B, and GAS.

### ***Project Goals***

The goal of this project is to develop a rapid POC diagnostic test that can simultaneously determine whether an individual is infected with influenza virus (types A and B) or GAS or both. The test should be simple, cost effective, non-invasive, demonstrate sensitivity and specificity greater than or comparable to the current POC tests, and have a potential of high throughput (running many samples at once for rapid testing). The test should employ reagents that can be stored under ambient conditions, and be compatible with U.S. regulatory guidelines for testing and validation. The final product should be compatible with POC use by healthcare personnel and field use by emergency responders, provide an instant color-coded readout preferably by direct observance or a portable electric/battery-operated analyzer for field use. Potential of such kit for use in home settings is desired but not required in Phase 1.

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

Phase I activities can include but are not limited to:

1. Review of literature and preparation of a report about the current status of POC influenza type A and B, and GAS tests available in the market or reported in published literature. The report should also include information about test sensitivity, specificity, merits and limitations and the knowledge gap associated with these diagnostic tests.

2. Development of new reagents or modification of currently available reagents that can be stored at ambient temperature.
3. Test development to enable one-step simultaneous specific detection of influenza type A and type B, and GAS.
4. Validation of test specificity and sensitivity greater than or comparable to current tests
5. Test kit development, including instructions for use and result interpretation.

### ***Impact***

This research has potential to develop a rapid test that is easy to use in home, field and health care settings for simultaneous detection of influenza viruses and GAS in patient samples. These pathogens that have a substantial impact on human health and our economy at community and global level. The sensitive and specific test when developed could improve the public health preparedness and healthcare system's appropriate response to a potential epidemic.

### ***Commercialization Potential***

There is a strong commercialization potential as the innovative research will lead to the development of a simple and rapid test to use in a home, field and health care settings for simultaneous detection of influenza viruses and GAS.

## 13 APPENDICES

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

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

PDF (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.pdf>)

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

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

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

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

MS Word (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixC.docx>)

PDF (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixC.pdf>)

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

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

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

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

MS Word (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixE.docx>)

PDF (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixE.pdf>)

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

MS Word (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixF.docx>)

PDF (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixF.pdf>)

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

MS Word (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixG.docx>)

PDF (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixG.pdf>)

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

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

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

Fillable PDF (<https://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixH.2.pdf>)

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

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

Fillable PDF (<https://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixH.3.pdf>)

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

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