AMENDMENT FOUR (4)

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PURPOSE OF SOLICITATION AMENDMENT

The purpose of this amendment is to:
- Remove and replace Page 5 of the solicitation, to revise NIA Topic 010 title, as attached; and,
- Respond to Questions received regarding the solicitation.

The hour and date specified for receipt of Offers remains unchanged.
Except as provided herein, all terms and conditions of the solicitation remain unchanged and in full effect.

Questions: Section 12 Component Instructions and Technical Topic Descriptions

NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES (NCATS)
NCATS TOPIC 024- Small Manufacturing Systems to Produce Research Grade Pharmaceutical Intermediates

Question 1: The Solicitation sates under the "Phase I Activities and Expected Deliverables (up to 1 year)" description of the topic:

c. Offerors may provide the intended synthetic route and associated intermediates list for demonstration, with strong justification for fit-for-purpose. Emphasis should be on synthetic simplicity, flexibility to produce many other intermediate targets from a common set of reactions, and on-board process monitoring. Proposed synthetic routes and targets must be approved by NCATS. Alternatively, offerors may select from a list of intermediate targets and associated synthetic routes provided by NCATS.

Do I need approval prior to submission? Or should I write the proposal more generally recognizing that NCATS will shape the direction of the work? If not, who do I speak with regarding route and target approval?

Answer 1: Approval is not required prior to submission. Please refer to the solicitation; NCATS will not be shaping the direction of the work.

NATIONAL CANCER INSTITUTE (NCI)

NCI Topic 461: Ultra-Fast Dose Rate (FLASH) Radiation Detectors and Safety Systems for Cancer Treatment

Questions 1: The solicitation indicates that solutions "unable to be validated and traced to NIST sources/dose definitions" will not be considered. Given that standard NIST guidelines for beam monitoring are usually based on ion chamber detectors, and that this solicitation is dependent on the understanding that ion chambers are not suitable technology for FLASH beam monitoring, can this statement please be clarified? Specifically, what test or standard should be used to meet the requirement of NIST source tracing?

Answer 1: There is no prohibition in the solicitation on the use of ion chambers. You would just need to be confident that you can make it work for the intended FLASH radiotherapy use case. Until NIST has a standard approach for FLASH, your device would have to be able to generate valid dosimetry measurements when used in a "slow" controlled state as an initial starting point, and we want offerors to design their device to ultimately work with any FLASH standard adopted by NIST in the future, if possible. What we are looking for is a commitment to the importance of a future NIST standard, not having it conform to such a standard today.

Question 2: Existing portal and dose monitoring systems in traditional radiation therapy modalities can be built as either a single point monitoring device or can measure dose distribution at many points across the beam as well as along the beam. For the purposes of this solicitation, would an ideal prototype work as a single-point dose measuring device or would a multi-point dose distribution measuring system be preferred?

Answer 2: This choice is yours to make. The goal is maximum data, but at the same time to be stable, affordable, and reliable.

Questions 3: Is the prototype supposed to work as replacement of (segmented) monitor chamber inside the FLASH machine or as a dosimeter inside a phantom?

Answer 3: Both. We want it to be incorporated into a safety system ultimately (mandated now) to stop the beam, or at least have it be known immediately that what was given was or was not FLASH. The goal is to stop the beam before any patient harm happens.

NATIONAL INSTITUTE ON AGING (NIA)

Please note the updated page 5 reflecting the revision to the title of NIA TOPIC 010 to *Technology to facilitate characterization of the **exposome** in under-resourced populations for AD/ADRD Studies*

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES (NIAID)

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

Question 1: **The announcement calls for a protype LF-IVD for detection of pathogen nucleic acids / proteins; however, it also mentions biomarker, and in this context, does this mean that an assay for detection of anti-HCV / anti-HIV antibodies would be responsive as well?**

Answer 1: Yes, an assay for detection of anti-HCV/anti-HIV antibodies would be responsive.

Question 2: **We have just successfully completed a Phase I contract that involved development of a device for qualitatively detecting anti-HCV antibodies in patient sera for self-testing in an at-home setting. Will this render us ineligible to submit a bid for an assay multiplexed for HCV / HIV?**

Answer 2: No. Overlap will be determined once the application is received.

Question 3: **For the Phase I feasibility and prototype development, would it be acceptable to first demonstrate feasibility and a demonstrate a functioning prototype using serum specimens procured from commercial repositories? We have obtained high quality, remnant serum specimens for such sources for our several of our federally funded projects, including the successfully completed NIH / NCI SBIR phase I effort. Given the time constraints imposed on the Phase I component, would it be acceptable if we used serum to demonstrate feasibility and prototype development in Phase I, and then translate the LF-IVD to whole-blood in Phase II?**

Answer 3: Yes, for Phase I it would be acceptable to demonstrate a functioning prototype use stored serum samples and translate/validate the LF-IVD using whole blood in Phase II.

NIAID TOPIC 128 - Adjuvant Development for Vaccines for Infectious and Immune-Mediated Diseases

Question 1: **Will topic NIH/NIAID 128 (Adjuvant Development for Vaccines for Infectious and Immune-Mediated Diseases) support the evaluation of different commercially available spray devices for intranasal delivery of our adjuvanted vaccine?**

Answer 1: Delivery is an important consideration for the development and optimization of vaccine adjuvants for use in vaccines. Topic NIH/NIAID 128 (Adjuvant Development for Vaccines for Infectious and Immune-Mediated Diseases) may support the evaluation and optimization of immunization delivery and regiments within the context of adjuvant development (e.g., pharmacokinetics, delivered dose). The topic will not support the development of platform technologies or delivery systems that have no immunostimulatory or tolerogenic activates themselves (e.g., development of an intranasal delivery device).

Question 2: **Is there flexibility with the company vs subcontractor split of a SBIR grant [contract]?**

Answer 2: Please refer to solicitation Section 4.2 Offeror Eligibility and Performance Requirements which states, “For Phase I, a minimum of two-thirds of the research or analytical effort must be performed by the awardee. For Phase II, a minimum

of one-half of the research or analytical effort must be performed by the awardee. The percentage of work will be measured by total award dollars."

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

NCHHSTP TOPIC 056 - EHR Algorithm to Identify Persons with HIV Not in Care

Question 1: Can you provide clarity about whether the expectation is that the algorithm has been developed and validated and has been implemented into an EHR via a dashboard; or whether the expected deliverable that the offeror could demonstrate that it is feasible to design an algorithm? With the expectation that validation and/or deployment of the algorithm might be funded under a Phase II proposal.

Answer 1: The expected deliverable for Phase I includes the dashboard. The expected deliverable will be the algorithm to identify PWH who are not engaged in care or are not virally suppressed using data available in EHR systems and create a dashboard to flag this information. As such, Phase I will address the feasibility of all aspects of the development and deployment of the algorithm. The contractor is expected to create and build a database management system and develop a prototype visual dashboard in Phase I.

NCHHSTP TOPIC 057 - Device for point-of-care nucleic acid purification and detection of HCV

Question 1: Where can we access a copy of the CDC workflow (U.S. Provisional Patent Application No. 63,489,519) that is mentioned in this topic?

Answer 1: Please see attached PDF of the CDC Workflow mentioned in this topic.

NATIONAL CENTER FOR IMMUNIZATION AND RESPIRATORY DISEASES (NCIRD)

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

Question 1: Does CDC have any additional sequences of the Alphaherpesvirinae, that would be released for research purposes?

Answer 1: It's recommended to look at GenBank. All sequences from CDC should be deposited there. A search with varicella would be able to obtain sequences from GenBank.

Question 2: Does this mean that CDC will supply a blind set of known positive and negative samples?

Answer 2: Yes, CDC is prepared to supply test panels of positive and negative specimens.

Question 3 What are the regulations for moving patient samples in addition to IRB compliance?

Answer 3: Moving patient samples between institutions will at minimum require a Materials Transfer Agreement to be established and depending on the institution. As for IRB compliance, it would depend on the regulations for the institution and the regulations covering how the specimens were collected. Any specimens collected as part of a study will depend on the language within the consent form and whether specimens are allowed to be used for further studies, and the nature of those future studies.

Replacement page 5 from solicitation

1 INTRODUCTION

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

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

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