

SOLICITATION OF
THE NATIONAL INSTITUTES OF HEALTH AND
THE CENTERS FOR DISEASE CONTROL
AND PREVENTION
FOR

SMALL
BUSINESS
INNOVATION
RESEARCH
CONTRACT PROPOSALS

PROPOSAL RECEIPT DATE
NOVEMBER 13, 2012

TABLE OF CONTENTS

PART I INSTRUCTIONS FOR PREPARING AND SUBMITTING A PROPOSAL	1
1. PROGRAM DESCRIPTION	1
1.1 PURPOSE OF SOLICITATION.....	1
1.2 THREE PHASE PROGRAM.....	1
1.3 AWARDING COMPONENTS	2
NATIONAL INSTITUTES OF HEALTH (NIH).....	2
CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC).....	3
1.4 SBIR PROGRAM ELIGIBILITY	3
1.5 REPORT FRAUD, WASTE AND ABUSE	5
2. AGENCY CONTACT FOR INFORMATION.....	5
3. DEFINITIONS	6
4. PHASE I PROPOSAL PREPARATION INSTRUCTIONS AND REQUIREMENTS.....	13
4.1 LIMITATIONS ON LENGTH OF PROPOSAL.....	13
4.2 TECHNICAL PROPOSAL FORMAT AND CONTENT REQUIREMENTS	13
4.2.1 TECHNICAL PROPOSAL COVER SHEET	13
4.2.2 ABSTRACT OF RESEARCH PLAN	13
4.2.3 RESEARCH PLAN	14
4.2.4 CURRENT AWARDS AND PENDING PROPOSALS/APPLICATIONS	15
4.2.5 PRIOR SBIR PHASE II AWARDS	16
4.2.6 PROPOSED COST BREAKDOWN	16
4.2.7 STREAMLINING THE CONTRACTING PROCESS	17
4.2.8 REQUIREMENT FOR ADEQUATE ASSURANCE OF PROTECTION OF HUMAN SUBJECTS	17
4.2.9 REQUIREMENT FOR ADEQUATE ASSURANCE OF COMPLIANCE WITH THE PHS POLICY ON HUMANE CARE AND USE OF LABORATORY ANIMALS	18
4.3 LIMITATIONS ON USE OF APPROPRIATED FUNDS.....	19
5. “FAST-TRACK” INITIATIVE.....	21
6. FAST-TRACK PHASE II PROPOSAL PREPARATION INSTRUCTIONS AND REQUIREMENTS	21
6.1 LIMITATIONS ON LENGTH OF PROPOSAL.....	21
6.2 TECHNICAL PROPOSAL FORMAT AND CONTENT REQUIREMENTS	22
6.3 BUSINESS PROPOSAL FORMAT AND CONTENT REQUIREMENTS	25
7. METHOD OF SELECTION AND EVALUATION CRITERIA	25
7.1 EVALUATION PROCESS	25
7.2 TECHNICAL EVALUATION CRITERIA	26
7.3 PROPOSAL DEBRIEFING	27
7.4 AWARD DECISIONS	27
8. CONSIDERATIONS	27
8.1 AWARDS	27
8.2 PROGRESS REPORTS.....	29
8.3 FINAL REPORT.....	29
8.4 PAYMENT	29
8.5 LIMITED RIGHTS INFORMATION AND DATA	30
8.6 PERFORMANCE OF RESEARCH AND ANALYTICAL WORK	32
8.7 ELECTRONIC AND INFORMATION TECHNOLOGY (SECTION 508)	33
8.8 ADDITIONAL INFORMATION	34
9. INSTRUCTIONS FOR PROPOSAL SUBMISSION	34
9.1 RECEIPT DATE.....	34

9.2	NUMBER OF COPIES	35
9.3	BINDING AND PACKAGING OF PROPOSAL.....	35
10.	CONTRACTING OFFICERS AND ADDRESSES FOR MAILING OR DELIVERY OF PROPOSALS	35
10.1	NATIONAL INSTITUTES OF HEALTH (NIH).....	35
	NATIONAL CANCER INSTITUTE (NCI).....	35
	NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES (NCATS)	36
	NATIONAL HEART, LUNG, AND BLOOD INSTITUTE (NHLBI)	36
	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES (NIAID)	36
	<i>EUNICE KENNEDY SHRIVER</i> NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT (NICHD).....	37
	NATIONAL INSTITUTE ON DRUG ABUSE (NIDA).....	37
10.2	CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC).....	37
	CENTER FOR GLOBAL HEALTH (CGH)	38
	NATIONAL CENTER FOR BIRTH DEFECTS AND DEVELOPMENTAL DISABILITIES (NCBDDD)	38
	NATIONAL CENTER FOR CHRONIC DISEASE PREVENTION AND HEALTH PROMOTION (NCCDPHP)....	38
	NATIONAL CENTER FOR EMERGING ZOO NOTIC AND INFECTIOUS DISEASES (NCEZID).....	38
	NATIONAL CENTER FOR HIV/AIDS, VIRAL HEPATITIS, STD, AND TB PREVENTION (NCHHSTP)	39
	NATIONAL CENTER FOR IMMUNIZATION AND RESPIRATORY DISEASES (NCIRD).....	39
	OFFICE OF PUBLIC HEALTH PREPAREDNESS AND RESPONSE (OPHPR)	39
11.	SCIENTIFIC AND TECHNICAL INFORMATION SOURCES.....	40
12.	RESEARCH TOPICS	40
NATIONAL INSTITUTES OF HEALTH	40	
	NATIONAL CANCER INSTITUTE (NCI)	40
	313 RNAi CANCER THERAPEUTICS USING NANOTECHNOLOGY	41
	314 DEVELOPMENT OF HUMAN TISSUE CULTURE SYSTEMS THAT MIMIC THE TUMOR MICROENVIRONMENT	43
	315 DEVELOPMENT OF COMPANION DIAGNOSTICS: ENABLING PRECISION MEDICINE IN CANCER THERAPY	45
	316 DEVELOPMENT OF CTC ISOLATION TECHNOLOGIES ENABLING DOWNSTREAM SINGLE CELL MOLECULAR ANALYSIS	47
	317 WOUND HEALING PREPARATIONS INCORPORATING NITRIC OXIDE-RELEASING MATERIALS (NIH TECHNOLOGY TRANSFER).....	49
	318 TEST TO PREDICT EFFECTIVENESS OF DOCETAXEL TREATMENT FOR PROSTATE CANCER (NIH TECHNOLOGY TRANSFER)	51
	319 TECHNOLOGY TO GENERATE ANTI-PEPTIDE CAPTURE REAGENTS FOR AFFINITY-ENRICHED PROTEOMIC STUDIES.....	53
	320 HIGH QUALITY CANCER-RELATED STANDARDS FOR METABOLOMICS RESEARCH	55
	321 CHEMICALLY DEFINED GLYCAN LIBRARIES FOR REFERENCE STANDARDS AND GLYCOMICS RESEARCH (JOINT NCI-NIGMS PROGRAM)	56
	322 REAL-TIME INTEGRATION OF SENSOR AND SELF-REPORT DATA FOR CLINICAL AND RESEARCH APPLICATIONS.....	59
	323 DEVELOPMENT OF RADIATION MODULATORS FOR USE DURING RADIOTHERAPY	62
	324 NOVEL IMAGING AGENTS TO EXPAND THE CLINICAL TOOLKIT FOR CANCER DIAGNOSIS, STAGING, AND TREATMENT	64
	325 INNOVATIVE RADIATION SOURCES FOR ADVANCED RADIOTHERAPY EQUIPMENT	66
	NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES (NCATS).....	68
	001 VISUALIZING KNOWLEDGE ABOUT HUMAN HEALTH AND THE PATHWAYS OF TRANSLATION	68
	002 BIOMARKER STUDY FOR CREATINE TRANSPORTER DEFECT DISORDERS	69
	003 AUTOMATED INSTRUMENT TO CLEAN MICROTITER PLATES	70
	004 ASSAY DEVELOPMENT FOR HIGH-THROUGHPUT SCREENING OF CHEMICALS OF TOXICOLOGICAL CONCERN.....	72
	NATIONAL HEART, LUNG, AND BLOOD INSTITUTE (NHLBI)	73
	072 NEW METHODS TO DETECT AND ASSESS MYOCARDIAL FIBROSIS.....	74
	073 EVALUATING OBSTRUCTIVE SLEEP APNEA DENTAL DEVICE TREATMENT COMPLIANCE	75

074	IMPROVING SAFETY AND EFFICACY OF RED BLOOD CELLS FOR TRANSFUSION.....	76
075	DEDICATED PEDIATRIC CARDIAC MRI RECEIVE COILS.....	77
076	MRI MYOCARDIAL BIOPSY FORCEPS	78
077	PASSIVE MRI GUIDEWIRE	80
078	TRANSTHORACIC CARDIAC ACCESS PORTS AND CLOSURE DEVICES	81
079	BIOABSORBABLE STENTS FOR PEDIATRIC PULMONARY ARTERY STENOSIS AND AORTIC COARCTATION.....	83
080	FLUORESCENT NANODIAMONDS FOR <i>IN VITRO</i> AND <i>IN VIVO</i> BIOLOGICAL IMAGING	84
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES (NIAID)		86
021	AEROSOLIZED DELIVERY OF ANTI-TUBERCULAR DRUGS	86
022	DEVELOPMENT OF LONG-ACTING FORMULATIONS OF HIV ANTI-RETROVIRALS	87
023	IMPROVED FORMULATIONS FOR APPROVED FIRST AND SECOND LINE ANTI- TUBERCULOSIS (TB) DRUGS	87
024	INTEGRATED MULTIPLEX MEDICAL DIAGNOSTICS PLATFORMS FOR INFECTIOUS DISEASES.....	88
EUNICE KENNEDY SHRIVER NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT (NICHD).....		89
023	NEURAL INTERFACES: IMPROVING FUNCTIONAL OUTCOMES.....	89
NATIONAL INSTITUTE ON DRUG ABUSE (NIDA)		91
147	A MOBILE APPLICATION TO HELP PATIENTS TAKE THEIR PILL MEDICATIONS AS PRESCRIBED: IMPROVING MEDICATION ADHERENCE.....	91
148	PRODUCTS FOR AT-HOME DEACTIVATION OF PSYCHOACTIVE PRESCRIPTION MEDICINES.....	94
149	DEVELOPMENT OF PREDICTIVE <i>IN VIVO</i> SCREENING SYSTEMS FOR PHENOTYPIC DRUG DISCOVERY FOR SMOKING CESSATION	96
150	VIDEO GAME TARGETING RELAPSE PREVENTION IN YOUTH WITH SUBSTANCE USE DISORDERS.....	102
CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)		104
CENTER FOR GLOBAL HEALTH (CGH).....		104
003	DIAGNOSTIC NEEDS FOR NEGLECTED TROPICAL DISEASES (NTD) PROGRAMS.....	104
004	RAPID SCREENING TESTS TO PREVENT CONGENITAL INFECTIONS AND ENSURE BLOOD SAFETY.....	105
005	DEVELOPMENT OF DIAGNOSTIC TESTS FOR STRONGYLOIDIASIS AND SCHISTOSOMIASIS.....	105
NATIONAL CENTER ON BIRTH DEFECTS AND DEVELOPMENTAL DISABILITIES (NCBDDD).....		106
016	IMPROVING DATA, IMPROVING CARE, MAKING IT COUNT	106
017	SMARTPHONE APPLICATION FOR GLOBAL BIRTH DEFECTS SURVEILLANCE	107
NATIONAL CENTER FOR CHRONIC DISEASE PREVENTION AND HEALTH PROMOTION (NCCDPHP)		108
033	A MOBILE PHONE APPLICATION (“APP”) FOR ADVANCING TEEN PREGNANCY PREVENTION ...	108
NATIONAL CENTER FOR EMERGING ZOOONOTIC AND INFECTIOUS DISEASES (NCEZID)		109
003	DEVELOPMENT OF NANOPARTICLE DENGUE DIAGNOSTIC TESTS	109
004	DEVELOPMENT OF TESTS IN A STANDARDIZED KIT FORMAT FOR DIAGNOSIS OF ARBOVIRAL INFECTIONS IN RESOURCE-LIMITED, PRIMARY HEALTH CARE SETTING	110
005	REDUCING ANTIMICROBIAL RESISTANCE THROUGH IMPROVED USE OF LABORATORY TESTING INFORMATION IN HEALTHCARE FACILITIES	111
NATIONAL CENTER FOR HIV/AIDS, VIRAL HEPATITIS, STD, AND TB PREVENTION (NCHHSTP).....		112
034	DEVELOPMENT OF BIOMEDICAL DEVICES TO ELICIT DURABLE PROTECTIVE IMMUNITY AGAINST HIV	112
035	DEVELOPMENT OF A PORTABLE MULTIPLEX ASSAY FOR DETERMINATION OF RECENT HIV-1 INFECTION.....	112
036	TESTING THE EFFICACY OF COMBINATION HIV PREVENTION STRATEGIES IN NONHUMAN PRIMATES	113
NATIONAL CENTER FOR IMMUNIZATION AND RESPIRATORY DISEASES (NCIRD)		114
025	DEVELOPMENT OF AN INACTIVATED ROTAVIRUS VACCINE FOR USE IN GLOBAL IMMUNIZATION	114
026	THERMOSTABLE DRY MEASLES VACCINE FORMULATION FOR SUBLINGUAL ADMINISTRATION.....	115
OFFICE OF PUBLIC HEALTH PREPAREDNESS AND RESPONSE (OPHPR).....		115
002	IMPROVED METHODS FOR COLLECTION, PRESERVATION, AND TRANSPORTATION OF BIOLOGICAL SPECIMENS.....	116

PART II HUMAN SUBJECTS RESEARCH GUIDANCE AND INFORMATION SUPPLEMENT	118
1. INTRODUCTION	118
2. SCENARIOS.....	118
3. INSTRUCTIONS FOR PREPARING THE SECTION ON PROTECTION OF HUMAN SUBJECTS.....	120
4. INSTRUCTIONS PERTAINING TO NON-EXEMPT HUMAN SUBJECTS RESEARCH	125
4.1 PROTECTION OF HUMAN SUBJECTS	125
4.1.1 RISKS TO HUMAN SUBJECTS	125
4.1.2 ADEQUACY OF PROTECTION AGAINST RISKS.....	126
4.1.3 POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO HUMAN SUBJECTS AND OTHERS....	126
4.1.4 IMPORTANCE OF THE KNOWLEDGE TO BE GAINED.....	126
4.1.5 DATA AND SAFETY MONITORING PLAN	127
4.1.6 CLINICALTRIALS.GOV REQUIREMENTS.....	127
4.2 INCLUSION OF WOMEN AND MINORITIES.....	128
4.2.1 ADDITIONAL INSTRUCTIONS AND REQUIREMENTS WHEN NIH-DEFINED PHASE III CLINICAL TRIALS ARE PROPOSED	130
4.3 INSTRUCTIONS FOR COMPLETING THE TARGETED/PLANNED ENROLLMENT TABLES FOR REPORTING RACE AND ETHNICITY DATA FOR SUBJECTS IN CLINICAL RESEARCH	130
4.4 INCLUSION OF CHILDREN.....	132
5. HUMAN SUBJECTS RESEARCH POLICY.....	133
5.1 PROTECTION OF HUMAN SUBJECTS	133
5.2 VULNERABLE POPULATIONS	134
5.3 DATA AND SAFETY MONITORING PLANS FOR CLINICAL TRIALS	135
5.4 IRB APPROVAL.....	135
5.5 REQUIRED EDUCATION IN THE PROTECTION OF HUMAN RESEARCH PARTICIPANTS	136
5.6 NIH POLICY ON THE INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH	136
5.7 NIH POLICY ON INCLUSION OF CHILDREN.....	136
5.8 NIH POLICY ON REPORTING RACE AND ETHNICITY DATA: SUBJECTS IN CLINICAL RESEARCH	137
5.9 RESEARCH ON TRANSPLANTATION OF HUMAN FETAL TISSUE.....	138
5.10 RESEARCH USING HUMAN EMBRYONIC STEM CELLS.....	138
5.11 CLINICALTRIALS.GOV REQUIREMENTS	138

APPENDIX A — PROPOSAL COVER SHEET - USE FOR PHASE I AND FAST-TRACK PROPOSALS

[MS Word \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.doc\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.doc)

[PDF \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.pdf\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.pdf)

APPENDIX B — ABSTRACT OF RESEARCH PLAN - USE FOR PHASE I, PHASE II, AND FAST-TRACK PROPOSALS

[MS Word \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixB.doc\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixB.doc)

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

APPENDIX C — PRICING PROPOSAL - USE FOR PHASE I, PHASE II AND FAST-TRACK PROPOSALS

[MS Word \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixC.doc\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixC.doc)

[PDF \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixC.pdf\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixC.pdf)

APPENDIX D — PHASE II TECHNICAL PROPOSAL COVER SHEET - USE FOR PHASE II AND FAST-TRACK PROPOSALS

[MS Word \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixD.doc\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixD.doc)

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

APPENDIX E — STATEMENT OF WORK SAMPLE FORMAT - USE FOR PHASE II AND FAST-TRACK PROPOSALS

[MS Word \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixE.doc\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixE.doc)

[PDF \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixE.pdf\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixE.pdf)

APPENDIX F — SUMMARY OF RELATED ACTIVITIES - USE FOR PHASE II AND FAST- TRACK PROPOSALS

[MS Word \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixF.doc\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixF.doc)

[PDF \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixF.pdf\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixF.pdf)

APPENDIX G — PROPOSAL SUMMARY AND DATA RECORD - USE FOR PHASE II AND FAST-TRACK PROPOSALS

[MS Word \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixG.doc\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixG.doc)

[PDF \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixG.pdf\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixG.pdf)

The Appendices noted above are in Microsoft Word and Adobe Acrobat Reader fillable format.

NOTE: Other software packages for completing these proposals may be available from other sources; however, it is essential that the type size and format specifications are met or the proposal may be returned without review.

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.

U. S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

**SOLICITATION OF THE NATIONAL INSTITUTES OF HEALTH AND THE
CENTERS FOR DISEASE CONTROL AND PREVENTION FOR
SMALL BUSINESS INNOVATION RESEARCH
CONTRACT PROPOSALS**

PART I INSTRUCTIONS FOR PREPARING AND SUBMITTING A PROPOSAL

1. PROGRAM DESCRIPTION

1.1 PURPOSE OF SOLICITATION

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](#), and to commercialize the results of that R&D, are encouraged to participate.

This solicitation is for Phase I contract proposals and also for Phase I/Phase II Fast-Track contract proposals (see specific topics listed in [Section 12](#) and awarding components identified as accepting Fast-Track proposals).

Included are instructions for offerors to prepare contract proposals, a description of the proposal review process, and some conditions of a contract award. **Contract proposals will be accepted only if they respond specifically to a research topic within this solicitation (see Section 12 “Research Topics”).** Otherwise, proposals will be returned to the offeror(s) without evaluation.

To apply for an SBIR GRANT rather than an SBIR CONTRACT, use the Omnibus Solicitation of the NIH, CDC, and FDA for Small Business Innovation Research Applications (<http://grants.nih.gov/grants/guide/pa-files/PA-12-088.html>).

The objectives of the SBIR program include stimulating technological innovation in the private sector, strengthening the role of small business in meeting Federal 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 Federal SBIR program is authorized under Public Laws 97-219, 99-443, 102-564, 106-554, and 112-81. The basic design of the NIH/CDC SBIR program is in accordance with the Small Business Administration (SBA) SBIR Program Policy Directive, 2002. This SBIR Contract solicitation strives to encourage scientific and technical innovation in areas specifically identified by the NIH/CDC awarding components shown in Section 1.3. 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.

1.2 THREE PHASE PROGRAM

The SBIR program consists of three separate phases. The award amount and contract’s duration listed below represent the guidelines of the SBIR program and, unless the research topic stating the award listed in Section 12 of the solicitation states otherwise, should be followed.

Phase I: Feasibility; \$150,000; 6 months

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 I awards normally may not exceed \$150,000 for direct costs, indirect costs, and profit (fixed fee) for a period normally not to exceed 6 months.

Phase II: Full R/R&D Effort; \$1,000,000; 2 years

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 II awards normally may not exceed \$1,000,000 for direct costs, indirect costs, and profit (fixed fee) for a period normally not to exceed two years. *Phase I contractors will be informed of the opportunity to apply for Phase II, if not submitted concurrently with the initial Phase I proposal under the Fast-Track procedure (described in Section 5). 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, where appropriate, 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 involve follow-on, non-SBIR funded R&D or production contracts for products or processes intended for use by the U.S. Government.

The competition for SBIR Phase I and Phase II awards satisfies any competition requirement of the Armed Services Procurement Act, the Federal Property and Administrative Services Act, and the competition in Contracting Act. Therefore, an agency that wishes to fund an SBIR Phase III project is not required to conduct another competition in order to satisfy those statutory provisions. As a result, in conducting actions relative to a Phase III SBIR award, 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).

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 former President Bush's [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](#)".

1.3 AWARDING COMPONENTS

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

National Institutes of Health (NIH)

- National Cancer Institute (NCI)
- National Center for Advancing Translational Sciences (NCATS)
- National Heart, Lung, and Blood Institute (NHLBI)
- National Institute of Allergy and Infectious Diseases (NIAID)
- *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)

- National Institute on Drug Abuse (NIDA)

Centers for Disease Control and Prevention (CDC)

- Center for Global Health (CGH)
- National Center for Birth Defects and Developmental Disabilities (NCBDDD)
- National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP)
- National Center for Emerging Zoonotic and Infectious Diseases (NCEZID)
- National Center for HIV/AIDs, Viral Hepatitis, STD, and TB Prevention (NCHHSTP)
- National Center for Immunization and Respiratory Diseases (NCIRD)
- Office of Public Health Preparedness and Response (OPHPR)

1.4 SBIR PROGRAM ELIGIBILITY

Organizational Criteria: Each organization submitting a proposal under the SBIR program must qualify as a small business concern as defined in [Section 3](#). In determining whether an offeror is a small business concern, an assessment will be made of several factors, including whether or not it is independently owned and operated and whether or not it is an affiliate of a larger organization whose employees, when added to those of the offeror organization, exceed 500. In conducting this assessment, all appropriate factors will be considered, including common ownership, common management, and contractual relationships.

In accordance with 13 CFR 121.103, affiliation exists when "... one concern controls or has the power to control the other ... control may be affirmative or negative, ...it does not matter whether control is exercised, so long as the power to control exists." One of the circumstances that would lead to a finding that an organization is controlling or has the power to control another organization involves sharing common office space and/or employees and/or other facilities (e.g., laboratory space). 13 CFR 121.103 also states that control or the power to control exists when "... key employees of one concern organize a new concern ... and serve as its officers, directors, principal stockholders, and/or key employees; and one concern is furnishing or will furnish the other concern with subcontracts, financial or technical assistance, and/or other facilities, whether for a fee or otherwise." Where there is indication of sharing of common employees, a determination will be made on a case-by-case basis of whether or not such sharing constitutes control or the power to control.

Joint ventures and limited partnerships are eligible provided the entity created qualifies as a small business concern as defined in [Section 3](#) of this solicitation.

If it appears that an offeror does not meet eligibility requirements, the NIH/CDC will request an eligibility determination of the organization from the cognizant SBA Government Contracting Area Office. The evaluation of the proposal for scientific merit will be deferred until the SBA provides a determination.

Project Director/Principal Investigator Criteria. The primary employment of the Project Director/Principal Investigator (PD/PI) must be with the offeror at the time of contract award and during the conduct of the proposed project. The PD/PI is the single individual designated in the proposal with responsibility for the scientific and technical direction of the project. Primary employment means that *more than one half of the PD/PI's time* is spent in the employ of the small business concern. *Primary employment with a small business concern precludes full-time employment at another organization.*

In the event that the PD/PI: (1) is a less-than-full-time employee of the small business, (2) is concurrently employed by another organization, or (3) gives the appearance of being concurrently employed by another organization, whether for a paid or unpaid position, at the time of submission of the proposal, *it is essential that documentation be submitted with the proposal to verify his/her eligibility.* If the PD/PI also is employed or appears to be employed by an organization other than the offeror (e.g., a university, a nonprofit research institute, or

another company), a letter must be provided by the *non-offeror organization* confirming that the PD/PI will, if awarded an SBIR contract, become a less-than-half-time employee of such organization and will remain so for the duration of the SBIR project. If the PD/PI is employed by a university, the Dean's Office must provide such a letter. If the PD/PI is employed by another for-profit organization, the corporate official must sign the letter. This documentation is required for every proposal that is submitted, even one that is a revision of a previously submitted proposal.

Multiple Principal Investigators. Offerors may propose a multiple Project Director/Principal Investigator (PD/PI) model to direct the project or program to be supported by the contract. The multiple PD/PI model is intended to supplement, and not replace, the traditional single PI model. Ultimately, the decision to submit a proposal using the multiple PD/PI versus single PD/PI is the decision of the investigators and their organizations. The decision whether to employ multiple PDs/Pis should be consistent with and justified by the scientific goals of the project.

The offeror organization may designate multiple individuals as principal investigators (PD/Pis) who share the authority and responsibility for leading and directing the project, intellectually and logistically. When multiple principal investigators are named, each is responsible and accountable to the offeror organization, or as appropriate, to a collaborating organization for the proper conduct of the project or program including the submission of all required reports. The presence of more than one PD/PI on a proposal or award diminishes neither the responsibility nor the accountability of any individual PD/PI.

For Multiple PD/PI proposals: The first PI listed must be affiliated with the small business concern organization submitting the proposal and will serve as the **Contact PD/PI**. For both SBIR Phase I and SBIR Phase II, the *primary employment of the "Contact PD/PI" must be with the small business concern at the time of award and during the conduct of the proposed project.*

Performance Site Criteria. For both Phase I and Phase II, the research or R&D project activity *must be performed in its entirety in the United States* (see [Part I, Section 3. Definitions](#)).

Access to special facilities or equipment in another organization is permitted (as in cases where the SBIR awardee has entered into a subcontractual agreement with another institution for a specific, limited portion of the research project). However, research space occupied by an SBIR contractor organization must be space that is available to and under the control of the SBIR contractor for the conduct of its portion of the project.

Whenever a proposed SBIR project is to be conducted in facilities other than those of the offeror, a letter must be submitted *with* the proposal stating that leasing/rental arrangements have been negotiated for appropriate research space (i.e., space that will be available to and under the control of the SBIR contractor organization).

This letter must be signed by an *authorized official of the organization whose facilities are to be used for the SBIR project*. It also must include a description of the facilities and, if appropriate, equipment that will be leased/rented to the offeror organization.

Market Research. *The NIH/CDC will not support any market research under the SBIR program.* Neither will it support 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.

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.

1.5 REPORT FRAUD, WASTE AND ABUSE

The Office of Inspector General Hotline accepts tips from all sources about potential fraud, waste, abuse and mismanagement in Department of Health & Human Services programs. The reporting individual should indicate that the fraud, waste and/or abuse concerns an SBIR/STTR grant or contract, if relevant.

[Report Fraud](#)

2. AGENCY CONTACT FOR INFORMATION

Web Site. The NIH SBIR/STTR Web site at <http://sbir.nih.gov> offers electronic access to SBIR solicitations, abstracts of ongoing SBIR projects, the latest updates on the SBIR program, hyperlinks to sources of business assistance, and other useful information.

Technical Questions about Solicitation Topics or Contract Administration. Technical questions about a particular contract topic and general questions on the administration of an SBIR contract should be directed to the appropriate contracting officer listed in [Section 10. Contracting Officers and Addresses for Mailing and Delivery of Proposals](#).

General Questions about the NIH SBIR Program

Matthew E. Portnoy, Ph.D.
NIH SBIR/STTR Program Coordinator
6705 Rockledge Drive
Rockledge I, Room 3540
Bethesda, MD 20892-7963
Phone: 301-435-2688 Fax: 301-480-0146
E-mail: sbir@od.nih.gov

Robert Vinson
NIH SBIR/STTR Program Analyst
6705 Rockledge Drive
Rockledge I, Room 3522
Bethesda, MD 20892-7963
Phone: 301-435-2713 Fax: 301-480-0146
E-mail: sbir@od.nih.gov

General Questions about the CDC SBIR Program

Juliana Cyril, Ph.D., M.P.H.
Deputy Director, Office of Science Quality
Office of the Associate Director for Science
Phone: 404-639-4639
Fax: 404-639-4903
E-mail: JCyril@cdc.gov

Sean David Griffiths, M.P.H.
Science Policy, Office of Science Quality
Office of the Associate Director for Science
Phone: 404-639-4641
Fax: 404-639-4903
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Listserv. The NIH maintains a Listserv e-mail broadcast service. To stay in touch with SBIR opportunities and receive notices about upcoming conferences and solicitations, subscribe by sending an e-mail to LISTSERV@LIST.NIH.GOV with the following text in the message body: subscribe SBIR-STTR your name. (LISTSERV will get your e-mail address from the "From:" address of your e-mail message.)

3. DEFINITIONS

Affiliate. This term has the same meaning as set forth in 13 CFR part 121 – Small Business Size Regulations, §121.103, “*What is affiliation?*”

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 21 years. 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.

DHHS Regulations (45 CFR part 46, Subpart D, Sec.401-409 (<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartd>)) provide additional protections for children involved as subjects in research, based on this definition: "Children are persons who have not attained the legal age for consent to treatments or procedures involved in research, under the applicable law of the jurisdiction in which the research will be conducted." Generally, state laws define what constitutes a “child.” Consequently, the age at which a child's own consent is required and sufficient to participate in research will vary according to state law. For example, some states consider a person age 18 to be an adult and therefore one who can provide consent without parental permission.

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 studies, or (d) development of new technologies.

(2) Epidemiologic and Behavioral Studies.

(3) Outcomes Research and Health Services Research.

Studies falling under Exemption 4 for human subjects research are not considered clinical research by this definition.
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Clinical Trial. The NIH defines a clinical trial as a prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices).

Clinical trials are used to determine whether new biomedical or behavioral interventions are safe, efficacious, and effective.

Behavioral human subjects research involving an intervention to modify behavior (diet, physical activity, cognitive therapy, etc.) fits this definition of a clinical trial.

Human subjects research to develop or evaluate clinical laboratory tests (e.g. imaging or molecular diagnostic tests) might be considered to be a clinical trial if the test will be used for medical decision making for the subject or the test itself imposes more than minimal risk for subjects.

Biomedical clinical trials of experimental drug, treatment, device or behavioral intervention may proceed through four phases:

- *Phase I* clinical trials test a new biomedical intervention in a small group of people (e.g., 20-80) for the first time to evaluate safety (e.g., to determine a safe dosage range and to identify side effects).

- *Phase II* clinical trials study the biomedical or behavioral intervention in a larger group of people (several hundred) to determine efficacy and to further evaluate its safety.
- *Phase III* studies investigate the efficacy of the biomedical or behavioral intervention in large groups of human subjects (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions as well as to monitor adverse effects, and to collect information that will allow the intervention to be used safely.
- *Phase IV* studies are conducted after the intervention has been marketed. These studies are designed to monitor effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use.
- *NIH-Defined Phase III Clinical Trial.* For the purpose of the Guidelines an NIH-defined Phase III clinical trial is a broadly based prospective Phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or controlled intervention or comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care. The definition includes pharmacologic, non-pharmacologic, and behavioral interventions given for disease prevention, prophylaxis, diagnosis, or therapy. Community trials and other population-based intervention trials are also included.

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

- (1) 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
- (2) 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 DHHS 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>.)

Commercialization. The process of developing markets and producing and delivering products for profit (whether by the originating party or by others). As used here, commercialization includes both government and private sector 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, grantees 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.

Data and Safety Monitoring Plan. For each clinical trial, NIH requires a data and safety monitoring plan that will provide oversight and monitoring to ensure the safety of participants and the validity and integrity of the data. The level of monitoring should be commensurate with the risks and the size and complexity of the clinical trial. A detailed data and safety monitoring plan must be submitted to the contractor's IRB and subsequently to the funding IC for approval prior to the accrual of human subjects. The reporting of Adverse Events must be reported to the IRB, the NIH funding Institute or Center, and other required entities. This policy requirement is in addition to any monitoring requirements imposed by 45 CFR part 46 (<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>).

Data and Safety Monitoring Board (DSMB). NIH requires the establishment of a Data and Safety Monitoring Board (DSMB) for multi-site clinical trials involving interventions that entail potential risk to the participants, *and generally for Phase III clinical trials*.

8(a) Small Business Concern. A small business concern that is owned and controlled by a socially and economically disadvantaged individual and that has been approved by the U.S. Small Business Administration as part of the 8(a) Business Development Program (see [13 CFR 124](#)).

Essentially Equivalent Work. This term is meant to identify "scientific overlap," which occurs when: (1) substantially the same research is proposed for funding in more than one contract proposal or grant application submitted to the same Federal agency; OR (2) substantially the same research is submitted to two or more different Federal agencies for review and funding consideration; OR (3) a specific research objective and the research design for accomplishing that objective are the same or closely related in two or more proposals or awards, regardless of the funding source.

Exemptions. The six categories of research exempt from the DHHS human subject regulations are:

Exemption 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.

Exemption 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.

Exemption 2 for research involving survey or interview procedures or observation of public behavior, does not apply to research with children (see 45 CFR part 46, Subpart D (<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartd>)), except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

Exemption 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.

Exemption 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.

The human subjects regulations decision charts

(<http://www.hhs.gov/ohrp/policy/checklists/decisioncharts.html>) of the Office for Human Research Protection (OHRP) will determine whether the research falls under the human subjects regulations and if so, whether it meets the criteria for Exemption 4. The NIH Office of Extramural Research Web site also contains information that is helpful for determining whether human subjects research meets the criteria for Exemption 4. See <http://grants.nih.gov/grants/policy/hs/index.htm>.

Research that meets the criteria for Exemption 4 is not considered “clinical research” as defined by NIH. Therefore the NIH policies for inclusion of women, minorities and children in clinical research, and targeted/planned enrollment tables, do not apply to research projects covered by Exemption 4.

Exemption 5: Research and demonstration projects that are conducted by or subject to the approval of Department or Agency heads and that 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.

Exemption 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.

Feasibility. The extent to which a study or project may be done practically and successfully.

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

Gender. Refers to the classification of research subjects into either or both of two categories: male and female. In some cases, representation is unknown, because gender composition cannot be accurately determined (e.g., pooled blood samples or stored specimens without gender designation).

HubZone Small Business Concern. A small business concern that appears on the List of Qualified HUBZone Small Business Concerns maintained by the Small Business Administration (13 CFR 126.103). HUBZone Small Business Concerns are located in historically underutilized business zones, in an effort to increase employment opportunities, investment, and economic development in those areas.

Human Subjects. The DHHS regulations “Protection of Human Subjects” ([45 CFR part 46](http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html) (<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>), 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 systems.

Innovation. Something new or improved, including research for: (1) development of new technologies, (2) refinement of existing technologies, or (3) development of new applications for existing technologies. For the purposes of PHS programs, an example of “innovation” would be new medical or biological products for improved value, efficiency, or costs.

Intellectual Property. The separate and distinct types of intangible property that are referred to collectively as “intellectual property,” including but not limited to: patents, trademarks, copyrights, trade secrets, SBIR technical data (as defined in this section), ideas, designs, know-how, business, technical and research methods, and other types of intangible business assets, and including all types of intangible assets either proposed or generated by an SBC as a result of its participation in the SBIR program.

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)).

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

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: <http://www.hhs.gov/ohrp/policy/cdebiol.html>.)

Joint Venture. An association of concerns with interests in any degree or proportion by way of contract, express or implied, consorting to engage in and carry out a single specific business venture for joint profit, for which purpose they combine their efforts, property, money, skill, or knowledge, but not on a continuing or permanent basis for conducting business generally. A joint venture is viewed as a business entity in determining power to control its management.

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:

1. *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.
2. *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.
3. *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.

- 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.
4. *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.

Obtains. In general, obtaining identifiable private information or identifiable specimens includes, but is not limited to:

- (a) observing or recording private behavior;
- (b) using studying, or analyzing for research purposes identifiable private information or identifiable specimens provided to investigators from any source; and
- (c) using, studying, or analyzing for research purposes identifiable private information or identifiable specimens already in the possession of the investigators.

Principal Investigator, Program Director, or Project Director (PD/PI). The individual(s) designated by the applicant organization to have the appropriate level of authority and responsibility to direct the project or program to be supported by the award. The applicant organization may designate multiple individuals as principal investigators (PDs/PIs) who share the authority and responsibility for leading and directing the project, intellectually and logistically. When multiple principal investigators are named, each is responsible and accountable to the applicant organization, or as appropriate, to a collaborating organization for the proper conduct of the project or program including the submission of all required reports. The presence of more than one PD/PI on an application or award diminishes neither the responsibility nor the accountability of any individual PD/PI.

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))

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

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; or
- 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.

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

SBIR Technical Data Rights. The rights a small business concern 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.

Senior/Key Personnel. The PD/PI and other individuals who contribute to the scientific development or execution of the project in a substantive, measurable way, whether or not salaries or compensation are requested under the contract.

Typically these individuals have doctoral or other professional degrees, although individuals at the masters or baccalaureate level should be included if their involvement meets the definition of senior/key personnel. Consultants and those with a postdoctoral role should also be included if they meet the definition of senior/key personnel. Senior/key personnel must devote measurable effort to the project whether or not salaries or compensation are requested--"zero percent" effort or "as needed" are not acceptable levels for those designated as senior/key personnel.

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 veteran. Status as a Service-Disabled Veteran-Owned Small Business Concern is determined in accordance with 13 CFR Parts 125.8 through 125.13; also see [19.307](#).

Significant Difference. For purposes of NIH policy, a "significant difference" is a difference that is of clinical or public health importance, based on substantial scientific data. This definition differs from the commonly used "statistically significant difference," which refers to the event that, for a given set of data, the statistical test for a difference between the effects in two groups achieves statistical significance. Statistical significance depends upon the amount of information in the data set. With a very large amount of information, one could find a statistically significant, but clinically small difference that is of very little clinical importance. Conversely, with less information one could find a large difference of potential importance that is not statistically significant.

Small Business Concern. A concern that, on the date of award for both Phase I and Phase II funding agreements:

1. is organized for profit, with a place of business located in the United States, which operates primarily within the United States or which makes a significant contribution to the United States economy through payment of taxes or use of American products, materials or labor;
2. is in the legal form of an individual proprietorship, partnership, limited liability company, corporation, joint venture, association, trust or cooperative, except that where the form is a joint venture, there can be no more than 49 percent participation by foreign business entities in the joint venture;
3. is at least 51 percent owned and controlled by one or more individuals who are citizens of, or permanent resident aliens in, the United States, except in the case of a joint venture, where each entity to the venture must be 51 percent owned and controlled by one or more individuals who are citizens of, or permanent resident aliens in, the United States; and
4. has, including its affiliates, not more than 500 employees.

Control can be exercised through common ownership, common management, and contractual relationships. The term "affiliates" is defined in greater detail in 13 CFR 121, as is the process for calculating "number of employees."

Business concerns include, but are not limited to, any individual (sole proprietorship), partnership, corporation, joint venture, association, or cooperative. Further information may be obtained by contacting the Small Business Administration Size District Office at <http://sba.gov/size>.

Socially and Economically Disadvantaged Individual. A member of any of the following groups: Black Americans; Hispanic Americans; Native Americans; Asian-Pacific Americans; Subcontinent Asian Americans; other groups designated from time to time by the Small Business Administration (SBA) to be socially disadvantaged; or any other individual found to be socially and economically disadvantaged by SBA pursuant to Section 8(a) of the Small Business Act, 15 U.S.C. 637(a).

Socially and Economically Disadvantaged Small Business Concern. A socially and economically disadvantaged small business concern is one that is at least 51% owned by (a) an Indian tribe or a native Hawaiian organization, or (b) one or more socially and economically disadvantaged individuals; **and** whose management and daily business operations are controlled by one or more socially and economically disadvantaged individuals.

Subcontract. Any agreement, other than one involving an employer-employee relationship, entered into by a Federal Government prime contractor calling for supplies or services required solely for the performance of the prime contract or another subcontract.

United States. The 50 states, territories and possessions of the U.S., Commonwealth of Puerto Rico, Trust Territory of the Pacific Islands, and District of Columbia.

Women-Owned Small Business Concern. A small business concern that is at least 51% owned by a woman or women who also control and operate it. "Control" in this context means exercising the power to make policy decisions. "Operate" in this context means being actively involved in the day-to-day management.

4. PHASE I PROPOSAL PREPARATION INSTRUCTIONS AND REQUIREMENTS

4.1 LIMITATIONS ON LENGTH OF PROPOSAL

SBIR Phase I proposals shall not exceed 50 single-sided, single-spaced pages for the entire proposal, all inclusive [including all pages, cover sheet(s), tables, CVs, resumes, references, pictures/graphics, and all enclosures, appendices or attachments, etc.]. 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). Two sided pages count as two pages. There are NO exclusions to the page limit – the complete proposal shall not exceed 50 pages. Pages in excess of the page limitation will be removed from the proposal and will not be read, considered, or evaluated.

4.2 TECHNICAL PROPOSAL FORMAT AND CONTENT REQUIREMENTS

4.2.1 Technical Proposal Cover Sheet - Complete the form identified as Appendix A ([MS Word \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.doc\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.doc) | [PDF \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.pdf\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.pdf)), and use it as the first page of the proposal. *No other cover sheet should be used.*

If submitting a proposal reflecting Multiple Project Directors/Principal Investigators (PDs/Pis), the individual designated as the Contact PI should be entered here.

- **Topic Number.** Provide the appropriate numerical designator of the research topic for which your proposal is being submitted. If your proposal is responsive to a subtopic, provide both the topic and subtopic numbers. (A numerical or alphabetical designator precedes each topic and subtopic.)
- **Project Title.** Select a title that reflects the substance of the project. Do not use the title of the topic that appears in the solicitation.

4.2.2 Abstract of Research Plan - Complete the form identified as Appendix B ([MS Word \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixB.doc\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixB.doc) | [PDF \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixB.pdf\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixB.pdf)), and insert it as the second page of each proposal. Do not include any proprietary information as abstracts of successful proposals will be published by NIH. 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.

4.2.3 Research Plan

Beginning on page three of the proposal, discuss in the order indicated the following elements:

- a. **Identification and Significance of the Problem or Opportunity.** Provide a clear statement of the specific technical problem or opportunity addressed.
- b. **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.
- c. **Work Plan.** 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. For specific guidance and instructions related to Human Subjects research, please see the section entitled, "[Human Subjects Research and Protection from Risk](#)" and the "[Human Subjects Research Guidance and Information Supplement](#)."
- d. **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.*
- e. **Relationship with Future R&D.**
 1. State the anticipated results of the proposed approach, assuming project success.
 2. Discuss the significance of the Phase I effort in providing a foundation for the Phase II R/R&D effort.
- f. **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.
- g. **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.

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.

- h. **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 from each individual confirming his/her role in the project must be included. Small business concerns must perform a minimum of

two-thirds for Phase I of the research and/or analytical effort (i.e., total contract price less profit/fee) conducted under the resulting contract. The Contracting Officer must approve deviations from this requirement in writing after consultation with the agency SBIR Program Manager/Coordinator.

- i. **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.

Whenever a proposed SBIR project is to be conducted in facilities other than those of the offeror, a letter must be submitted *with* the proposal stating that leasing/rental arrangements have been negotiated for appropriate research space (i.e., space that will be available to and under the control of the SBIR contractor organization).

This letter must be signed by an *authorized official of the organization whose facilities are to be used for the SBIR project.* It also must include a description of the facilities and, if appropriate, equipment that will be leased/rented to the offeror organization.

List the most important equipment items already available for this project, noting location and pertinent capabilities of each.

Any equipment and products purchased with Government funds shall be American-made, to the extent possible.

Title to Equipment. 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 research proposal involving the collection of information, such as surveys or interviews, of 10 or more public respondents will require clearance by the U.S. Office of Management and Budget. Therefore, it is not practical to propose such an activity for Phase I, which normally has only a six-month duration.

4.2.4 Current Awards and Pending Proposals/Applications

A small business concern may not submit both a contract proposal and a grant application for essentially the same project to the same or different awarding component(s) of the NIH/CDC. The only exception would be the submission of a grant application after a contract proposal has been evaluated and is no longer being considered for award. A firm that receives a Phase I SBIR contract may submit a Phase II grant application and vice versa.

A Phase I contractor is eligible to submit a Phase II contract or grant proposal. Phase I contractors will be informed of the opportunity to apply for Phase II.

While it is permissible, with proposal notification, to submit identical proposals or proposals containing a significant amount of essentially equivalent work (as defined in this solicitation) 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 before award.

If a firm elects to submit identical proposals or proposals containing a significant amount of essentially equivalent work under other Federal program solicitations, include a statement in each such proposal indicating the information requested in items a-j set forth below.

In addition, provide the information requested in items a-j on (1) active funding through contracts, grants, and cooperative agreements from public or private sponsors; (2) contract proposals and grant and cooperative agreement applications pending review or funding; and (3) contract proposals and grant and cooperative agreement applications about to be submitted.

- a. Name and address of the funding source.
- b. Type of award (contract, grant, cooperative agreement) and identifying number.
- c. Title of research project.
- d. Name and title of Principal Investigator(s) or Project Manager(s).
- e. Hours per week on the project by the Principal Investigator(s) or Project Manager(s).
- f. Annual costs proposed or awarded.
- g. Entire period of support.
- h. Date of proposal/application submission or date of award.
- i. Title, number, and date of solicitations under which proposals or applications were submitted or awards received.
- j. The specific applicable research topic for each SBIR proposal or application submitted or award received. *Specifically identify those projects that are SBIR.*

4.2.5 Prior SBIR Phase II Awards

If the small business concern has received more than 15 Phase II awards in the prior 5 fiscal years, submit name of awarding agency, date of award, funding agreement number, amount, topic or subtopic title, follow-on agreement amount, source, and date of commitment and current commercialization status for each Phase II.

This information must be submitted with the proposal.

4.2.6 Proposed Cost Breakdown

Complete the form identified as Appendix C (Contract Pricing Proposal) ([MS Word \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixC.doc\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixC.doc) | [PDF \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixC.pdf\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixC.pdf)). The cost breakdown should appear as the last section of the proposal. *If some items on this form do not apply to the proposed project, they need not be completed.*

- Under “Government Solicitation No.,” enter “PHS 2013-1.”
- If supplies are proposed, provide the quantities and the price per unit.
- Under “Direct Labor,” *list all senior/key personnel by name*. Support personnel may be consolidated into categories or labor classes, e.g., research assistants or data processing clerks.
- Cost for travel funds must be justified and related to the needs of the project. If travel is proposed, provide the following details on “Exhibit A – Supporting Schedule”: destination(s); duration of trip(s); number of travelers; and cost per trip, broken down by cost elements, e.g., airfare, lodging, and meals.
- If consultants are proposed, provide name(s), rate(s), and number of hours/days.
- If a subcontract is proposed, provide the same type of detailed cost breakdown as required for Appendix C. *Also provide a copy of the subcontractual agreement.*
- Use “Exhibit A – Supporting Schedule” to itemize and justify all major cost elements. If more space is needed, use Page 3 of Appendix C.
- Small business concerns must perform a minimum of two-thirds of the research and/or analytical effort (i.e., total contract price less profit/fee) conducted under the resulting contract. The Contracting Officer must approve deviations from this requirement in writing after consultation with the agency SBIR Program Manager/Coordinator.

4.2.7 Streamlining the Contracting Process

The NIH uses special “*Just-in-Time*” procedures that are designed to reduce the administrative burden on offerors without compromising the information needed during the initial evaluation of proposals. Certain documents that would previously have been required for submission with the Phase II proposal will be requested at a later stage in the evaluation process. The following documentation is part of the “Just-in-Time” procedures and offerors who elect to submit proposals under the “*Fast-Track*” initiative below are not required to submit this documentation with their initial Phase II business proposal:

- **Travel Policy.** The offeror's written travel policy.
- **Annual Financial Report.** The offeror's most recent annual financial report.
- **Total Compensation Plan.** Salary and fringe benefits of professional employees under service contracts.
- **Data Substantiating the Costs and Prices Proposed.** That is, payroll documentation, vendor quotes, invoice prices, etc.

4.2.8 Requirement for Adequate Assurance of Protection of Human Subjects

The DHHS regulations for the Protection of Human Subjects, 45 CFR 46 (as amended), provide a systematic means, based on established ethical principles, to safeguard the rights and welfare of individuals who participate as subjects in research activities supported or conducted by the DHHS. *The requirement is that an approved assurance of compliance with the regulations must be on file with the Office for Human Research Protections (OHRP), DHHS (<http://www.hhs.gov/ohrp>) before a DHHS award can be made.*

Neither an Institutional Review Board (IRB) review nor an OHRP-approved Assurance is required at the time the proposal is submitted or at the time that the proposals are peer reviewed.

Human Subjects Research and Protection from Risk

Instructions and Required Information

This information must be submitted with the proposal.

Create a section heading entitled “**Human Subjects Research.**” Place it immediately following the “Research Plan” section of the proposal.

In the Human Subjects Research section, you must provide sufficient information for reviewers to determine that the proposed research meets (1) the requirements of the DHHS regulations to protect human subjects from research risks ([45 CFR part 46 \(http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html\)](http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html)), (2) the requirements of NIH policies for data and safety monitoring of clinical trials, and (3) the requirements of NIH policies on inclusion of women, minorities, and children.

Provided in the [Human Subjects Research Guidance and Information Supplement](#) are six possible research scenarios, and links to the instructions for providing information on human subjects protection information and the inclusion of women, minorities, and children specific to each scenario. All research will fall into one of these six scenarios. Determine which scenario the proposed research falls into, then go to the specific instructions applicable to that scenario in Section 3 of the Supplement. Where appropriate, Section 3 provides instructions on addressing the Inclusion of Women and Minorities, the Targeted/Planned Enrollment Table, and the Inclusion of Children. All definitions related to human subjects research are linked to text found in Part I, Section 3, Definitions. Section 5 of this Part includes descriptions of and links to the DHHS Human Subjects Protections regulations and NIH policies that apply to clinical research.

Much of the information on the protection of human subjects that you are required to provide in this section is identical to information that will be required for IRB review.

4.2.9 Requirement for Adequate Assurance of Compliance with the PHS Policy on Humane Care and Use of Laboratory Animals

Instructions and Required Information

This information must be submitted with the proposal.

Create a section heading entitled “**Vertebrate Animals.**” Place it immediately following the “Research Plan” section of the proposal (or after Human Subjects Research section, if applicable).

Under the Vertebrate Animals heading, address the following five points. In addition, when research involving vertebrate animals will take place at collaborating site(s) or other performance site(s), provide this information before discussing the five points. Although no specific page limitation applies to this section of the proposal, be succinct.

1. Provide a detailed description of the proposed use of the animals in the work outlined in the Research Design and Methods section. Identify the species, strains, ages, sex, and numbers of animals to be used in the proposed work.
2. Justify the use of animals, the choice of species, and the numbers to be used. If animals are in short supply, costly, or to be used in large numbers, provide an additional rationale for their selection and numbers.
3. Provide information on the veterinary care of the animals involved.
4. Describe the procedures for ensuring that discomfort, distress, pain, and injury will be limited to that which is unavoidable in the conduct of scientifically sound research. Describe the use of analgesic, anesthetic, and tranquilizing drugs and/or comfortable restraining devices, where appropriate, to minimize discomfort, distress, pain, and injury.
5. Describe any method of euthanasia to be used and the reasons for its selection. State whether this method is consistent with the recommendations of the Panel on Euthanasia of the American Veterinary Medical Association. If not, present a justification for not following the recommendations.

Guidance and Additional Instructions

NIH no longer requires Institutional Animal Care and Use Committee approval of the proposed research before NIH peer review of a proposal (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-064.html>).

In August, 2002 NIH announced an IACUC “Just-in-Time” process for applications submitted for the October 1, 2002 deadline or other deadlines where the applications had a May/June 2003 Council review. The PHS policy requirement that no award may be made without an approved Assurance and without verification of IACUC approval remains in effect. The new policy gave institutions flexibility in the timing of IACUC review relative to the submission of a proposal and the verification of IACUC review. The policy does not require that IACUC approval be deferred. Institutional officials retain the discretion to require IACUC approval prior to NIH peer review in circumstances of their choosing if deemed necessary. As part of the NIH peer review process, the scientific review group will continue to address the adequacy of animal usage and protections in the review of a proposal and will continue to raise any concerns about animal welfare issues. Verification of IACUC approval will be required in a “Just-in-Time” fashion prior to award.

The *PHS Policy on Humane Care and Use of Laboratory Animals* 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 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. This policy does not affect applicable state or local laws or regulations

that impose more stringent standards for the care and use of laboratory animals. All institutions are required to comply, as applicable, with the Animal Welfare Act as amended (7 U.S.C. 2131 et sec.) and other Federal statutes and regulations relating to animals. These documents are available from the Office of Laboratory Animal Welfare, National Institutes of Health, Bethesda, MD 20892, (301) 496-7163.

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."

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. 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.

4.3 LIMITATIONS ON USE OF APPROPRIATED FUNDS

Every year since 1990 Congress has legislatively mandated a provision limiting the direct salary that an individual may receive under an NIH grant or contract.

Salary Rate Limitation

For FY 2012, the *Consolidated Appropriations Act, 2012* (Public Law 112-74) signed into law on December 23, 2011, restricts the amount of direct salary to Executive Level II of the Federal Executive Pay scale. The Executive Level II salary is \$179,700.

Anti-Lobbying

"(a) No part of any appropriation contained in this Act shall be used, other than for normal and recognized executive-legislative relationships, for publicity or propaganda purposes, for 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. (b) No part of any appropriation contained in this Act shall be used to pay the salary or expenses of any grant or contract recipient, or agent acting for such recipient, related to any activity designed to influence legislation or appropriations pending before the Congress or any State legislature."

Restriction on Distribution of Sterile Needles

"None of the funds contained in this Act may be used to distribute any needle or syringe for the purpose of preventing the spread of blood borne pathogens in any location that has been determined by the local public health or local law enforcement authorities to be inappropriate for such distribution."

Acknowledgment of Federal Funding

"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, all grantees receiving Federal funds included in this Act, including but not limited to State and local governments and recipients of Federal research grants, shall clearly state: (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) percentage and dollar amount of the total costs of the project or program that will be financed by non-governmental sources."

Restriction on Abortions

“(a) None of the funds appropriated under this Act, and none of the funds in any trust fund to which funds are appropriated in this Act, shall be expended for any abortion. (b) None of the funds appropriated in this Act, and none of the funds in any trust to which funds are appropriated in this Act, shall be expended for health benefits coverage that includes coverage of abortions. (c) The term “health benefits coverage” means the package of services covered by a managed care provider or organization pursuant to a contract or other arrangement.”

Ban on Funding of Human Embryo Research

“(a) None of the funds made available in this Act may be used for: (1) the creation of a human embryo or embryos for research purposes; or (2) 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. 289g(b)). (b) For purposes of this section, 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.”

Limitation on Use of Funds for Promotion of Legalization of Controlled Substances

“(a) None of the funds made available in this Act may be used for any activity that promotes the legalization of any drug or other substance included in schedule I of the schedules of controlled substances established by section 202 of the Controlled Substances Act except for normal and recognized executive-congressional communications. (b) The limitation in subsection (a) shall not apply when 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.”

NIH Public Access Requirement

“The Director of the National Institutes of Health shall require that all investigators funded by the NIH submit or have submitted for them to the National Library of Medicine’s PubMed Central an electronic version of their final, peer-reviewed manuscripts upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication: *Provided*, that the NIH shall implement the policy in a manner consistent with copyright law.”

Further information on the implementation of NIH’s Public Access Requirement is available in NIH Guide Notice [NOT-OD-08-033 \(http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-033.html\)](http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-033.html) published on January 11, 2008.

Dissemination of False or Deliberately Misleading Scientific Information

“None of the funds made available in this Act may be used to disseminate scientific information that is deliberately false or misleading.”

While this mandate has not been included in past appropriations acts, it is similar to existing requirements concerning research integrity, fraud, and false claims, and as such, NIH does not expect this new requirement to impact significantly the business practices at most institutions. Grantees and contractors are advised to review their implementation of the PHS Policies on Research Misconduct contained in 42 CFR Part 93 and the Civil False Claims Act (31 U.S.C. 3729(a)), Criminal False Claims Act (18 U.S.C. 287 and 1001), and Program Fraud and Civil Remedies Act (31 U.S.C. 3801 et seq.).

Restriction on Employment of Unauthorized Alien Workers

“None of the funds in this Act may be used to employ workers described in section 274A(h)(3) of the Immigration and Nationality Act.”

While this mandate has not been included in past appropriations acts, it is similar to existing requirements contained in the Immigration and Nationality Act (18 U.S.C. 1324a), and as such, NIH does not expect this new

requirement to impact significantly the business practices at most institutions. Grantees and contractors are advised to review their current hiring and employment practices to ensure compliance.

5. “FAST-TRACK” INITIATIVE

(Applicable Only to Proposals Submitted to NIH)

The “Fast-Track” initiative is a parallel review option available to those small business concerns (offeror organizations) whose proposals satisfy additional criteria that enhance the probability of the project's commercial success. This initiative is applicable only to NIH and only if an awarding component indicates it is accepting Fast-Track proposals for a particular topic. (Refer to [Section 12. “Research Topics,”](#) for notation.)

The Fast-Track initiative is an opportunity for small business concerns to submit both a Phase I and Phase II proposal for concurrent peer review. This initiative also has the potential to minimize any funding gap between Phase I and Phase II.

Phase I and Phase II are considered separate funding agreements under the Fast-Track Initiative. Therefore, Phase I Fast-Track awardees must recertify that they meet all of the eligibility criteria for an SBIR award prior to issuance of the Phase II award.

Fast-Track Proposal Process

To identify the proposals as Fast-Track, check the box marked “Yes” next to the words “Fast-Track Proposal” shown on the Phase I Proposal Cover Sheet, Appendix A ([MS Word \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.doc\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.doc) | [PDF \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.pdf\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.pdf)).

The small business concern must submit both a Phase I and a Phase II proposal for concurrent initial peer review and evaluation. The Fast-Track proposal must consist of the following parts:

1. **Phase I Proposal.** Prepared in accordance with Section 4. Phase I Proposal Preparation Instructions and Requirements, and addressing all factors stated in the evaluation criteria (Section 7) for Phase I proposals.
2. **Phase II Proposal.** Prepared in accordance with Section 6, Fast-Track Phase II Proposal Preparation Instructions and Requirements and addressing all factors stated in the evaluation criteria (Section 7) for Phase II proposals.
3. **Commercialization Plan.** Prepared in accordance with instructions in Section 6.2.

The Phase I and Phase II proposals are separate proposals and will be scored individually.

Fast-Track Phase II proposals may be funded following submission of the Phase I final report, and a determination that the Phase I objectives were met, feasibility was demonstrated, and funds are available.

6. FAST-TRACK PHASE II PROPOSAL PREPARATION INSTRUCTIONS AND REQUIREMENTS

6.1 LIMITATIONS ON LENGTH OF PROPOSAL

SBIR Phase II proposals shall not exceed a total of 150 single-spaced pages, including all enclosures and attachments. Pages should be of standard size (8.5” x 11”) with a font size of 11 points (or larger). Excluded from the page limitation are cover letters and letters from collaborators and consultants. Pages in excess of the page limitation will be removed from the proposal, and will not be read, considered, or evaluated.

6.2 TECHNICAL PROPOSAL FORMAT AND CONTENT REQUIREMENTS

1. **Phase II Technical Proposal Cover Sheet** - Use Appendix D ([MS Word \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixD.doc\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixD.doc) | [PDF \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixD.pdf\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixD.pdf)).
2. **Table of Contents**
3. **Abstract of the Research Plan** - Use Appendix B ([MS Word \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixB.doc\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixB.doc) | [PDF \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixB.pdf\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixB.pdf)). State the broad, long-term objectives and specific aims. Do not include any proprietary information. Briefly and concisely describe the research design and methods for achieving these goals.
4. **Anticipated Results of Phase I Effort** - Briefly discuss and summarize the objectives of your Phase I effort, the research activities to be carried out, and the anticipated results.
5. **Research Plan**
 - a. *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. Offerors using [Human Subjects](#) or [Vertebrate Animals](#) in their research should refer to the specific instructions provided in this solicitation.
 - b. *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.*
 - c. *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.)*
 - d. *Other considerations* - Provide a brief narrative of any unique arrangements, safety procedures in place, animal welfare issues, human subjects, etc. Note: If the research plan includes the use of human subjects or animals, refer to paragraphs [Sections 4.2.8 and 4.2.9](#) of this solicitation for further guidance.
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.

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, etc.), this must be explained in the proposal. See http://grants.nih.gov/grants/policy/data_sharing/data_sharing_faqs.htm.

1. *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 \(http://grants.nih.gov/grants/policy/data_sharing/\)](http://grants.nih.gov/grants/policy/data_sharing/) or <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html>.

2. *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 \(http://grants.nih.gov/grants/policy/model_organism/index.htm\)](http://grants.nih.gov/grants/policy/model_organism/index.htm), and [NIH Guide NOT-OD-04-042 \(http://grants.nih.gov/grants/guide/notice-files/NOT-OD-04-042.html\)](http://grants.nih.gov/grants/guide/notice-files/NOT-OD-04-042.html).

3. *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 \(http://www.nih.gov/grants/guide/notice-files/NOT-OD-07-088.html\)](http://www.nih.gov/grants/guide/notice-files/NOT-OD-07-088.html), and <http://gwas.nih.gov/>.

e. *Appendices*

(1) **Work Statement** – The Contracting Officer may require the offeror to develop a Statement of Work similar in format to the sample in Appendix E ([MS Word \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixE.doc\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixE.doc) | [PDF \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixE.pdf\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixE.pdf)). Create this from your detailed approach and methodology. It will be incorporated into the final contract document. Do not include proprietary information.

(2) **Commercialization Plan** – Required for the Phase II portion of ALL Fast-Track proposals.

The Phase II portion of Fast-Track proposals must include a succinct Commercialization Plan. The Commercialization Plan is limited to *12 pages*. Be succinct. There is no requirement for offerors to use the maximum allowable pages allotted to the Commercialization Plan.

Create a section entitled, “Commercialization Plan,” and 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:
- Letter of commitment of funding.
 - Letter of intent or evidence of negotiations to provide funding, should the Phase II project be successful and the market need still exist.
 - Letter of support for the project and/or some in-kind commitment, e.g., to test or evaluate the innovation.
 - Specific steps you are going to take to secure Phase III funding.
- f. **Production and Marketing Plan.** Describe how the production of your product/service will occur (e.g., in-house manufacturing, contract manufacturing). Describe the steps you will take to market and sell your product/service. For example, explain plans for licensing, internet sales, etc.
- g. **Revenue Stream.** Explain how you plan to generate a revenue stream for your company should this project be a success. Examples of revenue stream generation include, but are not limited to, manufacture and direct sales, sales through value added resellers or other distributors, joint venture, licensing, service. Describe how your staffing will change to meet your revenue expectations.

Offerors are *encouraged to seek commitment(s) of funds and/or resources from an investor or partner organization for commercialization* of the product(s) or service(s) resulting from the SBIR contract.

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

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

6. **Summary of Related Activities** - Use Appendix F ([MS Word \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixF.doc\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixF.doc) | [PDF \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixF.pdf\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixF.pdf)).
7. **Number of Copies** - Submit an original and 9 copies.

6.3 BUSINESS PROPOSAL FORMAT AND CONTENT REQUIREMENTS

1. **Cover Page** - Use NIH Form 2043, Proposal Summary and Data Record, Appendix G ([MS Word \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixG.doc\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixG.doc) | [PDF \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixG.pdf\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixG.pdf)).
2. **Proposed Cost Breakdown – For Phase I**, use Appendix C ([MS Word \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixC.doc\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixC.doc) | [PDF \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixC.pdf\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixC.pdf)). Explain the basis for all costs and submit documentation to support all proposed costs. Prepare a separate Appendix C for each year of the contract and a summary of the entire project. **For Phase II Fast-Track**, use Appendix C. Prepare a separate Appendix C for each year of the contract and a summary of the entire project.
3. **NIH Policy on Threshold for Negotiation of Facilities and Administrative (F&A)/Indirect Costs (IDC) Rates for SBIR proposals** - SBIR offerors who propose in the contract an F&A/IDC rate of 40 percent of total direct costs or less will not be required to provide further justification at the time of award, and F&A/IDC costs will be awarded at the requested rate. However, the Division of Financial Advisory Services (DFAS) will retain the authority to require well-documented proposals for F&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) should be used when calculating proposed F&A/ID 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 F&A/ID 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 F&A/ID costs to projects cannot exceed the awarded rate unless the SBC negotiates an indirect cost rate(s) with DFAS. DFAS will negotiate F&A/IDC rates for SBCs receiving awards if the requested rate is greater than 40 percent of total direct costs.
4. **Number of Copies** - Submit an original and 5 copies.

7. METHOD OF SELECTION AND EVALUATION CRITERIA

All Phase I and Fast-Track proposals will be evaluated and judged on a competitive basis. Using the technical evaluation criteria in Section 7.1, a panel of scientists, consisting primarily of nongovernment experts knowledgeable in the disciplines or fields under review, will evaluate proposals to determine the most promising technical and scientific approaches. Each proposal will be judged on its own merit. The Agency is under no obligation to fund any proposal or any specific number of proposals in a given topic. It also may elect to fund several or none of the proposed approaches to the same topic or subtopic.

7.1 EVALUATION PROCESS

Your proposal will be peer reviewed by a panel of scientists selected for their competence in relevant scientific and technical fields. Each peer review panel will be responsible for evaluating proposals for scientific and technical merit. When relevant, reviewers will be instructed to comment on the reasonableness of the following Resource Sharing Plans, or the rationale for not sharing the following types of resources. However, reviewers will not factor the proposed resource sharing plan(s) into the determination of scientific merit or priority score. Program staff within the funding organization will be responsible for monitoring the data sharing policy.

- Data Sharing Plan [http://grants.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm]
- Sharing Model Organisms [<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-04-042.html>]
- Genome Wide Association Studies (GWAS) [<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-07-088.html>]

The peer review panel provides a rating, makes specific recommendations related to the scope, direction and/or conduct of the proposed research, and for those proposals recommended for award, may provide a commentary about the funding level, labor mix, duration of the proposed contract project, vertebrate animal and human subject

research issues. The Institute program staff of the awarding component will conduct a second level of review. Recommendations of the peer review panel and program staff are based on judgments about not only the technical merit of the proposed research but also its relevance and potential contributions to the mission and programs of the awarding component and commercial potential. A Phase I or Fast-Track contract may be awarded only if the corresponding proposal has been recommended as technically acceptable by the peer review panel. *Funding for any/all acceptable proposals is not guaranteed.*

7.2 TECHNICAL EVALUATION CRITERIA

In considering the technical merit of each proposal, the following factors will be assessed:

FACTORS FOR PHASE I PROPOSALS	WEIGHT
1. The soundness and technical merit of the proposed approach and identification of clear measurable goals (milestones) to be achieved during Phase I. (Preliminary data are not required for Phase I proposals.)	40%
2. The qualifications of the proposed PDs/PIs, supporting staff, and consultants. For proposals designating multiple PDs/PIs, is the leadership approach, including the designated roles and responsibilities, governance, and organizational structure, consistent with and justified by the aims of the project and the expertise of each of the PDs/PIs?	20%
3. The potential of the proposed research for technological innovation.	15%
4. The potential of the proposed research for commercial application. The commercial potential of a proposal will be assessed using the following criteria: <ul style="list-style-type: none"> a. Whether the outcome of the proposed research activity will likely lead to a marketable product or process. b. The offeror's discussion of the potential barriers to entry and the competitive market landscape. 	15%
5. The adequacy and suitability of the facilities and research environment.	10%

FACTORS FOR PHASE II PROPOSALS (FOR FAST-TRACK ONLY)	WEIGHT
1. The scientific/technical merit of the proposed research, including adequacy of the approach and methodology, and identification of clear, measurable goals to be achieved during Phase II.	30%
2. The potential of the proposed research for commercialization, as documented in the offeror's Commercialization Plan and evidenced by (a) the offeror's record of successfully commercializing its prior SBIR/STTR or other research projects, (b) commitments of additional investment during Phase II and Phase III from private sector or other non-SBIR funding sources, and (c) any other indicators of commercial potential for the proposed research.	30%

FACTORS FOR PHASE II PROPOSALS (FOR FAST-TRACK ONLY)	WEIGHT
<p>3. The qualifications of the proposed PDs/PIs, supporting staff and consultants.</p> <p>For proposals designating multiple PDs/PIs, is the leadership approach, including the designated roles and responsibilities, governance, and organizational structure, consistent with and justified by the aims of the project and the expertise of each of the PDs/PIs?</p>	25%
<p>4. The adequacy and suitability of the facilities and research environment.</p>	15%

7.3 PROPOSAL DEBRIEFING

Offerors will be notified promptly in writing if their proposals are no longer being considered for award. Offerors may request a debriefing by submitting a written request to the Contracting Officer within three days of receipt of the notification. Untimely requests may be accommodated at the Government's discretion.

7.4 AWARD DECISIONS

For proposals recommended for award, the awarding component considers the following:

1. Ratings resulting from the scientific/technical evaluation process;
2. Areas of high program relevance;
3. Program balance (i.e., balance among areas of research); and
4. Availability of funds.

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. The SBIR contract projects do not require establishing a competitive range or requesting final proposal revisions before reaching source selection decisions.

8. CONSIDERATIONS

8.1 AWARDS

1. The award instrument will be a contract.
2. A profit or fixed fee may be included in the proposal, as specified in Federal Acquisition Regulation (FAR) Part 15.404-4. The fee will be negotiated as an element of the potential total contract amount over and above allowable costs.
3. Phase I awards will be firm fixed price contracts. Normally, Phase II awards will be cost-plus-fixed-fee contracts.
4. Unless specified differently in Section 12, the total cost for Phase I contracts may not normally exceed \$150,000. Phase II contracts may not exceed \$1,000,000 - including direct costs, indirect costs, and negotiated fixed fee.
5. 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 your proposal. Cost-sharing is an explicit arrangement under which the contractor bears some of the burden of reasonable, allocable, and allowable contract cost. If cost-sharing is proposed, it should be reflected in your budget summary.

Approximate number of Phase I contract awards:

AWARDING COMPONENTS	NO. OF AWARDS	ESTIMATED TIME OF AWARD
National Institutes of Health (NIH) National Cancer Institute (NCI)	37-51	Scientific and Technical Merit Review: March-May 2013 Anticipated Award Date: August-September 2013
National Institutes of Health (NIH) National Center for Advancing Translational Sciences (NCATS)	6-7	Scientific and Technical Merit Review: February-March 2013 Anticipated Award Date: September 2013
National Institutes of Health (NIH) National Heart, Lung, and Blood Institute (NHLBI)	15-17	Scientific and Technical Merit Review: February-April 2013 Anticipated Award Date: July-September 2013
National Institutes of Health (NIH) National Institute of Allergy and Infectious Diseases (NIAID)	5-9	Scientific and Technical Merit Review: March 2013 Anticipated Award Date: August 2013
National Institutes of Health (NIH) <i>Eunice Kennedy Shriver</i> National Institute of Child Health and Human Development (NICHD)	1-2	Scientific and Technical Merit Review: February-April 2013 Anticipated Award Date: July-September 2013
National Institutes of Health (NIH) National Institute on Drug Abuse (NIDA)	8-11	Scientific and Technical Merit Review: March 2013 Anticipated Award Date: August 2013
Centers for Disease Control and Prevention (CDC) Center for Global Health (CGH)	3	Scientific and Technical Merit Review: May-June 2013 Anticipated Award Date: August 2013
Centers for Disease Control and Prevention (CDC) National Center for Birth Defects and Developmental Disabilities (NCBDDD)	2	Scientific and Technical Merit Review: May-June 2013 Anticipated Award Date: August 2013
Centers for Disease Control and Prevention (CDC) National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP)	1	Scientific and Technical Merit Review: May-June 2013 Anticipated Award Date: August 2013

AWARDING COMPONENTS	NO. OF AWARDS	ESTIMATED TIME OF AWARD
Centers for Disease Control and Prevention (CDC) National Center for Emerging Zoonotic and Infectious Diseases (NCEZID)	3	Scientific and Technical Merit Review: May-June 2013 Anticipated Award Date: August 2013
Centers for Disease Control and Prevention (CDC) National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (NCHHSTP)	3	Scientific and Technical Merit Review: May-June 2013 Anticipated Award Date: August 2013
Centers for Disease Control and Prevention (CDC) National Center for Immunization and Respiratory Diseases (NCIRD)	2	Scientific and Technical Merit Review: May-June 2013 Anticipated Award Date: August 2013
Centers for Disease Control and Prevention (CDC) Office of Public Health Preparedness and Response (OPHPR)	1	Scientific and Technical Merit Review: May-June 2013 Anticipated Award Date: August 2013

8.2 PROGRESS REPORTS

Contractors will be required to submit progress reports during Phase I and Phase II along with their invoices at intervals (typically monthly or quarterly) stipulated in the terms and conditions of award.

8.3 FINAL REPORT

A final report is required of all Phase I and Phase II contractors. It should include a detailed description of the project objectives, the activities that were carried out, and the results obtained. **An original and two copies** of this report must be submitted as directed by the Contracting Officer not later than the expiration date of the Phase I contract.

Each Phase II "Fast-Track" contractor must submit semi-annual progress reports. A final report is required no later than the expiration date of the Phase II contract. *All reports must be submitted as specified in the contract or as directed by the Contracting Officer.*

8.4 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 Central Contractor Registration (CCR) database before the award of a contract. Offerors must access the CCR through the System for Award Management (SAM) located at www.sam.gov.

Payments on Phase I contracts may be made on a monthly advance basis. Invoices/financing requests submitted for costs incurred under Phase II cost reimbursement contracts will be on a monthly basis unless otherwise authorized by the contracting officer.

8.5 LIMITED RIGHTS INFORMATION AND DATA

Proprietary Information. Information contained in unsuccessful proposals will remain the property of the offeror. The Government, however, may retain copies of all proposals. Public release of information in any proposal will be subject to existing statutory and regulatory requirements.

The Department of Health and Human Services (DHHS) recognizes that, in responding to this solicitation, offerors may submit information that they do not want used or disclosed for any purpose other than for evaluation. Such data might include trade secrets, technical data, and business data (such as commercial information, financial information, and cost and pricing data). The use or disclosure of such information may be restricted if offerors identify it and the Freedom of Information Act (FOIA) does not require its release. For information to be protected, offerors must identify in the Notice of Proprietary Information (on the Proposal Cover Sheet) the page(s) on which such information appears. Any other Notice may be unacceptable to the Government and may constitute grounds for removing the proposal from further consideration without assuming any liability for inadvertent disclosure.

Unless disclosure is required by the FOIA, as determined by FOI officials of the DHHS, data contained in those portions of a proposal that have been identified as containing restricted information, in accordance with the Notice of Proprietary Information, shall not be used or disclosed except for evaluation purposes.

The DHHS may not be able to withhold data that has been requested pursuant to the FOIA, and the DHHS FOI officials must make that determination. The Government is not liable for disclosure if the DHHS has determined that disclosure is required by the FOIA.

If a contract is awarded to the offeror as a result of, or in connection with, the submission of a proposal, the Government shall have the right to use or disclose the data to the extent provided by law. Proposals not resulting in a contract remain subject to the FOIA.

Rights to Data Developed Under SBIR Funding Agreement. Rights to data, including software developed under the terms of any funding agreement resulting from a contract proposal submitted in response to this solicitation, shall remain with the awardee. However, the Government shall have the limited right to use such data for Government purposes only.

- (1) Each agency must refrain from disclosing SBIR technical data to outside the Government (except reviewers) and especially to competitors of the Small Business Concern (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 (3) of this section, the agency obtains permission to disclose such SBIR technical data from the awardee or SBIR offeror. 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, dated September 24, 2002. 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.

Copyrights. The awardee may normally copyright and publish (consistent with appropriate national security considerations, if any) material developed with PHS support. The awarding component receives a royalty-free license for the Federal Government and requires that each publication contain an acknowledgement of agency support and disclaimer statement, as appropriate. An acknowledgement shall be to the effect that: "This publication was made possible by contract number _____ from (DHHS awarding component)" or "The project described was supported by contract number _____ from (DHHS awarding component)."

Patents. Small business concerns normally retain the principal worldwide patent rights to any invention developed with Government support. Under existing regulations, 37 CFR 401, the Government receives a royalty-free license for Federal Government use, reserves the right to require the patent-holder to license others in certain circumstances, and requires that anyone exclusively licensed to sell the invention in the United States must normally manufacture it substantially in the United States.

To the extent authorized by 35 U.S.C. 205, the Government will not make public any information disclosing a Government-supported invention for a four year period to allow the awardee a reasonable time to file a patent application, nor will the Government release any information that is part of a patent application.

Inquiries or information about additional requirements imposed by 37 CFR 401 should be obtained from local counsel or from:

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) 435-0679
Fax: (301) 480-0272
E-mail: jpkim@nih.gov

Inventions must be reported promptly—within two months of the inventor's initial report to the contractor organization—to the Division of Extramural Inventions and Technology Resources, NIH, at the address above. 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.

Awardees are encouraged to submit reports electronically using Interagency Edison (<http://www.iedison.gov>). Information from these reports is retained by the NIH as confidential and submission does not constitute any public disclosure. Failure to report as described at 37 CFR Section 401.14 is a violation of 35 U.S.C. 202 and may result in loss of the rights of the recipient organization. In addition to fulfilling reporting requirements, Edison notifies the user of future time sensitive deadlines with enough lead-time to avoid the possibility of loss of patent rights due to administrative oversight. Edison can accommodate the invention reporting need of all organizations. For additional information about this invention reporting and tracking system, visit the Edison home page cited above or contact Edison via e-mail at Edison@od.nih.gov.

Resource Sharing Plan(s). NIH considers the sharing of unique research resources developed through NIH-sponsored research an important means to enhance the value of, and advance 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, etc.), this must be explained in the Resource Sharing section of the proposal. See http://grants.nih.gov/grants/policy/data_sharing/data_sharing_faqs.htm.

(a) *Data Sharing Plan*: Investigators 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.) Offerors are encouraged to discuss data-sharing plans with their program contact. See [Data-Sharing Policy \(http://grants.nih.gov/grants/policy/data_sharing/\)](http://grants.nih.gov/grants/policy/data_sharing/) or <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html>.

(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 and related resources, or state appropriate reasons why such sharing is restricted or not possible. See [Sharing Model Organisms Policy \(http://grants.nih.gov/grants/policy/model_organism/index.htm\)](http://grants.nih.gov/grants/policy/model_organism/index.htm), and [NIH Guide NOT-OD-04-042 \(http://grants.nih.gov/grants/guide/notice-files/NOT-OD-04-042.html\)](http://grants.nih.gov/grants/guide/notice-files/NOT-OD-04-042.html).

(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 provide an appropriate explanation why submission to the repository is not possible. A genome-wide association study 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 \(http://www.nih.gov/grants/guide/notice-files/NOT-OD-07-088.html\)](http://www.nih.gov/grants/guide/notice-files/NOT-OD-07-088.html), and <http://gwas.nih.gov/>.

Royalties. If royalties exceed \$1,500, you must provide the following information on a separate page for each separate royalty or license fee:

1. Name and address of licensor.
2. Date of license agreement.
3. Patent numbers.
4. Patent application serial numbers, or other basis on which the royalty is payable.
5. Brief description (including any part or model number of each contract item or component on which the royalty is payable).
6. Percentage or dollar rate of royalty per unit.
7. Unit price of contract item.
8. Number of units.
9. Total dollar amount of royalties.
10. If specifically requested by the Contracting Officer, a copy of the current license agreement and identification of applicable claims of specific patents (see FAR 27.204 and 31.205-37).

8.6 PERFORMANCE OF RESEARCH AND ANALYTICAL WORK

For Phase I projects, small business concerns must perform a minimum of two-thirds or 67% of the research and/or analytical effort (i.e., total contract price less profit/fee) conducted under the resulting contract.

For Phase II projects, small business concerns must perform a minimum of one-half or 50% of the research and/or analytical effort (i.e., total contract price less profit/fee) conducted under the resulting contract.

The Contracting Officer must approve deviations from these requirements in writing after consultation with the agency SBIR Program Manager/Coordinator.

Contractor Commitments. Upon award of a contract, the contractor shall be required to make legal commitments through acceptance of Government contract clauses in the Phase I contract. The outline that follows is illustrative of the types of provisions required by the Federal Acquisition Regulations that shall be included in the Phase I contract. This is not a complete list of provisions to be included in Phase I contracts, nor does it contain specific wording of these clauses. Copies of complete terms and conditions applicable to your contract are available upon request.

1. **Standards of Work.** Work performed under the contract must conform to high professional standards.
2. **Inspection.** Work performed under the contract is subject to Government inspection and evaluation at all times.
3. **Termination for Convenience.** The Government may terminate the contract at any time for convenience 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.
4. **Disputes.** Any dispute concerning the contract that cannot be resolved by agreement shall be decided by the contracting officer with right of appeal.
5. **Equal Opportunity.** The contractor will not discriminate against any employee or applicant for employment because of race, color, religion, sex, or national origin.
6. **Affirmative Action for Veterans.** The contractor will not discriminate against any employee or applicant for employment because he or she is a disabled veteran or veteran of the Vietnam era.
7. **Affirmative Action for Handicapped.** The contractor will not discriminate against any employee or applicant for employment because he or she is physically or mentally handicapped.
8. **Gratuities.** The Government may terminate the contract if any gratuities have been offered to any representative of the Government to secure the contract.
9. **American-made Equipment and Products.** When purchasing equipment or products under an SBIR contract award, the contractor shall purchase only American-made items whenever possible.
10. **Examination of Records.** The Comptroller General (or a duly authorized representative) shall have the right to examine any directly pertinent records of the contractor involving transactions related to this contract.
11. **Default.** The Government may terminate the contract for default if the contractor fails to perform the work described in the contract and such failure is not the result of excusable delays.
12. **Contract Work Hours.** The contractor may not require an employee to work more than eight hours a day or forty hours a week unless the employee is compensated accordingly (i.e., overtime pay).
13. **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.
14. **Patent Infringement.** The contractor shall report each notice or claim of patent infringement based on the performance of the contract.

8.7 ELECTRONIC AND INFORMATION TECHNOLOGY (SECTION 508)

- a. Pursuant to Section 508 of the Rehabilitation Act of 1973 (29 U.S.C. 794d), as amended by the Workforce Investment Act of 1998, all electronic and information technology (EIT) products and services developed, acquired, maintained, or used under the resultant contract must comply with the "Electronic and Information Technology Accessibility Provisions" set forth by the Architectural and Transportation Barriers Compliance Board (also referred to as the "Access Board") in 36 CFR part 1194. Information about Section 508 provisions is available at <http://www.section508.gov/>. The complete text of Section 508 Final Standards can be accessed at <http://www.access-board.gov/sec508/standards.htm>.
- b. The contractor shall submit electronic reports/documents that meet the requirements of Section 508 of the Rehabilitation Act of 1973, as amended by the Workforce Investment Act of 1998. Conformance shall be

verified by producing electronic reports/documents that satisfy the HHS Section 508 Checklists and Standards. (See [HHS Section 508 Checklists and Standards](#).) For further guidance, please see <http://www.hhs.gov/web/508/index.html>.

8.8 ADDITIONAL INFORMATION

1. This solicitation is intended for informational purposes and reflects current planning. If there is any inconsistency between the information contained herein and the terms of any resulting SBIR contract, the terms of the contract are controlling.
2. Prior to award of an SBIR contract, the Government may request the offeror to submit certain organizational, management, personnel and financial information to assure responsibility of the offeror to receive an award.
3. The Government is not responsible for any expenditures of the offeror in advance and in anticipation of an award. In a cost reimbursement contract, reimbursement of costs by the Government may be made only on the basis of costs incurred by the contractor after award and during performance.
4. This solicitation is not an offer by the Government and does not obligate the Government to make any specific number of awards. Awards under this program are contingent upon the scientific/technical merit of proposals and the availability of funds.
5. The SBIR contract program is not intended as a mechanism to invite unsolicited proposals. Unsolicited SBIR contract proposals shall not be accepted under the SBIR program in either Phase I, Phase II, or Fast-Track.
6. If an award is made pursuant to a proposal submitted in response to this SBIR solicitation, the contractor will be required to certify that he or she has not previously been, nor is currently being, paid for essentially equivalent work by any agency of the Federal Government.
7. Prior to award of a contract, the contractor will be required to provide a Data Universal Numbering System (DUNS) number. A DUNS number may be obtained immediately, at no charge, by calling Dun and Bradstreet at 1-866-705-5711 or via the Internet at <http://fedgov.dnb.com/webform>. The contractor must also be registered in the Central Contractor Registry (CCR) prior to award of a contract. Offerors must access the CCR through the System for Award Management (SAM) located at www.sam.gov.

9. INSTRUCTIONS FOR PROPOSAL SUBMISSION

9.1 RECEIPT DATE

The deadline for receipt of all contract proposals submitted in response to this solicitation is:

5:00 p.m., Eastern Time
Tuesday, November 13, 2012

Any proposal, modification or revision received at the offices designated below after the exact time specified for receipt is "late" and will not be considered unless it is received before award is made, and

1. There is acceptable evidence to establish that it was received at the Government installation designated for receipt of offers and was under the Government's control prior to the time set for receipt of offers; or
2. It is the only proposal received.

Acceptable evidence to establish the time of receipt at the Government installation includes the time/date stamp of that installation on the proposal wrapper, other documentary evidence of receipt maintained by the installation, or oral testimony or statements of Government personnel.

If an emergency or unanticipated event interrupts normal Government processes so that proposals cannot be received at the office designated for receipt of proposals by the exact time specified in the solicitation, and urgent Government requirements preclude amendment of the solicitation, 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.

Proposals may be withdrawn by written notice received at any time before award. Notwithstanding above, a proposal received after the date and time specified for receipt may be considered if it offers significant cost or technical advantages to the Government and it was received before proposals were distributed for evaluation, or within 5 calendar days after the exact time specified for receipt, whichever is earlier.

Note: Modifications or revisions to proposals that result in the proposal exceeding the stated page limitations will not be considered.

9.2 NUMBER OF COPIES

For Phase I, submit the original and 5 copies of each proposal. The Principal Investigator and a corporate official authorized to bind the offeror must sign the original. The 5 copies of the proposal may be photocopies of the original.

For Fast-Track Phase II, submit the original and 9 copies.

For Phase I and Fast-Track Phase II business proposals, submit an original and 5 copies.

In addition to the paper submissions, proposers are also encouraged to submit two CD-Rom's containing a PDF (Adobe Acrobat) copy of the entire proposal (Technical and Business). This does not replace the paper copies but is in addition to them. The paper copy is the official copy for recording timely receipt of proposals. By signing the proposal, the offeror certifies that, as part of the offer, the information in the paper copy is exactly the same as that which is contained on the electronic media.

9.3 BINDING AND PACKAGING OF PROPOSAL

Send all copies of a proposal in the same package. Do not use special bindings or covers. Staple the pages in the upper left corner of each proposal.

10. CONTRACTING OFFICERS AND ADDRESSES FOR MAILING OR DELIVERY OF PROPOSALS

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.

10.1 NATIONAL INSTITUTES OF HEALTH (NIH)

National Cancer Institute (NCI)

Ms. Anita Hughes
Phone: (301) 435-3805
Fax: (301) 480-0309
E-mail: anita.hughes@nih.gov

Proposals to the NCI, if mailed through the U.S. Postal Service, must be addressed as follows:

Ms. Anita Hughes
Procurement Analyst/Contracting Officer
Office of Acquisitions
National Cancer Institute

6120 Executive Blvd., EPS, Room 6038
Bethesda, MD 20892-7193 *

**Change the city to Rockville and the zip code to 20852 if hand-delivered or delivered by an overnight service to the NCI.*

National Center for Advancing Translational Sciences (NCATS)

Mr. Richard Phillips
Phone: (301) 402-6462
Fax: (301) 480-3432
E-mail: phillipr@nhlbi.nih.gov

Proposals to the NCATS, if mailed through the U.S. Postal Service, must be addressed as follows:

Office of Review
National Center for Advancing Translational Sciences
National Institutes of Health, DHHS
6701 Democracy Blvd, Room 1072
Bethesda, MD 20892-4874 *

**Change the zip code to 20817 if hand-delivered or delivered by an express or other courier service to the NCATS.*

National Heart, Lung, and Blood Institute (NHLBI)

Mr. John Taylor
Phone: (301) 435-0327
Fax: (301) 480-3338
E-mail: taylorjc@nhlbi.nih.gov

Proposals to the NHLBI, if mailed through the U.S. Postal Service, must be addressed as follows:

Review Branch
Division of Extramural Research Activities
National Heart, Lung, and Blood Institute
Rockledge 2, Room 7195
6701 Rockledge Drive, MSC 7924
Bethesda, MD 20892-7924 *

**Change the zip code to 20817 if hand-delivered or delivered by an express or other courier service to the NHLBI.*

National Institute of Allergy and Infectious Diseases (NIAID)

Mr. Richard Hartmann
Phone: (301) 496-0612
Fax: (301) 480-4675
E-mail: Richard.Hartmann@nih.gov

Proposals to the NIAID, if mailed through the U.S. Postal Service, must be addressed as follows:

Mr. Richard Hartmann
Branch Chief MD-A
Office of Acquisitions, DEA
National Institute of Allergy and Infectious Diseases
6700-B Rockledge Drive, Room 3154
Bethesda, MD 20892-7612 *

**Change the city to Rockville, MD and the zip code to 20817 for hand-delivery or overnight delivery service.*

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

Louis A. Quatrano, Ph.D.
Phone: (301) 402-4221
Fax: (301) 402-0832
E-mail: quatrano@mail.nih.gov

Proposals to the NICHD, if mailed through the U.S. Postal Service, must be addressed as follows:

Lynn Salo, Contracting Officer
NICHD Contracts Management Branch
6100 Executive Blvd., Rm. 7A07, MSC 7510
Bethesda, Maryland 20892-7510*

**Change the city to Rockville and the zip code to 20852 if hand-delivered or delivered by an overnight service to the NICHD.*

National Institute on Drug Abuse (NIDA)

Mr. Brian O'Laughlin
Phone: (301) 443-6677
Fax: (301) 443-7595
E-mail: bo50d@nih.gov

Proposals to the NIDA must be mailed or delivered to:

Mr. Brian O'Laughlin
NIDA R&D Contracts Management Branch
Neurosciences Office of Acquisition
6001 Executive Boulevard
Room 4211, MSC 9559
Bethesda, MD 20892-8402 *

**Change the city to Rockville and the zip code to 20852 if hand-delivered or delivered by an overnight service to the NIDA.*

10.2 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

Juliana Cyril, Ph.D., M.P.H.
Deputy Director, Office of Science Quality
Office of the Associate Director for Science
Phone: (404) 639-4639
Fax: (404) 639-4903
E-mail: JCyril@cdc.gov

Sean David Griffiths, M.P.H.
Office of Science Quality
Office of the Associate Director for Science
Phone: 404-639-4641
Fax: 404-639-4903
E-mail: SGriffiths@cdc.gov

Center for Global Health (CGH)

Carlos Smiley
Contracting Officer
Phone: (770) 488-1517
Fax: (770) 488-2688
E-mail: CSmiley1@cdc.gov

Proposals to CGH must be mailed or delivered to:

Carlos Smiley
Contracting Officer
Centers for Disease Control and Prevention
Procurement and Grants Office
2920 Brandywine Road
Atlanta, GA 30341

National Center for Birth Defects and Developmental Disabilities (NCBDDD)

Natasha Y. Rowland
Contracting Officer
Phone: (770) 488-2601
Fax: (770) 488-2671
Email: hee5@cdc.gov

Proposals to the NCBDDD must be mailed or delivered to:

Natasha Y. Rowland
Contracting Officer
Centers for Disease Control and Prevention (CDC)
Procurement and Grants Office (PGO)
2920 Brandywine Road
Atlanta, GA 30341

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

Natasha Y. Rowland
Contracting Officer
Phone: (770) 488-2601
Fax: (770) 488-2671
Email: hee5@cdc.gov

Proposals to the NCCDPHP must be mailed or delivered to:

Natasha Y. Rowland
Contracting Officer
Centers for Disease Control and Prevention (CDC)
Procurement and Grants Office (PGO)
2920 Brandywine Road
Atlanta, GA 30341

National Center for Emerging Zoonotic and Infectious Diseases (NCEZID)

Theresa Routh-Murphy
Contracting Officer
Phone: (770) 488.2173
E-mail: TRN3@cdc.gov

Proposals to NCEZID must be mailed or delivered to:

Theresa Routh-Murphy
Centers for Disease Control and Prevention
Procurement and Grants Office
2920 Brandywine Road
Atlanta, GA 30341

National Center for HIV/AIDs, Viral Hepatitis, STD, and TB Prevention (NCHHSTP)

Julio Lopez
Contracting Officer
Phone: (770) 488-2892
Fax: (770) 488-2868
E-mail: jlopez3@cdc.gov

Proposals to NCHHSTP must be mailed or delivered to:

Julio Lopez
Centers for Disease Control and Prevention
Procurement and Grants Office
2920 Brandywine Road
Atlanta, GA 30341

National Center for Immunization and Respiratory Diseases (NCIRD)

Alan Sims
Contracting Officer, Lead
Phone: (770) 488-2647
Fax: (770) 488-2670
E-mail: ASims1@cdc.gov

Proposals to NCIRD must be mailed or delivered to:

Alan Sims
Contracting Officer
Centers for Disease Control and Prevention
Procurement and Grants Office
2920 Brandywine Road
Atlanta, GA 30341

Office of Public Health Preparedness and Response (OPHPR)

Donna Myler
Contracting Officer, Lead
Phone: (770) 488-2861
Fax: (770) 488-2670
E-mail: DMyler@cdc.gov

Proposals to OPHPR must be mailed or delivered to:

Donna Myler
Contracting Officer
Centers for Disease Control and Prevention
Procurement and Grants Office
2920 Brandywine Road
Atlanta, GA 30341

11. SCIENTIFIC AND TECHNICAL INFORMATION SOURCES

Health science research literature is available at academic and health science libraries throughout the United States. Information retrieval services are available at these libraries and Regional Medical Libraries through a network supported by the National Library of Medicine. To find a Regional Medical Library in your area, visit <http://nmlm.gov/> or contact the Office of Communication and Public Liaison at publicinfo@nlm.nih.gov, (301) 496-6308.

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

National Technical Information Service
1-800-553-6847
<http://www.ntis.gov>

National Technology Transfer Center
Wheeling Jesuit College
1-800-678-6882
<http://www.nttc.edu/>

12. RESEARCH TOPICS

NATIONAL INSTITUTES OF HEALTH

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 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 II 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 \$3M for a period of up to three additional years to assist promising small business concerns with the challenges of commercialization. The specific requirements for the previously-

offered Phase IIB Bridge Award can be reviewed in the full RFA announcement (<http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-12-001.html>).

The NCI expanded the Phase IIB Bridge Award program in FY2011 to allow previous SBIR Phase II contract awardees to compete for SBIR Phase IIB Bridge Awards. Pending its planned continuation, it is anticipated that the Phase IIB Bridge Award program will be open to contractors that successfully complete a Phase I award as a result of this solicitation, and who are subsequently awarded a Phase II contract (or have an exercised Phase II option under a Fast-Track contract). Provided it is available in the future, 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 SBIR Technology Transfer

The NCI SBIR Technology Transfer program pilot began in FY 2011 through the solicitation of two topics as part of PHS 2011-1, Solicitation for SBIR Contract Proposals. This program is continuing in FY 2013 through the inclusion of two NIH NCI Technology Transfer topics in this solicitation ([Topic 317](#) and [Topic 318](#)). The Technology Transfer program is modeled after an effort launched by the National Institute of Standards and Technology (NIST) that has successfully demonstrated that this program can help move federal research inventions toward the marketplace. The two NIH NCI Technology Transfer topics included in this solicitation are based on employee invention reports (EIRs) from NCI intramural employees, and are backed by patent applications submitted by the NCI Technology Transfer Center (TTC). The goal of each SBIR-TT topic is to identify a small business to work under research and commercialization licenses and perform the necessary R&D to advance the technology towards commercialization with SBIR funding. Please refer to the project goals of each individual topic ([Topic 317](#) and [Topic 318](#)) for additional information on these topics including pre-submission webinars, licensing information, and information on the role of and level of interaction with the inventor. To find out the date of the 2012 webinar, please visit (<http://sbir.cancer.gov/news/upcoming/>).

NCI Topics:

This solicitation invites Phase I (and in certain topics Fast-Track) proposals in the following areas:

313 RNAi Cancer Therapeutics using Nanotechnology

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 3-5

Budget (total costs): Phase I: \$200,000 for 9 months; Phase II: \$1,000,000 for 2 years

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

Summary

In 2011, the SBIR Development Center hosted an industry roundtable to solicit inputs from life science industry professionals on emerging areas that are ripe for technology development by the small business community. Participants at this meeting expressed strong interest in using the SBIR mechanism to foster and encourage the development of novel RNA interference (RNAi) delivery platforms, particularly as a strategy for addressing therapeutic targets previously deemed “undruggable” by small molecules. Such therapeutics are gaining prominence due to their versatility and efficiency in treating cancer, as well as a variety of other genetic diseases; however, treating patients with RNAi has proven challenging, as it is difficult to achieve intracellular delivery to specific tissues and organs expressing the target gene. In particular, cellular uptake of naked RNAi is extremely inefficient owing to its polyanionic nature. The majority of intravenously administered RNAi is removed from circulation by hepatic and renal clearance, and the remaining RNAi is subject to degradation by nonspecific nucleases in the blood. Moreover, injecting large quantities of RNAi may elicit an immune response, and other

“off-target” effects may result in toxicity. While RNAi delivery to tumor cells poses these and other challenges, the ability to overcome these challenges is expected to facilitate the development of new and highly efficacious anti-cancer agents. Nanoparticle-based delivery systems are especially attractive as such strategies afford the opportunity to target specific cell, tissue, and organ types, while also increasing circulation half-life and shielding RNAi from degradation. Importantly, ongoing clinical trials are successfully utilizing nanoparticle-based delivery systems for cancer-related RNAi therapeutics, indicating that nanotechnology-based approaches hold great promise. To accelerate such efforts, the National Cancer Institute (NCI) requests proposals for the development of novel, commercially viable nanotechnology-based platforms for the delivery of RNAi cancer therapeutics.

Project Goals

Proposals submitted under this contract topic should involve the design, fabrication, characterization, and preclinical evaluation of novel nanoparticle-based drug formulations capable of delivering candidate RNAi therapeutics for the treatment of cancer. Of particular interest are delivery systems that can achieve targeted delivery of RNAi to tumor cells, favorable pharmacokinetics and circulation times, and efficient uptake of RNAi by tumor cells. Nanotechnologies which minimize immune responses and/or off-target effects of RNAi are also desirable.

Nanotechnology-based RNAi therapeutic agents acceptable under this contract topic include siRNA, shRNA, miRNA, other ncRNA(s) and combinations thereof. Antisense oligonucleotides are also acceptable. This contract topic is not intended to fund basic research to identify molecular targets for RNAi therapy, conduct exhaustive comparative studies of multiple nanoparticle delivery systems, or establish new animal models. Concepts delivering DNA, messenger RNA, and/or proteins are also not acceptable candidates for this topic, nor are viral delivery platforms for RNAi.

The RNAi-nanoparticle constructs under development may incorporate additional functionalities to supplement or enhance the therapeutic RNAi. Such functionalities may include, but are not necessarily limited to, the following:

- Novel nanoparticle delivery vehicles
- Constructs involving novel tumor targeting
- Novel RNAi loading and releasing schemes
- Nanoparticle constructs capable of crossing the blood-brain barrier, penetrating pancreatic stroma, overcoming multi-drug resistance, or treating metastatic cancer
- Combination therapies utilizing multiple RNAi payloads (e.g., RNAi-based Logic Circuits)
- Other combination therapies utilizing at least one RNAi therapeutic and one conventional chemotherapeutic agent (i.e., non-nucleic acid agent)

Phase I Activities and Expected Deliverables

- Provide a detailed experimental strategy to develop and deliver the RNAi/nanotherapeutic, and identify an appropriate cancer indication(s) for the nanoconstruct containing the RNAi(s)
- Encapsulate and/or attach the selected RNAi therapeutic agent(s) to the nanoparticle
- Demonstrate nanoconstruct stability *in vitro*, and demonstrate controlled release of the RNAi therapeutic agent(s) from the nanoconstruct
- Perform *in vitro* efficacy studies in the relevant cancer cell line(s): (a) quantitate knockdown of the target gene transcript(s) and demonstrate a $\geq 70\%$ reduction in the corresponding protein product(s) (knockdown of multiple gene products is encouraged but not required); and (b) evaluate appropriate correlative endpoints / phenotypic effects (e.g., cell death, cell cycle arrest, cell differentiation)

- Establish specificity of the RNAi therapeutic and its phenotypic effects using appropriate controls (e.g., mutational substitution, cDNA rescue, scrambled RNAi sequences)
- Perform a small *in vivo* efficacy study in a relevant animal model of cancer: (a) quantitate knockdown of the target gene transcript (i.e., at least one gene) and demonstrate a $\geq 70\%$ reduction in the corresponding protein product; (b) evaluate appropriate correlative endpoints / phenotypic effects

Phase II Activities and Expected Deliverables (include at least three of the following)

- Provide a plan and timeline to complete preclinical development for the RNAi/nanotherapeutic, culminating in the filing of an IND with the FDA
- Demonstrate *in vivo* preclinical efficacy (properly powered studies)
- Demonstrate acceptable safety (i.e., toxicity in rodents and/or large animals)
- Demonstrate acceptable pharmacokinetics and pharmacodynamics
- Conduct process development to support clinical manufacturing (e.g., scale-up feasibility)
- Conduct other R&D activities needed to complete an IND application, carried out in a suitable pre-clinical environment

314 Development of Human Tissue Culture Systems that Mimic the Tumor Microenvironment

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 3-5

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

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

Summary

There is a critical need to improve the accuracy of preclinical drug efficacy screening and testing through the development of *in vitro* culture systems that more effectively mimic the *in vivo* environment. Currently, two-dimensional (2D) *in vitro* culture systems or *in vivo* animal models are the primary tools used to test cancer cell responses to drugs. However, drug sensitivity data obtained via 2D culture systems can be misrepresentative, while animal models are expensive, time-consuming, and not always predictive of the effects on human tumors in their native environment. Three-dimensional (3D) culture systems that mimic the tumor microenvironment using human tissue could be a better tool for drug screening by providing a more accurate, *in vivo*-like structure and organization than 2D culture systems, without the cost and time associated with using animal models. In addition, culture systems using human tissue may produce responses more predictive of humans than animal models. Advances in bioengineering and 3D cell culture models have led to *in vitro* systems that better replicate the structure, physiology, and function of tissues seen *in vivo*. 3D models more accurately mimic the *in vivo* milieu than current 2D *in vitro* culture systems by recreating the morphology and arrangement of individual cells, concentration gradients of signaling molecules and therapeutic agents, and the composition, structure, and mechanical forces of extracellular matrix around cells. The use of 3D systems that recreate the human tumor microenvironment could improve drug development in at least two ways: 1) speed decision-making for whether a particular therapeutic agent is worth pursuing in an animal model, reducing the time and cost of development; 2) lead to fewer clinical trial failures because of earlier, more relevant results from human tissue.

Properly representing the tumor microenvironment is particularly critical for testing the effectiveness of anti-cancer therapeutic agents. For example, extravascular transport in solid tumors is a fundamental determinant of the efficacy of both locally and systemically administered cancer agents. Large diffusion distances in tumor tissues, elevated interstitial fluid pressure, and interactions between anti-cancer drugs, tumor tissue, and normal tissue

are factors that significantly limit drug diffusion in the extravascular compartment. Additionally, due to rapid proliferation and poor blood supply to tumor cells, the tumor microenvironment is often acidic and hypoxic, which can lead to the resistance of tumor cells to both drug and radiation therapy. Thus, systems to properly recreate the tumor microenvironment are essential to advance the discovery and development of effective anti-cancer agents.

Project Goals

The focus of this topic is the development of 3D human tissue model culture systems that accurately mimic the tumor microenvironment, including factors affecting tumor cell responses such as vascularization and interactions with heterogeneous cell types. The project goal is to produce a system that is validated against known effective anti-cancer agents to demonstrate the system's utility as a predictive tool and screening assay. It is anticipated that the development of 3D systems representative of human tumor microenvironments will lead to an increase in the quality of and reduction in the timelines and costs associated with screening drugs, and enhancement in efficacy information for regulatory decisions.

Essential characteristics of an *in vitro* tumor microsystem should include all or some of the following features: 1) multicellular architecture that represents physiologically relevant characteristics of the tumor and tissue of origin; 2) reproducible and viable operation with simple and clear protocols; 3) ability to examine multiple aspects of cancer, such as tumor growth, angiogenesis, cell proliferation, migration, and/or invasion; and 4) compatibility with high content screening platforms that include multiple molecular read-outs, such as genomic, proteomic, metabolomic, or epigenomic analyses. System development should permit scale-up production such that the system can be reliably reproduced at a cost with reasonable expectation for market success. An eventual goal for such systems may include the ability to incorporate individual patient tumor biopsies to test patient-specific responses to available agents.

It is important to note that full 3D tumor microenvironment systems will consist of more than just an extracellular matrix containing tumor cells and will facilitate the inclusion of various cell types to mimic tumor cell interaction with surrounding normal cells and their effects on cancer aggressiveness and response to anti-cancer drugs. Examples include stromal cells that can induce chemoresistance and encourage metastasis, as well as endothelial cells that can carry therapeutics to the cancer. This topic is not intended to fund microphysiological organ systems for the study of toxicity, though tumor culture systems developed under this topic may be combined as a module with systems such as those being developed through the collaborative program between NIH, FDA, and DARPA: <http://www.ncats.nih.gov/research/reengineering/tissue-chip/tissue-chip.html>.

Phase I Activities and Expected Deliverables

- Develop 3D culture system prototype that incorporates human tumor cells
 - System should include:
 - Co-culture with multiple cell types, such as stromal cells, endothelial cells, etc.
 - Components to address cell-cell or cell-extracellular matrix (ECM) adhesion
 - Method to deliver and control necessary growth factors
 - Use a tumor cell line or biopsy tissue that is readily available and well characterized
 - Model should be developed using or easily adapted for use with high content screening platforms for sample analysis
 - Develop standardized protocol to enable reproducible culture of tumor cells in 3D microenvironment
 - Recapitulate tissue-tissue interfaces, spatiotemporal chemical gradients (e.g. oxygen, nutrients, and/or growth factors), and mechanical context of tumor microenvironment
- Submit a statement to NCI that specifies metrics used and criteria for prediction of clinical efficacy prior to demonstration of accurate prediction of clinical efficacy

- Identify specific biomarkers (e.g. gene expression patterns, cell surface proteins) that characterize cell types and tumors used
- Specify criteria for assessing whether the tumor microenvironment is representative of human physiological environment
- Specify markers of tumor activity
- Specify metrics that will be used to evaluate efficacy and milestones for desired efficacy
- Demonstrate accurate prediction of clinical efficacy in the developed prototype
 - Test at least one anti-cancer agent with a known clinical profile using the developed prototype (e.g., agent used may be from the NCI Developmental Therapeutics Program [DTP] Approved Oncology Drugs Set) (http://dtp.cancer.gov/branches/dscb/oncology_drugset_explanation.html)
 - Benchmark performance in developed system against 2D (e.g., NCI-60 Human Tumor Cell Line), and currently available 3D culture systems (e.g., tumor spheroids, hollow-fiber bioreactors)

Phase II Activities and Expected Deliverables

- Benchmark performance in developed system against applicable *in vivo* animal model(s) and known clinical performance
 - Test multiple agents with known clinical profiles in the developed prototype
 - Test at least one agent that has proven efficacious in animal trials but not in clinical trials
 - Assess genomic, proteomic, metabolomic, and epigenomic profile of the tumor system
 - Use validated markers and/or evaluative criteria from *in vivo* histologic analysis
 - Genomic data may be compared to The Cancer Genome Atlas (<http://cancergenome.nih.gov>)
 - Compare dose-response relationships of known anti-cancer agents
- Demonstrate the ability to scale-up the system for use in high-throughput therapeutic agent screening assays
 - Demonstrate the ability to perform high-throughput quantitative analysis on samples, such as simple harvesting and/or automated imaging.

315 Development of Companion Diagnostics: Enabling Precision Medicine in Cancer Therapy

(Fast-Track proposals will be accepted.)

Number of Anticipated Awards: 4

Budget (total costs): Phase I: \$300,000 for 9 months; Phase II: \$1,500,000 for 2 years

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

Summary

The demand for companion diagnostics has greatly increased with the recognition that matching the right patient to the right drug at the right time can improve patient care and may decrease health care costs. More than a dozen companion diagnostic tests have been approved by the FDA to guide the prescription of products in oncology, cardiovascular disease, and infectious disease. Among them, tests of the Philadelphia chromosome, tumor-associated EGFR overexpression, and HER2 protein overexpression have been identified by the FDA as "required" for the identification of candidate cancer patients to receive Gleevec, Erbitux (cetuximab), and Herceptin (trastuzumab), respectively, for certain indications. In 2011, the FDA approved two pairs of new

oncology drugs and their companion diagnostic tests simultaneously. These decisions suggest that the era of companion diagnostics has arrived.

Despite initial success, many therapies in the cancer arena (both primary and adjuvant treatments) still lack prediction and guidance from companion diagnostics. Many patients die from recurrence and metastasis as a result of unpredicted resistance to drugs or radiation developed during therapy, or due to pre-existing tumor insensitivity to the drugs or radiation therapy. Guidance towards effective and safe therapy is greatly needed and can be provided by companion diagnostics, which include tests developed after a drug has come to market, tests developed in conjunction with the development of a therapeutic agent, and tests to predict the interaction of novel agents with existing standard of care therapies, such as radiation or cytotoxic chemotherapy. This topic seeks to stimulate research, development, and commercialization of innovative tests and technology platforms for all types of companion diagnostic applications. Companies with advanced biomarkers are particularly encouraged to apply.

Project Goals

The goal of this contract topic is to develop companion diagnostic assays that identify patients for which a particular therapeutic regimen, including radiation therapy, existing drugs, and drugs in clinical development will be safe and effective.

Tests for monitoring the response to treatment for the purpose of adjusting treatment (e.g., schedule, dose, discontinuation) to achieve improved safety or effectiveness are also acceptable under this contract topic. Though the examples mentioned above are for targeted therapies, tests may also encompass therapeutics outside of this class. These tests include, but are not limited to, tumor RNA/protein expression or overexpression, gene mutation or deletion/insertion, allelic variation, and enzymatic deficiency. Noninvasive and minimally invasive sampling methods (e.g., body fluids and mouth swab) are preferred. Other sampling methods are also acceptable if they provide significantly improved predictive value, accuracy, and clinical applicability.

This topic is not intended to support the development of assays that do not provide predictive/prognostic information for a therapy. For example, the development of an assay for the sole purpose of measuring whether the drug hits its intended target (e.g., pharmacodynamic assay) would not be considered responsive under this contract topic. A novel test/device providing information that is useful in cancer diagnostics or prognostics, but not a determining factor for the safe and effective use of a therapeutic product, would also not be considered responsive.

Phase I Activities and Expected Deliverables

- Develop a working companion diagnostic test that meets the criteria described above
- Characterize the variation, reproducibility, and accuracy of the test, and implement a QA/QC plan
- Demonstrate the suitability of the test for use in the clinic, and conduct benchmarking studies against current tests (if available); algorithms must be tested with datasets other than those used for their development
- In cases where the drug for which the companion diagnostic test being developed is not yet commercially available (i.e., approved for marketing), the applicant must provide proof of collaboration or partnership with the entity that is developing the therapeutic agent or with an established diagnostic company
- All offerors must establish a collaboration or partnership with a diagnostic and/or pharmaceutical company and/or clinical/research institution that can provide relevant clinical trial specimens; offerors must provide a letter of support from the partnering organization in the Phase II application
- Deliver the SOP of the working test to NCI for evaluation

Phase II Activities and Expected Deliverables

- Demonstrate clinical utility and value by testing sufficient numbers of patients from multiple sites to unequivocally prove statistical significance with regards to patient selection for the therapy

- If the primary conclusions reached during the Phase I studies were based on animal experiments or *ex vivo* modeling, then a correlation study between these models and treatment in human subjects is expected
- Establish marketing partnership or alliance with the company developing the therapy, unless the therapy is already approved for marketing
- It is preferred that the test be performed in at least one independent CLIA-certified laboratory
- Deliver the final SOP to NCI for evaluation

316 Development of CTC Isolation Technologies Enabling Downstream Single Cell Molecular Analysis

(Fast-Track proposals will be accepted.)

Number of Anticipated Awards: 4

Budget (total costs): Phase I: \$300,000 for 9 months; Phase II: \$1,500,000 for 2 years

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

Summary

Circulating tumor cells (CTCs) are cancer cells shed from either the primary tumor or its metastases and are circulating in the peripheral blood. While metastases are directly responsible for the majority of cancer deaths, CTCs may constitute seeds for metastases and may be instrumental for the spread of the disease. Many studies have shown that the presence of CTCs in peripheral blood or bone marrow is of prognostic significance in different types of solid tumors, and that the number and molecular changes of CTCs may help predict or monitor response to treatment. An increasing number of studies have shown large molecular and cellular heterogeneity of CTCs from the same types of cancer and even from CTCs from the same patient. This phenomenon has made the interpretation of cancer status very difficult. Current FDA-approved CTC analysis is based on immunological capture of CTCs by magnetic beads. This method does not capture all types of CTCs, and the recovery of the captured cells for subsequent molecular or cellular analysis is limited; hence, it is important to develop improved methodologies for CTC isolation that enable subsequent genomic, proteomic, or metabolomic analysis at the single cell level in order to understand the origin and role of these subpopulations of CTCs in cancer progression and treatment response. Enabling CTC analysis at the single-cell level will significantly contribute to cancer research and the selection of treatment options for patients based on changes in CTC numbers and molecular characteristics before and during treatment.

Project Goals

The long-term goal of the project is to integrate new or established technologies to enable molecular characterization and analysis of individual CTCs isolated from blood or bone marrow. An ideal system will be a modular platform combining a CTC capture and separation module with several other modules for downstream molecular analysis such as genomic, metabolomic, proteomic and mutation analysis at the individual cell level. Non-modular systems will also be acceptable. The short-term goal is to demonstrate the technical viability of the proposed technology to isolate and analyze CTCs at the single-cell level in an experimental setting. If molecular analysis is not performed with the proposed device, a detailed description about compatible downstream analysis technology(/ies), including manufacturers and model numbers, is required.

Acceptable studies include but are not limited to:

- CTC isolation and enrichment technologies such as magnetic separation, microfluidics, size separation, and negative or positive selection
- Integrated CTC devices which combine CTC capture and molecular analysis

- Viable CTC cell isolation and/or culturing for treatment assessment
- Low-cost multichannel scanning, imaging, flow cytometry, spectral analysis or equivalent technologies for CTC molecular analysis with the potential to combine with innovative single-cell isolation (e.g. micro dissection)
- Non-separation-based technologies for CTCs that enable molecular analysis

Phase I Activities and Expected Deliverables

- Develop a method for CTC isolation or identification amenable to downstream single-cell analysis
- The technology/device should be able to isolate or identify CTCs from samples with CTC counts as low as one cell/ml of blood (for Phase I, seeding experiments are acceptable)
- The technology/device should be able to perform single-cell molecular analysis (or whole genome amplification) for more than 100 CTCs, or isolate more than 100 CTCs individually in a format and volume that is compatible with existing downstream single-cell molecular analysis
 - In the latter case, please specify the format, volume, and intended downstream analysis
- Characterize the variation, reproducibility, and accuracy of the method; the method must demonstrate at least 80% recovery and 70% purity
- When applicable (e.g., when downstream analysis is gene expression), determine the viability of CTCs
- Demonstrate feasibility that the device (including imaging, spectral analysis or equivalent technologies) can provide CTCs for molecular analysis at the single-cell level, and at least 10 biomarkers (including markers to confirm that the isolated cells are CTCs) can be measured (preferably simultaneously) for the same cell
- Implement a QA/QC plan
- The establishment of a collaboration or partnership with established diagnostic or pharmaceutical companies is strongly encouraged
- Provide the NCI with SOPs, including sample collection, shipping, storage conditions, consumables used, and molecular analysis, for evaluation
- Provide the NCI detailed design specifications (including components) and estimations of the cost of producing the proposed devices and/or reagents, including an analysis/breakdown of vendors and/or sources of raw materials

Phase II Activities and Expected Deliverables

- Develop a prototype of the device incorporating the technology demonstrated in Phase I with at least two of the applications below or other applications with significant clinical utility:
 - Single CTC whole genome sequencing
 - Single CTC molecular phenotyping
 - Single CTC proteomic analysis
 - Single CTC metabolomic analysis
 - Single CTC targeted multiplex gene expression analysis
 - Single CTC targeted multiplex mutation analysis
 - Single CTC targeted multiplex epigenetic analysis

- Culture of individual CTCs with sufficient percent of viable cells for *ex vivo* analysis (e.g. drug treatment)
- Test the device with a sufficient number of patient samples to demonstrate clinical utility and advantages, with appropriate consideration of statistical significance
- Establish a marketing partnership or alliance with an established diagnostic or device company

317 Wound Healing Preparations Incorporating Nitric Oxide-Releasing Materials (NIH Technology Transfer)

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

Number of Anticipated Awards: 1

Budget (total costs): Phase I: \$200,000 per award for 1 year; Phase II: \$1,500,000 per award for 2 years

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

Summary

Non-healing wounds can pose significant problems for cancer patients (e.g., in cases where multiple operations are required for local recurrence, when large wounds are slow to close, and especially when patients receive radiation at sites requiring surgery). In addition, the effects of chemotherapy, nutritional deficits along with co-morbidities (e.g., diabetes), and infections can complicate wound healing. Therefore, the cancer patient population has the potential for non-healing wounds due to the nature and effects of the oncologic disease process and its treatments (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2206003/>). Improved methods are thus needed for treating non-healing wounds that often result in lengthy hospital stays, application of multiple types of dressings and ointments, and hyperbaric methods.

Nitric oxide (NO) is an important bio-signaling molecule whose role has been extensively recognized in the body's endogenous immune, inflammatory, and tissue regenerative responses. Therapeutic application of exogenous topical NO-generating agents has been shown to provide powerful, broad-spectrum antimicrobial action, and NO is capable of providing numerous wound-healing benefits if delivered at the proper concentrations. However, since NO is an easily oxidized gas, controlled topical delivery of NO to a desired area is difficult. The National Cancer Institute (NCI) has developed a family of polymers based on poly(acrylonitrile) that are capable of storing NO bound in a stable chemical functionality, called a diazeniumdiolate group, and releasing NO under aqueous conditions. The next logical step in the utilization of these materials for biomedical applications is the incorporation of these NO-releasing poly(acrylonitrile)-based compositions into suitable, biocompatible dressings for application to wounds to fight infection, modulate inflammation, and promote angiogenesis and collagen synthesis in order to accelerate wound closure and/or otherwise improve functional outcomes.

This invention is the subject of issued patents [US 7,968,664](#) and [US 8,093,343](#), and HHS Reference Number [E-188-2004](#).

Project Goals

The ultimate goal of this effort is to develop a commercially viable wound-healing dressing, utilizing this NCI-developed technology, to alleviate the suffering and costs caused by non-healing wounds, thereby establishing a precedent for supportive care for cancer while quickly creating a product of merit. The short-term goal of this project is to develop a prototype of such a dressing and to provide data that clearly demonstrate the potential of this stable NO-releasing material/formulation. The work scope may include design and fabrication of the material with *in vitro* evaluation (e.g., product stability testing) and preliminary *in vivo* assessment of its efficacy and final prototype development. These data will support the continued development of the experimental medical device to the point of filing an Investigational Device Exemption (IDE). The long-term goal of this topic is to enable a small

business to bring a fully developed product incorporating NCI's NO-releasing polymer technology to the clinic and the market.

The dressing to be developed under this contract should demonstrate the ability to maintain the stability of the diazeniumdiolate group during storage and sterilization, and to release NO when triggered by any mechanism related to wound contact (e.g., thermal or aqueous stimuli, biochemical interaction, etc.), or triggered by the health care provider (e.g., light source, chemical mixing, etc.). Since one of the major potential benefits of sustained and controlled release of therapeutic NO is the reduced frequency with which the care provider must contact the wounded skin to apply therapeutics and change the dressing, any stable, NO-releasing formulation will be considered including, but not limited to, fabric-based "traditional" dressings incorporating poly(acrylonitrile) as one of the textile components, hydrogels, creams, gels, nanomaterials, meshes, films, coatings, etc.

This is an NIH TT (Technology Transfer) contract topic from the NCI. This is a program whereby inventions from the NCI Intramural Research Program (Center for Cancer Research, CCR) are licensed to qualified small businesses with the intent that those businesses develop these inventions into commercial products that benefit the public. The contractor funded under this contract topic shall work closely with the NCI CCR inventors of this technology. The inventors will provide assistance in a collaborative manner with reagents and discussions during the entire award period. Between the time this contract topic is published and the time an offeror submits a contract proposal for this topic, no contact will be allowed between the offeror and the NCI CCR inventors. However, a pre-submission public briefing and/or webinar will be given by NCI staff to explain in greater detail the technical and licensing aspects of this program (for further information, see <http://sbir.cancer.gov/news/upcoming/>). In addition, a list of relevant technical, invention, and licensing-related questions and answers (including those from the public briefing) will be posted, maintained, and updated online (<http://sbir.cancer.gov/news/upcoming/>) during this time period.

The awarded contractor will automatically be granted a royalty-free, non-exclusive license to use NIH-owned and patented background inventions only within the scope and term of the award. However, an SBIR offeror or SBIR contractor can apply for an exclusive or non-exclusive commercialization license to make, use, and sell products or services incorporating the NIH background invention. Offerors submitting an SBIR contract proposal in response to this topic are strongly encouraged to submit concurrently an application for a commercialization license to such background inventions. Under the NIH NCI TT program, the SBIR contract award process will be conducted in parallel with, but distinct from, the review of any applications for a commercialization license.

To apply for a commercialization license to develop this NIH invention, an SBIR offeror or contractor must submit a license application to the NIH Licensing and Patenting Manager: Betty Tong Ph.D., tongb@mail.nih.gov or 301-594-6565. A license application and model license agreements are available at <http://www.ott.nih.gov/pdfs/LicApp.pdf> and http://www.ott.nih.gov/forms_model_agreements/forms_model_agreements.aspx#LAP.

This license application provides NIH with information about the potential licensee, some of the terms desired, and the potential licensee's plans for development and/or commercialization of the invention. License applications will be treated in accordance with Federal patent licensing regulations as provided in 37 CFR Part 404. A further description of the NIH licensing process is available at http://www.ott.nih.gov/licensing_royalties/intra_techlic.aspx. NIH will notify an SBIR offeror who has submitted an application for an exclusive commercialization license if another application for an exclusive license to the background invention is received at any time before such a license is granted.

Any invention developed by the contractor during the course of the NIH TT contract period of performance will be owned by the contractor subject to the terms of Section 8.5.

Phase I Activities and Expected Deliverables

- Prepare one or more dressings or other formulations incorporating NO-releasing poly(acrylonitrile) materials
- Produce a prototype product meeting minimum essential characteristics

- Quantifiable NO release durations should range from acute time periods (minutes) to 24 hours or longer to support an adequate therapeutic window
- NO storage and release should be quantified via standard electrochemical or chemiluminescent assays routinely used in characterizing NO-based materials
- Characterize the material's:
 - total NO release potential
 - triggered NO release kinetics
- Conduct proof of concept *in vitro* studies in the appropriate models and environments
- Conduct *in vivo* efficacy studies to demonstrate potential therapeutic benefit of the lead candidate NO-releasing preparation in an appropriate model

Phase II Activities and Expected Deliverables

- All studies in Phase II shall be conducted with the ultimate aim of producing a product acceptable to the FDA, and shall thus follow the recommendations contained in the FDA document "Guidance for Industry: Chronic Cutaneous Ulcer and Burn Wounds-Developing Products for Treatment" published June 2006 and available for download from the FDA website: (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071324.pdf>)
- Conduct appropriate stability studies, including thermal stability at sterilization temperatures and shelf life characterization
- Provide quantitative evidence of improved wound healing over the current standard-of-care
- Demonstrate capability for commercial production of the product
- Demonstrate capability to manufacture and sterilize the lead candidate in an industrial setting
- Prototype should demonstrate the ability to provide medical benefit, robust stability, and commercial potential

318 Test to Predict Effectiveness of Docetaxel Treatment for Prostate Cancer (NIH Technology Transfer)

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

Number of Anticipated Awards: 1

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

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

Summary

Over the past two years, medical oncologists have added three new therapies to the therapeutic arsenal against Castration-Resistant Prostate Cancer (CRPC): abiraterone, Siplucec-T, and cabazitaxel. Before approval of these agents, docetaxel was the only life-extending therapeutic option for men with CRPC, and docetaxel remains the standard of care for men who can tolerate chemotherapy. Moreover, there are several promising agents that are likely to be FDA-approved for CRPC in coming years (i.e., MDV-3100, EPI-001, and TOK-001). Therefore, the commercial availability of a method to determine which CRPC patients will have a superior response to docetaxel therapy (and which CRPC patients will not respond), will allow medical oncologists to consider other approved options in certain patients, thereby "personalizing" CRPC therapy.

The National Cancer Institute (NCI) has developed a genotype test that can indicate the duration of survival following docetaxel therapy in men with CRPC. The test detects a genetic variant in cytochrome P450 1B1 (*CYP1B1**3; 4326C>G) that encodes a leucine-to-valine amino acid substitution, L432V, in the translated protein. This genetic polymorphism causes *P450 1B1* *3 to synthesize higher than normal concentrations of a reactive estrogen species (e.g., estradiol-3,4-quinone [E2-3,4Q]) that reduces docetaxel activity via two distinct mechanisms. Firstly, E2-3,4Q binds directly to docetaxel at biological pH, thereby reducing docetaxel potency. Secondly, E2-3,4Q antagonizes the mechanism of action of docetaxel (i.e., microtubule stabilization), by destabilizing the interaction between tubulin thiol groups that are required to form microtubules. Therefore, a simple genotypic test can determine whether or not a patient will respond to docetaxel, or whether treatment with other newly-approved anticancer agents is warranted. The genetic marker *CYP1B1**3 could be used as a prognostic tool to predict survival rate and propensity to respond to docetaxel treatment.

This invention is the subject of filed patent applications [US20100280084A1](#) and [EP1943358](#), and HHS Reference Number [E-307-2005/0](#).

Project Goals

The focus of this topic is to advance development of this genetic test which would provide rapid and useful *a priori* predictions of the clinical outcome of docetaxel patients and guide the therapeutic strategy for each patient. The short-term goals of this project are to: (i) develop a rapid and reproducible assay for the *CYP1B1**3 variant; (ii) provide additional preclinical evidence necessary for carrying the *CYP1B1**3 genotype test into the clinical setting; and (iii) determine if cabazitaxel activity is related to the *CYP1B1**3 allele and reactive estrogen species. The long-term goal of this project is obtain FDA approval for the test, to establish broader utility for the *CYP1B1**3 test in treatment of other cancer types, implement the test in conjunction with alternate therapeutics that act via modulation of this estrogen responsive pathway, and to further translate the utility of the genotype test to wider clinical use. This technology, once demonstrated in the field of prostate cancer, could be applied to breast and lung cancer genetic markers that have clinical application in defining the chemotherapeutic treatment schedules for individual patients.

Phase I deliverables include technique development, further demonstration of the mechanism of *CYP1B1**3 interference, validation that genotype is related to survival using retrospective CRPC patient samples, and identification of the percentage of samples with the variant. A future Phase II SBIR award would include a genotype-directed prospective clinical trial with docetaxel and/or cabazitaxel to demonstrate improved taxane outcomes in genotyped patients.

This is an NIH TT (Technology Transfer) contract topic from the NCI. This is a program whereby inventions from the NCI Intramural Research Program (Center for Cancer Research, CCR) are licensed to qualified small businesses with the intent that those businesses develop these inventions into commercial products that benefit the public. The contractor funded under this contract topic shall work closely with the NCI CCR inventor of this technology. The inventor will provide assistance in a collaborative manner with reagents and discussions during the entire award period.

Between the time this contract topic is published and the time an offeror submits a contract proposal for this topic, no contact will be allowed between the offeror and the NCI CCR inventor. However, a pre-submission public briefing and/or webinar will be given by NCI staff to explain in greater detail the technical and licensing aspects of this program (for further information, see <http://sbir.cancer.gov/news/upcoming/>). In addition, a list of relevant technical, invention, and licensing-related questions and answers (including those from the public briefing) will be posted, maintained, and updated online (<http://sbir.cancer.gov/news/upcoming/>) during this time period.

The awarded contractor will automatically be granted a royalty-free, non-exclusive license to use NIH-owned and patented background inventions only within the scope and term of the award. However, an SBIR offeror or SBIR contractor can apply for an exclusive or non-exclusive commercialization license to make, use, and sell products or services incorporating the NIH background invention. Offerors submitting an SBIR contract proposal in response to this topic are strongly encouraged to submit concurrently an application for a commercialization license to such background inventions. Under the NIH NCI TT program, the SBIR contract award process will be conducted in parallel with, but distinct from, the review of any applications for a commercialization license.

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This license application provides NIH with information about the potential licensee, some of the terms desired, and the potential licensee's plans for development and/or commercialization of the invention. License applications will be treated in accordance with Federal patent licensing regulations as provided in 37 CFR Part 404. A further description of the NIH licensing process is available at http://www.ott.nih.gov/licensing_royalties/intra_techlic.aspx. NIH will notify an SBIR offeror who has submitted an application for an exclusive commercialization license if another application for an exclusive license to the background invention is received at any time before such a license is granted.

Any invention developed by the contractor during the course of the NIH TT contract period of performance will be owned by the contractor subject to the terms of Section 8.5.

Phase I Activities and Expected Deliverables

- Develop a simple array-based genotyping technique for *CYP1B1*3* in which a genotype call is conferred to the patient within two days following the receipt of a blood sample
- Extend the proof-of-concept that *CYP1B1*3* interferes with docetaxel activity via formation of estrogen quinones using cellular assays and/or tumor-bearing mice
- Validate that the genotype is related to survival in retrospective samples obtained from patients with CRPC undergoing therapy with docetaxel (The NCI intramural laboratory can aid in getting samples)
- Identify the percentage of patient samples with the *CYP1B1*3* variant
- Determine if cabazitaxel is subject to the same interaction with E2-3,4Q (The NCI intramural laboratory has synthesized frozen E2-3,4Q and can provide some of the quinone estrogen species; it is unlikely that the NCI laboratory could provide any retrospective samples)
- Deliver data to the NCI

Phase II Activities and Expected Deliverables

- Conduct a genotype-directed prospective clinical trial with docetaxel and/or cabazitaxel to demonstrate improved taxane outcomes in genotyped patients (The NCI may provide samples from retrospective studies and assist with getting more samples)
- Identify the percentage of patients with the *CYP1B1*3* variant
- Translate the test to the commercial clinical setting in a manner sufficient to pass CLIA certification
- Develop a commercially-viable prototype

319 Technology to Generate Anti-Peptide Capture Reagents for Affinity-Enriched Proteomic Studies

(Fast-Track proposals will be accepted.)

Number of Anticipated Awards: 4

Budget (total costs): Phase I: \$200,000 for 9 months; Phase II: \$1,000,000 for 2 years

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

Summary

Anti-peptide capture reagents can be used to identify and quantify proteins containing a target peptide sequence with a number of applications in biological research and bioassay development. For instance, they are used routinely in techniques such as immunoprecipitation, Western blot, and immunohistological identification and protein localization. A recently-developed application of such reagents is Stable Isotope Standards and Capture by Anti-Peptide Antibodies (SISCAPA), which utilizes antibodies to enrich peptides from complex matrices for quantitation of proteins by stable isotope dilution mass spectrometry. SISCAPA has the potential for simultaneous quantification of multiple targets from a given sample. There is growing interest in the development of such multiplex protein assays, including large-scale biomarker candidate verification studies and analyses of targeted biological pathways. Concurrent quantification of multiple protein analytes is highly desirable in these applications to minimize sample requirements, handling, and assay costs per analyte, while maximizing throughput.

Project Goals

The goal of this project is to develop new technologies that generate reproducible, well-characterized anti-peptide capture reagents for use in affinity-enriched proteomic studies for the cancer research community. An important characteristic of the desired reagents is the ability to immunoprecipitate their target peptide with high affinity. These reagents should be comparable or superior to ELISA-based antibody technologies in terms of specificity, affinity, and sensitivity and be reproducibly generated in a cost-effective and efficient (e.g. renewable) manner. Currently, mice are often used to generate monoclonal antibodies or alternative capture reagents, but peptides do not always elicit a potent immune response, which can result in low yield of antibodies to effectively immunoprecipitate the target peptides. The desired technology will likely be one that produces a strong immune response to peptide antigens, and may include the use of species other than mice for the generation of antibodies, since other species may have more diverse epitope recognition and improved immune response to small-size epitopes.

The development of these affinity capture reagents will be done in coordination with NCI's Clinical Proteomic Technologies for Cancer (CPTC) (<http://proteomics.cancer.gov>). A list of proteins or proteotypic peptides derived from cancer biomarker candidates may be requested from CPTC. Furthermore, these capture reagents must be made available as a resource to the scientific community. The suggested choices of performance platforms that the affinity reagents must be compared to include mass spectrometry-based quantitative assays, immunoprecipitation, ELISA-based assays, Western blot, and immunohistochemistry. In addition, other considerations should include sensitivity/specificity/affinity information for the reagents, and method comparison with gold standard practices, precision, and LOD/LOQ.

Phase I Activities and Expected Deliverables

- Develop proof-of-concept strategies and/or technologies that reliably generate anti-peptide capture reagents that can immunoprecipitate the target peptides; this includes, but is not limited to, strategies/technologies that can produce stronger immune responses to peptide antigens than current technologies
- Demonstrate that the capture reagents developed through this technology can repeatedly and reproducibly immunoprecipitate the target peptides
- Work with the Clinical Proteomic Technologies for Cancer (CPTC) community (<http://proteomics.cancer.gov>), private and public sector to identify appropriate minimum characterization criteria for validation of the assays
- In coordination with CPTC program staff, select and generate affinity reagents to at least ten proteotypic peptides and demonstrate high affinity (K_d of 10^{-9} M or better), specificity and immunoprecipitation performance
- If requested, be prepared to make available to NCI sufficient reagents to perform 10 test runs for each of the ten peptides for independent evaluation

- Present findings to an NCI CPTC Evaluation Panel and demonstrate any additional characteristics (e.g. capture of corresponding full-length protein) and how the capture reagents have improved cost effectiveness and throughput capabilities in production and method feasibility of screening of large numbers of hybridomas while conserving time and resources
- Propose quantitative feasibility milestones

Phase II Activities and Expected Deliverables

- Implement the new fully functional anti-peptide capture reagent development strategies/technologies and project plan for development of at least 100 anti-peptide capture reagents capable of immunoprecipitation in coordination with CPTC program staff
 - Reagents should be able to capture the target peptides of interest from complex biological mixtures such as blood, plasma, or tissue
- Demonstrate whether the antibodies can immunoprecipitate full-length proteins
- Test performance criteria against affinity, specificity, immunoprecipitation and affinity-enriched SRM-MS (Selected Reaction Monitoring-Mass Spectrometry) platforms or clinical-grade ELISA tests if available
- Work with CPTC to integrate capture reagents into proteomic research platforms

320 High Quality Cancer-Related Standards for Metabolomics Research

(Fast-Track proposals will be accepted.)

Number of Anticipated Awards: 3-5

Budget (total costs): Phase I: \$200,000 for 9 months; Phase II: \$1,000,000 for 2 years

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

Summary

The metabolome is a measure of the output of biological pathways and, as such, is often considered more representative of the functional state of a cell than other 'omics measures such as genomics or proteomics. In addition, metabolites are conserved across various animal species, facilitating the extrapolation of research findings in laboratory animals to humans. Despite early promise, challenges remain before the full potential of metabolomics can be realized – including the limited availability of high quality metabolite standards and of companies/core facilities that provide metabolomics services. The NIH Common Fund is currently developing a multi-component program to help increase metabolomics research capacity. SBIR contracts that focus on identifying and synthesizing reliable metabolite standards will complement this effort by attracting current and emerging small businesses to develop these much needed tools – which in turn will contribute towards achieving an important NIH Common Fund goal of increasing the repertoire of high quality and authentic standards for identification, characterization and quantization of metabolites. Entities that wish to compete for such contracts must be cognizant of the current cost and intellectual property rights challenges that have restricted the use of said tools in basic, pre-clinical, and translational research alike and consequently make reasonable efforts to make said standards and corresponding product sheets widely accessible to the metabolomics community at large.

Project Goals

The short and long-term project goals involve the development of both isotopically labeled (i.e., ^{15}N , ^{13}C or ^2H) and unlabeled metabolite standards for use with mass spectrometry (MS) and/or nuclear magnetic resonance spectroscopy (NMR), respectively. Compounds need to be synthesized in GLP labs with ISO 9000 certification, and purified by either chromatographic methods or crystallization to >95% purity.

Classes of metabolites that require standards for metabolite identification include, but are not limited to:

1. Glycolytic and other energy intermediates
2. Amino acid metabolism
3. Lipids (phospholipids, glycerolipids, sphingolipids, glycolipids, oxylipins)
4. Acylcarnitines and acylglycines
5. Secondary drug metabolites
6. Secondary food metabolites
7. Fatty acids

Offerors should focus their proposals on developing at least one set of metabolite standards, where all compounds in the set are linked to one cancer-related metabolic pathway

Phase I Activities and Expected Deliverables

- Synthesize, as appropriate for any given metabolic pathway, a range of 10-1000 labeled or unlabeled compounds under GLP conditions on a pilot scale sufficient to run at least 10 MS or NMR analyses
- Verify structures of the synthesized compounds
- Purify compounds using either chromatographic methods or crystallization to >95% purity
- Investigate formulation issues and whether the compounds in the metabolite standards set can stably be packaged together versus separately
- Run pilot MS or NMR validation tests of the metabolite standards set to evaluate its performance

Phase II Activities and Expected Deliverables

- Scale up of synthesis, purification, and formulation/packaging/chemical stability of Phase I deliverables to allow for more extensive product validation.
- Validate the metabolite standards set for reproducible performance in MS or NMR as appropriate.
- Provide letters of interest from potential customers, and later letters of commitment from customers to purchase the product developed under this contract.

321 Chemically Defined Glycan Libraries for Reference Standards and Glycomics Research (Joint NCI-NIGMS Program)

(Fast-Track proposals will be accepted.)

Number of Anticipated Awards: 4-6

Budget (total costs): Phase I: \$300,000 for 9 months; Phase II: \$1,000,000 for 2 years

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

Summary

Glycans play important roles in cell recognition, motility, signaling processes, cell differentiation, cell adhesion, microbial pathogenesis, and immune recognition. Carbohydrate-based high throughput assays (e.g. glycan microarrays, nanoparticles) hold great promise for the rapid analysis of carbohydrate binding proteins (CBPs), elucidation of CBP biology, and the development of diagnostics, vaccines, and therapeutics for a number of diseases, including cancer. However, the utility of these high throughput assays is limited by the paucity of robust

biologically relevant glycan libraries available for screening. Glycan standards are also needed to perform structural analysis, especially for monitoring changes in glycosylation that can significantly affect protein function and the safety and efficacy of bio-therapeutics.

NCI participates in trans-NIH initiatives to further glycomics research as part of the Alliance of Glycobiologists for Detection of Cancer, which partners with NCI's Early Detection Research Network, as well as the Glycomics and Glycotechnology Biomedical Technology Research Centers and the Consortium for Functional Glycomics which are funded by NIGMS. Small businesses that develop new glycan libraries for defining the specificities of CBPs, probing the immune response, screening for cancer-associated glycan biomarkers, and enabling glycan structural analysis will more rapidly advance the field of glycomics.

Contract offerors must be cognizant of the current cost and intellectual property rights challenges that have restricted the use of chemical libraries in basic, preclinical, and translational research, and be willing to abide by NIH policies pertaining to the sharing and dissemination of unique research resources developed with NIH funding. Abiding by the NIH [Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources](#) will ensure that libraries and data generated from them will be deposited into existing repositories and databases that will serve as resources for the entire glycobiology community for non-commercial research purposes.

Project Goals

The goals of this program are to support the synthesis and commercial distribution of robust, well-characterized new carbohydrate libraries that are amenable to being functionalized/linkered for use in high throughput assays, are useful as standards in mass spectrometry (MS) and nuclear magnetic resonance (NMR) applications, and can be used to expand existing screening platforms, structural assays, and additional tool development. These libraries would need to be made with appropriate quality control documentation, and at reasonable cost.

The *Expanding the Chemical Space for Carbohydrates: Roadmap to Automated Synthesis* workshop report, presented to the NIGMS National Advisory Council in 2011, highlights the critical need for comprehensive chemically-defined glycan libraries for: development of screening platforms with sufficient numbers of structures and diversity to cover the major sectors of mammalian glycomes, use as analytical standards, use as substrates for enzymology, and use as building blocks to increase the glycan chemical space with newly identified enzymes. For analytical standards, biologically relevant groups of related structures with emphasis on isomers will be most useful. Compound collections that provide a basis for development of MS or NMR-based experimental conditions for differentiation of closely related structures are highly desirable. Based on current literature, a 10k-12k glycan collection is needed to represent the functional human glycome, and populate a comprehensive glycan array in a manner that would significantly move the field of glycomics forward. Presently, estimates suggest that only 1000 or so glycans have been synthesized for research purposes, and of these, only a few hundred are commercially available.

A number of NIH institutes (NIGMS, NCI, NIAID, NHLBI) support specific efforts in glycomics and several others (NIDDK, NIDCR, NICHD, NIAMS) also have interests in glycobiology. Discovery labs in The Alliance of Glycobiologists for Detection of Cancer (<http://glycomics.cancer.gov>), supported by NCI have a current need for libraries of glycans to facilitate structural studies and high-throughput analysis of carbohydrates derived from biological sources. SBIR contracts focused on synthesis of chemically defined glycan libraries that represent important subsets of the human glycome including representative N- and O- linked glycan libraries, glycan structures found on glycosphingolipids, and libraries of glycosaminoglycan oligomers, would speed progress towards a comprehensive mammalian glycan library. Ready access to these reagents is expected to speed progress in the emerging field of glycomics. Compounds must be synthesized and purified utilizing best practices to >98% purity as established by NMR.

It is recommended that offerors focus their proposals on developing at least one robust glycan library of significant complexity. Libraries of free, reducing-end glycans required include, but are not limited to:

Hybrid-type and complex N-glycan core structures with various multiples of antennae

- Hybrid-type N-glycans with all combinations of mannose cores

- Complex-type N-glycans with basic structures of bi-, tri- tetra-antennary, and bisected versions of those, terminating in either sialic acid, galactose, or N-acetylglucosamine. Further elaboration of antennae might include lactosamine extensions, fucosylation, or sulfation. Variability of these features in the antennae is also required to distinguish topological isomers.
- High mannose-type glycans and isomers.

O-glycans

- O-glycan Cores 1 and 2, as well as O-glycans bearing fucosylated and sialylated lactosamines of various lengths and degrees of internal fucosylation.

Human Blood Group Antigens

- ABO blood group (N-Acetylgalactosamine, galactose) antigens (ABO(H) and their variations - A1, A2, H-type 1, H-type 2, H-type 3, H-type 4, etc.).
- Lewis blood group (human fucose-containing) antigens (sLex, Lex, Lea, sLea, repeating Lex, etc., on glycolipid, N- and O-glycan backbones, etc.).

Glycosphingolipid head groups

- Ganglioside-, globoside-, lactosamine-, and neo-lactosamine-based core structures

Phosphorylated mannose glycans

- P-Man-R and GlcNAc-P-Man-R

Glycosaminoglycans (GAGs)

- Glycosaminoglycan fragments (especially heparan sulfate oligosaccharides) of 4 to 8 saccharides with/without defined sulfation.

Glycopeptides

- O-linked core structures on building blocks (such as Fmoc, Ser, or Thr) that can be utilized in peptide synthesis.

Phase I Activities and Expected Deliverables

- Synthesize a defined library of free reducing-end glycans (20-50 compounds) representative of a sector(s) of the mammalian glycome that is not presently commercially available, under GLP conditions on a pilot scale (~ 200 µg/compound)
- Purify these compounds using best practices to >98% purity
- Verify structures of the synthesized compounds by NMR
- Investigate any packaging issues for the compounds
- Provide samples (~50 µg) of all synthesized compounds to an NIGMS-designated screening center for printing on glycan arrays, appropriate validation testing, and subsequent use in NIGMS-funded screening assays
- Provide the spectra used to confirm each glycan's structure as part of product information

Phase II Activities and Expected Deliverables

- Expand the reducing glycan libraries representative of a sector(s) of the mammalian glycome and not presently commercially available to at least 100 compounds
- Verify structures of the synthesized compounds by NMR
- Scale up the synthesis, purification, structural verification, and packaging of all compounds in the libraries
- Provide the spectra used to confirm each glycan's structure as part of product information
- In collaboration with an NIGMS-designated screening center: provide ~ 50 µg of each of the newly synthesized compounds made to expand the libraries for printing on glycan arrays, appropriate validation testing, and subsequent use in NIGMS-funded screening assays
- Provide letters of interest from potential customers to purchase the product developed under this contract

322 Real-Time Integration of Sensor and Self-Report Data for Clinical and Research Applications

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 2-3

Budget (total costs): Phase I: \$200,000 for 9 months; Phase II: \$1,000,000 for 2 years

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

Summary

Wireless sensors, and mobile devices and applications are increasingly marketed for health monitoring or interventions in consumer and clinical settings for prevention or management of chronic disease. A rapidly expanding market segment of technologies are focused on objective measures of health related behaviors (e.g., physical activity, sleep, diet, medication adherence, etc.). These mobile health technologies offer the capability to collect tremendous volumes of high quality health data, with continuous monitoring or event recording functions, in near real time. The expanding use of behavioral monitoring technologies, applications and mobile messaging provides new opportunities within consumer health, clinical care, and research. However, meaningful interpretation of the high volume of data generated from monitoring technologies is a challenge for the patient, care team and the researcher. Further, health monitoring technologies are often criticized for lacking additional contextual data to facilitate their interpretation.

Added to data from sensors and monitoring technology, self-reported measures can provide invaluable psychosocial, contextual, and environmental health-related information. Patient-reported outcomes in physical, mental or social health domains include physical abilities, fatigue, pain, depression, and social interactions. The expanded use of smartphone technologies lends itself to private, convenient, real-time data collection of self-reported measures. However, development or optimization of cross-platform mobile applications and scalable, efficient, cloud-based server platforms for rapid and real-time self-reporting and monitoring of these measures is needed.

Real-time integration of objective and patient-reported data could improve understanding and clinical management of acute and time-varying symptoms such as fatigue, pain, or depression experienced by cancer and other chronic disease patients. The integrated collection of objective and self-reported data can stimulate innovation within clinical and research settings, including clinical trials, clinical care, case-management, interventions, surveillance, and epidemiologic studies. For example, temporal integration of medication monitoring technologies, such as smart pill cases and sensor-based activity and sleep data, with patient-reported measures of depression, fatigue, or pain could enhance pharmaceutical clinical trial results. However, efficient systems and platforms for the capture, storage, integration, visualization, and reporting of these data streams are extremely limited or non-existent.

Project Goals

This topic's short-term goal is the development of innovative, secure, privacy-compliant mobile applications and paired analytic systems to control the collection, transfer, integration, analysis and reporting of objective and self-reported health-related measures. Longer term goals include the integration of these data systems and layers in health care and research settings to support customized monitoring and feedback loops, alerts, or alarms for consumers, patients, or members of the health care team.

Responses to this topic are expected to address the development of efficient methods and platforms to:

1. Collect data from behavioral health monitoring technologies and self-reported behavioral, psychosocial, environmental, and contextual measures.
2. Demonstrate integration with various wireless sensors.
3. Appropriately secure data at each stage of collection, transfer, and storage.
4. Temporally integrate information from multiple data sources.
5. Visualize data using customizable tools.
6. Analyze and report on (patient identified or de-identified) individual or group level data using customizable tools and reporting systems.
7. Maintain compliance with HIPAA, privacy, and consent management protocols as required for platform specific applications.

The resulting platform's utility extends from consumer health to clinical care and research settings for behavioral monitoring and prevention or management of disease. This topic encourages development of innovative, secure, privacy compliant mobile applications and 2-way mobile messaging techniques to facilitate and control the collection and transport of temporal data inputs from behavioral health monitoring technologies, self-reported measures, and associated metadata. The data acquisition systems described above must be paired with efficient, scalable back-end systems for data importation, storage, integration, visualization, analyses, and output reporting. Data elements may include (but are not limited to) wireless physical activity or sleep sensors/monitors, physiologic sensors, adherence monitors, sensor-based measures of stress or fatigue, dietary intake measures, geospatial location tags or linkages, images, text based annotations, speech recording and recognition; and self-reports of behavioral, psychosocial, environmental, and contextual data.

An essential task for each proposal is the development of transparent and customizable analytic tools for temporal data integration, visualization, and summary reporting of individual or group level measures. Recommended short term targets for system outputs are to provide reports to patients/participants, clinicians/researchers, and health systems; with longer term targets to provide reports directly to electronic medical records and public health surveillance systems. Recommended reports are consistent with current health outcomes policy priorities and objectives in the Meaningful Use Matrix for electronic health records established by the Health Information Technology Policy Committee (see <http://healthit.hhs.gov/portal/server.pt>).

Phase I Activities and Expected Deliverables

- Establish a project team including proven expertise in: sensor technology for behavioral and physiological monitoring, wireless sensor integration with mobile devices (smartphones, tablets, etc.), self-reported and/or sensor-based psychosocial, environmental, and contextual measures, secure wireless transport of health data using standards based protocols, secure cloud-based computing models, data visualization, and systems architecture that will effectively address all objectives of the current topic
- Provide a report including detailed description and/or technical documentation of the proposed:
 - Database structure for the proposed system's self-reported and sensor-based data inputs and metadata requirements
 - Data standards for collection, transport, importation, and storage of self-reported and sensor-based data inputs

- Data types for exchange of health-related behaviors such as physical activity, sleep, diet, and medication adherence between mobile platforms and secure servers
- Data integration approaches to leverage multiple data input streams
- Data visualization, feedback, and reporting systems for population or clinical monitoring and research applications
- Expected sensor(s), mobile platform(s) and mobile device(s) compatibility matrix for front- end mobile application and back-end server systems to be developed
- Develop a functional prototype system that includes:
 - Front-end mobile application(s) to facilitate and control the collection and transport of self-reported and sensor-based data inputs and any associated metadata used within the system
 - Integration with several wireless sensors including wireless physical activity monitors and other physiologic, geospatial, indoor location, proximity, environmental, or compliance related sensors
 - Automated data screening and importation protocols for data transferred from the mobile application to the back-end server systems
 - Software systems user interface (web- or computer-based)
 - Back-end user-interface controls for custom data integration and visualization for individual or group-level data
- Provide a report detailing output reporting systems feasibility, proposed timelines, data standards, and communication architecture for reporting summary outputs to patients/subjects, clinicians/researchers, electronic medical records, and health surveillance systems
- Finalize database formats and structure, data collection, transport, and importation methods for targeted data inputs
- Include funds in budget to present Phase I findings and demonstrate the final prototype to an NCI evaluation panel

Phase II Activities and Expected Deliverables

- Beta-test and finalize front-end mobile applications developed in Phase I
- Beta-test and finalize automated file transfer, screening, and database importation protocols and systems
- Develop, beta-test, and finalize data integration and visualization tools developed in Phase I
- Develop, beta-test, and finalize care team/researcher user-interface systems
- Develop and beta-test output reporting systems capabilities for multiple system output targets listed above
- Demonstrate system compatibility with sensor(s), mobile platform(s), and mobile device(s), included in the Phase I compatibility matrix
- Perform regression testing for both front-end and back-end system functions
- Conduct usability testing of consumer/patient-facing mobile applications and any associated web portals and care team/researcher-facing user interface features including system management, analyses, and reporting applications
- Develop systems documentation where applicable
- In the first year of the contract, provide the program and contract officers with a letter(s) of commercial interest

- In the second year of the contract, provide the program and contract officers with a letter(s) of commercial commitment

323 Development of Radiation Modulators for Use During Radiotherapy

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 3-5

Budget (total costs): Phase I: \$250,000 for 9 months; Phase II: \$1,500,000 for 2 years

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

Summary

Radiotherapy is employed in the treatment of over half of all cancer patients. Many of those patients suffer adverse effects during and/or after treatment. Additionally, tumors recur in approximately half the patients treated with curative intent. Enhancing specific tumor killing and minimizing normal tissue damage from radiotherapy would improve tumor control and patient quality of life. An ideal intervention would both enhance radiation effects in tumors and protect the normal tissues.

Radiosensitizers are agents that are intended to enhance tumor cell killing while having a minimal effect on normal tissues. Recently, two new radiation sensitization drugs have proven clinically effective: Temozolomide treatment with radiotherapy for glioblastoma and Cetuximab treatment combined with radiation for head and neck squamous cell cancers. There is significant potential for further development of novel radiosensitizing agents.

Conventionally, *radioprotectors* are defined as agents given before radiation exposure to prevent or reduce damage to normal tissues, while *mitigators* refer to those agents given during or after a patient's prescribed course of radiation therapy to prevent or reduce imminent damage to normal tissues. Both radioprotectors and mitigators are also being developed as potential countermeasures against radiological terrorism and several have shown promise in pre-clinical testing. In order for these to be developed and useful in clinical radiation therapy applications, it is imperative to demonstrate that they do not protect cancer cells.

The importance of developing agents that sensitize tumor cells, protect or mitigate radiation-induced damage in normal tissue, improve survival, quality of life, and palliative care in cancer patients was emphasized in a recent NCI workshop on *Advanced Radiation Therapeutics - Radiation Injury Mitigation* held on January 25th 2010 (Movsas B, et al. [Decreasing the adverse effects of cancer therapy: National Cancer Institute guidance for the clinical development of radiation injury mitigators](#). Clin Cancer Res. 2011 Jan 15;17(2):222-8. Epub 2010 Nov 3. PMID: 21047979), and in a workshop on *Radiation Resistance in Cancer Therapy: Its Molecular Bases and Role of the Microenvironment on its Expression* held Sept 1-3, 2010. Prior workshops have dealt with sensitization, protection, or radiation effects assessment (Colevas AD, et al. Radiation Modifier Working Group of the National Cancer Institute. [Development of investigational radiation modifiers](#). J Natl Cancer Inst. 2003 May 7;95(9):646-51. Review. PMID:12734315; Stone HB, et al. [Models for evaluating agents intended for the prophylaxis, mitigation and treatment of radiation injuries. Report of an NCI Workshop, December 3-4, 2003](#). Radiat Res. 2004 Dec;162(6):711-28. PMID: 1554812.)

This contract topic encourages the development of innovative and promising radioprotectors, mitigators, or sensitizers that either selectively protect normal tissues (but not tumors) against ionizing radiation or selectively sensitize tumors, thereby increasing the therapeutic ratio of radiation. Proposals for radiation modulators are solicited that include preclinical and/or early phase clinical studies demonstrating safety, efficacy, dose, schedule, pharmacokinetics (PK), pharmacodynamics (PD), and metabolism. Proposals should also demonstrate a clear understanding of regulatory requirements, and should include a regulatory plan including key steps such as a pre-IND meeting with FDA, submission of an investigational new drug (IND) application, approval of clinical trial design, and ultimately drug registration.

Project Goals

The goal is to stimulate collaborations among academic institutions, small businesses, and contract research organizations in order to promote the rapid development of innovative radioresponse modifiers that will decrease normal tissue injury and/or enhance tumor killing, thereby improving radiotherapy outcomes. The long-term goal is to enable small businesses to fully develop, license, and/or market radioresponse modifiers for clinical use.

The contract proposal must describe:

Phase I

- A quantitative estimate of the patient population that will benefit from the availability of such radioresponse modifiers.
- A plan for generating evidence that the proposed compound(s) protects at least one relevant normal tissue from radiation-induced injury, and/or sensitizes at least two relevant tumor models.
- Either:
 1. A plan for generating evidence that the proposed radioprotector(s)/mitigator(s) does not significantly protect cancer cells, OR
 2. A plan for generating evidence that the proposed radiosensitizer(s) does not significantly sensitize normal cells and tissues.
- The plans must include the methodologies proposed to evaluate the preferential effects on normal tissues or tumors by the compound(s) *in vivo* (including appropriate biomarkers and endpoints as determined during early interactions with the FDA).
- Determination of the optimal dose and schedule *in vivo* based upon preclinical pharmacodynamic and pharmacokinetic studies.
- Statistical validation of the proposed study endpoints including where appropriate, power calculations and rationale for proposed sample sizes.

Phase II

- The approach to early-phase human trials designed to take into account relevant molecular pathways and targets, and aim to gather pharmacodynamic and pharmacokinetic data to confirm the compound's observed behavior in animal studies.

The approach and experiments to assess the safety and efficacy of the compound(s) in early-phase human trials employing, as appropriate, physician-reported endpoints as well as patient-reported outcomes.

Deliverables

Phase I may include primarily preclinical studies. Phase II or Fast-Track proposals must contain a section entitled "Regulatory Plan" detailing plans for early involvement of the FDA. There should be a description of how the applicant plans on meeting the requirements to: 1) define suitable biomarkers and endpoints, 2) file IND and 3) design and perform phase 0-2 clinical trials in preparation for product transition to phase 3 clinical trials by groups such as the Radiation Therapy Oncology Group (<http://www.rtog.org/>).

Where cooperation of other partners is critical for implementation of the proposed methodology, the applicant should provide evidence of such cooperation (through partnering arrangement, letters of support, etc.).

The following deliverables may be required depending on a compound's maturity in the developmental pipeline:

Phase I

- Selection and approval of cell line panels for *in vitro* testing
- Demonstration of drug solubility and uptake using cultured normal and transformed cells
- Study design for determining clonogenic survival or approved alternative tailored to the mechanism of each tested compound
- Clonogenic survival data or approved alternative validating lack of drug toxicity in normal cells, efficacy and specificity of radioprotection for normal cells and/or efficacy and specificity of radiosensitization for tumor cells
- Preliminary evidence for lack of *in vivo* toxicity in normal cells or organisms
- Documentation providing a top-level description of the protocols and the testing results should be provided to NCI as part of the Phase I progress report

Phase II

For advanced pre-clinical work:

- Design of NCI and Institutional Animal Care and Use Committee (IACUC)-approved *in vivo* experimentation plan including statistical validation of experimental design, and sample size determination including power calculations
- Selection and approval of tumor cell panel and normal tissues for *in vitro* testing
- Demonstration of bioavailability PK and PD in rodent model
- For radiation protectors/mitigators: demonstration by physiologic testing and histological assessment that irradiated normal tissues are spared over a 6-month period
- Demonstration of effects (sensitization or lack of protection as appropriate) on tumors using *in vivo* radiation regrowth delay assays
- Collection of data validating lack of drug toxicity, efficacy, and specificity for normal cells over tumor cells in the case of radiation protectors/mitigators
- Documentation of the testing protocol and testing results should be provided to NCI as part of the Phase II progress report for pre-clinical studies

For proposals advancing to early-phase human trials:

- Identify GMP drug source
- Obtain IND approval
- Provide evidence of established clinical collaboration
- Submit protocol for IRB approval
- Define suitable clinical endpoints and patient-oriented outcomes

324 Novel Imaging Agents to Expand the Clinical Toolkit for Cancer Diagnosis, Staging, and Treatment

(Fast-Track proposals will be accepted.)

Number of Anticipated Awards: 3-5

Budget (total costs): Phase I: \$250,000 for 9 months; Phase II: \$1,500,000 for 2 years

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

Summary

Medical imaging plays a key role in the clinical management of cancer patients. Cancer imaging agents are used in conjunction with medical imaging equipment, and, by highlighting the contrast between normal and malignant tissues, they allow the collection of information on cancer presence, spread, and metabolism.

Recent scientific advances in nanotechnology, radiochemistry, reporter gene imaging, cancer stem cell imaging, and other fields enable the development of novel imaging agents for:

- Early detection and diagnosis of cancer.
- Differentiation of benign disease from malignancy.
- Stratification of patients for the purpose of selecting a cancer therapy.
- Surgical planning.
- Evaluation of tumor response to chemotherapy and radiation therapy.
- Detection of cancer recurrence.

Despite significant preclinical scientific progress, very few cancer imaging agents are available in the clinic. This SBIR contract topic seeks to stimulate the commercialization of novel imaging agents, including but not limited to: nanotechnology-based imaging agents, radiopharmaceuticals for positron emission tomography (PET) and single photon emission computed tomography (SPECT), targeted contrast agents for X-ray, computed tomography (CT), and magnetic resonance imaging (MRI), optical contrast agents, and reporter gene imaging technologies.

One specific area of interest under this topic is the development of single-domain antibody fragments used to target radionuclides for imaging and targeted radiotherapy of cancer. Single-domain antibody fragments are comprised of the single variable region of naturally-occurring antibodies that lack a light chain or engineered antibody fragments. This type of small protein or peptide has advantages over conventional antibodies and antibody fragments in terms of favorable and tunable clearance kinetics, ability to recognize hidden or uncommon epitopes, agent format flexibility, and ease of manufacture. Therefore, developing an imaging technology for early diagnosis of cancer at the molecular level based on single domain antibody fragments will be encouraged.

Project Goals

The short-term goal of this SBIR contract topic is to support research and development activity at small businesses that are developing cancer imaging agents. The imaging agent should be novel and, when appropriate, have high affinity and specificity against tumor targets. It should also display fast *in vivo* clearance, rapid tumor accumulation, sufficient *in vivo* stability and good bioavailability, and low immunogenicity and toxicity. The work scope may include animal testing, formulation, GMP production, pharmacokinetic studies, pharmacodynamic studies, and toxicological studies. These data will support the rationale for continued development of the experimental medical imaging agent to the point of filing an Investigational New Drug application (IND).

The long-term goal of this contract topic is to enable small businesses to bring novel classes of fully developed cancer imaging agents to the clinic and the market. Therefore, businesses are encouraged to submit applications for development of lead compounds representing novel technology platforms.

Phase I Activities and Expected Deliverables

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

Expected activities may include:

- Prepare an imaging agent that produces a high signal-to-noise ratio
- Demonstrate capabilities enabled by the imaging agent
- Quantify imaging signals to determine agent affinity and specificity
- Perform proof of concept pre-clinical studies
- Perform preliminary toxicological studies
- Prepare a development plan that describes in detail the experiments necessary to file an IND or an exploratory IND
- Present Phase I results and development plan to NCI staff

Phase II Activities and Expected Deliverables

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

Expected activities may include:

- Complete all pre-clinical experiments according to the development plan
- Demonstrate fast *in vivo* clearance, rapid tumor accumulation, sufficient *in vivo* stability, good bioavailability, and low immunogenicity/toxicity of the imaging agent
- Demonstrate high reproducibility and accuracy of the imaging technology in several animal models
- When appropriate, demonstrate similar or higher specificity and sensitivity of the technology compared to other imaging technologies
- When appropriate, demonstrate capabilities to monitor efficacy of drugs in tumor cell lines and/or animals
- Produce sufficient amount of clinical grade material suitable for an early clinical trial
- If warranted, file an IND or an exploratory IND for the candidate imaging agent
- Complete small-scale clinical study

325 Innovative Radiation Sources for Advanced Radiotherapy Equipment

(Fast-Track proposals will be accepted.)

Number of Anticipated Awards: 2-3

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

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

Summary

Radiation therapy is an important tool in the cancer treatment arsenal. Conventional radiotherapy with photons is currently used to treat 50% of all cancer patients. The success of radiation therapy and the risk of side effects depend heavily on the ability to concentrate radiation in the tumor while not injuring adjacent normal tissues. Recent developments in radiation therapy instrumentation have increased the ability to direct radiation energy, thereby improving the clinical utility of this treatment.

Although significant progress has been made, one of the limiting factors in the development of novel radiotherapy approaches is the size and cost of radiation sources. For many types of modern advanced radiotherapy, the equipment needed to produce such radiation is bulky and extremely expensive. At the same time, continuing advances in particle acceleration approaches enable breakthrough innovations in this field. An example of such advancement is the development of technologies for charged particle acceleration using high-power lasers (laser-plasma acceleration). New technologies enable the construction of compact, cost-efficient external beam accelerators, and facilitate new applications of radiotherapy. Another potential class of applications is the development of fiber-optics-based systems for endoscopic delivery of gamma or electron beams. These and other technologies present key opportunities in enabling next-generation radiation therapy instruments.

Project Goals

This contract topic seeks to stimulate research, development, and commercialization of innovative radiation sources that could be used to reduce the cost and footprint of radiation treatment systems, and thus enable novel routes for radiotherapy delivery.

It is expected that the proposed innovation be driven by clinical practice. Therefore, in addition to standard proposal components, the contract proposal must contain specific discussion of:

1. Evidence of an existing clinical problem that is addressed by the proposed radiation source
2. Analysis of competitive methods to address the same problem and explanation of competitive advantages of proposed system.

The short-term goal of the project is to perform proof-of-principle technical feasibility demonstration of innovative radiation source or source components. The long-term goal of the project is to develop a robust, reliable radiation source and to incorporate it into a radiotherapy system.

Phase I Activities and Expected Deliverables

Phase I activities should support the technical feasibility of the innovative approach.

- Design and build proof-of-principle prototype system
- Characterize beam parameters, including energy spectra, spatial distribution, and flux
- Demonstrate that the prototype has a high probability of development into a clinically-relevant radiation source in Phase II, based on measured beam parameters
- Provide documentation of the prototype system design, characterization protocol, and testing results to NCI as part of the Phase I progress report

Phase II Activities and Expected Deliverables

Phase II activities should support development of a full-scale prototype of a radiation source with beam parameters appropriate for the clinical application.

- Design and develop a prototype radiation source with parameters (e.g., beam energy, flux, stability, etc.) that are acceptable for clinical radiation oncology application

- Demonstrate that the system is capable of delivering a treatment dose in a clinically acceptable period of time in an anthropomorphic phantom
- Provide a data sheet detailing performance of the developed system to NCI as part of the Phase II progress report

Where cooperation with other equipment manufacturers is critical for implementation of proposed technology, company should provide evidence of such cooperation (through partnering arrangement, collaboration, or letters of intent) as part of the Phase II proposal.

NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES (NCATS)

The mission of the National Center for Advancing Translational Sciences 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. NCATS supports the entire spectrum of clinical and translational research.

This solicitation invites proposals in the following areas.

001 Visualizing Knowledge about Human Health and the Pathways of Translation

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 2

Translational science is very complex and can be characterized in a multitude of ways. Publications, grant applications, progress reports, funding, specific aims, study designs, hypotheses, outcomes, scientific evidence, experts, collaborations, organizations, and networks, as well as many other factors reflect the complex activity of translational and clinical research. These elements are interlinked and often are represented by massive heterogeneous data, e.g. thousands of papers are produced weekly. To make sense of these data and to aid in seeing the big picture, new methods are needed. Data visualization techniques (e.g. maps, networks, clusters, time series) expose patterns, trends and correlations and are proven to be useful for extracting information from abundant data. NCATS invites SBIR proposals that will facilitate the introduction of visualization technology into understanding the big picture of translational science, the evidence behind the knowledge about human health, and interdisciplinary communication of complex scientific information.

Main requirements

The outcome of this contract is expected to be software that assists in exploring multidimensional data and understanding complex concepts. The software should:

- visualize high-dimensional data from potentially diverse data sources
- enable data exploration, change of displayed dimensions, and semantic zooming
- create personalized views
- work with complex data dimensions, utilizing the elements of principal component analysis (PCA) or other appropriate techniques
- have transparent, validated, and well-documented protocols for all steps of data processing (cleansing, filtering, analysis, visualization, personalization, etc.)
- be accompanied by documentation of data processing algorithms, data accuracy, precision, and other features necessary for the most accurate interpretation of the produced visualization
- take advantage of the existing tools and technologies whenever possible

- have Application Programming Interface (API) that does not require programming skills

Sample areas of interest to NCATS include

- Landscape of knowledge about human health with underlying evidence
- Knowledge gaps, discrepancies
- Comparative evidence
- Provenance of information about human health, therapeutics and diagnostics
- Translational Pathways: from discovery to clinical practice
- The patterns of self-care and health literacy in various cultures and communities
- Uncertainty of information about human health coming from clinical practice, research and consumers
- Propensity scores in observational studies
- Human subject research design
- Complex and distributed resources and on-going research activities, e.g. among Clinical and Translational Science Award (CTSA) institutions or NIH Institutes

Deliverables

The deliverable of Phase I is a visualization of a test dataset(s), which is made meaningful and valuable to NCATS through the process of interactive learning with minimal burden on the NCATS experts. It is envisioned that the offeror's representative will gather initial information from publically available sources, and then fine-tune it via observing NCATS activities and interactions with NCATS staff to ensure that the presentation of data and analysis is tailored to NCATS interests and facilitates actions, discussions, feedback, and further learning.

The Phase II deliverable is web-enabled software that can be used for multidimensional data exploration and analysis, can work with multiple data sources, and can be personalized to the customer needs via generalized interactive learning methodology of Phase I.

Data sources

The analysis should be done using a number of various data sources, e.g., publications, social media, NIH databases. The identification of appropriate sources is determined by the offeror. The choices must be justified, analyzed, and well documented with advantages and limitations of every source.

Other project clarifications

The offerors are encouraged to utilize the multiple principal investigator option to bring in experts from academia http://grants.nih.gov/grants/multi_pi/.

002 Biomarker Study for Creatine Transporter Defect Disorders

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 1

Creatine Transporter Deficiency (CTD) is a severe x-linked linked mental retardation disorder. It is caused by mutations in the creatine transporter gene (SLC68A). Mutations in this gene result in an inability to move creatine across the blood brain barrier. This inability to transport creatine across the blood brain barrier results in a severe deficit of creatine in the CNS and this lack impacts energy homeostasis. Currently, diagnostic biomarkers rely on

comparing urinary levels of creatine/creatinine; however these readings rarely provide definitive enough data for a CTD diagnosis. While there are only a few hundred patients who have been accurately diagnosed with this disorder it is estimated that there are upwards of 40,000-50,000 individuals that are now labeled with x-linked mental retardation or autism. Clinical research of potential therapeutics will rely on the availability of a pool of patients, as well as attempts to better understand the extent and progression of the disease through natural history studies. This initiative seeks to develop a biomarker for use in Creatine Transporter Defect disease. This biomarker would correlate to the nature of CTD and allow its use to identify patients suitable for inclusion in clinical trials. There is the potential that this biomarker could find utility as a diagnostic after validation.

Main requirements

The outcome of this contract is expected to be a biomarker to monitor the effects of creatine depletion in the CNS. This biomarker would be most useful if it could be tracked in blood or urine but cerebral spinal fluid markers would also be acceptable. This biomarker would have a large impact on patients if banked tissue and blood samples could be examined as well. This biomarker must show a difference between normal volunteer, diagnosed CTD patients and the difference from other autistic or cognitively impaired patients whose symptoms are not related to creatine transporter deficiency. This assay should be able to be performed in reasonable throughput.

Deliverables Phase 1

A biomarker assay that meets the requirements listed above and also meets the following:

- Develop a working assay
- Characterize the variability, reproducibility and accuracy of the detection
- Demonstrate the utility of the assay by characterizing differences between normal volunteer, diagnosed CTD patients and the difference from other autistic or cognitively impaired patients whose symptoms are not related to creatine transporter deficiency
- Deliver the SOP of the working test to NCATS

Deliverables Phase 2

- Demonstrate clinical utility by testing a large number of patient samples or banked tissue or plasma samples
- Establish a relationship with companies developing therapeutics for the creatine transporter deficiency patients
- Deliver final SOP to NCATS for evaluation

003 Automated Instrument to Clean Microtiter Plates

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

Number of anticipated awards: 1

This initiative seeks to develop an automated piece of instrumentation that can be used to clean previously used microtiter plates, making them suitable for reuse. Given the large quantities of microtiter plates required for high throughput screening any such device developed has the potential of a viable commercial market. Currently in high throughput screening the rule of thumb is to treat every Society for Biomolecular Sciences (SBS) standard assay plate that gets run in a screen as a consumable that gets used only once and is then discarded due to the risk of cross contamination. That being the case, the relationship of assay plates to compound plates to be screened is a 1 to 1 association, meaning as your compound library grows, your demand for assay plates increases, driving costs upwards. Due to this 1 to 1 relationship, for many assays the most expensive part of the

screen are the assay plates themselves. In addition to the cost of the plates, these plates are typically made of non-biodegradable plastics (polystyrene, polypropylene, etc.) that will eventually end up in a landfill once discarded. A piece of instrumentation that could utilize some technique to clean used assay plates would allow each plate to be treated as a resource instead of as a consumable, which could greatly reduce screening costs in addition to the amount of solid waste generated. Also, as an automated device this instrument could be used as part of the screening process itself, which would reduce the amount of start up time and system real estate required for plate storage for large scale screens. Another benefit of the instrument being automated is it would remove the need for large scale screens to be run in batches, since one set of assay plates could be used for the entire screen allowing for continuous system operation.

Given the potential for cost and environmental savings and the high degree of automated instrumentation used in biological laboratory settings any instrument developed that could allow for the reuse of microtiter plates could potentially have a commercial market.

Project Goals

The preliminary goal of this project is to develop a functional prototype of an instrument capable of removing both biological reagents and compounds from a used SBS standard assay plate, specifically geared towards biochemical assays. The final product will be an instrument, or set of instruments, that could be integrated as a component of a high throughput screening system in an automated fashion, capable of cleaning plates regardless of the number of sample wells. The long term goal of this project is to bring this instrument to market to meet the needs of those researchers using high quantities of assay plates, for both biochemical and ideally cell based assays.

Phase I Activities and Expected Deliverables

- Develop a prototype instrument or a detailed plan for a device that meets the following specifications:
 - Can handle 96, 384, or 1536 plate formats;
 - Has the ability to utilize multiple potential cleaning solutions while minimizing the need for large quantities of reagent;
 - Has the capacity to completely dry a cleaned plate;
 - Does not involve any abrasive touching of the interior of each well, the bottom in particular, that could negatively affect the physical integrity of each well;
 - Has a maximum clean cycle time of 5 minutes total.
- Demonstrates a cleaning process for plates to be used within a biochemical assay with the ability to:
 - Remove over 99% of a biological reagent such as a BSA solution using different assay detection modes, within the dynamic range of the assay in question (absorbance, luminescence, fluorescence, etc.) to verify wash results (e.g. an absorbance assay utilizing Bradford staining solution);
 - Remove over 99% of a chemical compound such as Tannic Acid using different assay detection modes, within the dynamic range of the assay in question to verify wash results (e.g. a luminescence based assay utilizing a dose response curve of Tannic Acid as a control to quantify any residual Tannic Acid left in the sample area of the plate);
 - Does not degrade assay performance with repeated wash cycles, capable of withstanding up to 50 wash cycles total;
 - Although not a specific requirement towards Phase I completion, there should be some ability or plan to quantify a Sterility Assurance Level (SAL), geared towards later work in Phase II when some focus is given towards the ability to clean cell based assay plates to ensure there is no contamination between uses.
- Cost estimates to manufacture a device capable of meeting the specifications listed above.

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

Phase II Activities and Expected Deliverables

- Build a prototype instrument that meets the Phase I specifications in addition to several others geared towards the device working as part of a larger automated process:
 - Is accessible enough to have a plate automatically loaded into the device by standard laboratory robotic equipment;
 - Has a remote programmatic interface allowing the instrument to be controlled by an external software application through standard laboratory communication protocols (RS-232, TCP/IP, etc.);
 - Can reliably operate for extended periods of time in an automated fashion (overnight usage with a constant plate throughput limited by the duration of the load/unload time of the device and the cleaning process itself).
- Develop detailed procedures to be able to quantify the instruments cleaning effectiveness:
 - Provide detailed protocols to show the effectiveness of the instrument in removing biological reagents from a used assay plate;
 - Provide detailed protocols to show the effectiveness of the instrument in removing chemical compounds from a used assay plate;
 - Develop procedures to potentially allow for the cleaning of cell based assay plates, assuming these plates did not require any additional coating to promote cell adhesion.
- Demonstrate the ability of the prototype instrument to run the cleaning procedures as described above in an automated fashion:
 - A set of assay plates should be run for multiple cycles and show no residual biological or chemical contamination from previous uses;
 - The assay performance should remain close to constant despite using the same plates repeatedly;
 - The assay performance should be comparable to using new assay plates;
 - Multiple assay detection modes should be tested as described in Phase I.
- Develop a robust manufacturing plan for the instrument, using off the shelf OEM components where possible to minimize expense.
- Provide NCATS with all data resulting from Phase II Activities and Deliverables.

004 Assay Development for High-Throughput Screening of Chemicals of Toxicological Concern

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 2-3

Adverse human health outcomes – a.k.a., “toxicity” – caused by pharmaceutical or environmental compounds are a major cause of drug development failure and public health concern. Methods to evaluate the potential of chemical compounds to induce toxicity are based largely on animal testing, are low-throughput and expensive while giving little insight into mechanisms of toxicity, and have not changed appreciably in the last 50 years despite enormous advances in science. Multiple efforts, including Tox21 in the U.S., REACH in the E.U., and multiple industrial collaborations, are attempting to develop *in vitro* methods to assess chemical toxicity. These programs must assess toxicity potential in every organ system and identify pathways and/or targets affected. Given the protean nature of these effects, it is likely that hundreds of *in vitro* assays will need to be developed and tested for their ability to read out chemical effects on particular cell types and pathways. Progress in the field is currently limited by the relatively small number of pathways and cell types that have been developed into high-throughput screening (HTS)-ready assays, and the artificial nature of many of the assays that have been

developed (e.g., immortalized/transformed cell lines, heterologous expression with lack of physiologically accurate regulation).

The development of HTS-ready assays which can report on particular pathways and cellular phenotypes across the full spectrum of pathway space and toxicological outcomes is needed. Such assays would need to meet strict performance criteria of robustness, reproducibility, and physiological relevance. The assays developed would need to be capable of being run in 384-well or (ideally) 1536-well format and must allow the testing of >100,000 samples per week.

Main requirements

The outcome of this contract is expected to be one or more novel assays for targets, pathways, and cellular phenotypes related to any type of xenobiotic toxicity. These assays would utilize human cells, including immortalized cell lines, primary cells, and stem cell derived cells, and must be functional in multiwell format with characteristics suitable for automated high-throughput screening. Such assays should be novel, reflecting new pathways or cellular endpoints than are currently available, and be clearly connected to some type of human toxicological response. Such assays could find utility as in chemical assessment and risk management after validation.

Deliverables Phase 1

An assay that meets the requirements listed above and also meets the following:

- Develop a working assay in 96-well or denser (384, 1536) microwell format
- Characterize the sensitivity, specificity, variability, reproducibility, signal: background, dynamic range, and accuracy of the assay, utilizing standard positive and negative controls, Z' values >0.5
- Demonstrate the utility of the assay by characterizing its ability to detect the effects of compounds known to affect the pathway/cellular phenotype, with a throughput of at least 10,000 samples/day with workstation automation
- Are not duplicative of assays already available commercially
- Deliver the assay/SOP to NCATS for evaluation

Deliverables Phase 2

- Demonstrate miniaturization of assay to work in at least 384-well (preferably 1536-well) format with same technical specifications as listed above
- Demonstrate amenability for HTS by successful testing of >100,000 samples/day in fully automated robotic format with maintenance of assay performance
- Deliver final assay/SOP to NCATS for evaluation.

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, blood vessel, lung, and blood diseases 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 program, visit our website at:
<http://www.nhlbi.nih.gov/funding/sbir/index.htm>

This solicitation invites proposals in the following areas.

072 New Methods to Detect and Assess Myocardial Fibrosis

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 3-5

Budget (total costs): Phase I: \$200,000 for 12 months; Phase II: \$1,000,000 for 3 years

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

Summary

Myocardial fibrosis is a crucial marker of adverse cardiac remodeling. Research suggests a strong correlation between the extent of myocardial fibrosis and adverse myocardial remodeling that occurs after ischemic injury or during the progression of cardiomyopathies and heart failure. Diffuse myocardial fibrosis is thought to provide a high-risk substrate for the development of atrial and ventricular arrhythmias. Therefore, early detection of myocardial fibrosis might be prognostic for the development of heart failure and increased risk of both atrial and ventricular heart rhythm disorders. In addition, a means to easily assess the development of myocardial fibrosis is expected to provide a more effective way to monitor therapeutic efficacy of interventions intended to slow or halt the progression of these cardiac disorders. Although present methods can detect “frank” fibrosis, new methods that target the early stages of fibrogenesis are expected to be extremely useful as they may be more effective in guiding interventions that block further development of fibrosis and prevent the onset of myocardial remodeling associated with heart failure and arrhythmias.

Project Goals

The goal of this initiative is to significantly advance non-invasive methods to detect, image, and monitor myocardial fibrosis *in vivo*. Myocardial fibrosis is a hallmark of adverse cardiac remodeling associated with development of heart failure and life-threatening cardiac arrhythmias. Early detection of myocardial fibrosis is essential to development of effective ways to diagnose, treat, and prevent these cardiac disorders. Current methods for detection of myocardial fibrosis, however, are either invasive (e.g., biopsy-based) or unable to detect early fibrogenesis or diffusively distributed fibrosis in the myocardium. This initiative encourages researchers to develop innovative myocardial fibrosis detection methods that overcome current challenges and demonstrate their utility in appropriate experimental models.

Phase I Activities and Expected Deliverables

Phase I activities are expected to be aimed at demonstration of the method’s feasibility. The studies may be conducted in established animal models or human tissue samples. Examples of Phase I research and expected deliverables may include, but are not limited to:

- Design, synthesis and development of fibrosis-targeted imaging agent(s) and demonstration of the ability to detect cardiac fibrosis in well-established animal models
- Design and development of MRI-based technology/method to detect diffuse myocardial fibrosis in established experimental models
- Identification of serum biomarker(s) of myocardial fibrosis (e.g., extracellular matrix protein fragments, matrix metalloproteinases, microRNAs, post translational modified protein or glycoprotein fragments, etc.) and their limited validation using established animal models or human tissue samples

Phase II Activities and Expected Deliverables

Phase II research activities are expected to include development, optimization and validation of the product/method, including research work leading to regulatory filing (IND or IDE) and help attract funding from non-federal sources. Examples of expected deliverables may include, but are not limited to:

- Development of fibrosis-targeted imaging agent(s) and data demonstrating capability to detect and quantify cardiac fibrosis in established animal models using appropriate clinical imaging platforms
- Development of MRI-based methods that enable detection and quantification of diffuse myocardial fibrosis and data demonstrating the method's utility in established experimental models
- Validation of serum biomarker(s) for assessment and monitoring of myocardial fibrosis progression in appropriate human studies

073 Evaluating Obstructive Sleep Apnea Dental Device Treatment Compliance

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 3

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

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

Summary

As a therapeutic option, an array of existing oral appliances are approved for the medical treatment of snoring and mild to moderate obstructive sleep apnea but lack specific capabilities necessary to fulfill regulatory requirements and conduct population-based effectiveness research. Integration of oral appliance and electronic monitoring technologies is needed to develop enhanced oral devices capable of addressing regulatory requirements and facilitating population-based research and clinical trials monitoring adherence and effectiveness of sleep apnea treatment.

Project Goals

Adapt therapeutic oral appliances currently used to maintain an open airway during sleep with electronic and sensor technologies to quantitatively monitor and evaluate patient adherence and the effectiveness of treatment. Validate the implementation of monitoring technologies as needed to fulfill regulatory requirements. Since oral appliances vary in how an open airway is maintained, it is anticipated that 2-3 different oral appliances with integrated monitoring capability. Proposals to develop an oral appliance treatment as opposed to integrate monitoring capabilities into an existing technology will not be considered responsive to this request.

Phase I Activities and Expected Deliverables

Development of a prototype oral appliance with an integrated capability of monitoring treatment adherence and efficacy up to 24 hours independent of external power sources and connections. The enhanced oral appliance must be should not change acceptance of the device by patients, interfere with therapeutic efficacy of the device, increase patient burden, or introduce potential electrical or biological risks to patient safety over the anticipated life of the instrument. The prototype must demonstrate that the proposed design specifications including sensitivity and longevity of sensor technology have been achieved for successful completion of phase I activities.

Phase II Activities and Expected Deliverables

A sufficient number of working devices and procedures for deployment and field testing must be developed. These procedures should validate the capabilities of the monitoring technology, demonstrate adherence to therapy, and the efficacy of treatment fulfilling regulatory requirements of the commercial transportation industry.

Validation includes field testing in a representative cohort of middle-age men and women diagnosed with sleep apnea and physician-recommended treatment using an oral appliance. The cohort must be designed to allow a stratified analysis of the device capabilities among apnea patients with Epworth Sleepiness Scale scores greater than or equal to 10 compared to apnea patients with scores below 10. The results obtained from device monitoring should be compared with correlative measures such as actigraphy, daytime sleepiness and psychomotor vigilance task to establish that the monitoring capabilities of the integrated device can be used to accurately predict functional outcomes. Proposals to enhance standard medical practice in diagnosis or treatment of sleep apnea will not be considered responsive.

074 Improving Safety and Efficacy of Red Blood Cells for Transfusion

(Fast-Track proposals will be accepted.)

Budget (total costs): Phase I: \$200,000 for 6 months; Phase II: \$1,500,000 for 2 years

Number of anticipated awards: 3

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

Summary

Red blood cell (RBC) products for transfusion undergo metabolic and physical changes in both the cellular and plasma fractions during storage (RBCs can be stored up to 42 days currently) which may be associated with non-infectious risks and reduced tissue oxygenation capacity. The changes that occur during storage have been referred to in the literature as the RBCs "storage lesion". Many of these changes have been characterized and include increasing levels of microparticles and potassium; free hemoglobin release; decrease in pH, adenosine triphosphate, and 2,3-diphosphoglycerate; loss of RBC membrane flexibility; and changes in enzymatic functionality resulting in a loss of nitric oxide (NO) signaling. Current research suggests that the storage lesion may result in extravascular hemolysis and inflammation, vasoconstriction, and potentially suboptimal tissue oxygenation. Many retrospective and prospective studies, including a recent meta-analysis of 21 studies, have demonstrated that the transfusion of RBC units which have been stored for longer periods (up to 42 days) appears to be associated with increased recipient morbidity and mortality; but these associations may be confounded by severity of illness. Two large blinded, multi-center randomized trials are currently underway in the United States and in Canada to determine if "younger" vs. "older" or "standard age" blood is equally safe and effective in complex cardiovascular surgery and ICU patients, respectively, but the results of these studies will not be known for several years.

While it is unclear at this stage whether the RBC storage lesion results in serious adverse clinical outcomes in transfusion recipients, it would seem biologically plausible that a reduction in the number of potentially toxic elements in RBC supernatants, as well as an increase in the concentration of well-preserved RBCs, would be beneficial in many ways. These potential benefits could include 1) improved effectiveness of RBC products; 2) markedly reduced adverse events; and 3) optimal tissue oxygenation by fully functioning RBCs. Developing improved blood bank storage and transfusion processes and practices to mitigate the RBCs "storage lesion", improve the effectiveness of transfusion, and safely maintain the shelf-life of RBC components at or near the current FDA mandated maximal storage limit of 42 days, will be important to assuring blood availability for future public health needs.

There is scientific evidence that some of the RBC storage lesion changes might be reduced, restored or mitigated by changes in blood storage conditions and/or through manipulation prior to transfusion with processes such as washing, filtration and/or reinitiation. Multiple strategies may be needed because targeting any single parameter may be insufficient to markedly improve RBC product quality.

The National Blood Collection and Utilization Survey Report estimates that a total of 17.3 million blood units were collected and 14.6 million RBCs units were transfused in the United States in 2008. Except for pediatric transfusions, blood banks always deliver the oldest available RBC units when a RBC transfusion is requested to optimize their inventory management. It is anticipated that a product and/or process developed for this contract

topic could be utilized by all, or a portion of, the patients needing a transfusion in the U.S. and internationally. Depending on the product, the market may be any or all of the following: blood centers, blood banks, and hospitals as these are the facilities that collect, produce and/or transfuse RBC component units.

Applicants are encouraged to explore utilization of the NHLBI SMARTT program (<https://www.nhlbismartt.org/>) to assist with the preclinical and early clinical study planning and regulatory support for IND/IDE applications associated with this contract topic.

Project Goals

The purpose of this SBIR contract solicitation is to develop new additive solutions, storage bags and/or new processes to enhance RBCs function and survival after storage and transfusion and/or reduce non-infectious complications associated with allogeneic RBC component transfusions.

Accepted products, devices or technologies for the contract topic include, but are not limited to:

- New additive solutions for RBC component storage,
- Novel RBC component storage bags or modification of current storage bags,
- Small footprint cell washer and associated disposables for use in hospital blood banks and transfusion services,
- Pre- or post-storage processes and systems that will deliver a more therapeutic, less toxic transfused RBC component,
- Development of kits, including combinatorial approaches such as devices and technologies, to achieve the project goals.

Development of products and/or procedures for the sole purpose of leukoreduction will not be considered responsive to this solicitation.

Phase I Activities and Expected Deliverables

In Phase I, the investigator(s) are expected to complete proof-of-concept, become knowledgeable of regulatory requirements for required IND/IDE approval, and present the Phase I results and the development plan to NHLBI staff. The Phase I research plan must contain specific, quantifiable, and testable feasibility milestones along with alternate approaches if unexpected data are generated. The new technology needs to result in a demonstrable reduction in the development of the RBC storage lesion such as a decrease in the number of red blood cell microparticles and/or better preserved RBC rheology.

Phase II Activities and Expected Deliverables

Phase II should follow the development plan laid out in the Phase I if the FDA has approved the approach and feasibility has been demonstrated. Phase II studies should focus on developing the required technologies and working towards the initiation of clinical testing.

Deliverables include the provision of evidence of having initiated the process leading to IND/IDE submission (and hopefully approval), and the documentation that the plan is feasible and that there are alternate approaches if any contradictory data are generated. When appropriate, it must be documented that production of sufficient amount of clinical grade material suitable for an early clinical trial can occur. The Phase II research plan must contain specific, quantifiable, and testable feasibility milestones.

075 Dedicated Pediatric Cardiac MRI Receive Coils

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: \$225,000 for 12 months; Phase II: \$600,000 for 1 year

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

Summary

Clinical MRI systems use local surface receive devices (coils) to provide optimized signal to noise and enable fast imaging using parallel imaging techniques. These surface coils are designed for adult patients and function poorly for pediatric patients. Pediatric coils are targeted at a certain age group and due to the wide range of pediatric patient sizes (from neonates to preadolescents) it is not possible to design one set of surface coils that fit all pediatric patients. In this solicitation we seek a set of dedicated cardiac MRI coils that will cover the entire range of pediatric patients.

Project Goals

The aim is to create a set of four (4) different pediatric cardiac MRI receive coil arrays to cover the size ranges of the pediatric population: 1) Neonate/Premie, 2) 3 months – 2 years, 3) 4-8 years, 4) 10-12 years. The coils could consist of a semi-rigid shell in the shape of the pediatric torso and multiple receiver coil elements will be placed on the shell. Optimal design in terms of coil element sizes and placement needs to be determined (through simulation and prototyping) during the project. The goal is to have coils with a large number of coil elements (16-64) optimized for parallel imaging (rate 4 for 2D imaging and rates 4-8 for 3D imaging). We envision an iterative development process where prototype coils are refined and optimized based on actual experiments in pediatric patients at the NHLBI operated MRI system at Children's National Medical Center (Phase I). Commercial products will be developed based on the prototypes (Phase II).

Phase I Activities and Expected Deliverables

Phase I will be focused on developing and fine-tuning prototypes. The end goal of the project (after phase II) is to have a commercial set of 4 coils, but for phase I, two (2) coils will be expected (e.g. sizes 1 and 4 above). Phase I will be initiated with discussions between the vendor and NHLBI about coil sizes, element counts, and parallel imaging performance expectations. The deliverables for Phase I are:

- Initial survey of reasonable coil geometries for the 4 body sizes mentioned above.
- Simulations of optimal element size and count for all 4 coil sizes.
- Two prototype coils (sizes 1 and 4). Compatible with a Siemens 64-channel, 1.5T Aera MRI system (Dual Density Signal Transfer system).
- Coil test data needed for a) Siemens safety compliance, b) NHLBI NMR Safety Committee approval for human use.

Phase II Activities and Expected Deliverables

Phase II represents the final commercialization of the set of four (4) coils. Expected deliverables:

- One set of (4) coils approved for human use.

076 MRI Myocardial Biopsy Forceps

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: \$150,000 for 12 months; Phase II: \$1,000,000 for 2 years

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

Summary

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

Image-guided myocardial biopsy using MRI might enhance the diagnostic utility and safety of myocardial biopsy in inflammatory or infiltrative cardiomyopathies. This solution would be especially attractive in pediatrics, where the risk of and need for biopsy is higher than in adults, yet the need more frequent.

Project Goals

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

The deliverable would likely have fixed development costs and low marginal production costs, and therefore is suitable for commercialization after initial SBIR investment.

Phase I Activities and Expected Deliverables

A phase I award would develop and test a bioptome prototype. The awardee deliverable would be tested *in vivo* in the contracting Division of Intramural Research (DIR) lab (cardiovascular intervention program).

The specific deliverable would be:

- Biopsy forceps catheter with an outer diameter 6-7 French
- Bioptome sharpness equivalent or superior to commercially available stainless steel myocardial biopsy forceps catheters
- Able successfully to cut endomyocardial biopsy specimens 1-2mm x 2-3mm each
- Deflectable curve or shapeable to impart a curve analogous to Stanford-style endomyocardial bioptome
- Suitable for transjugular or transfemoral biopsy of the right ventricle or transfemoral retrograde aortic biopsy of the left ventricle
- Free from clinically-important heating (20C at 1W/kg SAR) during MRI at 1.5-3.0T
- Visibility during MRI. If visible using magnetic susceptibility phenomena, the tip should be distinctly visible, and at least the distal 40cm of the shaft should also be visible. In general, susceptibility markers should be > 3mm in diameter using commonly used steady state free precession or fast gradient echo MRI techniques.
- There should be a characteristic imaging signature that distinguishes the “open” from the “closed” position of the biopsy forceps, using MRI
- Proposals for alternative visualization strategies, such as “active” or “inductively-coupled” receiver coils, are welcomed.

Phase II Activities and Expected Deliverables

A phase II award would allow mechanical and safety testing and regulatory development for the device to be used in human investigation, whether under Investigational Device Exemption or under 510(k) marketing clearance.

The contracting DIR lab would perform an IDE clinical trial at no cost to the awardee. IDE license or 510(k) clearance would constitute the deliverable.

The specific deliverable would be:

- Biopsy forceps catheter with an outer diameter 6-7 French
- Biopptome sharpness equivalent or superior to commercially available stainless steel myocardial biopsy forceps catheters
- Able successfully to cut endomyocardial biopsy specimens 1-2mm x 2-3mm each
- Deflectable curve or shapeable to impart a curve analogous to Stanford-style endomyocardial biopptome
- Suitable for transjugular or transfemoral biopsy of the right ventricle or transfemoral retrograde aortic biopsy of the left ventricle
- Free from clinically-important heating (20C at 1W/kg SAR) during MRI at 1.5-3.0T
- Visibility during MRI. If visible using magnetic susceptibility phenomena, the tip should be distinctly visible, and at least the distal 40cm of the shaft should also be visible. In general, susceptibility markers should be > 3mm in diameter using commonly used steady state free precession or fast gradient echo MRI techniques.
- There should be a characteristic imaging signature that distinguishes the “open” from the “closed” position of the biopsy forceps, using MRI
- Proposals for alternative visualization strategies, such as “active” or “inductively-coupled” receiver coils, are welcomed.

077 Passive MRI Guidewire

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: \$150,000 for 12 months; Phase II: \$1,000,000 for 2 years

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

Summary

MRI-guided catheter procedures can avoid radiation and may allow surgery to be avoided in a range of applications. A safe clinical guidewire is not commercially available. A complex “active” electronic MRI guidewire is being developed by DIR. However, a more simple and versatile “passive” MRI guidewire also is valuable to be used as part of multi-step procedures (such as catheter exchange), but is neither commercially available nor attractive to manufacture in DIR. Several prototypes have been reported in the literature but none have been commercialized. Such a device would have utility in cardiovascular and in non-cardiovascular applications.

This contract solicitation is to obtain an exchange-length guidewire that is safe for operation during MRI.

Project Goals

The goal of the project is to develop an exchange-length guidewire that is safe for operation during MRI. First a prototype would be developed and tested in animals, and ultimately a clinical-grade device would undergo regulatory development for clinical testing at NIH.

The deliverable would likely have fixed development costs and low marginal production costs, and therefore is suitable for commercialization after initial SBIR investment.

Phase I Activities and Expected Deliverables

A phase I award would develop and test a guidewire prototype. The awardee deliverable would be tested *in vivo* in the contracting DIR lab (cardiovascular intervention program).

The specific deliverable would be:

- 0.035" outer diameter x 2.6-3.0 meters length allowing unencumbered catheter exchange
- Mechanical properties matching up to two commercially available X-ray guidewires, in descending priority order: (1) Wholey {steerable and torquable angled guidewire}, (2) Supra-Core {steerable and torquable shapeable soft-tip and stiff-shaft}
- Shapeable tip is strongly preferred over a J tip
- Free from clinically-important heating (20C at 1W/kg SAR) during MRI at 1.5-3.0T
- Visibility during MRI. If using individual susceptibility markers, they should be positioned at the tip and along the shaft in a pattern that allows the operator to delineate/differentiate them. Susceptibility markers should be > 3mm in diameter using commonly used steady state free precession or fast gradient echo MRI techniques
- Proposals for alternative visualization strategies, such as "active" or "inductively-coupled" receiver coils, are welcomed.

Phase II Activities and Expected Deliverables

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

The specific deliverable would be:

- 0.035" outer diameter x 2.6-3.0 meters length allowing unencumbered catheter exchange
- Mechanical properties matching up to two commercially available X-ray guidewires, in descending priority order: (1) Wholey {steerable and torquable angled guidewire}, (2) Supra-Core {steerable and torquable shapeable soft-tip and stiff-shaft}
- Shapeable tip is strongly preferred over a J tip
- Free from clinically-important heating (20C at 1W/kg SAR) during MRI at 1.5-3.0T
- Visibility during MRI. If using individual susceptibility markers, they should be positioned at the tip and along the shaft in a pattern that allows the operator to delineate/differentiate them. Susceptibility markers should be > 3mm in diameter using commonly used steady state free precession or fast gradient echo MRI techniques
- Proposals for alternative visualization strategies, such as "active" or "inductively-coupled" receiver coils, are welcomed.

078 Transthoracic Cardiac Access Ports and Closure Devices

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: \$200,000 for 12 months; Phase II: \$1,500,000 for 2 years

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

Summary

Implanting large appliances, such as mitral valve replacement, currently requires cardiac surgery and cardiopulmonary bypass. Minithoracotomy access remains high risk. NHLBI has shown early feasibility of direct transthoracic large-port access to the beating heart, and effective closure using nitinol appliances in animal models. The objective of this contract solicitation is to support the commercial development of purpose-built access ports and closure devices for direct transthoracic cardiac access to the left and right ventricles.

Project Goals

Safe non-surgical access to the beating heart would be attractive to implant large appliances (such as mitral valve replacement), to repair complex congenital or structural heart defects, or to deliver smaller appliances such as transcatheter aortic valve replacement in the large minority of patients ineligible for transvascular delivery.

NHLBI DIR has demonstrated early feasibility of this approach using MRI guidance and off-the-shelf nitinol closure devices. A purpose-built device would be necessary for safe and robust transthoracic access port and closure.

Phase I Activities and Expected Deliverables

A phase I award would develop and test a port and closure device system prototype. The awardee deliverable would be tested *in vivo* in the contracting DIR lab (cardiovascular intervention program).

Applicants are directed to several publications from NHLBI regarding this topic in calendar year 2011 (Pubmed ID: 21234923, 22192372, and 2192373), accessible from www.ncbi.nlm.nih.gov/pubmed?term=21234923,22192372,2192373.

The specific deliverables include:

- **Access Port**
 - Access port in at least two sizes, one being 32Fr and another 24Fr, to accommodate implantation of large prostheses
 - The port (“introducer sheath”) should incorporate features to assure retention inside the endocavitary space once delivered, to avoid inadvertent exit from the targeted ventricular cavity.
 - The port should have a mechanism to protect against damage to endoventricular contents (papillary muscles, chordae tendinae, valve leaflets) during delivery.
 - The system should have a hemostatic valve or equivalent mechanism to allow large appliances to be introduced into the heart from a transthoracic access port without significant blood loss and without entry of air.
 - The system should feature sufficient taper, rigidity, and curvature to be introduced into the left or right ventricle via intercostal and subxiphoid trajectories, and characteristics to accomplish non-surgical intercostal separation if necessary.
 - The system should allow delivery into the heart through the chest initially over a 0.035” guidewire
 - The port should have length sufficient to reach the mid-left atrium or proximal ascending aorta from a transthoracic (subxiphoid and intercostal) access route in most patients.
 - The system should be conspicuous under multiple imaging modalities, including ultrasound and MRI.
 - The entire system should be MRI compatible (free from magnetic displacement and from significant magnetic susceptibility artifact) based on materials compatibility.

- The system should be curved to allow operation within a large-bore (70cm diameter) MRI system.
- **Myocardial Closure System**
 - The myocardial port must be closed with high reliability, immediate hemostasis, and with a reliable bail-out mechanism in case of failure. Targeted clinical reliability will be successful deployment and immediate hemostasis in 99.9% of attempts.
 - Anticipated closure mechanisms include permanent implants with suitable fixation mechanisms or suture-delivery. Any closure mechanism must assure high reliability of deployment, high reliability of success, robust immediate hemostasis, extremely low risk of late erosion or pseudoaneurysm, and trivial or no degradation of myocardial function.
 - One minimal mechanism of bailout is a parallel guidewire that allows a bailout/temporizing hemostatic mechanism to be inserted quickly and reliably should hemostasis fail, to allow controlled surgical rescue. Other options are invited.
 - The design should be safe from early and late myocardial erosion.
 - The proposal should include a risk/failure analysis
 - Operational considerations should be described, including whether the closure system is deployed at the beginning of the transcatheter procedure (“pre-close”) or at the conclusion.
- Strategies should be defined for use and withdrawal of secondary drainage catheters after the access port is closed.

Phase II Activities and Expected Deliverables

A phase II award would allow mechanical, fatigue, and biocompatibility testing and regulatory development for the device to be used in human investigation, under Investigational Device Exemption. We expect the device will require a PMA for marketing, which is expensive. The contracting DIR lab would perform an IDE clinical trial at no cost to the awardee.

The specific Phase II deliverables are as described under Phase I.

- The phase II award would consist of the contractor obtaining an IDE based on the design finalized in phase I.

079 Bioabsorbable Stents for Pediatric Pulmonary Artery Stenosis and Aortic Coarctation

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: \$200,000 for 12 months; Phase II: \$1,500,000 for 2 years

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

Summary

Mechanical stents to relieve obstructive cardiovascular lesions could have great utility in pediatric cardiology, but are unsuitable for small children. Commercially available stents limit vessel growth and require future surgical removal. Absorbable stents might revolutionize the treatment of congenital heart disease in children. Small children require small delivery systems for devices that are larger than adult coronary arteries. Specific target diseases include aortic coarctation and pulmonic stenosis, which currently require open surgical repair or multiple X-ray-guided catheter procedures in early childhood.

Project Goals

These are transcatheter stents to be delivered using conventional interventional cardiovascular techniques including guiding catheters or sheaths, transluminal guidewires, and balloon-expandable or self-expanding delivery systems. Conventional and novel approaches are welcomed.

Specific requirements of the stents include small delivery systems (5-6 French or smaller); sufficient radial force to resist elastic recoil for the two applications; sustained radial strength suited to the application for at least 6 months; controlled degradation within 6-12 months; inflammatory response that does not cause significant stenosis, restenosis, or aneurysm; resistance to downstream embolization or toxicity; and nominal calibers suitable for the most common lesions (pulmonary artery stenosis and aortic coarctation, see below) .

Proposed stent nominal geometry should be diameter (6-10mm), length (range 10-25mm), delivery system (5-6 French or smaller). The radial hoop strength of the deployed device should approach that of commercial balloon-expandable stent such as the Cordis Palmaz Genesis. Percutaneous vascular access routes for the pulmonary artery application include femoral and jugular venous. Percutaneous vascular access routes for aortic coarctation application include transvenous-transeptal antegrade and retrograde transfemoral artery. The implant or the delivery system should be conspicuous under the intended image-guidance modality. Offerings should specifically provide the high radial force required to overcome immediate recoil of the intended applications, and should allow "direct stent" treatment technique for native and iatrogenic lesions.

Phase I Activities and Expected Deliverables

Phase I should focus on mechanical and biological performance of the proposed biodegradable stents in the intended use for pulmonary artery stenosis and aortic coarctation, taking into account mechanical strength required for the application; geometry of the access vessels and geometry and morphology of target vessels including tapering and branching; strategies to avoid inflammatory restenosis or constriction; and delivery, 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 sponsoring NHLBI laboratory is willing 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

At the conclusion of phase II, the offeror should obtain an investigational device exemption (IDE), and a supply of devices provided, for a first-in-human research protocol, involving at least 10 subjects, to be performed by the sponsoring NHLBI laboratory. The sponsoring NHLBI laboratory is willing to perform a limited number of *in vivo* proof-of-principal experiments in swine (by mutual agreement). NHLBI offers 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.

The specific Phase II deliverables are as described under Phase I.

- The phase II award would consist of the contractor obtaining an IDE based on the design finalized in phase I.

080 Fluorescent Nanodiamonds for *In Vitro* and *In Vivo* Biological Imaging

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: \$150,000 for 6 months; Phase II: \$1,500,000 for two years

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

Summary

There is a need to develop a biocompatible fluorescent label that never photobleaches or blinks, and that is brighter than commonly used dyes. Fluorescent nanodiamonds (FNDs) are 10 to 100 nm sized biocompatible particles with indefinite photo-stability that make them superior imaging probes for a wide range of applications. Whereas organic dyes and quantum dots are neither biocompatible nor photo-stable as they photobleach and blink, and gold nanoparticles exhibit weak, size and shape dependent fluorescence, FNDs do not photo-bleach or blink and can provide bright fluorescence. In particular, their near-infrared fluorescence and biocompatibility make them ideally suited for *in vivo* diagnostic applications. The commercial potential for fluorescent nanodiamonds is enormous. Because of their superior fluorescence characteristics and inherent biocompatibility, FNDs could replace the most commonly used optical probes; quantum dots (QDs) and organic fluorophores.

The nanodiamond fluorescence comes from nitrogen-vacancy (N-V) centers, point defects in the diamond structure. By adjusting the number of N-V centers created in a particle, its brightness can be tuned for a desired application. FND near-infrared emissions are not only optimal for *in vivo* imaging but also can be used as an optical readout of magnetic resonance. Furthermore, the relatively long fluorescence lifetime (~17 ns) of FNDs compared to ~1-2 ns lifetime of *in vivo* autofluorescence makes FNDs ideal background-free agents for time-gated imaging of, for instance various, cardiac myopathies or blood malignancies where typically blood hemoglobin interference in fluorescence spectrum has limited the uses of optical imaging for these pathologies. At the single-molecule level, they can be used to track labeled biomolecules over extended periods of time, and due to their wide excitation spectra, can be used as stable multispectral fiducial markers for ultra high resolution microscopy across multiple wavelengths to study sub cellular structures with nm precision. While these are just a few of the biomedical applications of FNDs, the energy level structure and electron spin coherence of N-V centers have potential novel applications in ultra-low magnetic field detection, ultra-sensitive NMR, ultra-low power consuming spin-based spintronics, and quantum computing. The commercial routes to develop this product for are numerous and highly profitable.

Project Goals

Currently there is no commercial source of fluorescent nanodiamonds appropriate for biomedical imaging applications. This is a rapidly emerging field that would be well served by a source of well characterized FNDs that could be further processed by the end user for a wide range of applications in biomedical imaging and nanotechnology.

Phase I Activities and Expected Deliverables

In Phase I, we expect 100 grams of fluorescent nanodiamonds. The mean diameter of the nanodiamonds should be in the range of 10 to 80 nm, with a coefficient of variation not to exceed 60%. The peak fluorescence emission of the nanodiamonds will be in the range of 650-750 nm and they will be photostable, i.e., not photobleach, under continuous laser excitation of 20 mW or less in the range of 500-600 nm. A minimum of 50% of the fluorescent nanodiamonds will be at least 10 times brighter (i.e., 10-fold higher fluorescence emission at the peak emission wavelength with an optical bandwidth of 30 nm) than Alexa680, which is a commonly used near infrared dye. These specifications can be confirmed with total internal reflection fluorescence microscopy (TIRFM) measurements in which the brightness of fluorescent nanodiamonds and Alexa680 can be compared side-by-side under identical conditions. We are prepared to assist with these measurements if requested. We have successfully made fluorescent nanodiamonds (~30 nm diameter), but their brightness must be improved with optimization of the N-V center creation and annealing process. The contracting company will be expected to optimize the process, deliver well-characterized fluorescent nanodiamonds, and provide a description of the irradiation, annealing, and any additional processing such that an expert in the field could reproduce the process. We can assist the company with the characterization of the nanodiamonds.

Phase II Activities and Expected Deliverables

In Phase II, the deliverables will be a range of FNDs with different levels of brightness and different sizes. Furthermore, the more challenging deliverable in Phase II will be a high-yield product with narrow size and brightness distributions. These well-defined distributions can either be achieved by determining a method that generates the desired distributions directly, or by separating the fluorescent nanodiamonds based on size and brightness after the fact, a technique that would solve a problem that the fields of nanotechnology and molecular imaging have been struggling with.

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 <http://www.niaid.nih.gov/about/whoWeAre/Pages/moreWhoWeAre.aspx>.

021 Aerosolized Delivery of Anti-Tubercular Drugs

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1-2

Budget (total costs): Phase I: \$225,000 for up to 1 year; Phase II: \$1,500,000 for up to 3 years

Background

Many currently existing drugs for the treatment of TB, especially MDR TB are moderately potent, show restrictions with absorption or oral bioavailability, and have toxicity profiles that make patient management difficult. Aerosolized delivery offers the potential to bypass these barriers to drug efficacy by achieving high drug concentrations in the infected pulmonary tissue with lower systemic exposure and by bypassing first-pass hepatic metabolism, thus allowing increased immediate potency. Given these potential benefits, an easy to use, aerosolized delivery system would represent a significant advance in the treatment of tuberculosis. Though anti-tubercular drugs have been formulated into aerosolized particles by multiple research groups and numerous papers are available in the literature on formulating inhaled therapies for TB, no formulation has yet to be commercialized.

Project Goal

The goal of this solicitation is to develop an inexpensive, easy to use, aerosolized delivery system of a combination of anti-tubercular drugs that could be used for the treatment of MDR TB.

Phase I activities

1. Development of an aerosolized formulation of a combination of anti-tubercular drugs
2. Development of an inexpensive, easy to use platform for delivery of said formulation
3. Initial testing to quantitatively assess for drug efficacy, toxicity and pharmacokinetics including required in-vitro studies.

Phase II activities

1. Preclinical studies including required in-vivo testing in a standardized, reproducible, validated small animal model.
2. Development of a well-defined formulation and delivery platform under good manufacturing practices (GMP);
3. Uniformity from lot to lot and be certified under quality control;

4. Scale-up and production for future Phase I clinical study.

022 Development of Long-Acting Formulations of HIV Anti-Retrovirals

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 2-3

Budget (total costs): Phase I: \$225,000 for up to 1 year; Phase II: \$1,500,000 for up to 3 years

Background

Effective treatment of HIV-infected individuals requires strict adherence to a multi-component regimen of antiretroviral agents that currently must be taken daily on a life-long basis. Non-compliance with recommended dosing regimens is a significant factor contributing to the incomplete suppression of HIV and to the development of drug resistance. The development of long-acting formulations that might significantly simplify the dosing requirements potentially could facilitate improvements in patient adherence. Long-acting formulations also would have utility as components of drug regimens provided to uninfected individuals for pre-exposure prophylaxis (PrEP) purposes. Some orally administered antiretrovirals readily penetrate and accumulate in rectal and female genital tract mucosa and achieve concentrations in those tissues higher than in plasma. Formulations based on antiretrovirals with these properties might have utility both as systemic and PrEP agents and thus are particularly attractive as formulation development candidates.

Project Goals

The goal of this SBIR contract solicitation is to support small businesses interested in developing novel formulations of antiretroviral drugs that can achieve clinically relevant systemic or tissue concentrations and maintain these levels for an extended period of time. Formulations that need only be administered once per month are of particular interest; however, formulations that extend the dosing interval to once a week or better still might be valuable additions to current or future PrEP and treatment strategies. Antiretroviral agents selected for formulation development should either be FDA-approved or in mid- to late-stage preclinical development (estimated time to clinical evaluation of 1-3 years). Offerors will be responsible for obtaining the parent antiretroviral compounds for their formulation efforts and for resolving any intellectual property issues that might arise regarding use of these compounds.

Phase I Activities

1. Develop prototype formulations that address the goals of this solicitation.
2. Develop analytical assays that can be used to assess formulation purity and stability.
3. Assess the pharmacokinetic profile and safety of the formulations in an uninfected animal species.
4. Submit promising formulations to NIAID, if requested, for evaluation in either *in vitro* HIV-inhibition assays or small animal models of infection.

Phase II Activities

1. Scale-up the formulations (activity need not be compliant with cGMP) for further preclinical studies.
2. Conduct additional pharmacology and toxicology evaluations of the formulations in uninfected animals.
3. Conduct bioequivalence studies in uninfected animals.

023 Improved Formulations for Approved First and Second line anti-Tuberculosis (TB) Drugs

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1-2

Budget (total costs): Phase I: \$225,000 for up to 1 year; Phase II: \$1,500,000 for up to 3 years

Background

There is an urgent need to develop alternative formulations of approved first and second line anti-TB drugs for pediatric use and also to simplify administration.

There are few child-friendly formulations of pediatric first and second-line anti-TB medications available to practitioners in the US and globally. It is standard practice to cut or crush un-scored adult tablets and administer them to children in juice or other palatable substances. This has significant potential to deliver incorrect and highly variable doses to children, contributing to ineffective treatment. While consideration of pediatric applications is a recent regulatory requirement for novel drugs in general, this requirement does not apply to approved, TB drugs that are off patent and manufactured as generics. Additionally, treatment of adult and pediatric patients may include the administration of TB drugs that are only available as injectable agents. This often requires that the patient be hospitalized to facilitate administration or visit health centers on a daily basis interfering with employment obligations and compromising adherence.

Project Goal

The goal of this project is to develop improved formulations for currently approved TB drugs for pediatric use and also to develop alternative formulations for drugs currently administered by injection. The final product should be simple to manufacture, stable under ambient conditions, and ready for testing in Phase I bioequivalence and PK studies. NIAID clinical contract resources could be used to facilitate evaluation of these formulations in target populations at the end of the SBIR contract period.

Phase I Activities

- Development of prototype formulations that address the goals of this solicitation.
- Development of analytical assays to characterize chemical composition, purity and stability of prototype formulations.
- Assessment of the pharmacokinetic profile and safety of the formulations in an uninfected animal species.
- Development or conduct of drug potency assays for bioequivalence studies.

Phase II Activities

- Scale-up of the formulations (activity need not be compliant with cGMP) for further preclinical studies.
- Conduct of additional pharmacology and toxicology evaluations of the formulations in uninfected animals.
- Conduct of bioequivalence studies in uninfected animals or infected animals as appropriate.

024 Integrated Multiplex Medical Diagnostics Platforms for Infectious Diseases

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1-2

Budget (total costs): Phase I: \$225,000 for up to 1 year; Phase II: \$1,500,000 for up to 3 years

Background

NIAID supports integrated multiplex medical diagnostics platforms capable of simultaneously identifying multiple pathogens in clinical specimens (swabs, sputum, blood, serum, cerebrospinal fluid, urine, stool, etc.). Platforms that provide diagnostic information on potential early, non-specific symptoms and determine pathogen drug sensitivities are of high priority.

Project Goal

The final integrated diagnostic product should be capable of aiding healthcare providers in diagnosing individuals exposed to and/or infected with infectious agents. The product should be developed with the ultimate goal of obtaining FDA clearance. Consequently the product should demonstrate sensitivity and specificity equivalent to or exceeding FDA-cleared tests for similar agents. The proposed diagnostic must provide rapid, shortened time from sample to diagnosis (30-40 minutes); offer high sensitivity and specificity; and be easy to use. Importantly, it should not incorporate nucleic acid amplification to detect pathogens, toxins or infectious diseases. The product should function as an integrated, closed sample-to-answer system with automated data analysis and output. It should be capable of integrating new assays and detection of modified or new targets and be cost-effective.

Phase I activities should include one or more of the following:

- Development and integration of novel methods for sample preparation and concentration into the platform.
- Development and integration of novel detection technologies into the platform that do not involve nucleic acid amplification.
- Development, optimization, integration, and validation of multiplex assays.
- Integration and validation of internal process controls.
- Development of software for controlling the platform, displaying the results of the diagnostic tests, and transferring results to laboratory information systems (LIMS).

Phase II activities should include one or more of the following:

- Continuation of Phase I activities.
- Process development for the manufacturing of diagnostic components, including Quality Assurance/Quality Control methods for reagent recovery, characterization, purification, identity, and stability.
- Validation of the integrated multiplex medical diagnostic platform. Tests for use on human samples may consider benchmarks required for FDA approval (<http://www.fda.gov/cber/devices.htm>).

EUNICE KENNEDY SHRIVER NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT (NICHD)

The NICHD, established by Congress in 1962, conducts and supports research on topics related to the health of children, adults, families, and populations. Some of these topics include: reducing infant deaths; improving the health of women, men, and families; understanding reproductive health and fertility/infertility; learning about growth and development; examining, preventing and treating problems of birth defects and intellectual and developmental disabilities; and enhancing well-being of persons through the lifespan with rehabilitation research.

For additional information about scientific areas of interest to the NICHD, please visit our home page at <http://www.nichd.nih.gov>.

023 Neural Interfaces: Improving Functional Outcomes

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

Number of anticipated awards: 1-2

Budget (total costs): Phase I \$150,000 for 6 months. Phase II \$1,000,000 per year for 2 years.

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

Summary

The long term goal of neural interfaces for medical rehabilitation purposes is to replace lost functionality for people with physical disabilities. While great strides have been made in the neuroprosthetics field, the state of the art falls far short of complete restoration of function. For example, there is no consensus on the best modality for extracting signals from the central nervous system, peripheral nervous system, or the musculoskeletal system. There is insufficient evidence of reliable, long-term neural interfaces in human subjects. There are no decoding algorithms that allow for quick, natural, and diverse use of multiple degrees of freedom in the end effector. There is insufficient use of sensory input to close the feedback loop. There are no common measures for training and testing of neural interfaces and human subjects.

Technical areas of particular interest that address unmet challenges in neuroscience, medicine, materials, and engineering include: (1) Novel, reliable, and scalable biotic-abiotic interfaces for recording neural or muscle signals; innovation in tissue interface systems that demonstrate high-levels of neural-information extraction, low levels of error, and long functional lifetimes are highly encouraged. (2) Reliable, effective, and clinically viable algorithms for decoding limb-control signals; new algorithmic approaches that maximize the amount and rate of limb-control information while reducing the error, degree of pre-processing, and need for recalibration over time are highly encouraged. (3) Novel, reliable, and scalable biotic-abiotic interfaces for providing sensory stimulation. Proposals should address novel methods that go beyond conventional neural stimulation approaches in order to extend the clinical applications of neural stimulation. Approaches may include, but are not limited to electronic, photonic, tactile, ultrasonic, or chemical stimulation platforms. (4) Training and testing methods; identification of common metrics related to function that would allow systematic investigation of signal processing is encouraged.

Applications for this RFP should address one or more of these technical areas.

Project Goals

The purpose of the proposed RFP is to accelerate research in the field of neural or muscle interfaces with the emphasis on a more naturally controlled prosthesis for people with movement impairments by improving the person/device interface. This solicitation seeks novel approaches for the fusion of neural data with the intent of controlling extracorporeal systems. Proposals designed to capture neural-control signals from central nervous system (CNS) and non-CNS sources (e.g., peripheral nervous system, neuro-musculature system, etc.) are encouraged. The long term goal of the project is to create platform software packages with novel algorithms that can be integrated with one or more modular rehabilitation devices.

Phase I Activities and Expected Deliverables

Phase I research should generate scientific data confirming the clinical potential of the proposed software. Some of the expected activities are:

- Design and development of a prototype system(s).
- Development of innovative algorithms to improve neural signal processing methods for guided interventions for individuals with movement impairments.
- Demonstration of the capabilities of the software.

Final Phase I report should include plans for future work and commercialization.

Phase II Activities and Expected Deliverables

Production of a laboratory or clinic ready hardware and software package with user friendly graphical interface.

Draft user manual.

NATIONAL INSTITUTE ON DRUG ABUSE (NIDA)

NIDA's mission is to lead the nation in bringing the power of science to bear on drug abuse and addiction, through support and conduct of research across a broad range of disciplines and by ensuring rapid and effective dissemination and use of research results to improve prevention, treatment, and policy.

This solicitation invites proposals in the following areas:

147 A Mobile Application to Help Patients Take their Pill Medications as Prescribed: Improving Medication Adherence

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

Number of anticipated awards: 2-3

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

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

Drugs don't work in patients who don't take them.

— C. Everett Koop, M.D., former U.S. Surgeon General

Medication adherence is described as the extent to which patients take medications as prescribed by their health care providers.

A World Health Organization (WHO) report confirms that almost half of patients with chronic illnesses do not take medications as prescribed. Low medication adherence greatly lowers efficacy; and it leads to preventable prolongation of illnesses, re-hospitalizations and sometimes death. Approximately 125,000 Americans die annually (342 people every day) due to poor medication adherence. Every day, prescription non-adherence costs more than \$270 million in additional hospitalization and other medical costs. Nine out of every 10 outpatients are taking prescribed medicines improperly, contributing to prolonged or additional illness. Cost of non-adherence to medications is estimated approximately \$100 billion a year in the U.S. In addition, other forms of medication non-adherence such as misuse, underuse or overuse (abuse) also have negative consequences in individuals.

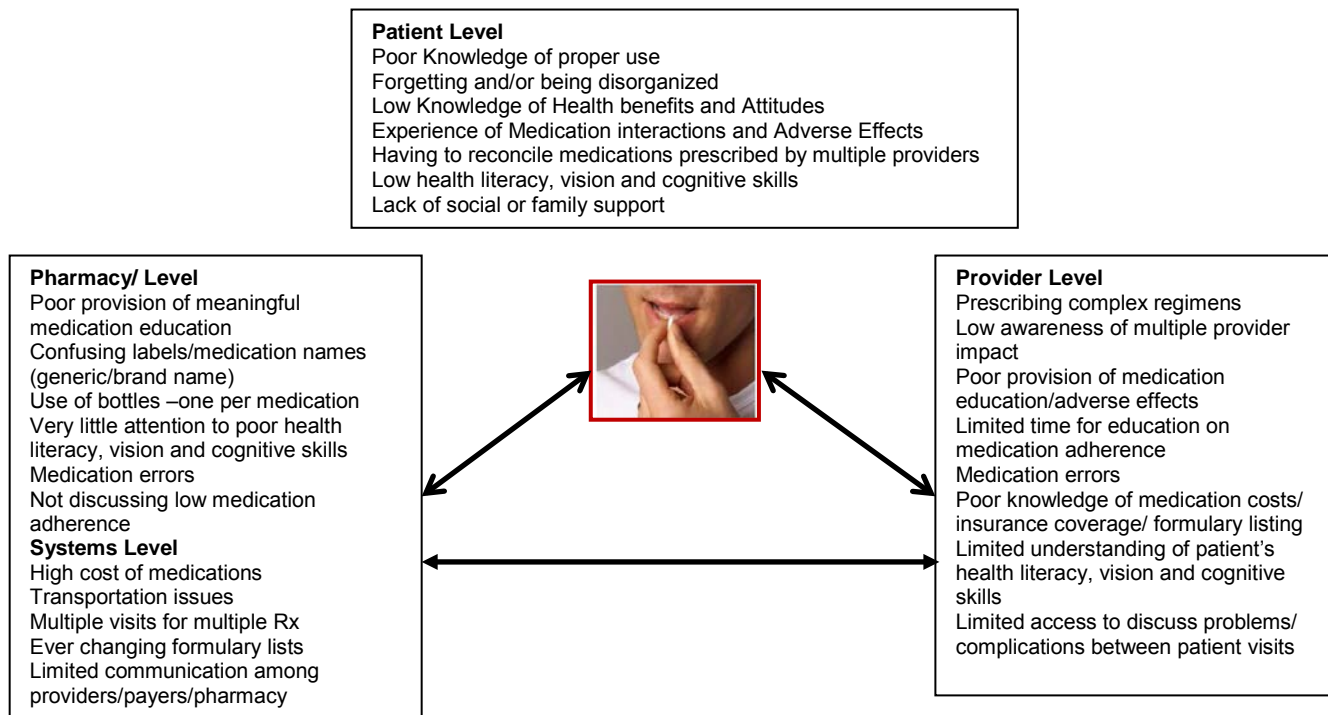
Medication non-adherence is especially burdensome to patients with substance use disorders who are prescribed medications for psychiatric and medical conditions. In addition, approximately 50% of patients prescribed Buprenorphine for opioid dependence and NRT/other medications for smoking cessation report taking medications as prescribed.

NIDA seeks to develop and test prototype mobile/tablet technology-based application to provide a low-cost, highly personalized, interactive patient-centric medication adherence tool that improves upon currently available mobile technology-based medication adherence applications.

Background Information

The WHO, Institute of Medicine (IOM), National Institute of Health (NIH), American Heart Association (AHA) and advocacy organizations have all acknowledged that this is both a complex and a difficult issue to solve but the time for action is now.

Barriers to medication adherence are complex, variable and reside at multiple levels: the patient, the provider, the healthcare system and their interactions.



Systematic reviews have found that existing medication adherence interventions yield only modest benefits and while simple reminder systems do work, most of the systems were complex, cost-prohibitive and labor-intensive greatly limiting generalizability.

Adherence is an active process but existing low-cost solutions are passive. Examples of commercially available apps for Android and Apple devices: Pillbox Alert, Med Minder, Med Helper - Prescription App, MyMedSchedule, Dosecast, RxmindMe, Intelcare. They are typically simple to use and employ visual aids but are limited by patient input of their medications; sole reliance on reminders; predominant focus on the use of English language; and not always Health Insurance Privacy and Portability Act of 1996 (HIPPA) and Health Information Technology for Economic and Clinical Health (HITECH) Act compliant.

Other solutions use electronic pillboxes which record pill use by the patient and in some cases, provide reminders: MEMS cap, Wisepill device, Med-eMonitor, etc. These products have limited main stream application due to high costs of these stand-alone devices that typically record one medication per container; with limited links to real-time and interactive feedback or education; and most have limited programming capacity.

The newer FDA approved medical devices such as the SIMpill® Medication Adherence System and the PillStation® medication adherence system are more complex and offer adherence reminders and organization solutions but do not provide tailored interventions based on the patient's baseline, nor do they address adverse effects, other barriers to medication adherence.

Phase I Activities and Expected Deliverables

Develop and test the acceptability and feasibility of a mobile/tablet-based technology application prototype that improves medication adherence by successfully addressing the barriers to medication adherence and contain the following features:

- Allow multiple user input and interaction (i.e. between physician, pharmacy, patient, caregiver/parent) and superiority to existing mobile applications and electronic pillbox/medication monitoring tools;

- The core medication adherence enhancement solution is to be a mobile application. However, hybrid solutions that link to external systems will be preferred, e.g. demonstrate capacity to link to external electronic databases, such as pharmacy, laboratory and/or medication information systems; other existing stand alone medication monitoring tools such as electronic pillboxes, etc.;
- Account for low health literacy and visual impairment needs of patient;
- Demonstrate capabilities for GIS, GPS, SMS, phone, Bluetooth, online, video and other platforms of real-time communication;
- Eliminate patient need to enter medication information (i.e. names and doses of medications) through the use of barcodes, photo/camera capabilities and similar technologies;
- Demonstrate capabilities to link to patient's record in EMR, EHR, pharmacy database and other healthcare systems (e.g. appointment scheduling systems, provider locations, etc.);
- Use computational modeling, branching logic and/or query functions to develop sophisticated adherence solution algorithms for the software;
- Provide a baseline ecological momentary assessment of patient's status (such psychiatric and/or physical symptoms, mood states, drug cravings/drug use) and its impact on medication adherence, so that customized interventions can be delivered to the patient, based on their ability;
- Offer a menu of customizable adherence strategies, based on each individual's baseline rate of medication adherence, ranging from simple to complex (and provide some rating mechanism for the strategies offered);
- Offer tailored medication education content suited for adult learning and links to reliable information databases;
- Link to social media sites, email and other communication resources to enable caregiver, parent, significant other person support/monitoring;
- Build in incentives (financial and other positive reinforcements) for meeting medication adherence goals;
- Demonstrate scalability and cost-effectiveness;
- Must be HIPPA and HITECH Act compliant;
- Demonstrate feasibility, acceptability and preliminary efficacy in improving medication adherence: test the application on 9 patients receiving a FDA approved medication to gather preliminary data on the reliability of the system and its ease of use by patients, providers and caregivers;
- Demonstrate that the proposed research activity will likely lead to a marketable product or process, including consideration of the potential barriers to entry and the competitive market landscape. This may include a letter of commitment for additional investment or support from a private sector party or other non-SBIR funding sources.

Phase II Activities and Expected Deliverables

Develop and validate a production model prototype by using the system in substance abusing patients undergoing treatment with an FDA approved medication either for treating addiction such as buprenorphine or a psychiatric disorder such as Major Depressive Disorder.

Provide evidence for commercialization potential, i.e., record of successfully commercializing prior SBIR/STTR or other research projects, commitments of additional investment from private sector or other non-SBIR funding sources, and any other indicators of commercial potential for the proposed research.

148 Products for at-home Deactivation of Psychoactive Prescription Medicines

(Fast-Track proposals will be accepted.)

Number of Anticipated Awards: 2-3

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

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

Objective: This topic addresses the need to fund research and development activities to promote the commercial development and testing of an inexpensive prescription medicine disposal system that would provide a simple means for patients (prescription drug “end-users” defined by the Drug Enforcement Administration) or members of their household to safely render prescription drugs unusable and effectively contained in order to minimize the potential for diversion or accidental exposure to children or pets. Methods proposed may include approaches or agents that mechanically destroy or chemically neutralize prescription drugs for either safe home disposal or safe transit for disposal by another facility. For example, such a product or agent could be distributed by practitioners and pharmacies along with scheduled medications. As an ancillary benefit, such a product holds the potential to minimize drugs entering the watershed and other adverse environmental effects.

Background

Last year in America, 210 million prescriptions for opioids were written- enough medication for every American to have a 30-day supply. Nearly every American household will at some time be in possession of controlled substances. A large percentage of prescription medicines are never used or are used in much smaller quantities than prescribed. For example, a recent study showed that among upper extremity surgery patients, who were prescribed an average dose of 30 narcotic pills, approximately half only used 2 days worth of pills or fewer (Rodgers et al 2012). This illustrates how leftover medicine is a large problem. Death of an elderly family member or medication changes can also result in surplus controlled substances in the home.

Results from the most recent (2010) National Survey on Drug Use and Health (NSDUH) show prescription drug misuse is generally initiated via “diversion”- when people are given psychoactive pills (or steal) from friends or relatives. Accordingly, safe drug disposal is a pillar of the President’s Prescription Drug Strategy (http://www.whitehouse.gov/sites/default/files/ondcp/issues-content/prescription-drugs/rx_abuse_plan_0.pdf (page 7) and Drug Enforcement Administration (DEA) is in the process of rulemaking on the Secure and Responsible Drug Disposal Act of 2010. This rulemaking likely will involve a combination of take-back and other means to return medication to facilities with incinerators.

Aside from cost, one problem with all such programs is the drug remains available to use/misuse/abuse until incineration or other final disposal. Currently, DEA provides labor-intensive prescription drug disposal “takeback” programs that visit sites to collect unused medications from households (e.g. http://www.deadiversion.usdoj.gov/drug_disposal/non_registrant/transcript_diposalmtg_011911.pdf). Federal sponsorship of this program underscores the high interest in this problem.

Although there are products like drug shredding machines that are deployed in nursing homes and other care-giving venues (www.ultimateproducts.us/DrugShredder.htm#features), there are few alternatives for safe medication removal by patients in the home. For most scheduled medicines, the Food and Drug Administration (FDA) recommends mixing the medicines with coffee grounds or kitty litter and then throwing these medicines in the trash. This process presumes availability of such material in the household. Notably, in addition to risk of diversion, household disposal of some medications in solid waste (especially in transdermal patches) (<http://www.fda.gov/Drugs/DrugSafety/ucm300747.htm>) can create hazards to children and pets.

FDA has recommended that only a subset of medications be flushed - (<http://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/ensuringsafeuseofmedicine/safedisposalofmedicines/ucm186187.htm>). Flushing some types of unused medications into the water supply can

create environmental hazards and is only recommended for medications that pose the most imminent risk if accidentally ingested.

An in-home prescription medicine deactivation or disposal system would meet the goal of having an immediate method to render unused medicine harmless. Recent advances in technology offer the opportunity for companies to add technology-based features such as mobile phone applications that could include medication expiration dates and disposal reminders.

Families with small children and pets are likely audiences for this product in terms of prevention of poisoning. As such, sales of this product may benefit from positioning by child-proofing and pet-proofing products. Parents of teenagers (particularly teens who are known to have experimented with alcohol or marijuana) are likely consumers of this product as well. At home drug test kits are routinely sold in pharmacies, and positioning this product near opioid test-kits is a natural marketing strategy. Finally, “green” consumers, interested in reducing their environmental impact may consider such a product for its environmental benefits.

Phase I Activities and Expected Deliverables

This SBIR topic will help address the need for safe, at-home deactivation of divertible medications for home disposal in solid or liquid waste or before transit for third-party disposal. It is expected that potential offerors can demonstrate with preliminary data that agents or devices in their proposals (such as chemical-based drug-deactivating agents, nanomaterials or mechanical processes) will inactivate the proposed chemical class of psychoactive medication and its medium of delivery (e.g. tablet, capsule, or patch) in direct application (not embedded in a device or product). It is not expected that a single agent or device would be suitable or capable of deactivating all classes of medication or deactivating across all forms of medication delivery.

Specifically, the contractor will be provided with funding to develop this agent or device into a consumer-friendly, low-cost, and simple-to-use product for home use that contains the drug-deactivating device or agent, into which medication may be dropped, inserted, mixed or adhered for inactivation and disposal.

Phase I testing should include testing the product for ease of portability, storage, and use. The device or product should be able to be handled and transported by an elderly or physically-challenged consumer. Because repeat use of this type of product hinges on the user experience being at minimum not unpleasant, focus groups may address ease of use and aesthetic factors for the “disposal system”. Phase I may also include development and testing of materials such as instruction sets, educational materials, calendars, and mobile applications to facilitate use the product.

Deliverables will include:

1. Product usability testing to establish that the product can be easily used by the targeted users, including elderly patients and their caregivers, families with young and teenage children (particularly women). For example, testing should assess the degree to which having to open the medication container for inactivation of its contents paradoxically introduces exposure and toxicity risk. Additionally, tests should ensure the product provides an optimized aesthetic experience (i.e., does not emit unpleasant or noticeable odors) and is amenable to cleaning, if the product is a reusable device.
2. Market research to determine how the proposed product could either compete with, compliment, or assist existing drug-disposal schemes, like in-person drop-off boxes at participating pharmacies or programs that provide mailers to consumers to mail unused medications to an incineration service. This research should be geared toward determining whether the product would have a market for direct sales to families, or would be best distributed by pharmacies as part of the costs of scheduled drug dispensing. Notably, the product should have a unit cost low enough to be either sold readily directly to consumers or distributed routinely with medications and prescriptions along with patient information sheets.
3. Risk-assessment and solutions for product liability issues with regard to incompletely-deactivated medications, such as from misuse of the product.

4. Toxicology assessment to demonstrate that the agent or product itself (or as an amalgam with a medication), is non-toxic and either directly disposable or eligible for transport by the postal service or other commercial carriers.

Phase II Activities and Expected Deliverables

Projects that demonstrate feasibility, safety, and marketability of the product/device in Phase I may be extended into Phase II. In Phase II, the offeror will be expected to have packaged the deactivating agent or device in a deployable form for mass-distribution. In addition, in Phase II the offeror will be expected to conduct assays, tests or surveys to assess:

1. Degree of adherence by prescribers, pharmacies, and/or home users
2. Whether use under normal household conditions improves outcomes (e.g., reduces calls to poison centers, changes total medication reported used or total medication reported destroyed). Such a test should include random or quasi-random assignment of patients and families typically prescribed narcotics and likely to have leftover medicine (e.g., acute injury patients or patients undergoing orthopedic surgery.) Because certain individuals are at high risk for substance misuse it is recommended investigators stratify assignment based on whether people have a history of a substance use disorder, chronic pain, or mental illness.
3. The classes of chemical compositions or delivery systems of medicines (transdermal patch, tablets, capsules) for which the device or agent is most effective or exclusively effective. This might be specific individual medicines.
4. Adverse events from use of the product
5. The durability or shelf-life of the product, so as to establish and provide expiration dates of products that use chemical or nano-particle based inactivating agents.
6. Development of ancillary materials to ensure adoption and consistent use- such as educational and public-awareness materials, a programmable adherence application for a mobile phone, or paper reminder calendars.

149 Development of Predictive *in vivo* Screening Systems for Phenotypic Drug Discovery for Smoking Cessation

(Fast-Track or Phase I proposals will be accepted.)

Number of Anticipated Awards: 2

Budget (total costs): Phase I: \$350,000 for one year; Phase II: \$1,500,000 for 2 years. Total budget for Fast-Track: \$1,850,000 for 3 years.

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

Summary

Phenotypic drug discovery is a complement to target-based drug discovery and provides an alternative approach that begins by querying more complex cellular or physiological systems instead of specific targets. The possible advantage resides in the fact that a relevant biological context is interrogated without predisposed bias toward mechanism(s). Thus, an opportunity is created to identify compounds that may interact with one or more targets or pathways not anticipated by a single mechanism-driven hypothesis. In essence, phenotypic approaches screen multiple mechanisms and targets simultaneously. This solicitation for Small Business Innovation Research (SBIR) contract proposals invites contract proposals from small business concerns (SBCs) for a multi-pronged research program to develop and evaluate a weighted battery of animal behavioral tests that can be used for the phenotypic drug discovery and development of smoking cessation medications. The battery should be, preferably, high- or medium- throughput and designed to improve the predictive validity of *in vivo* screening of drug candidates. Since people continue to smoke for many different reasons - withdrawal relief, pleasure, taste, improvement in concentration, weight control, stress control, arousal, etc. - the battery should be capable of

assessing the multiple components (reinforcement, affective, cognitive, etc.) that underlie smoking. The offeror is expected to identify and propose the behavioral domains of particular importance to human tobacco dependence, and to develop the necessary animal behavioral protocols to test multiple processes believed to be contributing to smoking in humans. It is not necessary that the behavioral measures model the aspects of smoking in precise fashion. That is, this contract solicitation focuses on the predictive (and construct) validity of the behavioral battery, not on its face validity. The SBC must screen in uniform fashion and, then, build a large database of pharmacological signatures of currently available medications (with known anti-smoking efficacy in humans) comprised of measures reflecting the reinforcement, affective, cognitive, etc. functions. The critical part of this solicitation is the focus on biostatistical/computational solutions and modeling. Bioinformatics algorithms are to be developed which will complement and enhance the statistical power to recognize phenotypic profiles of drugs. Proposals are expected to include animal behavior tests only.

Background Information

Despite major developments in computational, *in vitro* and *ex vivo* model systems, *in vivo* animal testing remains a necessary part of drug development. This solicitation invites offers from SBCs interested in developing a weighted battery of animal behavioral tests/assays (rat or mouse) to function as a screening system for preclinical development of smoking cessation medications.

In this solicitation, behavioral assay is defined as a means of qualifying a dependent biological variable. In this solicitation, animal model is defined as a theoretical description of the way a system (or disease) works. The animal model induces under- or over-expression of a biological variable which assay quantifies. This solicitation seeks to establish a battery of carefully selected behavioral tests/assays that will provide a comprehensive behavioral assessment of domains of particular importance in tobacco smoking and quitting. A battery must be comprised of currently used and available tests whose appropriateness and validation could be assessed through literature search. Applications proposing new animal models or assays are not allowed.

This assay battery will be used to obtain standardized data on the responses to existing first-line pharmacotherapies that have been approved by FDA as aids for smoking cessation (i.e. varenicline, bupropion), and second-line pharmacotherapies (i.e. clonidine, nortriptyline). Measuring several domains and several medications will result in obtaining a rich dataset, which is to be systematically analyzed for identification of critical parameters or axes, selecting the most useful features and identifying underlying variables. The critical parameters in each domain are to be selected to be combined into final, "lean", standardized and validated battery of assays, with the goal to provide superior reliability, greater statistical power and higher throughput than standard methods. This validated battery of assays will be used for *in vivo* screening of anti-smoking drug candidates to advance future research and discovery in this area.

Because of the importance of tobacco-dependence treatment to national tobacco control efforts, the National Cancer Institute and the National Institute on Drug Abuse (NIDA) convened a meeting, entitled "Translational Medication Development for Nicotine Dependence Workshop." Participants from industry, academia and government agencies provided their views on the greatest opportunities for accelerating the translational efforts in the area of nicotine dependence. One of the challenges in medications development for addictive disorders is to determine the predictive validity of preclinical and clinical pharmacology models of various aspects of drug dependence. Several pharmacotherapies are, in fact, available to support treatment of nicotine (tobacco) dependence, including ones with an overt nicotinic mechanism of action, such as nicotine replacement therapies and varenicline (Chantix®, Champix®), others, in which nicotinic mechanisms may be a component, such as bupropion (Zyban®), and still others, for which there is no obvious nicotinic component to their action (e.g., the second-line medication clonidine, an α_2 adrenergic agonist). Each of these drugs significantly improves the quit-rate compared to placebo. With these currently available medications, however, only about 20% of smokers are able to maintain long-term abstinence, and more efficacious pharmacotherapies need to be developed promptly.

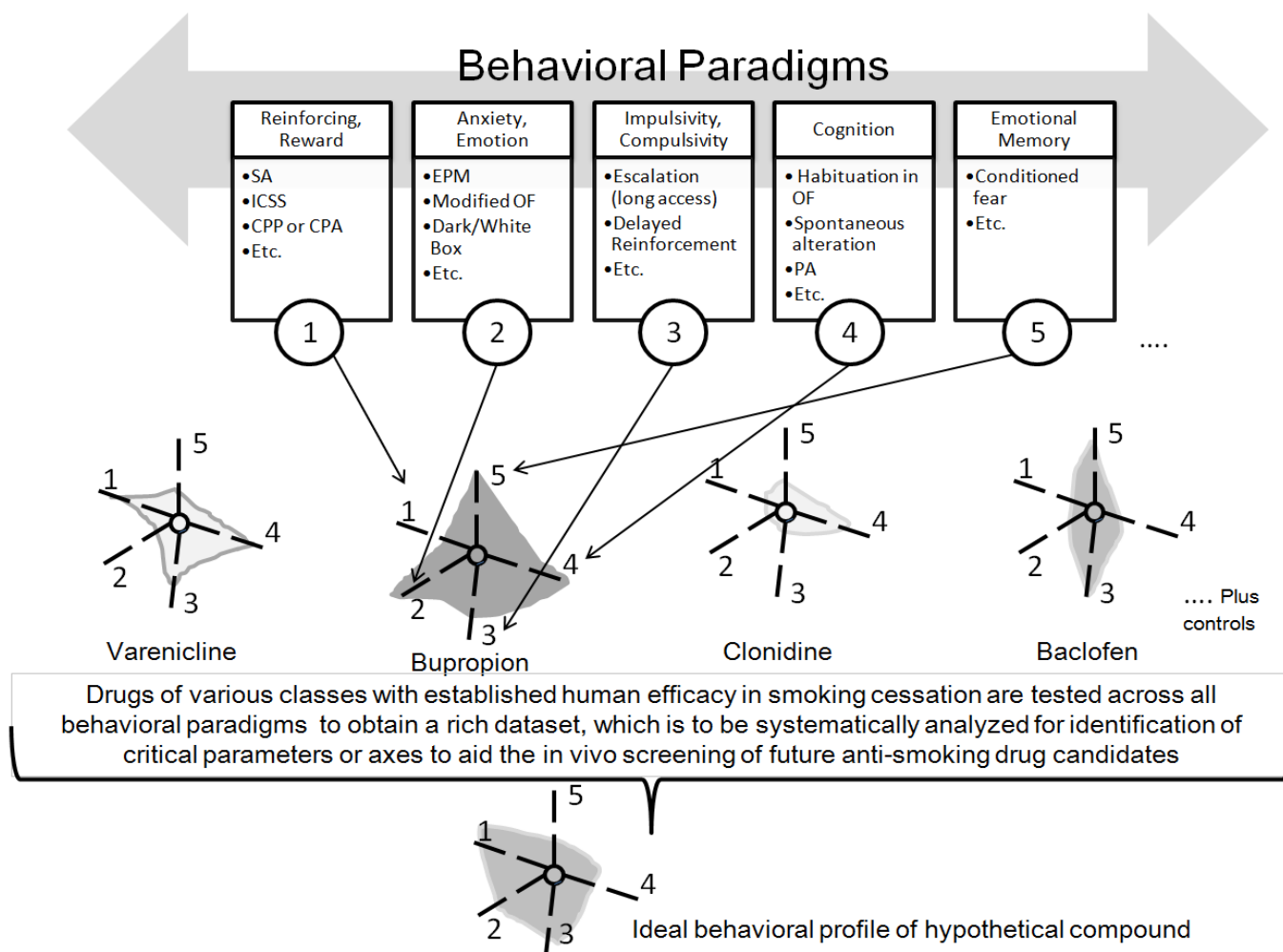
Scientific knowledge to be achieved through research supported by this contract

Basic research into the mechanisms of nicotine addiction has the benefit of the availability of a wide array of preclinical animal behavioral models and assays. A number of these tests have seen extensive use as research tools, and, as a result, they are known to have utility in studying the mechanisms and processes related to

addiction and drug abuse relapse. In addition, some of these models, such as drug-self administration and drug discrimination, have demonstrated translational utility in providing preclinical data in support of the development of varenicline. However, given that varenicline is the only smoking cessation pharmacotherapy to have been developed through the typical pharmaceutical industry drug discovery approach, there is little evidence for the predictive validity of any of these animal behavioral models for medication development for drug addiction. Indeed, since inadequate efficacy remains a significant cause of failure in the drug development process, improvements in the ability to predict efficacy at various stages across the drug development process are warranted. The intent of this contract solicitation is to fund small business concerns (SBCs) capable to undertake screening of anti-smoking medications (with various mechanisms of action and known to demonstrate some efficacy in humans) in multiple animal behavior paradigms. Although addiction is frequently and preferentially conceptualized in terms of reward and reinforcement, this contract solicitation seeks to collect data simultaneously in other domains that may be relevant to drug addiction and drug abuse relapse, namely cognition and affect. For each of these domains, there exist well-established assays and models that have validity within the domain (e.g., for reward and reinforcement – drug self-administration, intra-cranial self-stimulation; for cognition - pre-pulse inhibition, 5 choice serial reaction time; affect - open-field test, elevated plus-maze). It is important to note that these examples are not intended to be exclusive or prescriptive; other models may be worthy of validation in this effort. The purpose of this initiative is to support research to estimate if individually and/or collectively these tests are predictive of medication efficacy in clinical trials.

A critical part of this solicitation focuses on improving the reproducibility of preclinical data which will be obtained. Given the high cost of clinical drug development, factors such as low reproducibility and translatability, or heterogeneity in study design that hinder the comparison of preclinical data are major disincentives for investment in development of novel treatments. Diseases of addiction are not among the priorities for pharmaceutical companies. In addition, a major concern highlighted in other CNS- and non-neurologic disease areas is the poor reproducibility of preclinical data for compounds progressing from academic laboratories to industrial development programs and, ultimately, to clinical trials. The reasons for these obstacles are multiple and varied, but methodological issues related to the design, execution, and reporting of preclinical studies are important components. Thus, offerors are expected to meticulously address methodological issues in their applications and, if successfully selected, in execution of this contract.

Fig 1 illustrates the basics of the concept. Please note that the examples of behavioral paradigms are not intended to be exclusive or prescriptive. The offeror is expected to identify and propose the behavioral domains of particular importance, and to develop the necessary animal behavioral protocols to test multiple processes believed to be contributing to smoking in humans.



In general, the tests chosen should be ones that have been used pre-clinically, so that reliability of the data generated has been established and that there exists some conceptual understanding of what the test measures. In addition, while considering models for the reward and positive reinforcement domain, investigators must be aware that certain animal behavioral tests appear not to generate reliable data with nicotine, and these should not be proposed (e.g., conditioned place preference, nicotine-primed reinstatement). Equally, it is important to highlight the fact that this contract solicitation is not intended as a mechanism to support the development of new behavioral models, assays or tests, or to uncover novel behavioral processes or neurobiological mechanisms. Nor is it intended to be directed only to investigators with addiction research expertise. NIDA welcomes the interest of small businesses who have expertise with animal models that have not seen wide use in addiction research (e.g., potentiated startle, elevated plus maze), but that might be useful as part of a screening battery.

Offerors must provide the rationale for:

- **Selecting the model system.** A detailed description of the animal model characteristics such as a definition of study population using a common strain and individual commercial stock designations of each animal provider, diet, housing conditions, microbial status and handling should be described. Before using compounds in the rat or mouse, detailed information about the cross-reactivity of the compounds with the target in the rat or mouse is necessary. For example, lower binding affinity in mice would require higher dosing which, in turn, might compromise target specificity and affect the results of testing. In addition, other interspecies differences should be taken into consideration. Bupropion is metabolized differently in the rat compared to human and mouse. Therefore, offerors need to specify how they will

address this and similar species differences (e.g., comparison of dosing with bupropion compared to its metabolite over a sufficient dose/time range).

- **Selecting the assays/models for the behavioral domains to be studied.** Provide the rationale for the selected domains, assays, models and end points. The proposed tests must be validated for their specificity and selectivity to measure clinically relevant symptom(s) or physiological parameters. It is expected that, regardless of the model or assay chosen for testing, investigators will propose an approach that is sensitive to the need for relatively high throughput assessment. Approaches that require lengthy training or assessment periods will be deemed not feasible. For behavioral domains different from Reward, testing in nondependent animals is expected. Testing in animal models of nicotine dependence is not required, although may be proposed if justified and deemed consistent with high- and medium-throughput. There are a variety of behavioral tests in the behavioral neuroscience field that could be adapted to this purpose of phenotypic drug screening. For the selection and validation of the tests, it is important to recognize that some drugs that provide similar phenotypic effects have differential effectiveness in aiding smoking cessation. For example, nicotine improves attentional function and does help with smoking cessation, whereas amphetamine also improves attentional function but there is no evidence for it aiding smoking cessation. Bupropion is an antidepressant and aids smoking cessation but sertraline which also is an antidepressant has not been found to help smoking cessation. It is thus important to integrate the phenotypic information with the neuropharmacological information to help develop a more integrated neurobehavioral approach. Importantly, the selected behavioral tests/models must provide internal behavioral validation such as learning rate or habituation which offers assurance that the conditions of the tests are appropriate.
- **Adequacy of controls.** Verification that interventional drugs reached and engaged the target. A potential concern about the specificity of drug effects in this screen – establishing a balance between sensitivity and specificity- should be addressed through selection of appropriate drug controls. The evaluation of both of these components, sensitivity and specificity, of predictive validity is vital in work of this type to avoid costly clinical studies of false-positive drugs that affect behaviors in preclinical screens but are ineffective in humans that are addicted to tobacco.
- **Selecting the dose, timing and route of administration for the medications being tested.** A drug administration and dose regimen that is adapted to the pharmacokinetic properties of the drug, and to the duration of the study requires careful consideration. The rationale for dosing the animal must be evident from appropriate pharmacodynamic and pharmacokinetic assays, published in the literature or obtained in applicants' laboratories. The route of administration is important not only because of animal welfare, but also out of consideration that the oral route is the desired route of administration in humans. Hence, oral dosing is preferable whenever possible. Frequent subcutaneous, intraperitoneal or intravenous injections lead to considerable stress in the animals and could influence test outcome. Assistant application devices, such as minipumps, should be avoided wherever possible, as they require surgery, additional control groups and can cause technical complications. For testing, a minimum of 3 doses of first and second line medications should be proposed. All of the medications are to be screened in each model proposed for evaluation.
- **Selecting the experimental design.**
 - Must describe methods of blinding, strategies for randomization and /or stratification. To improve the reliability of the proposed studies, the offeror must use randomization to eliminate systematic differences between treatment groups; induce the condition under investigation without knowledge of whether or not the animal will get the drug of interest; and assess the outcome in a blinded fashion.
 - Demonstrate the reconciliation between statistical needs for the detection of biological effects and constraints of animal welfare, cost and time. To guard against 'underpowered' studies, researchers must calculate the number of animals required to have a reasonable chance of detecting the anticipated effect given the expected variance of the data. A detailed discussion about the use of appropriate statistics must be provided, including the evidence that applicants consulted a statistician to obtain information about the sufficient group size, and the appropriate statistical method to be

applied for data analysis for each behavioral test and adapting the statistical approach for combining data across behavioral tests in developing an optimized predictive 'screening system.'

- Detailed description of statistical methods used in analysis and interpretation of results
- **Guidelines on nicotine dose selection for *in vivo* research.** If the models, in which *in vivo* nicotine dosage is warranted, are selected for this project, an evidence for species-specific nicotine dosage ranges must be presented. Nicotine dose ranges tolerated by humans and their animal models provide guidelines for experiments intended to extrapolate to human tobacco exposure through cigarette smoking or nicotine replacement therapies. Just as important are the nicotine dosaging regimens used to provide a mechanistic framework for acquisition of drug-taking behavior, dependence, tolerance, or withdrawal in animal models. The literature is replete with reports in which a dosaging regimen chosen for a specific nicotine-mediated response was suboptimal for the species used. **Guidelines on nicotine dose selection for *in vivo* research must be consulted (Psychopharmacology (2007) 190:269–319).**

Phase I Activities and Expected Deliverables

- Select the behavioral assays and models representing the behavioral domains of particular importance believed to be contributing to smoking and quitting in humans.
- Develop the necessary animal behavioral protocols to test multiple processes in those identified domains. Must finalize the selection of model systems, controls, experimental design, the dose, timing and route of administration, and provide verification that interventional drugs reached and engaged the target.
- Demonstrate that the selected behavioral tests are capable of high or medium throughput.
- Must agree and comply with good reporting practices, such as ARRIVE Guidelines. The ARRIVE guidelines consist of a checklist of 20 items describing the minimum information that all scientific publications reporting research using animals should include, such as the number and specific characteristics of animals used (including species, strain, sex, and genetic background); details of housing and husbandry; and the experimental, statistical, and analytical methods (including details of methods used to reduce bias such as randomization and blinding). All the items in the checklist have been included to promote high-quality, comprehensive reporting to allow an accurate critical review of what was done and what was found (see: ***Improving Bioscience Research Reporting: The ARRIVE Guidelines for Reporting Animal Research, PLoS Biology, 2010, Volume 8, issue 6, 1-5.***)
- To eliminate bias, all results, negative and positive, must be reported.
- Must provide data interpretation, including alternative interpretations. Must include the review of relevant literature in support or in disagreement with results.

Phase II Activities and Expected Deliverables

- Establish the battery of carefully selected behavioral tests.
- Demonstrate that the battery of carefully selected behavioral tests is capable of high or medium throughput. Demonstrate that this battery can make data collection and analysis more efficient without compromising the quality of the phenotypic assessment.
- Demonstrate that the battery of carefully selected behavioral tests is sufficiently sensitive to produce a comprehensive behavioral assessment in functional domains of cardinal importance for tobacco dependence.
- In selected model systems, using appropriate controls, experimental design, the dose, timing and route of administration, obtain standardized data on the responses to existing first-line pharmacotherapies that have been approved by FDA as aids for smoking cessation (i.e. varenicline, bupropion), and second-line pharmacotherapies (i.e. clonidine, nortriptyline).

- Establish, test and validate the bioinformatics algorithms/processes which are able to quickly and reliably recognize phenotypic profiles produced by varenicline, bupropion, clonidine and nortriptyline. The proposed bioinformatic approach must aid the predictions of the therapeutic effect of candidate compounds for smoking cessation to be developed in the future.
- Confirm that multivariate and/or bioinformatics algorithms are able to discriminate between varenicline-, bupropion-, clonidine- and nortriptyline-treated animals and at least two positive and two negative controls.
- Demonstrate the compliance with good reporting practices, such as ARRIVE Guidelines. The ARRIVE guidelines consist of a checklist of 20 items describing the minimum information that all scientific publications reporting research using animals should include, such as the number and specific characteristics of animals used (including species, strain, sex, and genetic background); details of housing and husbandry; and the experimental, statistical, and analytical methods (including details of methods used to reduce bias such as randomization and blinding). All the items in the checklist have been included to promote high-quality, comprehensive reporting to allow an accurate critical review of what was done and what was found (see: *Improving Bioscience Research Reporting: The ARRIVE Guidelines for Reporting Animal Research, PloS Biology, 2010, Volume 8, issue 6, 1-5.*)
- Collect and report all results, negative and positive.
- Must provide data interpretation, including alternative interpretations. Must include the review of relevant literature in support or in disagreement with results.
- Creating the all-inclusive platform which is comprised of hardware that evaluates the behaviors of domains of importance, and software that recognizes and analyzes behavior is encouraged.

150 Video Game Targeting Relapse Prevention in Youth with Substance Use Disorders

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

Number of Anticipated Awards: 2-3

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

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

Objective

This topic addresses the need for improved relapse rates among adolescent substance abusers. A video game should be designed for substance using adolescents in a commercializable and compelling package, for the purpose of reinforcing and maintaining behavior changes (e.g., skills development) accomplished through a theory-driven and evidence-based therapy. The video game may be compatible with an off the shelf commercially available gaming system. The project may, depending on the console selected, also involve development of peripherals for use with the system. The technology used must be familiar and accessible to youth, and developmentally appropriate.

Background

Despite advances in the development of treatments for adolescents with substance use disorders, relapse remains a significant concern. Although approaches to adolescent substance abuse almost exclusively focus on abstinence, relapse is likely to occur for one third to one half of youth, within 12 months of treatment completion (Grella, Joshi & Hser, 2004; Winters, Botzet, & Fahnhorst, 2011). Some studies report that less than half of adolescents are abstinent 3 months after discharge from outpatient treatment programs (Brown et al., 2001, Dennis et al., 2004, Kaminer et al., 2002, Winters, 2003). In the study of adolescent relapse risk, continuing care

and aftercare have repeatedly been shown to reduce the likelihood of relapse and enhance the maintenance of treatment gains (Burlison, Kaminer, & Burke, 2012; Winters et al., 2011).

Digital media and communication technology is pervasive in youth culture. Developing a video game for the purpose of maintaining treatment gains, using technology that is appealing, accessible and familiar to youth, and developmentally-appropriate, has the potential to greatly improve relapse rates in this population. This technology could improve engagement and reach, as well as reduce the cost and time burden of implementation on community treatment providers. Recent research by Girard et al (2009) has shown that participating in video game sessions that included behaviors that were incompatible with smoking cigarettes (crushing virtual cigarettes), within a virtual environment was more efficacious for smoking cessation than a similar game in which patients found and crushed virtual balls. The mechanism of this treatment is not well understood and it may be a form of extinction, counter conditioning, exposure with response prevention, or re-evaluative conditioning. Nonetheless, such practice in a “game” environment may be uniquely helpful because it can deliver a large “dose” of alternative practice in a manner that people not just tolerate but also enjoy. The fact Girard et al’s short duration gaming experience could improve outcomes in comparison with a “placebo” control suggests that video games may hold great promise for treating addiction.

Phase I Activities and Expected Deliverables

- Modification of an existing game or development of a new therapeutic game for use by one or several players (e.g., internet based, social networking opportunity)
- Development of peripherals to interact with the game as needed
- The game should provide opportunities for participants to practice skills learned in treatment or other opportunities that reinforce behavior changes/gains made through treatment
- The game should allow for personalization when appropriate (e.g., selection of drug of choice, or multiple drugs)
- The game should include a variety of difficulty levels of increasing intensity, with opportunities for participants to refine skills
- The game should be able to recognize and keep track of the participant’s performance over time so the participant can experience improvement in game play
- The game should record, store, and provide for downloading into a database, information regarding system use by each player such as time played, used to determine the extent of adherence and the “dose” required
- The game may allow for cooperation and interaction with other participants when the game is played as a group exercise
- A pilot study with a small group of adolescent substance abuse treatment completers (N=9)
 - The study will expose participants to the game weekly for 30 minutes a session, for 4 weeks
 - Measures collected at baseline will include drugs of choice, and timeline follow-back
 - Measures collected following each game exposure session will include acceptability, suggestions for improvement, AES/SAES, craving ratings, urine drug screening and cotinine screening (for smokers) and treatment engagement data
 - Measures collected 1 month after treatment entry will include timeline follow-back
 - The pilot testing may be done in an iterative fashion so that multiple small focus groups are exposed to the program and it is modified in response to their comments

Phase II Activities and Expected Deliverables

Modification of program developed in Phase I, in response to customer feedback followed by an RCT Pilot clinical study evaluating the effectiveness of the newly developed video game (TAU + 1 month of access to the video game vs. TAU alone). Outcomes collected will include AEs, SAEs, system use information (durations, preferred contexts/levels, times accessed), initial abstinence/use via urine screening, follow up abstinence/use via time-line follow back.

CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

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 Internet site: <http://www.cdc.gov/globalhealth/>

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

003 Diagnostic Needs for Neglected Tropical Diseases (NTD) Programs

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

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

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

Background: Neglected tropical diseases (NTDs) are bacterial and parasitic infections that disproportionately affect poor and marginalized populations around the world. A subset of NTDs, including lymphatic filariasis, onchocerciasis, schistosomiasis, trachoma and intestinal helminth infections, can be targeted effectively through mass chemotherapy. These NTDs are not considered to cause appreciable mortality; however, they are associated with high levels of morbidity because of the chronic nature of many of the infections. Blindness and disability due to these NTDs increase in prevalence with age, reducing the productivity of adults. Intestinal helminths, among the commonest of infections, have profound effects on the growth and cognitive development of children. The past five years have seen significant increases in the number of countries implementing NTD programs and in the number of persons being treated. These increases are the direct result of generous donations of drugs from pharmaceutical manufacturers and new funding support from the US Agency for International Development (USAID) and the Department for International Development (DFID), among others. Reducing the morbidity caused by NTDs is an objective of the Global Health Initiative (GHI) and the global elimination of lymphatic filariasis and trachoma are specific GHI targets. Available diagnostic tools for lymphatic filariasis (LF), trachoma, schistosomiasis, onchocerciasis and intestinal helminth infections do not at present meet the needs of the control programs.

Project Goal: Diagnostic tests are needed to guide programmatic decisions on community treatment for diseases addressed by mass drug administration (MDA). Despite the molecular revolution in biology, little of the new found knowledge of parasite genes and gene products is being translated into tools that can be used in the field to guide program decisions. Tools for mapping and monitoring program impact are still conventional parasitologic methods, based on microscopy. These tests lack sensitivity and are not adequate for NTD programs

with elimination endpoints. New antibody tests could provide more sensitive tools to monitor transmission, facilitate decision-making, and conduct surveillance. The potential advantages of antibody-based tests for post-MDA surveillance supports the efforts to develop a standard platform therefore opening opportunities for integrated surveillance for NTDs.

Impact: Development of improved diagnostic tools will address one of CDC's efforts to address lymphatic filariasis (LF in the Americas) and the GHI targets on NTDs. They will also enhance the commitment of donors and policy makers to the control and elimination programs for NTDs by providing higher quality information and increased confidence that public health goals are being met. Significant savings in human and financial resources could be obtained through the development of improved diagnostic tools.

004 Rapid Screening Tests to Prevent Congenital Infections and Ensure Blood Safety

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

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

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

Background: During the past decade, several companies have developed lateral flow immunochromatographic devices to detect antibodies to individual communicable diseases. More recently, these platforms have also been adapted to detect specific antigens associated with these infections. These inexpensive point-of-care (POC) tests offer considerable advantages over conventional laboratory tests, since they can be performed in remote, peripheral settings with little or no instrumentation by primary health care workers. This also allow for counseling (and treatment if appropriate) at the initial consultation. Point-of-care (POC) tests have been used successfully to screen pregnant women for HIV and syphilis to prevent vertical transmission of these infections and therefore prevent congenital disease. In addition, in areas remote from formal, organized blood banks, these and other POC tests have been used to screen potential blood donors to prevent transfusion related infections. Unfortunately, these tests are usually performed as individual tests for antibodies or antigens for single infections. This results in a series of test strips being run in parallel, which may have different flow characteristics, buffers and run times that may lead to confusion and potential inaccuracies.

Project Goal: CDC is seeking the development of a highly sensitive, highly specific, rapid and easy to use, disposable multiplex immunochromatographic screening device to detect Hepatitis BsAg and malarial antigen together with antibody to Human Immunodeficiency Virus 1 and 2 (HIV 1/2) and syphilis in a single finger-stick sample of whole blood. The purpose is for screening pregnant women with the intent to prevent vertical transmission of infection. CDC is also interested in a single device to detect Hepatitis BsAg and malarial antigen together with antibody to Hepatitis C Virus (HCV), Human Immunodeficiency Virus 1 and 2 (HIV 1/2) and syphilis in a single finger-stick sample to screen blood donors for transfusion-related infections in settings where conventional laboratory facilities are not available. Optimization of assays to detect both antibodies and specific antigens in the same cassette device on a single specimen is strongly encouraged.

Impact: It is anticipated that the development of these two multiplex immunochromatographic test cassettes could result in a significant reduction in rates of congenital HIV and syphilis, together with other infections that can be transmitted from mother to child. In addition, these tests would help make blood transfusions safer in areas where laboratory testing is either not available, or of poor quality.

005 Development of Diagnostic Tests for Strongyloidiasis and Schistosomiasis

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

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

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

Background: Schistosoma and Strongyloides parasites affect an estimated 100 million people worldwide, putting international travelers at risk for infections with these organisms. In a 10-year period from 1997 to 2008, over 400 cases of schistosomiasis were reported in travelers to the international travelers' health surveillance network (GeoSentinel). In addition, the United States resettles 50,000-80,000 refugees annually from around the world. It is estimated that the prevalence rates of parasites, such as Strongyloides and Schistosoma in many U.S.-bound refugee groups are between 20 and 40%. Diagnosis of these infections in returning travelers and refugees in the United States is difficult because patients often present initially with a constellation of vague symptoms and thus, diagnoses of strongyloidiasis and schistosomiasis typically rely on confirmatory laboratory testing. The availability of parasitic serology testing in the United States is limited to six commercial laboratories and the CDC reference laboratory. Most commercial laboratories use reagents prepared by one or two manufacturers. To further complicate diagnosis, the reliability of these reagents and tests are variable and typically not FDA-cleared. To improve laboratory diagnosis of parasitic diseases, reliable serological tests are needed, especially for schistosomiasis and strongyloidiasis.

Project Goal: CDC is particularly interested in the development, validation, and FDA clearance of serological tests for diagnosis of strongyloidiasis and schistosomiasis. Use of recombinant protein targets instead of native parasite materials for detection of parasite specific antibodies will reduce variability and availability and should be considered. All submissions must include validation and FDA clearance as deliverables.

Impact: Availability of reliable commercial tests for strongyloidiasis and schistosomiasis will improve clinical management of these diseases.

NATIONAL CENTER ON BIRTH DEFECTS AND DEVELOPMENTAL DISABILITIES (NCBDDD)

The mission of the CDC's National Center on Birth Defects and Developmental Disabilities (NCBDDD) is to promote the health of babies, children and adults and enhance the potential for full, productive living. To achieve its mission, NCBDDD works to: Identify the causes of birth defects and developmental disabilities; helps children to develop and reach their full potential; and, promotes health and well-being among people of all ages with disabilities, including blood disorders.

NCBDDD Web site: <http://www.cdc.gov/ncbddd/index.html>

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

016 Improving Data, Improving Care, Making it Count

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

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

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

Background: The number of people affected by complex childhood rare conditions (CCRC), such as spina bifida (SB), is estimated to be 1/1500 globally. While the prevalence of these conditions is low, they have high impact in terms of health care costs and impact on the family and the community. Reliable and valid clinical data are scarce and insufficient to identify and evaluate clinical practices that lead to the best outcomes in care for these populations. Diagnosis-specific Electronic Medical Records (EMRs) offer an important opportunity for specific clinical populations and their providers. Currently, most spina bifida clinics are required to enter data in both their institution's EMR, as well as in the spina bifida electronic medical record (SB-EMR). A software application that will eliminate double data entry and allow each institution to maintain its electronic medical record while also populating a diagnosis-specific record will allow the extraction of data that can be used to measure and evaluate

quality of care. This in turn has the potential to significantly impact the health and cost of care of people with spina bifida and other rare disorders.

Project Goal: CDC is seeking software that will build on the existing spina bifida electronic medical record (SB-EMR) being used by 19 clinics in the National Spina Bifida Patient Registry (NBSPR). Funding will support the development of intraoperative software to extract relevant data from an institution's legacy medical record system and input it into the SB-EMR, significantly reducing the resources needed to collect the condition-specific information critical for research. Data can then be used to evaluate the effectiveness of various treatment and prevention approaches for SB patients. Any software product developed as a part of this proposal must follow the Enterprise Performance Life Cycle process for project management, producing each of the required artifacts for a gate review prior to moving to the next stage in the process. Also, it must obtain Authority to Operate (ATO) from the Office of the Chief Information Security Officer (CISO), CDC.

Impact: The proposed software tool has applications for other health condition and clinical practices. For example, other registries (e.g., ALS) could use this tool for recording and tracking patient information. In addition, state and local health departments could use a similar tool to avoid double data entry into multiple surveillance systems. Labor and associated resources at the clinic level could be reduced dramatically while improving the quality of data needed to identify health care trends and best practices for care. This project will build on the current expansion of technology and use of EMR as they are rapidly being implemented in health systems across the country. If successful, the technology and tools developed will result in a more efficient and effective data entry operation by which clinical care and prevention can be improved.

017 Smartphone Application for Global Birth Defects Surveillance

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

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

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

Background: Every year approximately 8 million children are born worldwide with severe birth defects. Currently, data about the magnitude of birth defects prevalence in low and middle income countries are either nonexistent or severely underestimated, creating difficulties for health strategic planners to convince policy makers of the burden and the public health impact of birth defects in their countries. The use of smartphone technology has proven to be a useful tool in the collection of data that is otherwise not available, incomplete or not easy to capture. The use of smartphones is a novel, simple, efficient and instructive approach to the collection of data and offers great potential for encouraging health care personnel to contribute data using their mobile telephones. In particular, this technology would help address a critical need in large continental areas like Africa, South America and East Asia where birth defect registries are limited or do not exist and thus little is known about disease burden and service need. Use of smartphones to establish standard global surveillance data will help to more accurately identify the prevalence of birth defects and expand the reach and impact of clinical and public health services for affected children and their families.

Project Goal: CDC is seeking the development of smartphone technology for the implementation of birth defect registries in global settings. Application of smartphone technology has the potential to improve the accuracy of data collection, reduce the time and the cost of data transmission and retrieval, reduce data entry errors and synchronize collected information with a central database. Use of smartphone technology has the potential to address many of the issues involved in global birth defect surveillance such as the standardization of the data collection process. Built-in data quality indicators can assess key elements of data quality such as accuracy of diagnosis (providing clinical decision support to the health provider in the field), completeness of information of a minimal set of required variables, geographic information systems (GIS), timeliness of data transmission, availability of population denominator information, and evaluation of performance.

Impact: Many large countries have remote areas where the implementation of appropriate birth defect surveillance is very difficult. A smartphone application will strengthen surveillance by facilitating the standardization of birth defect collection, and storage, transmission and retrieval of data across worldwide communities. Local providers will have access to clinical information and guidelines for initial management of patients with birth defects. In addition, the technology will contribute to the awareness of the public health burden of birth defects, and the need for more targeted prevention strategies leading to a positive global health impact. Once developed, the smartphone application for birth defects registries has the potential to be easily converted into a collection tool for other existing epidemiological data registries with numerous uses and to further applications for insurance companies, government entities and private business.

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

The mission of the National Center for Chronic Disease Prevention and Health Promotion is leading efforts to promote health and well-being through prevention and control of chronic diseases. The vision is all people living healthy lives free from the devastation of chronic diseases.

Strategic Priorities

- Focus on Well-Being: Increase emphasis on promoting health and preventing risk factors, thereby reducing the onset of chronic health conditions.
- Health Equity: Leverage program and policy activities, build partner capacities, and establish tailored interventions to help eliminate health disparities.
- Research Translation: Accelerate the translation of scientific findings into community practice to protect the health of people where they live, work, learn, and play.
- Policy Promotion: Promote social, environmental, policy, and systems approaches that support healthy living for individuals, families, and communities.
- Workforce Development: Develop a skilled, diverse, and dynamic public health workforce and network of partners to promote health and prevent chronic disease at the national, state, and local levels.

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

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

033 A Mobile Phone Application ("App") for Advancing Teen Pregnancy Prevention

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

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

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

Background: The teen birth rate in the US remains high, particularly among racial/ethnic minorities compared with many other industrialized nations. The adverse consequences of teen pregnancy are substantial at individual, family, and community levels. A range of innovative tools and interventions is needed to foster an environment that enables teens to experience better reproductive health. In 2011, more than one-third of US teens ages 13-17 years and over 50% of young adults ages 18-24 years owned a smart phone. Evidence shows that teens access the internet for reproductive health information. Direct access to accurate, evidence-based, comprehensive, and teen-friendly information regarding pregnancy prevention that is also confidential and immediate can be made available with smart phone technology. While evidence related to the public health impact of smart phone apps is limited, similar technology-based tools, including internet-based and text-

messaging interventions, have been shown to be effective at increasing health-related knowledge, motivation, and behaviors.

Project Goal: CDC is seeking the design and development of complex mobile phone applications for multiple smart phone platforms. The applications should be developed with input from multiple stakeholders, including one or more leading teen pregnancy organizations that already maintain youth-friendly websites with relevant content. The development of the platforms should include a marketing plan for the app that targets teens, caregivers, youth-serving organizations, and health care providers. Teens and provider representatives must be involved in the testing of smartphone platforms, in line with standard practices in product development. The app should be interactive and comprehensive, including information about pregnancy and pregnancy prevention that may include quizzes, games, and other engaging means; a clinic “finder” feature that points users to clinics in their zip code; and a calendar and/or text-messaging feature to support both personal contraceptive use and service utilization. The app should be designed to be acceptable to teens, their caregivers, as well as youth-serving organizations and health care providers, who can promote its utilization in their services.

Impact: Mobile phone technology is an important underexplored tool to support the reproductive health of teen girls, with real potential to improve knowledge and attitudes about pregnancy prevention and increase uptake of relevant health services. The product is prime for rapid scalability, as it will be freely available through multiple channels to large numbers of teens with smart phones and can be integrated easily into a wide range of reproductive health programs and services for teen girls. Once launched, the product will be evaluated initially by tracking app downloads, website hits, and related technological means. Once developed, the application could have the potential to be adapted for other audiences.

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). NCEZID’s 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, NCEZID can attain better health for humans and animals and improve our environment.

NCEZID’s Web site: <http://www.cdc.gov/ncezid>

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

003 Development of Nanoparticle Dengue Diagnostic Tests

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

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

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

Background: Dengue is a major public health problem in global tropical and subtropical areas. Primary prevention of this mosquito vector-borne (transmitted) disease is limited because vaccines are only in the late-stage development phase and vector control has been thus far unsuccessful. Dengue presents as an acute febrile illness often without signs or symptoms that differentiate it from other common diseases such as influenza and leptospirosis. Some patients progress to severe dengue near the end of their febrile period, which can result in death. Good clinical management, early in the course of dengue, prevents excess morbidity and mortality. Yet, early clinical management requires accurate laboratory diagnosis to differentiate dengue from other similar presenting diseases (e.g., influenza, leptospirosis).

Until recently, dengue diagnostic testing was problematic because most patients present during the first days after onset of fever. Dengue virus (DENV) detection in serum is the only way to make the diagnosis, but anti-DENV IgM levels usually do not reach measurable levels until the critical phase. While molecular testing identifies most persons with dengue, this method is not widely available in developing countries where the disease is endemic. In addition, a soluble non-structural antigen (NS1) can be detected by immunoassay during this period, but is not as sensitive as molecular tests.

Nanoparticle-based technology significantly increases the sensitivity of antigen and antibody detection tests and can be used for molecular diagnostics and in multiplex formats. Microresonator constructs and nanowire-based field effect transistors allow this technology to detect biolytes at low femtomolar concentrations. Surface enhanced Raman scattering (SERS) and extrinsic Raman labels (ERLs) have been used with metal nanoparticles (gold, silver) organic reporter molecules to magnify the Raman response by $\sim 10^6$, which surpasses fluorescence.

Project Goal: To develop prototype dengue diagnostic tests that identify DENV by either molecular or immuno-detector systems (e.g., DENV specific nucleic acid, NS1 and E antigen) using nanoparticle-based technology that includes but is not limited to SERS and ERLs. The prototype test(s) should be developed as a biochip with a product profile that is amenable to a short-turn-around diagnostic result for use in resource constrained settings. Prototype test(s) would be judged as 'acceptable' if they detect a high proportion of dengue cases during the early phase of the febrile illness across all DENV serotypes, in primary and secondary infections and do not cross-react or misdiagnose other flavivirus infections or infections due to other causes of febrile illness that present with signs and symptoms similar to dengue.

Impact: The availability of dengue diagnostic tests with high sensitivity and specificity that detect DENV infection soon after the onset of fever would greatly change the public health impact of current secondary prevention activities by improving clinical outcomes, and would provide the basis for evaluation of dengue vaccines following introduction. The market for dengue diagnostic tests has not been estimated, however, it is estimated that 40-60% of the world's population reside in dengue endemic areas of the world (i.e., 100% cases of dengue are reported annually). Thus, one would expect there would be a many-fold great market for these tests each year.

004 Development of Tests in a Standardized Kit Format for Diagnosis of Arboviral Infections in Resource-Limited, Primary Health Care Setting

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

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

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

Background: Arthropod-borne virus infections may present with clinical symptoms similar to those of other bacterial or viral infections, such as a flu-like illness, encephalitis, or polio-like myelitis. Laboratory diagnosis is essential to determine etiology and calculate disease burden in order to guide treatment and control strategies, particularly if there is an effective vaccine available, such as for yellow fever and Japanese encephalitis. Detection of virus-specific immunoglobulin M (IgM) antibody in an enzyme-linked immunosorbent assay (MAC-ELISA) is the standard serological test for diagnosis of acute arbovirus infections. However, diagnostic tests are not available for many of these "neglected" but medically important arboviral diseases in resource poor laboratories. Samples must be sent to reference laboratories for testing, which delays diagnosis and reduces the number of laboratory-confirmed cases. "In-house" assays developed in reference laboratories are unsuitable for use in laboratories with limited technical capacity, due to the lack of standardized reagents and format.

Project Goal: The goal of this project is the development of a laboratory test based on IgM detection to diagnose arboviral infections in a standardized kit format. A prototype yellow fever virus MAC- ELISA should be developed initially showing proof-of-concept. The developed assays should have the characteristics of simplicity and robustness as described by the World Health Organization. The format should be designed so that the assay can easily be modified to test for other arboviruses by switching out a limited number of standardized and validated

reagents and controls. The variation, reproducibility, and accuracy of the test should be characterized and benchmarked against current tests. Suitability of the test for use in resource-limited surveillance laboratories should be demonstrated.

Impact: The test is meant to be a screening test used at primary health care level. A rapid diagnostic test is essential to support vaccination and surveillance programs by increasing the number of biologically confirmed cases, thus improving the accuracy of disease burden estimates. These data will in turn improve the effectiveness of vaccine programs for vaccine-preventable diseases such as yellow fever. The primary benefit of such diagnostics is intended for resource-poor countries. Such rapid arbovirus diagnostics can be incorporated into resource-poor countries as laboratory capacity-building efforts.

Innovative approaches such as “dipstick” technology that can be used in the clinic and the field are already being employed by manufacturers of commercial diagnostic assays for other medically important infectious diseases. Rapid diagnostics is an area that should be of particular interest to small business concerns. Laboratories in developing countries have either no alternative methods or only elaborate and inefficient methods to diagnose arbovirus infections at this time, a gap which a small business has the opportunity to fill.

005 Reducing Antimicrobial Resistance through Improved use of Laboratory Testing Information in Healthcare Facilities

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

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

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

Background: The reduction and eventual elimination of healthcare-associated infections (HAIs) and the combatting of antibiotic resistance in the pathogens causing these infections are national public health priorities as demonstrated in Department of Health and Human Services (HHS) national action plans. Public reporting of HAIs by hospitals using the National Healthcare Safety Network (NHSN) is mandated in over half of all states and the number of states is increasing annually. The public reporting of three HAIs is currently incentivized by the Centers for Medicare and Medicaid Services and this program is slated to expand dramatically in coming years. Meanwhile, as the crisis of antibiotic resistance continues to grow, the need for more detailed surveillance data will increase to preserve remaining drug activity. Electronic data submission provides the best method for meeting increasing informational needs while containing the costs of public reporting. Already several hundred hospitals are submitting electronic data to NHSN to meet present and future mandates for public reporting.

Project Goal: To develop a technical prototype for summarizing antimicrobial resistance data (as outlined on the NHSN website) using a laboratory or infection control information system and reporting to NHSN within the CDC clinical document architecture specifications (http://www.cdc.gov/nhsn/CDA_eSurveillance.html).

It is expected that a successful project will implement a research plan and evaluate (1) the validity (i.e., accuracy) of the data reported to NHSN and (2) the usability for hospital or regional-based collaborative efforts on reducing antimicrobial resistant infections.

Impact: Success of this project would demonstrate the value of electronic submission of antimicrobial resistance data to NHSN, therefore providing risk adjusted resistance patterns to guide infection prevention and antimicrobial stewardship activities at a facility. Infection control information systems and laboratory information systems that enable such electronic reporting will consider this functionality an attractive option to hospitals to comply with state mandates on reporting and adhering to emerging federal policies in this arena. If the experience of reporting HAI data electronically from vendor systems to NHSN is any indication, demonstrating the utility of such reporting for antimicrobial resistance data will be perceived by hospitals engaged in infection prevention activities, either by mandate or quality improvement programs, as an attractive option in making decisions regarding hospital-based health information systems.

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

The mission of the National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (NCHHSTP) is to maximize public health and safety nationally and internationally through the elimination, prevention, and control of disease, disability, and death caused by HIV/AIDS, Viral Hepatitis, other Sexually Transmitted Diseases, and Tuberculosis.

NCHHSTP Web site: <http://www.cdc.gov/nchhstp/>

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

034 Development of Biomedical Devices to Elicit Durable Protective Immunity against HIV

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

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

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

Background: Substantial progress has been made recently towards identifying effective HIV prevention strategies. The RV144 trial demonstrated that an HIV vaccine comprised of a recombinant ALVAC prime + gp120 boost regimen was partially efficacious (VE=31.2%), although its protective effects waned over the study period and study volunteers faced barriers related to transportation to clinic for the required multiple injections with vaccine. Thus, there is an urgent need to identify innovative approaches to elicit or to boost HIV vaccine-elicited immunity, via simplified immunization regimens. If identified, these approaches have the potential to increase the durability of vaccine-mediated protection against HIV acquisition. Use of platforms to sustainably deliver HIV vaccine antigens, which could also incorporate delivery of antiretroviral drugs, would potentially allow for co-delivery of biomedical preventions for HIV.

Project Goal: The goal of this project is to stimulate research and development of biomedical devices that elicit durable protective immunity against HIV. Specific areas of research interest include the development of novel devices to achieve sustained delivery of HIV vaccine antigens to mucosal surfaces for the purpose of priming antiviral immune responses and/or boosting prior vaccine-elicited immune responses with the goal of increasing the duration of protective immunity against HIV as well as reducing the need for multiple visits to a provider. Development of products based upon platforms that have (1) demonstrated high levels of safety, acceptance and adherence in human usage for sustained delivery (e.g. implants, vaginal rings) and (2) intrinsic flexibility for advanced development to incorporate co-delivery of antiretroviral compounds, other HIV microbicides, vaccine adjuvants, or hormonal contraceptives are highly encouraged.

The expected end-product is the design and construction of a device that could be used in humans to achieve sustained delivery of HIV vaccine antigens to mucosal surfaces and that is suitable for efficacy assessment in a relevant non-human primate model. It would be expected that there would be documentation providing a detailed description of all testing results, including *ex vivo* characterization of the device as well as pre-clinical assessment protocols and a preliminary efficacy trial design (including statistical power estimates).

Impact: Globally, more than 2.6 million new HIV infections occur each year (>50,000 in the US). As such, the need for efficacious biomedical preventions is needed to complement existing behavioral interventions. Products determined to be efficacious under this proposed evaluation have enormous market potential in HIV prevention.

035 Development of a Portable Multiplex Assay for Determination of Recent HIV-1 Infection

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

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

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

Background: The estimation of HIV incidence, or the rate of new infections in a population, is an important public health indicator that provides valuable information on the growth of the epidemic and the efficacy of various intervention strategies. Within the past 15 years, a new strategy for estimating HIV incidence has been employed based on the observation that certain biomarkers (mainly HIV-specific antibody levels and avidity) can distinguish recent from long-term infection. Since the immune response to HIV gradually develops post-infection, the immune profile of newly infected individuals will present differently from the immune profile of individuals with chronic infection. Although several laboratory tests have been developed for the purpose of identifying recent infection, most approaches rely on a single assay measure. Relying on a single measure of the immune response is subject to greater misclassification due to inherent immune variation among individuals. Recent studies have shown that a combination of antibody responses or immune measures may reduce misclassification rates and improve incidence estimates. Ideally, multiple immune responses should be measured in a single assay, since it is not always feasible or cost effective to require several different tests for accurate incidence estimates.

Project Goal: The goal of the proposed project is to develop a portable and cost-effective assay that is capable of measuring multiple immune responses at the same time (multiplexing). The assay should be able to provide a quantitative or semi-quantitative measure of HIV-specific antibody levels and avidity to multiple antigens using a relatively small volume of plasma ($\leq 20\mu\text{l}$). The assay should be similar in sensitivity to HIV antibody-based tests that are currently commercially available. While several technologies with multiplexing capability do exist, there are some limitations to the assay formats, as they are typically costly, technically complicated, and not accessible to all testing settings/ laboratories. The technology should be a portable, high-throughput, and a scalable multiplexing platform for determining recent infection.

Impact: The availability of a low-cost, portable assay that can measure multiple HIV-specific biomarkers will enhance accessibility to diverse laboratory or field settings, enabling large-scale use of HIV incidence by various public health entities to chart their respective epidemics. The platform may also be suitable for other infectious disease diagnostics.

036 Testing the Efficacy of Combination HIV Prevention Strategies in Nonhuman Primates

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

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

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

Background: Although substantial progress has been made to identify new biomedical HIV prevention strategies, including topical and oral antiretroviral drug pre-exposure prophylaxis (PrEP) regimens and vaccines, they are not yet approved for general use. However, these preventions (or related derivatives) are likely to be implemented widely in upcoming years. The identification of HIV preventions such as these, despite being only partially efficacious, offer an opportunity for small companies with flexible portfolios to consider the possibility of combining novel or existing biomedical preventions to generate a high probability for complete protection.

Because future clinical trials of HIV vaccines will likely incorporate control arms that include PrEP, there is also a need to model whether such combinations may result in additive, synergistic, neutral or even subtractive effects. Non-human primate modeling, to determine the efficacy and interactions of combinations of two partially effective, clinically relevant HIV biomedical prevention approaches, can directly inform clinical trial design and impact the implementation of biomedical preventions against HIV.

Project Goal: The long-term goal of this project is to determine, in non-human primates, whether two biomedical HIV preventions, such as vaccines and PrEP, may be combined to achieve additive or synergistic protective efficacy. Proposals are sought where small businesses will combine biomedical preventions, such as vaccines and drugs that are known to have efficacy (complete or partial), to prevent HIV infection in humans or animal models of HIV. In the event that one or both prevention modalities do not have extensive prior assessment in non-human primates or human clinical trials, demonstration of safety and scalability is of primary importance. Safety testing can include use of *in vitro* or small animal model testing. Proposals should include plans for the design, construction and characterization of prevention modalities suitable for efficacy assessments of the combination of partially effective interventions in a relevant non-human primate model. Proposals should also document a detailed description of the prevention modalities and pre-clinical assessment protocols.

Impact: Globally, more than 2.6 million new HIV infections occur each year (>50,000 in the US). As such, the need for efficacious biomedical preventions is urgently needed to complement existing behavioral interventions. This mechanism specifically enables small businesses to rapidly conduct relevant pre-clinical evaluation of combined HIV prevention products in a nonhuman primate model that presages the changing landscape of domestic HIV prevention trials to incorporate PrEP as a standard of care. Combined HIV prevention products in a nonhuman primate model could facilitate the identification of the most promising HIV prevention solutions early in the developmental pipeline, which would accelerate the pace at which they are translated into effective products to prevent HIV infections.

NATIONAL CENTER FOR IMMUNIZATION AND RESPIRATORY DISEASES (NCIRD)

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

NCIRD Web site: <http://www.cdc.gov/ncird/>

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

025 Development of an Inactivated Rotavirus Vaccine for Use in Global Immunization

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

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

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

Background: The currently licensed oral rotavirus vaccines Rotarix™ and Rotateq™ are effective in reducing cases of severe diarrhea among children in high and middle income countries, but are significantly less effective in low income countries. In addition, both vaccines are associated with a low risk of diarrhea and intussusception among infants who receive the first dose of vaccine. To improve the safety and efficacy of oral rotavirus vaccines, CDC scientists have developed a proprietary inactivated rotavirus vaccine (IRV) technology (new human strains and a novel method for rotavirus inactivation) and demonstrated the immunogenicity in mice and protective efficacy in piglets of this IRV by intramuscular (IM) administration.

CDC has demonstrated good immunogenicity of the IRV using an innovative microneedle patch technology, achieving comparable antibody titers with a 1/10th of the antigen dose compared to those induced by a full IM dose of vaccine. Microneedles provide a simple and painless method to administer vaccines without using hypodermic needles. They are inexpensive to manufacture and may not need the cold chain, a major advantage for immunization campaigns in the developing world. The findings from this study may allow us to enhance public health through the development of a low cost vaccine with an improved safety and efficacy profile and thus help achieve and sustain global immunization initiatives such as rotavirus vaccines.

Project Goal: With the establishment of proof of concept for intramuscular and skin immunization in animals, the CDC has licensed the technology to a number of vaccine manufacturers in the US and emerging developing countries for scale-up and clinical development as a stand-alone IRV first and then a combined pediatric vaccine. However, phase 1 safety data in the country of origin (USA in this case) is a prerequisite for vaccine manufacturers in developing countries to receive approval from their national regulatory agencies for clinical trials of a new vaccine. To meet this requirement, the goal of this project is to propose several specific research areas of interest, (1) production of a Vero cell bank, (2) production of two rotavirus seed banks and, (3) preparation of two pilot vaccine lots under Good Manufacturing Practice (GMP) conditions in partnership with a contract manufacturing organization (CMO). Pilot lots will include the preparation of an injectable IM vaccine first and microneedle patches for skin immunization, if enough funding is available.

Impact: Availability of GMP materials and phase I safety data will provide the opportunity to move this project forward, working with partners, to jointly develop this new and innovative IRV for use in children throughout the world. In long term, this IRV can be combined with other pediatric vaccines, such as IPV. Due to the parenteral administration, IRV will be equally effective in all settings, help save more lives, and ultimately increase global health impact through large immunization campaigns.

026 Thermostable Dry Measles Vaccine Formulation for Sublingual Administration

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

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

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

Background: Vaccines are one of the most powerful tools available for preventing disease. Measles vaccine has led to the elimination of endemic measles from the Western Hemisphere and a tremendous reduction in global mortality. However, the logistic difficulties inherent in vaccination by injection create barriers to high measles vaccine coverage. Vaccination by injection requires highly skilled vaccinators, maintenance of an expensive cold-chain, vaccine reconstitution with risks of contamination and bio-waste disposal of millions of syringes and needles to prevent reuse or injuries. Needle-free vaccine delivery would lower these barriers and expand the benefits of vaccination to a larger at-risk population.

Project Goal: Although sublingual drug delivery has been used for years, only recently has research begun to demonstrate the potential of sublingual vaccine delivery. Proposals are solicited for the development of a thermostable dry measles vaccine formulation to be administered sublingually in a melting tablet, wafer or strip format. The goal of this project is the development of the thermostability of the vaccine formulation in the selected format with < 1 log titer loss after 6 months at 37^o C and a clear demonstration of immunogenicity in a small animal model (i.e., cotton rat).

Impact: A thermostable sublingual measles vaccine would lower barriers to vaccination, especially in the developing world, by reducing the skill level required to vaccinate, eliminating cold chain requirements and the risks associated with reconstitution and injection. Dry sublingual vaccine would reduce shipping costs, cold chain costs and the direct cost of syringe and needles as well as many hidden costs (e.g., costs of vaccinator training, sharps disposal, disease from needle reuse or injury).

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.

PHPR carries out its mission by emphasizing accountability through performance, progress through public health science, and collaboration through partnerships.

OPHPR's Web site link: <http://www.cdc.gov/phpr/about.htm>

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

002 Improved Methods for Collection, Preservation, and Transportation of Biological Specimens

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

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

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

Background: CDC has both domestic and international laboratory programs that provide clinical specimen testing for the detection of known and emerging infections, chemical, or radiological agents that pose global health threats. Current methods for collection, storage, and transport of biological specimens are expensive and labor and material intensive. Clinical specimens are often collected by highly trained phlebotomists and other health professionals, transported to laboratories in compliance with shipping regulations for potentially infectious specimens, and shipped cold chain to ensure specimen integrity. There is a need for novel, minimally invasive, low-complexity specimen collection, and preservation technologies.

Project Goal: CDC is interested in improving capabilities in low-complexity methods to collect, preserve, and safely transport clinically relevant specimens or samples for endemic/outbreak surveillance and chemical or radionuclide exposure. Additionally, these technologies could translate well to low resource settings or home health care environments. High quality proposals must address the following priority area and preference will be given to proposals that can address any additional areas of interest. Specifically excluded is research that only incrementally advances the current state of the art. Proposals that aim to simply integrate existing methods and technologies will be considered non-responsive.

Priority Area of Interest:

Technologies/methods that allow for the self-collection of blood specimens in all point of care/contact settings without the necessity for trained personnel, require minimal materials/reagents, yet maintain the integrity of either nucleic acids (DNA and RNA), protein analytes (antigens, enzyme, and antibody), or both, at ambient temperature (0-40oC) for ≥ 14 days, and allow for inexpensive storage and transportation.

Nucleic acids and/or protein analytes must be compatible/interoperable with downstream assays including functional (activity) assays, real-time PCR, real-time RT-PCR, ELISA, sequencing, mass spectroscopy, and serology, as appropriate.

Additional Areas of interest:

Compatibility of the technologies/methods with additional biological specimens (e.g., serum, sputum, nasopharyngeal swabs/aspirates, whole blood or urine).

When warranted, inactivation of infectious agents by methods that do not interfere with detection/measurement of the diagnostic target, to allow laboratory testing under BSL2 conditions.

Suitability for testing a broad range of target analytes (including but not limited to, antibodies, antigens, cytokines, enzymes, carbohydrates, small molecules, metals, radionuclides, lipids, and nucleic acids) at clinically relevant concentrations.

Potential for FDA clearance or CLIA waiver for use with diagnostics in low resource settings, patient homes, and first responder use, Potential for Point of Care or Point of Need settings or laboratory environments.

Impact: Improved capabilities for specimen or sample collection, preservation, inactivation, and transportation will result in faster laboratory testing, reduce public health costs, and improve testing capabilities in low complexity settings. The impact of this initiative is broadly applicable to many CDC's "Winnable Battles" including HIV, food safety, obesity, achieving and sustaining global immunization goals, and eliminating lymphatic filariasis in the Americas. In addition, this improved capability will support core CDC surveillance programs such as the National Health and Nutrition Examination Survey, National Health Interview Survey, and the National HIV Behavioral Surveillance System. New technologies resulting from this project have commercialization potential within the growing home health testing market, global diagnostics, and traditional laboratory testing venues.

PART II HUMAN SUBJECTS RESEARCH GUIDANCE AND INFORMATION SUPPLEMENT

1. INTRODUCTION

A Protection of Human Subjects section of the Research Plan is required for all proposals. The information provided in the section on Protection of Human Subjects should be consistent with the information provided on the face page of the application.

For all research involving human subjects, the Scientific Review Group (SRG) will assess the adequacy of protections for research participants against research risks, and the appropriate inclusion of women, minorities, and children, based on the information provided in the application.

To assist in preparing the section on Protection of Human Subjects, six possible scenarios are provided in Section 2 below. All research projects will fall into one of these six scenarios (to help determine whether research that involves the use of human data or biological specimens is human subjects research, refer to this Web site <http://grants.nih.gov/grants/policy/hs>). Determine which scenario the proposed research falls into, then go to the specific instructions applicable to that scenario in [Section 3](#) of the Supplement. Where appropriate, Section 3 provides instructions on addressing the Inclusion of Women and Minorities, the Targeted/Planned Enrollment Table, and the Inclusion of Children. All definitions related to human subjects research are linked to text found in Part I, Section 3, [Definitions](#). [Section 5](#) of this Part includes descriptions of and links to the DHHS Human Subjects Protections regulations and NIH policies that apply to clinical research.

2. SCENARIOS

Scenario A. No Human Subjects Research

If no human subjects research is proposed in the proposal, check the box marked “No” on the Proposal Cover Sheet (Appendix A) and indicate “No” on the Proposal Summary and Data Record (Appendix G). If your proposed research involves the use of human data and/or biological specimens, you must provide a justification for your claim that no human subjects are involved in the Protection of Human Subjects section of the Research Plan.

See the [instructions for Scenario A](#).

Scenario B. Non-Exempt Human Subjects Research

If research involving human subjects is anticipated to take place under the award, check the box marked “Yes” on the Proposal Cover Sheet (Appendix A) and indicate “Yes” on the Proposal Summary and Data Record (Appendix G). Enter your Human Subjects Assurance Number.

In the Protection of Human Subjects section of the Research Plan, you must provide sufficient information for reviewers to determine that the proposed research meets (1) the requirements of the DHHS regulations to protect human subjects from research risks (45 CFR part 46), and (2) the requirements of NIH policies on inclusion of women, minorities, and children. Research involving a clinical trial will fall under either Scenario E or F below.

See the [instructions for Scenario B](#).

Scenario C. Exempt Human Subjects Research

If **all** of the proposed human subjects research meets the criteria for one or more of the exemptions from the requirements in the DHHS regulations (46.101(b)), check the box marked “Yes” on the Proposal Cover Sheet (Appendix A). Indicate “Yes” on the Proposal Summary and Data Record and insert E-1, E-2, E-3, E-4, E-5, or E-6 as appropriate, in the field for Exemption Number (Appendix G). Leave IRB Approval Date field blank since a Human Subjects Assurance Number is not needed for exempt research. Check “N/A” in field for “example of informed consent” and “Clinical Protocol” as these are not required for exempt research.

In the section on Protection of Human Subjects in the Research Plan, provide a justification for the exemption(s) containing sufficient information about the involvement of the human subjects to allow a determination by peer reviewers and NIH staff that claimed exemption(s) is/are appropriate.

The PHS will make a final determination as to whether the proposed activities are covered by the regulations or are in an exempt category, based on the information provided in the Research Plan. When in doubt, consult with the Office for Human Research Protections (OHRP), Department of Health and Human Services by accessing their Web site <http://www.hhs.gov/ohrp/> for guidance and further information.

The [exemptions](#) appear in Part I, Section 3, Definitions.

Please note: If the proposed research involves only the use of human data or biological specimens, you should first determine whether the research involves human subjects. The exemptions do not apply if the research does not involve human subjects. For help determining whether research that involves the use of human data or biological specimens is human subjects research, please refer to this Web site <http://grants.nih.gov/grants/policy/hs/>.

See the [instructions for Scenario C](#).

Scenario D. Delayed-Onset Human Subjects Research

If human subjects research is anticipated within the period of the award but plans for involvement of human subjects cannot be described in the application as allowed by the DHHS regulations (45 CFR part 46.118), check “Yes” to “This proposed project involves human subjects” on the Proposal Cover Sheet (Appendix A) and indicate “Yes” on the Proposal Summary and Data Record (Appendix G). In the section on Protection of Human Subjects in the Research Plan, you should either include an explanation of anticipated protections for human subjects or an explanation of why protections cannot be described.

Examples of delayed-onset of human subjects research include:

- Human subjects research is dependent upon the completion of animal or other studies; or
- Human subjects research protocols to be included will undergo an independent decision-making process (often defined by a FOA).

See [instructions for Scenario D](#).

Scenario E. Human Subjects Research Involving a Clinical Trial

If research involving human subjects is anticipated to take place under the award, and you intend to conduct a [clinical trial](#) during the project period, check the boxes marked “Yes” on the Proposal Cover Sheet (Appendix A) to “This proposed project involves human subjects,” and “Clinical Trial?” Indicate “Yes” on the Proposal Summary and Data Record (Appendix G). In addition, complete the items regarding the Institution’s General Assurance, Institution’s Review Board, informed consent and clinical protocol.

In the section on Protection of Human Subjects in the Research Plan, you must provide sufficient information for reviewers to determine that the proposed research meets:

- 1) the requirements of the DHHS regulations to protect human subjects from research risks (45 CFR part 46);
- 2) NIH policy requirements for Data and Safety Monitoring for Clinical Trials;
- 3) the ClinicalTrials.gov requirements if applicable;
- 4) the requirements of NIH policies on inclusion of women, minorities, and children; and
- 5) the requirements of NIH policy on reporting race and ethnicity data for human subjects in clinical research.

See [instructions for Scenario E](#).

Scenario F. Human Subjects Research Involving an NIH-Defined Phase III Clinical Trial

If research involving human subjects is anticipated to take place under the award, and you intend to conduct an [NIH-defined Phase III clinical trial](#) during the project period, check the boxes marked “Yes” to the following statement/questions on the Proposal Cover Sheet (Appendix A):

- This proposed project involves human subjects.
- Clinical Trial?
- Agency-Defined Phase III Clinical Trial?

Also indicate “Yes” on the Proposal Summary and Data Record (Appendix G) to the following question: Does this proposal involve human subjects research? In addition, complete the items regarding the Human Subjects Assurance Number, Institution’s Review Board, informed consent and Clinical Protocol.

In the section on Protection of Human Subjects in the Research Plan, you must provide sufficient information for reviewers to determine that the proposed research meets:

- 1) the requirements of the DHHS regulations to protect human subjects from research risks (45 CFR part 46);
- 2) NIH policy requirements for Data and Safety Monitoring for Clinical Trials;
- 3) the ClinicalTrials.gov requirements if applicable;
- 4) the requirements of NIH policies on inclusion of women, minorities, and children;
- 5) additional Requirements for NIH-defined Phase III clinical trials; and
- 6) the requirements of NIH policy on reporting race and ethnicity data for subjects in clinical research.

See [instructions for Scenario F](#).

3. INSTRUCTIONS FOR PREPARING THE SECTION ON PROTECTION OF HUMAN SUBJECTS

Scenario A. No Human Subjects Research Proposed

Criteria

Human Subjects Research	No
Exemption Claimed	No
Clinical Trial	N/A
NIH-Defined Phase III Clinical Trial	N/A

Instructions and Required Information

In the proposal narrative, create a heading labeled “Protection of Human Subjects” and include the following statement below the heading: “No Human Subjects Research is proposed in this proposal.”

If proposed studies using human data or biological specimens do not involve human subjects as described in the OHRP Guidance on Research Involving Coded Private Information or Biological Specimens (<http://www.hhs.gov/ohrp/policy/cdebiol.html>), provide an explanation of why the proposed studies do not constitute research involving human subjects.

The explanation could include: a description of the source of the data/biological specimens, and whether there is any intervention or interaction with the subjects in order to obtain the specimens and data; what identifiers will be associated; the role(s) of providers of the data/biological specimens in the proposed research; and the manner by which the privacy of research participants and confidentiality of data will be protected.

Research that does not involve intervention or interaction with living individuals, or identifiable private information, is not human subjects research (see Part I, Section 3, [Definitions](#)). Research involving the use of coded private information or biological specimens may not constitute human subjects research if the conditions of the OHRP Guidance on Research Involving Coded Private Information or Biological Specimens have been met (<http://www.hhs.gov/ohrp/policy/cdebiol.html>).

Research that only proposes the use of cadaver specimens is not human subjects research because human subjects are defined as “living individuals.” The use of cadaver specimens is not regulated by 45 CFR part 46, but may be governed by other Federal, State or local laws.

Scenario B. Non-Exempt Human Subjects Research

Criteria

Human Subjects Research	Yes
Exemption Claimed	No
Clinical Trial	No
NIH-Defined Phase III Clinical Trial	No

Instructions and Required Information

Although no specific page limitation applies to this section of the proposal, be succinct.

In the proposal narrative, create a section entitled “Protection of Human Subjects” and create a subheading for each of the following items.

Follow the instructions that are identified for each of the following topics and provide the information that is requested:

Protections for Human Subjects - [Section 4.1 - 4.1.4](#)

Inclusion of Women and Minorities - [Section 4.2](#)

Targeted/Planned Enrollment Table - [Section 4.3](#)

Inclusion of Children - [Section 4.4](#)

If the research involves collaborating sites or subprojects, provide the information identified above for each participating site.

Scenario C: Human Subjects Research Claiming Exemption 1, 2, 3, 4, 5, or 6

Criteria

Human Subjects Research	Yes
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Exemption Claimed	1, 2, 3, 4, 5, or 6
Clinical Trial	Yes or No
NIH-Defined Phase III Clinical Trial	No

Instructions and Required Information

Although no specific page limitation applies to this section of the proposal, be succinct. The [exemptions](#) appear in Part I, Section 3, Definitions.

Although the research may be exempt from the DHHS regulatory requirements, it is still research involving human subjects and the application must follow the instructions that are identified for each of the following topics and provide the information that is requested.

In the proposal narrative, create a heading entitled “Protection of Human Subjects” and include the following statement below the heading: “This Human Subjects Research falls under Exemption(s)”

Follow the instructions that are identified for each of the following topics and provide the information that is requested:

Justification for Claimed Exemption(s):

In this section, identify which exemption(s) (1, 2, 3, 4*, 5, or 6) you are claiming. Justify why the research meets the criteria for the exemption(s) that you have claimed.

If the research will include a clinical trial, even if exempt, include a Data and Safety Monitoring Plan – [Section 4.1.5](#), and address the ClinicalTrials.gov requirements if applicable – [Section 4.1.6](#).

Inclusion of Women and Minorities - [Section 4.2](#)

Targeted/Planned Enrollment Table - [Section 4.3](#)

Inclusion of Children - [Section 4.4](#)

*NOTE: If all the proposed research meets the criteria for Exemption 4, then the requirements for inclusion of women and minorities, targeted/planned enrollment table, and inclusion of children, do not need to be addressed.

Scenario D: Delayed-Onset Human Subjects Research

Criteria

Human Subjects Research	Yes
Exemption	Yes or No
Clinical Trial	Yes or No
NIH-Defined Phase III Clinical Trial	Yes or No

Instructions and Required Information

In rare situations, proposals are submitted with the knowledge that human subjects will be involved during the period of support, but plans are so indefinite that it is not possible to describe the involvement of human subjects

in the proposal. The kinds of activities that lack definite plans are often institutional awards where the selection of specific projects is the institution's responsibility, research training grants, and projects in which the involvement of human subjects depends upon completion of instruments, animal studies, or purification of compounds.

If the involvement of human subjects cannot be fully described, create a heading entitled "Protection of Human Subjects" and provide a detailed explanation why it is not possible to develop definite plans at this time. The explanation should be specific and directly related to the Specific Aims in the proposal. If the involvement of human subjects depends upon information that is not presently available (e.g., completion of instruments, animal studies, purification of compounds), be explicit about the information and the factors affecting the availability of the information. Describe the information that will be necessary in order to develop definite plans for the involvement of human subjects, why that information is not currently available, and when the information is expected to become available during the course of the project.

If an award is made, prior to the involvement of human subjects the grantee must submit to the NIH awarding office for prior approval either (1) detailed information as required in the Research Plan, Protection of Human Subjects (addressing risks to the subjects, adequacy of protection against risks, potential benefits of the proposed research, importance of the knowledge to be gained, and data and safety monitoring plan if applicable), OHRP Assurance (FWA) and certification of IRB approval, OR (2) if all of the research meets the criteria for one or more exemptions, identification of which exemption(s) is/are applicable to the research, and a justification for the exemption with sufficient information about the involvement of human subjects to allow a determination that the claimed exemption is appropriate. For clinical research, the request for prior approval must also address the inclusion of women and minorities, the inclusion of children, and provide completed targeted/planned enrollment tables as required in the Research Plan.

Under no circumstance may human subjects be involved in research until approval is granted by the awarding entity, and certification of IRB approval has been accepted by the agency.

In the proposal narrative, create a section entitled Protection of Human Subjects and a subheading for each of the following items. Follow the instructions that are identified for each of the following topics and EITHER provide as much of the information that is requested as possible; OR describe why it is not possible to provide the information due to delayed-onset of human subjects research:

Protection of Human Subjects - [Section 4.1 - 4.1.4](#)

If the research will include a clinical trial, even if exempt, include a Data and Safety Monitoring Plan - [Section 4.1.5](#), and address the ClinicalTrials.gov requirements if applicable – [Section 4.1.6](#).

Inclusion of Women and Minorities - [Section 4.2](#)

Targeted/Planned Enrollment Table - [Section 4.3](#)

Inclusion of Children - [Section 4.4](#)

Scenario E: Clinical Trial

Criteria

Human Subjects Research	Yes
Exemption	Yes or No
Clinical Trial	Yes
NIH-Defined Phase III Clinical Trial	No

Instructions and Required Information

In the proposal narrative, create a section entitled "Protection of Human Subjects" and include the following statement below the heading: "This Human Subjects Research meets the definition of a clinical trial." (See definition of "[clinical trial](#)" in Part I.) Create a subheading for each of the following items. Follow the instructions that are identified for each of the following topics and provide the information that is requested:

Protection of Human Subjects - [Section 4.1 - 4.1.6](#)

Inclusion of Women and Minorities - [Section 4.2](#)

Targeted/Planned Enrollment Table - [Section 4.3](#)

Inclusion of Children - [Section 4.4](#)

If the research involves collaborating sites or subprojects, provide the information identified above for each participating site.

Scenario F: NIH Defined Phase III Clinical Trial

Criteria

Human Subjects Research	Yes
Exempt	No
Clinical Trial	Yes
NIH-Defined Phase III Clinical Trial	Yes

Instructions and Required Information

In the proposal narrative, create a section entitled "Protection of Human Subjects" and include the following statement below the heading: "This Human Subjects Research involves an NIH-Defined Phase III Clinical Trial." (See "[NIH defined Phase III Clinical Trial](#)" in Definitions.)

Create a subheading for each of the following items. Follow the instructions that are identified for each of the following topics and provide the information that is requested:

Protection of Human Subjects - [Section 4.1 - 4.1.6](#)

Inclusion of Women and Minorities - [Section 4.2](#)

Additional Instructions and Requirements when NIH-Defined Phase III Clinical Trials are Proposed - [Section 4.2.1](#)

Targeted/Planned Enrollment Table - [Section 4.3](#)

Inclusion of Children - [Section 4.4](#)

If the research involves collaborating sites or subprojects, provide the information identified above for each participating site.

4. INSTRUCTIONS PERTAINING TO NON-EXEMPT HUMAN SUBJECTS RESEARCH

In your proposal narrative, **create a section entitled “Human Subjects.”** Although no specific page limitation applies to this section of the proposal, be succinct. Scientific Review Groups will assess each proposal as being acceptable or unacceptable with regard to the protection of human subjects. DHHS regulations and policies governing human subjects research are described and referenced in Section 5 below. **Use subheadings** to address the issues listed under items 4.1-4.4 below. If your research includes a clinical trial, include a subheading "Data and Safety Monitoring Plan" and follow the instructions in 4.2 below. If your research includes an NIH-Defined Phase III Clinical Trial, follow the additional instructions in 4.2.1 below.

4.1 PROTECTION OF HUMAN SUBJECTS

4.1.1 Risks to Human Subjects

a. *Human Subjects Involvement, Characteristics, and Design*

- Describe the proposed involvement of human subjects in the work outlined in the Human Subjects Research section.
- Describe and justify the characteristics of the subject population, including their anticipated number, age range, and health status if relevant.
- Describe and justify the sampling plan, as well as the recruitment and retention strategies and the criteria for inclusion or exclusion of any subpopulation.
- 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. Note that 'prisoners' includes all subjects involuntarily incarcerated (for example, in detention centers) as well as subjects who become incarcerated after the study begins.
- If relevant to the proposed research, describe procedures for assignment to a study group. As related to human subjects protection, describe and justify the selection of an intervention's dose, frequency, and administration.
- 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. Explain how data from the site(s) will be obtained, managed, and protected.

b. *Sources of Materials*

- Describe the research material obtained from living individuals in the form of specimens, records, or data.
- Describe any data that will be collected from human subjects for the project(s) described in the application.
- Indicate who will have access to individually identifiable private information about human subjects.
- Provide information about how the specimens, records, and/or data are collected, managed, and protected as well as whether material or data that include individually identifiable private information will be collected specifically for the proposed research project.

c. *Potential Risks*

- Describe the potential risks to subjects (physical, psychological, financial, legal, or other), and assess their likelihood and seriousness to the human subjects.
- Where appropriate, describe alternative treatments and procedures, including the risks and potential benefits of the alternative treatments and procedures, to participants in the proposed research.

4.1.2 Adequacy of Protection Against Risks

a. Recruitment and Informed Consent

- Describe plans for the recruitment of subjects (where appropriate) and the process for obtaining informed consent. If the proposed studies will include children, describe the process for meeting requirements for parental permission and child assent.
- 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. If a waiver of some or all of the elements of informed consent will be sought, provide justification for the waiver. Informed consent document(s) need not be submitted to the PHS agencies unless requested.

b. Protections Against Risk

- Describe planned procedures for protecting against or minimizing potential risks, including risks to privacy of individuals or confidentiality of data, and assess their likely effectiveness.
- Research involving vulnerable populations, as described in the DHHS regulations, Subparts B-D must include additional protections. Refer to DHHS regulations, and OHRP guidance:

Additional Protections for Pregnant Women, Human Fetuses and Neonates:

<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartb>

Additional Protections for Prisoners:

<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartc>

OHRP Subpart C Guidance: <http://www.hhs.gov/ohrp/policy/index.html#prisoners>

Additional Protections for Children:

<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartd>

OHRP Subpart D Guidance: <http://www.hhs.gov/ohrp/policy/index.html#children>

- Where appropriate, discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects. Studies that involve clinical trials (biomedical and behavioral intervention studies) must include a general description of the plan for data and safety monitoring of clinical trials and adverse event reporting to the IRB, the NIH and others, as appropriate, to ensure the safety of subjects.

4.1.3 Potential Benefits of the Proposed Research to Human Subjects and Others

- Discuss the potential benefits of the research to research participants and others.
- Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to research participants and others.

4.1.4 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 reasonably may be expected to result.

NOTE: Test articles (investigational new drugs, devices, or biologics) including test articles that will be used for purposes or administered by routes that have not been approved for general use by the Food and Drug Administration (FDA) must be named. State whether the 30-day interval between submission of applicant certification to the FDA and its response has elapsed or has been waived and/or whether use of the test article has been withheld or restricted by the FDA, and/or the status of requests for an Investigational New Drug (IND) or Investigational Device Exemption (IDE) covering the proposed use of the test article in the Research Plan.

4.1.5 Data and Safety Monitoring Plan

The NIH Data and Safety Monitoring Plan Policy is described and referenced in [Section 5.3](#).

- If the proposed research includes a clinical trial, create a heading entitled "Data and Safety Monitoring Plan."
- Provide a general description of a monitoring plan that you plan to establish as the overall framework for data and safety monitoring. Describe the entity that will be responsible for monitoring and the process by which Adverse Events (AEs) will be reported to the Institutional Review Board (IRB), the funding I/C, the NIH Office of Biotechnology Activities (OBA), and the Food and Drug Administration (FDA) in accordance with Investigational New Drug (IND) or Investigational Device Exemption (IDE) regulations. Be succinct. Contact the FDA (<http://www.fda.gov/>) and also see the following Web sites for more information related to IND and IDE requirements:
http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr312_01.html (IND)
http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr812_01.html (IDE)
- The frequency of monitoring will depend on potential risks, complexity, and the nature of the trial; therefore, a number of options for monitoring trials are available. These can include, but are not limited to, monitoring by a:
 - a. PD/PI (required)
 - b. Institutional Review Board (IRB) (required)
 - c. Independent individual/safety officer
 - d. Designated medical monitor
 - e. Internal Committee or Board with explicit guidelines
 - f. Data and Safety Monitoring Board (DSMB). NIH specifically requires the establishment of Data and Safety Monitoring Boards (DSMBs) for multi-site clinical trials involving interventions that entail potential risk to the participants, and generally for Phase III clinical trials. Although Phase I and Phase II clinical trials may also need DSMBs, smaller clinical trials may not require this oversight format, and alternative monitoring plans may be appropriate.
- A detailed Data and Safety Monitoring Plan must be submitted to the applicant's IRB and subsequently to the funding IC for approval prior to the accrual of human subjects (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html>). For additional guidance on creating this Plan, see the above reference.

4.1.6 ClinicalTrials.gov Requirements

Public Law 110-85 (also known as the FDA Amendments Act (FDAAA) of 2007) mandates registration and results reporting of certain "applicable clinical trials" in ClinicalTrials.gov. Under the statute these trials generally include: (1) Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase 1 investigations, of a product subject to FDA regulation; and (2) Trials of Devices: Controlled trials with health outcomes, other than small feasibility studies, and pediatric postmarket surveillance. Review the statutory definition of applicable clinical trial to identify if registration is required to comply with the law (See [PL 110-85](#), Section 801(a), adding new 42 U.S.C. 282(j)(1)(A)).

NIH encourages registration of ALL clinical trials whether required under the law or not.

Registration is accomplished at the ClinicalTrials.gov Protocol Registration System Information Web site (<http://prsinfo.clinicaltrials.gov/>). A unique identifier called an NCT number, or ClinicalTrials.gov registry number, will be generated during the registration process.

The NIH implementation of FDAAA requires:

- the registration of applicable clinical trials in ClinicalTrials.gov no later than 21 days after the first subject is enrolled,

- 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, and
- if an “applicable clinical trial” is funded in whole or in part by an NIH grant or cooperative agreement, grant and progress report forms shall include a certification that the responsible party has made all required submissions to ClinicalTrials.gov.

For competing (new and renewal) applications that include applicable clinical trials which require registration and, in certain cases, require results reporting under FDAAA, provide the NCT number/s, Brief Title/s (protocol title intended for the lay public – see [Definitions](#)), and the identity (name, organization) of the responsible party (or parties) and their contact information (e-mail address is required for internal administrative use only) in the human subjects section of the Research Plan under a section heading entitled ClinicalTrials.gov. If a new applicable clinical trial is proposed or if the contract will support an applicable clinical trial that is ongoing but not yet required to register under FDAAA (e.g. less than 21 days have passed since enrollment of the first patient), under the heading ClinicalTrials.gov include a clear statement that the application includes an applicable clinical trial which will require registration in ClinicalTrials.gov.

The entity responsible for registering the trial is the “responsible party.” The statute defines the responsible party as:

(1) the sponsor of the clinical trial (as defined in 21 CFR 50.3) (<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.3>), or

(2) the principal investigator of such clinical trial if so designated by a sponsor, grantee, contractor, or awardee (provided that “the principal investigator is responsible for conducting the trial, has access to and control over the data from the clinical trial, has the right to publish the results of the trial, and has the ability to meet all of the requirements” for submitting information under the law) (http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110.pdf). See PL 110-85, Section 801(a), (adding new 42 U.S.C. 282(j)(1)(A)(ix)).

For the complete statutory definitions of “responsible party” and “applicable clinical trial”, refer to [Elaboration of Definitions of Responsible Party and Applicable Clinical Trial](#).

The signature on the application of the Authorized Organizational Representative assures compliance with FDAAA.

Additional information can be found on the ClinicalTrials.gov Web site (http://grants.nih.gov/ClinicalTrials_fdaaa).

4.2 INCLUSION OF WOMEN AND MINORITIES

Create a section heading entitled "Inclusion of Women and Minorities" and place it immediately following the "Protection of Human Subjects" section. Although no specific page limitation applies to this section of the proposal, be succinct. The NIH Policy on the Inclusion of Women and Minorities in Clinical Research is described and referenced in [Section 5.6](#).

Scientific Review Groups will assess each proposal as being acceptable or unacceptable with regard to the inclusion of women and minorities in clinical research.

In this section of the Research Plan, address, at a minimum, the following four points:

1. The targeted/planned distribution of subjects by sex/gender and racial/ethnic groups for each proposed study or protocol using the format in the Targeted/Planned Enrollment Table. (Instructions for completing this table are provided below in 4.3.) If using existing specimens and/or data without access to information on the distribution of women and minorities, so state and explain the impact on the goals of the research as part of the rationale that inclusion cannot be described (item 3 below). Alternatively, describe the gender and

minority composition of the population base from whom the specimens and/or data will be obtained. Include the Targeted/Planned Enrollment Table in this section.

2. A description of the subject selection criteria and rationale for selection of sex/gender and racial/ethnic group members in terms of the scientific objectives and proposed study design. The description may include, but is not limited to, information on the population characteristics of the disease or condition under study.
3. A compelling rationale for proposed exclusion of any sex/gender or racial/ethnic group (see examples below).
4. A description of proposed outreach programs for recruiting sex/gender and racial/ethnic group members as subjects.

Examples of acceptable justifications for exclusion of:

A. *One gender:*

1. One gender is excluded from the study because:
 - inclusion of these individuals would be inappropriate with respect to their health;
 - the research question addressed is relevant to only one gender;
 - evidence from prior research strongly demonstrates no difference between genders; or
 - sufficient data already exist with regard to the outcome of comparable studies in the excluded gender, and duplication is not needed in this study.
2. One gender is excluded or severely limited because the purpose of the research constrains the applicant's selection of study subjects by gender (e.g., uniquely valuable stored specimens or existing datasets are single gender; very small numbers of subjects are involved; or overriding factors dictate selection of subjects, such as matching of transplant recipients, or availability of rare surgical specimens).
3. Gender representation of specimens or existing datasets cannot be accurately determined (e.g., pooled blood samples, stored specimens, or data-sets with incomplete gender documentation are used), and this does not compromise the scientific objectives of the research.

B. *Minority groups or subgroups:*

1. Some or all minority groups or subgroups are excluded from the study because:
 - inclusion of these individuals would be inappropriate with respect to their health;
 - the research question addressed is relevant to only one racial or ethnic group;
 - evidence from prior research strongly demonstrates no differences between racial or ethnic groups on the outcome variables;
 - a single minority group study is proposed to fill a research gap; or
 - sufficient data already exists with regard to the outcome of comparable studies in the excluded racial or ethnic groups and duplication is not needed in this study.
2. Some minority groups or subgroups are excluded or poorly represented because the geographical location of the study has only limited numbers of these minority groups who would be eligible for the study, and the investigator has satisfactorily addressed this issue in terms of:
 - the size of the study;
 - the relevant characteristics of the disease, disorder or condition; or
 - the feasibility of making a collaboration or consortium or other arrangements to include representation.

3. Some minority groups or subgroups are excluded or poorly represented because the purpose of the research constrains the applicant's selection of study subjects by race or ethnicity (e.g., uniquely valuable cohorts, stored specimens or existing datasets are of limited minority representation, very small numbers of subjects are involved, or overriding factors dictate selection of subjects, such as matching of transplant recipients or availability of rare surgical specimens).
4. Racial or ethnic origin of specimens or existing datasets cannot be accurately determined (e.g., pooled blood samples, stored specimens or data sets with incomplete racial or ethnic documentation are used) and this does not compromise the scientific objectives of the research.

4.2.1 Additional Instructions and Requirements When NIH-Defined Phase III Clinical Trials Are Proposed

If the proposed research includes an [NIH-Defined Phase III Clinical Trial](#), the section on Inclusion of Women and Minorities also must address whether clinically important sex/gender and/or race/ethnicity differences are expected from the intervention effect. The discussion may include supporting evidence and/or data derived from animal studies, clinical observations, metabolic studies, genetic studies, pharmacology studies, and observational, natural history, epidemiology and other relevant studies. The discussion of expected sex/gender and/or race/ethnicity differences in intervention effect must include selection and discussion of one of the following analysis plans:

- Plans to conduct valid analyses 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. (Representation of sex/gender and racial/ethnic groups is not required as subject selection criteria, but inclusion is encouraged.), *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 among subgroups.

4.3 INSTRUCTIONS FOR COMPLETING THE TARGETED/PLANNED ENROLLMENT TABLES FOR REPORTING RACE AND ETHNICITY DATA FOR SUBJECTS IN CLINICAL RESEARCH

The NIH Policy on Reporting Race and Ethnicity Data for Subjects in Clinical Research is described and referenced in [Section 5.8](#).

A. New Proposals

All new clinical research studies should collect and report information on participants with respect to two categories of ethnicity and five categories of race. The Inclusion Enrollment Report (http://grants.nih.gov/grants/funding/424/SF424R-R_enrollmentreport.doc) for reporting summary data on participants to NIH includes two categories of ethnicity and five categories of race and is based on the Office of Management and Budget (OMB) reporting standards for data on race and ethnicity. Investigators should review the instructions and Frequently Asked Questions about using the Enrollment Table format at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html>.

When reporting these data in the aggregate, investigators should report: (a) the number of research participants in each ethnic category; (b) the number of research participants who selected only one category for each of the five racial categories; (c) the total number of research participants who selected multiple racial categories reported as the "number selecting more than one race," and (d) the number of research participants in each racial category who are Hispanic or Latino. Investigators may provide the detailed distributions, including all possible combinations, of multiple responses to the racial designations as additional information. However, more detailed data should be compiled in a way that they can be reported using the required categories.

Instructions for Completing Targeted/Planned Enrollment Table

(http://grants.nih.gov/grants/funding/424/SF424R-R_enrollment.doc)

Provide the study title.

The “Total Planned Enrollment” means the number of subjects that are expected to be enrolled in the study, consistent with the definition in ClinicalTrials.gov.

The “Total Planned Enrollment” will be reported in two ways in the table: by “Ethnic Category” and by “Racial Categories.”

“Ethnic Category”: Provide the numeric distribution of the Total Planned Enrollment according to ethnicity and sex/gender in the top part of the table.

“Racial Categories”: Provide the numeric distribution of the Total Planned Enrollment, this time by racial categories and sex/gender, in the bottom part of the table. Note that Hispanic is an ethnic, not a racial, category.

If there is more than one study/protocol, provide a separate table for each.

List any proposed racial/ethnic subpopulations below the table.

Submitting Applications or Proposals Using Existing Data in Clinical Research with No Plans for Collecting New/Additional Data:

Investigators are instructed to provide plans for the total number of subjects proposed for the study and to provide the distribution by ethnic/racial categories and sex/gender using the Targeted/Planned Enrollment Table. Under these circumstances, investigators are not required to re-contact subjects solely to comply with the newly revised categories.

If Data Collection is Ongoing, Such that New Human Subjects Will be Enrolled and/or Additional Data Will be Collected from Human Subjects:

Investigators should report ethnicity/race and sex/gender sample composition using the Inclusion Enrollment Report.

If Data Collection is Complete, Such that No New/Additional Subject Contact is Planned:

Investigators should use the Inclusion Enrollment Report.

Research Conducted at Foreign Sites:

If proposed studies involve a foreign site, investigators are encouraged to design culturally sensitive and appropriate data collection instruments that allow research participants to self-identify their racial and ethnic affiliation. However, these items should be designed in a way that they can be aggregated into the OMB-required categories. Also, the investigator can report on any racial/ethnic subpopulations by listing this information in an attachment to the required table. This may be particularly useful when distinctive subpopulations are relevant to the scientific hypotheses being studied.

When completing the tables that describe research in foreign sites, investigators should asterisk and footnote the table indicating that data include research participants in foreign sites. If the aggregated data only includes participants in foreign research sites, the investigator should provide information in one table with an asterisk and footnote. However, if the study includes both domestic and foreign sites, the investigator should complete two separate tables – one for domestic and another for foreign participants.

B. Progress Reports

The Inclusion Enrollment Report (http://grants.nih.gov/grants/funding/424/SF424R-R_enrollmentreport.doc) must be used for reporting accrual data to the NIH. In annual progress reports, investigators conducting clinical research are required to provide the cumulative total enrollment of subjects to-date, showing the distribution by ethnic/racial categories and sex/gender on the Inclusion Enrollment Report, and must update the Targeted/Planned Enrollment Table as needed.

4.4 INCLUSION OF CHILDREN

The NIH Policy on Inclusion of Children is referenced and described in [Section 5.7](#). Instructions for this item under the “Human Subjects” heading of the Research Plan are as follows:

- Create a section entitled “Inclusion of Children” and place it immediately following the Targeted/Planned Enrollment Table.
- For the purpose of implementing these guidelines, a *child* is defined as an individual under the age of 21 years (for additional information see <http://grants.nih.gov/grants/funding/children/children.htm> and <http://grants.nih.gov/grants/guide/notice-files/not98-024.html>).
- Provide either a description of the plans to include children, or, if children will be excluded from the proposed research, application, or proposal, present an acceptable justification for the exclusion (see below).
- If children are included, the description of the plan should include a rationale for selecting a specific age range of children. The plan also must include a description of the expertise of the investigative team for working with children at the ages included, of the appropriateness of the available facilities to accommodate the children, and the inclusion of a sufficient number of children to contribute to a meaningful analysis relative to the purpose of the study.
- Scientific Review Groups will assess each proposal as being acceptable or unacceptable with regard to the age-appropriate inclusion or exclusion of children in the research project.
- When children are involved in research, the Additional Protections for Children Involved as Subjects in Research ([45 CFR part 46 Subpart D \(http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartd\)](#)) apply and must be addressed under the Protections Against Risk subheading (4.1.2.b).

Justifications for Exclusion of Children

For the purposes of this policy, all individuals under 21 are considered children; however, exclusion of any specific age group, such as individuals under 18, should be justified in this section. It is expected that children will be included in all clinical research unless one or more of the following exclusionary circumstances apply:

1. The research topic to be studied is not relevant to children.
2. Laws or regulations bar the inclusion of children in the research.
3. 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 needlessly redundant. Documentation of other studies justifying the exclusions should be provided. NIH program staff can be contacted for guidance on this issue if the information is not readily available.
4. A separate, age-specific study in children is warranted and preferable. Examples include:
 - a. The condition is relatively rare in children, as compared to adults (in that extraordinary effort would be needed to include children, although in rare diseases or disorders where the applicant has made a particular effort to assemble an adult population, the same effort would be expected to assemble a similar child population with the rare condition); or

- b. The number of children is limited because the majority are already accessed by a nationwide pediatric disease research network; or
 - c. Issues of study design preclude direct applicability of hypotheses and/or interventions to both adults and children (including different cognitive, developmental, or disease stages or different age-related metabolic processes). While this situation may represent a justification for excluding children in some instances, consideration should be given to taking these differences into account in the study design and expanding the hypotheses tested, or the interventions planned, to allow inclusion of children rather than excluding them.
5. 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). Although 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.
 6. Study designs are aimed at collecting additional data on pre-enrolled adult study subjects (e.g., longitudinal follow-up studies that did not include data on children).
 7. Other special cases can be justified by the investigator and found acceptable to the review group and the Institute/Center Director.

5. HUMAN SUBJECTS RESEARCH POLICY

Human Subjects Research Policy includes DHHS regulations for the protection of human subjects and the following NIH policies related to human subjects research.

5.1 PROTECTION OF HUMAN SUBJECTS

The Department of Health and Human Services (DHHS) regulations for the protection of human research subjects provide a systematic means, based on established, internationally recognized ethical principles, to safeguard the rights and welfare of individuals who participate as subjects in research activities supported or conducted by the DHHS. The regulations stipulate that the awardee organization, whether domestic or foreign, bears responsibility for safeguarding the rights and welfare of human subjects in DHHS-supported research activities. The regulations require that offeror organizations engaged in nonexempt human subjects research supported or conducted by the DHHS hold a Federal-wide Assurance (FWA) with the Office for Human Research Protections (OHRP), and establish appropriate policies and procedures for the protection of human subjects. These regulations, [45 CFR part 46 \(http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html\)](http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html), Protection of Human Subjects, are available from OHRP, Department of Health and Human Services, The Tower Building, 1101 Wootton Parkway, Suite 200, Rockville, MD 20852; telephone: 1-866-447-4777 (toll-free) or (240) 453-6900; e-mail: ohrp@osophs.dhhs.gov. In general, OHRP considers organizations that receive direct support from DHHS for the conduct of nonexempt human subjects research to be engaged in human subjects research (for more information on whether an institution is engaged in human subjects research, refer to: <http://www.hhs.gov/ohrp/policy/engage08.html>). When a research project is conducted by multiple organizations, each organization that is engaged in nonexempt human subjects research must hold an FWA and comply with the regulations at 45 CFR 46.

Nonexempt research involving human subjects may only be conducted under a DHHS award if the engaged organization(s) is operating in accord with an approved FWA and provides verification that an Institutional Review Board (IRB) that is registered under the specific FWA has reviewed and approved the proposed activity in accordance with the DHHS regulations. No award to an individual will be made unless that individual is affiliated with an assured organization that accepts responsibility for compliance with the DHHS regulations. Foreign offeror organizations must also comply with the provisions of the regulations unless a determination of equivalent protections is made in accord with 45 CFR 46.101(h).

Under DHHS regulations to protect human subjects, certain research areas are [exempt](#). However, if an offeror makes inappropriate designations of the noninvolvement of human subjects or of exempt categories of research, this may result in delays in the review of an application or an application not being reviewed. The PHS will make a

final determination as to whether the proposed activities are covered by the regulations or are in an exempt category, based on the information provided in the Research Plan. With the exception of research projects that meet the criteria for Exemption 4, studies that are exempt from the human subjects regulatory requirements must still address the inclusion of women, minorities and children in the study design.

Regulations of the Food and Drug Administration (21 CFR 50, 21 CFR 56) generally apply to biomedical research involving an unapproved drug, device or biologic and may apply to certain studies of approved products. Additional information on FDA regulations is available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/cfrsearch.cfm>. If work falls under FDA's regulatory requirements, the grantee must follow both DHHS and FDA human subject protection regulations.

The *National Institutes of Health Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)* apply to all projects (NIH-funded and non NIH-funded) involving recombinant DNA molecules that are conducted at or sponsored by an institution that receives NIH support for recombinant DNA research. As defined by the *NIH Guidelines*, recombinant DNA molecules are either: (1) molecules that are constructed outside living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate in a living cell; or (2) DNA molecules that result from the replication of those described in (1). The *NIH Guidelines* set forth principles and standards for safe and ethical conduct of recombinant DNA research and apply to both basic and clinical research studies. The *NIH Guidelines* should be carefully reviewed and implemented to ensure that proper biosafety and containment practices are employed for all projects involving recombinant DNA research, including review by an Institutional Biosafety Committee that meets the requirements of the *NIH Guidelines*. Further, the *NIH Guidelines* include special review and reporting requirements for the conduct of human gene transfer studies (under Appendix M). Failure to comply with the *NIH Guidelines* may result in suspension, limitation, or termination of NIH funds for recombinant DNA research at the organization or a requirement for NIH prior approval of any or all recombinant DNA projects at the organization. A copy of the *NIH Guidelines* is posted at the following URL: http://oba.od.nih.gov/rdna/nih_guidelines_oba.html and may be obtained from the NIH Office of Biotechnology Activities, 6705 Rockledge Drive, Suite 750, Bethesda, MD 20892, 301-496-9838.

Federal requirements to protect human subjects apply to most research on human specimens (such as cells, blood, and urine), residual diagnostic specimens, and medical information. Research involving existing data, documents, records, pathological specimens, diagnostic specimens, or tissues that are individually identifiable is considered "research involving human subjects." The NIH Office of Extramural Research Human Subjects Web site contains additional information and Frequently Asked Questions to help investigators understand how these federal requirements apply to their research. See <http://grants.nih.gov/grants/policy/hs/index.htm>.

The DHHS regulations require the NIH to evaluate all proposals involving human subjects (<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.120>). This independent evaluation is conducted at the NIH through the peer review system and NIH staff review, and, as required, will take into consideration the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained. On the basis of this evaluation, the NIH may approve or disapprove the proposal, or enter into negotiations to develop an approvable one.

5.2 VULNERABLE POPULATIONS

Investigators who conduct research involving pregnant women, human fetuses and neonates, prisoners (or subjects who become prisoners after the research has started), or children, must follow the provisions of the regulations in Subparts B, C, and D of [45 CFR part 46](http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html) (<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>), respectively. The subparts describe the additional protections required for conducting research involving these populations. Relevant information may be obtained at the OHRP Web site (<http://www.hhs.gov/ohrp/policy/index.html>).

REMINDER: DHHS regulations at [45 CFR part 46, Subpart C](http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartc) (<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartc>) describe requirements for additional protections for research involving prisoners as subjects *or* individuals who become prisoners after the research has started. Refer to: <http://www.hhs.gov/ohrp/policy/prisoner.html> for complete instructions.

[Exemptions 1-6](http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartc) do **not** apply to research involving prisoners or subjects who become prisoners (see [Subpart C](http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartc) (<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartc>)). Although Exemptions 1 and 3-6 apply to research involving children (see [Subpart D](http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartd) (<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartd>)), [Exemption 2](http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartd) can only be used for research involving educational testing or observations of public behavior when the investigator(s) do not participate in the activities being observed.

5.3 DATA AND SAFETY MONITORING PLANS FOR CLINICAL TRIALS

For each proposed clinical trial, NIH requires a data and safety monitoring plan that describes oversight and monitoring to ensure the safety of participants and the validity and integrity of the data. The level of monitoring should be commensurate with the risks and the size and complexity of the clinical trial. Prior to the accrual of human subjects, a detailed data and safety monitoring plan must be submitted to the offeror's IRB and to the funding entity for approval. Adverse Events must be reported to the IRB, the NIH funding Institute or Center, and other appropriate offices or agencies. This policy requirement is in addition to any monitoring requirements imposed by [45 CFR part 46](http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html) (<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>). NIH policy specifically requires the establishment of a Data and Safety Monitoring Board (DSMB) for multi-site clinical trials involving interventions that entail potential risk to the participants, and generally for Phase III clinical trials.

5.4 IRB APPROVAL

NIH does not require certification of IRB approval of the proposed research prior to NIH peer review of a proposal. See <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-031.html>.

Following NIH peer review, the offeror organization will be notified of the need for review and approval of the proposed research by an IRB that is registered under the institutional assurance with OHRP. See <http://www.hhs.gov/ohrp/> to register an IRB. Certification of IRB approval must be sent to the Grants Management Office identified in the notice requesting documentation. Certification of IRB review and approval must include: the PHS SBIR proposal number, title of the project, name of the program director /principal investigator, date of IRB approval, and appropriate signatures. Grantees may also use the optional form "Protection of Human Subjects - Assurance Identification/IRB Certification/Declaration of Exemption (Common Rule)" (OMB Form No. 0990-0263 <http://www.hhs.gov/ohrp/assurances/forms/of310.rtf>) to meet this requirement.

According to OHRP policy, in general, an institution is considered to be engaged in human subjects research when it receives an NIH award to support nonexempt human subjects research. See <http://www.hhs.gov/ohrp/policy/engage08.html>. All institutions engaged in human subjects research must obtain a Federalwide Assurance (FWA) from OHRP. Instructions for applying for a Federalwide Assurance (FWA) are available from the OHRP Web site at <http://www.hhs.gov/ohrp/assurances/index.html>.

DHHS human subject regulations at 45 CFR 46.103(f) require that each application for non-exempt HHS-supported human subject research be reviewed and approved by an IRB (see also <http://www.hhs.gov/ohrp/policy/conditionalapproval2010.html>). Only the date of approval of the application should be submitted to NIH. However, the IRB must ensure that any corresponding protocol(s) are consistent with the application, and must maintain documentation of IRB approval of all corresponding protocols, including those reviewed by consortium participants. For multi-site research, the primary grantee is expected to collect the certification from each subrecipient.

Any modifications to the Research Plan in the proposal, required by either NIH or by the IRB, must be submitted with follow-up certification of IRB approval to the NIH before the competing award is made. It is the responsibility of the PD/PI and the offeror organization to submit the follow-up documentation.

If more than a year will have elapsed between the initial IRB review date and the anticipated award date, the awarding unit staff shall require re-review by the IRB prior to award.

5.5 REQUIRED EDUCATION IN THE PROTECTION OF HUMAN RESEARCH PARTICIPANTS

NIH requires education on the protection of human research participants for all individuals identified in PHS applications as senior/key personnel who will be involved in the design or conduct of human subjects research, before funds are awarded for applications or contract proposals involving human subjects. For information relating to this requirement, see the following notices <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html> and <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-061.html>, and Frequently Asked Questions at: http://grants.nih.gov/grants/policy/hs_educ_faq.htm. Prior to award, offerors will be required to provide a description of education completed in the protection of human subjects for all senior/key personnel involved in the design or conduct of human subjects research. Although NIH does not endorse specific programs, there are curricula available that can provide guidance or that can be modified to provide training in this area. See <http://phrp.nihtraining.com/users/login.php> for computer-based training developed by NIH that can be downloaded at no charge. For information on facilitating education and developing curricula, see <http://www.nih.gov/sigs/bioethics>.

5.6 NIH POLICY ON THE INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH

NIH policy requires that women and members of minority groups and their subpopulations must be included in all NIH-supported biomedical and behavioral research projects involving [clinical research](#) unless a clear and compelling rationale and justification establishes to the satisfaction of the funding IC Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, 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 NIH-supported biomedical and behavioral research involving human subjects is defined as clinical research. This policy applies to research subjects of all ages.

The inclusion of women and members of minority groups and their subpopulations must be addressed in developing a research design appropriate to the scientific objectives of the study. The Research Plan should describe the composition of the proposed study population in terms of sex/gender and racial/ethnic group, and provide a rationale for selection of such subjects. Such a plan should contain a description of the proposed outreach programs for recruiting women and minorities as participants. See http://grants.nih.gov/grants/funding/women_min/women_min.htm.

5.7 NIH POLICY ON INCLUSION OF CHILDREN

Research involving children (see definition of “[child](#)”) must comply with the NIH Policy and Guidelines on the Inclusion of Children in Clinical Research. Investigators should obtain full copies of the Policy and Guidelines from NIH staff, or from <http://grants.nih.gov/grants/funding/children/children.htm>.

NIH policy requires that children (i.e., individuals under the age of 21) must be included in all clinical research, conducted or supported by the NIH unless there are clear and compelling reasons not to include them. Therefore, proposals for clinical research must include a description of plans for including children. If children will be excluded from the research, the proposal must present an acceptable justification for the exclusion.

The involvement of children as subjects in research must be in compliance with all applicable subparts of [45 CFR part 46](#) (<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>) as well as with other pertinent Federal laws and regulations.

IRBs have special review requirements to protect the well-being of children who participate in research. These requirements relate to risk, benefit, parental/guardian consent, and assent by children, and to research involving children who are wards of the state or of another institution. The local IRB approves research that satisfies the conditions set forth in the regulations.

5.8 NIH POLICY ON REPORTING RACE AND ETHNICITY DATA: SUBJECTS IN CLINICAL RESEARCH

The Office of Management and Budget (OMB) (http://www.whitehouse.gov/omb/fedreg_1997standards) defines minimum standards for maintaining, collecting and presenting data on race and ethnicity for all Federal reporting agencies (including NIH) in OMB Directive 15, http://www.whitehouse.gov/omb/fedreg_1997standards. The standards were revised in 1997 and include two ethnic categories (Hispanic or Latino and Not Hispanic or Latino) and five racial categories (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and White). Reports of data on race and ethnicity shall use these categories. The categories in this classification are social-political constructs and should not be interpreted as being anthropological in nature. NIH is required to use these definitions to allow comparisons to other federal databases, especially the census and national health databases. The following definitions apply to the minimum standards for the ethnic and racial categories.

Ethnic Categories:

Hispanic or Latino: A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term, "Spanish origin," can be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories:

American Indian or Alaska Native: A person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliation or community attachment.

Asian: A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American: A person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or Other Pacific Islander: A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White: A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

Ethnic/Racial Subpopulations: In addition to OMB ethnic and racial categories, NIH uses the following definition for ethnic/racial subpopulations:

Subpopulations: Each ethnic/racial group contains subpopulations that are delimited by geographic origins, national origins, and/or cultural differences. It is recognized that there are different ways of defining and reporting racial and ethnic subpopulation data. The subpopulation to which an individual is assigned depends on self-reporting of specific origins and/or cultural heritage. Attention to subpopulations also applies to individuals who self identify with more than one race. These ethnic/racial combinations may have biomedical, behavioral, and/or social-cultural implications related to the scientific question under study.

Guidance on Collecting Race and Ethnicity Data from Human Subjects

When an investigator is planning to collect data on ethnicity and race, the categories identified above should be used. The collection of greater detail is encouraged, for example on ethnic/racial subpopulations. However, any collection that uses more detail must be designed in a way that data can be aggregated into these minimally required categories. Use self-report or self-identification to collect this information by asking two separate questions – one on ethnicity and one on race. Collect ethnicity information first followed by the question on race and provide subjects with the option to select more than one racial category.

See NIH Policy on [Inclusion of Women and Minorities](#) and http://grants.nih.gov/grants/funding/women_min/women_min.htm.

5.9 RESEARCH ON TRANSPLANTATION OF HUMAN FETAL TISSUE

In signing the proposal Cover Page, the Authorized Organizational Representative/Corporate Official of the offeror organization certifies that if research on the transplantation of human fetal tissue is conducted, the offeror organization will make available, for audit by the Secretary, DHHS, the physician statements and informed consents required by section 498A (b)(2) and (c) of the Public Health Service Act, 42 U.S.C. 289g (b)(2) and (c), or ensure DHHS access to those records, if maintained by an entity other than the offeror organization.

5.10 RESEARCH USING HUMAN EMBRYONIC STEM CELLS

In signing the proposal Cover Page, the Authorized Organizational Representative/Corporate Official of the offeror organization certifies that if research using human embryonic stem cells (hESCs) is proposed, the offeror organization will identify hESCs to be used from the NIH Registry (<http://stemcells.nih.gov/research/registry/>), or, if a specific cell line cannot be referenced at the time of application, certify that one from the NIH Registry will be used, in accord with the NIH Guidelines on Human Stem Cell Research (<http://stemcells.nih.gov/policy/2009guidelines.htm>). See <http://stemcells.nih.gov/index.asp> for additional information on stem cells, and <http://stemcells.nih.gov/policy/guidelines.asp> for Federal policy statements and guidelines on federally funded stem cell research.

5.11 CLINICALTRIALS.GOV REQUIREMENTS

In signing the proposal Cover Page, the Authorized Organizational Representative/Corporate Official of the offeror organization certifies that if the research includes an applicable clinical trial under Public Law 110-85, the offeror organization will be in compliance with the registration and reporting requirements of Public Law 110-85, if applicable (http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110.pdf). The law, enacted 09/27/2007, amends the Public Health Service Act to expand the scope of clinical trials that must be registered in ClinicalTrials.gov. It also increases the number of registration fields that must be submitted, requires certain results information to be included, and sets penalties for noncompliance.

The trials that must be registered are called “applicable clinical trials.” Under the statute these trials generally include: (1) Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase 1 investigations, of a product subject to FDA regulation; and (2) Trials of Devices: Controlled trials with health outcomes, other than small feasibility studies, and pediatric postmarket surveillance. NIH encourages registration of ALL trials whether required under the law or not.

Additional information can be found on the ClinicalTrials.gov Web site (http://grants.nih.gov/ClinicalTrials_fdaaa/).