

REQUEST FOR LETTERS OF INTENT ON FORMATIVE RESEARCH

INTRODUCTION

The National Children's Study (NCS) has reframed the Vanguard Study scope of activity to focus on feasibility, acceptability, and cost of the elements that will form the NCS Main Study. This is the second in a planned series of announcements for letters of intent to augment Vanguard Study activities with efforts that will accelerate development and deployment of the Main Study. This call for Letters of Intent includes opportunities to develop and enhance study visit assessments; to develop methods to analyze and augment the utility of data collected through the Study; and to test promising methods in pilot studies or formative research with Study participants for possible inclusion in the Main Study.

The opportunities detailed below are intended to facilitate the development and evaluation of (1) linking NCS data with other data sources; (2) study visit measures and assessments; (3) recruitment and retention strategies, and (4) operational and logistical models. The intended results of these efforts are the design or enhancement of brief, scientifically robust materials, methods, tools, and measures to be made available to all NCS Study Centers, as well as the potential for other population-based studies. Any new method should demonstrate performance advantages to existing procedures.

Principal Investigators of all Vanguard Centers (VCs) and Study Centers (SCs) currently under contract with the NCS are eligible to respond to this call for Letters of Intent. As part of the submitted Letters of Intent, the Program Office encourages collaboration among SCs, VCs, subcontractors, and other eligible entities.

OPPORTUNITIES

1. Data Linkages

This request focuses on methodological studies and other development activities related to linking and validating data from participants with extant data sources at the national, state, and local level. These activities will include but will not be limited to 1) developing mechanisms to select and collect any additional information from participants necessary for making linkages, gauging and documenting the acceptability to participants of this approach and these activities, and developing relevant standardized informed consent language and materials; 2) identifying important extant databases and feasibility (in terms of technology, scalability and cost) of their linkage to NCS data at the personal record level and at an aggregate, geographic level; and 3) approaches to linking and validating data from participants in NCS databases with those of extant databases on an emerging and important topics (for example, linking with state health departments that might have records of H1N1 influenza immunizations). Study centers may also choose to cross-validate specific measures by comparing extant data sources to NCS participant data, such as the personal medical logs, or responses to questionnaire items. Note that all data linking must be done in accordance with the NCS Data Access and Confidentiality Committee (DACC) policies. For further details see

<http://www.nationalchildrensstudy.gov/about/organization/dacc/Pages/PolicyManualandDataUseAgreements.aspx>

These studies, conducted using either existing data in the public domain, generic data that is identical in structure and format to key datasets of interest, or Vanguard Study data as necessary, will provide a useful model to understand how NCS data can be linked to data in extant databases, what barriers exist in connecting these data sources, how acceptable these approaches are to NCS participants, and how feasible it will be to carry out these data linkages.

2. Development of Visit Assessments

Contractors are encouraged to submit letters related to a variety of specific measures and methods that fall under the broad category of study visit assessments. Study visit assessments include all scheduled questionnaires, measurements, specimens, and samples acquired during an NCS study visit. All proposed measures will be evaluated given scientific merit, brevity, appropriateness of use in a large-scale, population-based setting, and fit with Study design and goals. Upon selection, all copyright permissions for development and use are expected to be arranged with the affected publishers. Awardees proposing to enhance existing measures are expected to work closely with assessment developers.

Testing is not required to be conducted with NCS participants or within sampled segments but must be applicable to them. Any proposed data collection could be subject to Institutional Review Board (IRB) review and Office of Management and Budget (OMB) clearance as appropriate and applicable. Letters should detail proposed sampling strategies.

Conceptual domains to be considered are described in the current version of the Vanguard Study Protocol. Pending Institutional Review Board approval, a draft copy of the Vanguard Study Protocol can be obtained by Principal Investigators by request from the NCS Program Office. Examples of study visit assessments sought are described below.

MENTAL/MOTOR DEVELOPMENT: A brief, direct assessment of early childhood mental and motor development at ages 6 months, 12 months, 18 months, 24 months and 36 months that can be reliably administered on a large scale by lay field interviewers with limited scientific training. All assessments must permit criterion analysis and growth curve analysis. Although the NCS is particularly interested in the development of a short form of the Bayley Scales of Infant Development, III, proposals to develop short forms of other known, robust early childhood assessments are also of interest.

MENTAL HEALTH: Development of an assessment of parental mental health status including current symptoms and lifetime history. These items should be self-reported or must be administered reliably by field interviewers with limited scientific training. Such an assessment could be administered prenatally and after the birth of the child.

LANGUAGE ACQUISITION: Development or enhancement of measures of early language acquisition and dual language competency and growth are of interest. Measures appropriate for ages 2 through 7 are of particular interest. These measures must be administered reliably by field interviewers with limited scientific training, and permit criterion analysis and growth curve analysis.

SOCIAL ENVIRONMENT: Measures of racial/ethnic discrimination (experienced by mothers, fathers, other caregivers and later by children themselves), health care access and barriers, health literacy, life-stress coping skills, and neighborhood characteristics collected primarily through questionnaire administration.

NUTRITION: The study seeks an efficient means to collect nutrition data with improved precision and accuracy. Methodological studies of nutritional assessment in pregnant women and young children, such as assessing the feasibility (including cost effectiveness, participant burden, data quality) of utilizing new dietary recall instruments like the Automated Self-Administered 24 hour Dietary Recall (ASA24) which do not require in-person interviewer administration. If overall feasibility is demonstrated but modifications to the instrument are needed to promote successful NCS field implementation, appropriate modifications will also be part of this task.

BIRTH DEFECTS/DYSMORPHOLOGY: Standardized tools for screening for birth defects and dysmorphism suitable for administration by lay field interviewers and appropriate for use in a multi-center population-based study. The goal is for NCS field interviewers to perform a standardized assessment at the birth visit or shortly thereafter that could detect a potentially abnormal condition. Diagnostic specificity is not expected, but rather general recognition of abnormal findings. Most standardized birth defects screens are lengthy, meticulous examinations performed by experts and not practical for NCS field researchers in a hospital or home setting shortly after birth. The NCS seeks to develop a valid and reliable initial screening assessment that can be completed within a reasonable amount of time in the context of a NCS field visit to the home.

3. Alternate modes of data collection

Data collection in the NCS Vanguard Protocol is multi-modal and currently includes (1) in-person interviews, with both interviewer and self-administered components, with and without computer assisted interviewing (CAI) technology; (2) telephone interviews using paper-and-pencil instruments (PAPI) or CAI technology; and (3) self administered, PAPI questionnaires. New modalities under consideration include, but are not limited to text messaging, interactive voice response, web-based data collection, participant-collected biological specimens and environmental samples, and e-mail. Currently, in-person interviews using CAI technology are administered on a laptop computer that can be used as a tablet. New hardware platforms under consideration are smaller tablets, hand-held devices, and cell phones. There is particular interest in the use of modalities that could improve the quality of the data collected and the efficiency in which the data can be managed for analysis.

Outcomes of interest include but are not limited to acceptability, cost, completeness, and accuracy of data collection in comparison to current methodologies. In addition the NCS is interested in the effects of alternate data collection modes on participant retention. It will also be important to determine the utility of any technology by study phase and population (for example household listing, household enumeration, pregnancy screening, pre-pregnancy surveillance, post-enrollment, post-birth, etc.) As the main NCS will be conducted in multiple diverse populations across the country, testing of new technologies for data collection should occur under a variety of conditions among diverse populations.

Examples of the types of questions of interest include: Does acceptance and use of text messaging for data collection vary by age, race, income, and spoken language of the participant? Are respondents more likely to utilize a text messaging approach if the cell phone is supplied by the study? What incentive is required to gain cooperation by when cell phones are participant-owned? Will respondents initiate reporting of medical events through a web-based collection or are such events only reported when prompted to do so (for example by e-mail or text message)? Will participants report daily practices (for example exercise, diet, sleep) using a web based application for a defined period of time (for example two weeks)? Which assessments can be self-administered reliably (and securely) through electronic means, such as a hand-held device? Is self collection of biological specimens and environmental samples feasible and accurate? Is use of extant environmental databases a viable alternative or supplement to in-home environmental sample collection? If so, is there a means to model extant environmental data and apply it to the overall NCS study population? Are there biological indicators that serve as reliable, short- and long-term gauges of environmental exposure? Evaluations should include consideration for precision, accuracy and completeness to illustrate that these techniques do in fact provide superior performance.

Testing with NCS participants or within sampled segments is not required but proposed methods must be applicable to both. Any proposed data collection occurring with target populations outside of NCS segments may be subject to IRB and OMB review and clearance, and letters should detail proposed sampling strategies.

4. Methods for biospecimen collection and analysis and environmental exposure sensors

The goal of this effort is to identify, evaluate, select, and test technologies for either for the collection and analysis of biospecimens or for assessment of environmental exposures. Preferably, these technologies should be in an end stage of development or presently being used on a limited scale. The NCS would like to incorporate these technologies into the predetermined study visit assessments for additional testing of their feasibility, acceptability and cost advantages.

The NCS welcomes proposals for all technologies that are sufficiently developed, are likely to be available to the NCS, and can be easily incorporated into the NCS Vanguard Phase. The NCS plans to optimize data collection efforts through the identification and testing of these technologies.

Examples of emerging biospecimen collection and analysis methods technologies include: (1) rapid sampling of placental tissue for optimal recovery of nucleic acids; (2) methods for detection and quantification of environmental chemicals in placental tissue; (3) noninvasive, self-collected biospecimen sampling methods such as saliva collection; (4) methods for detection and quantification of environmental chemicals in saliva; (5) methods for optimal collection and recovery of human DNA in saliva.

Examples of emerging environmental sensor technologies include: (1) personal exposure monitoring devices; (2) chemical exposure sensor technologies; (3) accelerometers with Global Positioning System (GPS) capabilities, (4) or improved means of diet and nutrition assessment.

All responses need to include the following supporting information: (1) a defined sensor technology or biospecimen collection/analysis methods technology; (2) a description of the conditions under which the technology can be obtained by the NCS, such as through licensing; (3) a plan for a performance evaluation of the proposed technology under both controlled and actual field conditions that demonstrates the feasibility, acceptability and cost advantage of the technology; (4) a clear demonstration that the proposed technology meets or exceeds the performance capability of existing methods; and (5) evidence that the proposed technology is suitable for predetermined NCS study visit assessments, is feasible, acceptable, and scalable for the wide use in the NCS.

Testing with NCS participants or within sampled segments is not required but proposed methods must be applicable to both. Any proposed data collection occurring with target populations outside of NCS segments may be subject to IRB and OMB review and clearance, and letters should detail proposed sampling strategies.

5. *Fetal cell and DNA collection*

The NCS is interested in the possibilities offered by the bi-directional exchange of maternal and fetal cells during pregnancy for at least three purposes: Study of developmental genomic and other nucleic acid changes in fetal and maternal cells; the role of these cells in maternal and child auto-immune diseases; and possible identification of biomarkers of placental abnormalities.

The goal of this initiative is to obtain fetal cells serially from a variety of sources. The NCS is interested in post-conception collection using maternal and infant blood and/or urine, including (1) circulating fetal DNA (cell-free) from maternal blood (both plasma and serum) during all three trimesters of pregnancy; (2) fetal cells from maternal blood (plasma and serum) during all three trimesters of pregnancy; (3) circulating maternal DNA (cell-free) from infant blood (plasma and serum) and urine post-partum; and (4) maternal cells from infant blood (plasma and serum) and urine. Of additional interest is collection post-conception using fetal trophoblasts isolated from the cervix at birth.

The maternal circulation is a valuable source of embryonic and fetal cells from as early as seven weeks gestation. Nucleic acids and mitochondria may be extracted from these cells. Similarly, blood drawn from children may also be a potential source of maternal cells. The phenotype and purpose(s) of these maternal cells are unknown. While the NCS will have more than enough maternal biospecimens, identification of the nature of these maternal cells circulating in NCS babies' blood may be a vital source of data on possible developmental origins of adult disease. Newer studies have also shown that fetal trophoblasts are plentiful in the endocervical canal. Data on the efficacy of the least invasive method of trophoblast collection (for example vaginal swab) would be valuable

These embryonic, fetal, and maternal cells, their quantity, immunophenotype and presence in different secretory compartments (blood, urine, cervix) may provide insight into maternal and child autoimmune disease. These cells or cell-free DNA in the maternal blood may provide potential biomarkers of placental dysfunction which may presage abruption, preterm birth, and other related conditions.

Analyses of the embryonic, fetal, and maternal cells provide information into the developmental progression of epigenetics, Copy Number Variants (CNVs), histone de/acetylation and other changes in the human genome. These data in conjunction with environmental exposure measurements may permit association studies. Specific goals of this solicitation include, but are not limited to, identification and evaluation of circulating (cell-free) and cellular embryonic/fetal/neonatal/infant DNA, RNA, and mitochondria from maternal biospecimens. Similar studies from neonatal and infant blood and urine for evaluation of maternal nucleic acid containing species are also desired. Data which address questions regarding how early the target species are detectable, at what concentration, and how long they persist, are of particular interest.

Given that the data requested in this announcement may also contribute to future studies of the role of maternal and child micro-chimerism in autoimmune diseases, examination of the processing and storage of the target biospecimens for later studies using fluorescence-activated cell sorting (FACS) and other immunophenotyping techniques, would be of interest.

For this research, collaborations with clinical centers will be required. Submissions may propose partnerships with other Study Centers and subcontractors including commercial entities such as biotechnology companies.

6. Methods and Materials for Recruitment and Retention

The intended result of this effort is an evidenced-based tool-kit available to all NCS Study Centers, and potentially other population-based studies. These activities allow the study to understand and address critical issues, including attitudes and perceptions about participation; successful strategies for gaining cooperation and refusal conversion; acceptable methods for long-term surveillance of women who may become pregnant; and the utility of community members in recruitment and retention. Interested Study Centers are not limited to the above topics and may choose to identify other related topics.

Examples of methods may include the development of outreach materials and messaging (for example, brochures, posters, advance letters, etc.); field interviewer training programs (for example manuals, videos, in-person training materials/activities); interviewer scripts for use when contacting participants or other NCS stakeholders (for example in-person, telephone, e-mail, etc.), or other relevant methodologies.

As the NCS audiences are extensive and varied, submissions may be appropriate for a general community audience or targeted to a specific subgroup. Such subgroups may include: families with a currently enrolled child (or individuals within such families – mothers, fathers, grandparents, etc.); age-eligible women; pregnant minors; non-residential fathers; health care providers, or other stakeholders. Methods may be further targeted to particular regions, racial, ethnic or language groups, or other appropriate strata.

Testing with NCS participants or within sampled segments is not required but proposed methods must be applicable to both. Any proposed data collection occurring with target populations outside of NCS

segments may be subject to IRB and OMB review and clearance, and letters should detail proposed sampling strategies. Submissions may propose partnerships with other Study Centers, and subcontractors including commercial entities such as communication or social research organizations.

7. Analysis of Recruitment and Retention

As part of our effort to develop a comprehensive set of tools for participant recruitment and long-term retention in the National Children's Study, the NCS seeks to summarize and evaluate all efforts to date completed by the original seven Vanguard Centers. As a result of this evaluation, the Study assembly will document, understand, and better address critical issues, including (but not limited to) attitudes and perceptions about participation; successful strategies for gaining cooperation and refusal conversion; and the utility of community leaders in recruitment and retention.

Case management data will be made available by the Program Office for analysis. Contractors are also encouraged to propose collecting primary data (qualitative or quantitative) from Vanguard Center staff, members of community advisory boards, health care providers (local to the original seven Vanguard Centers), current NCS participants, those who declined participation, and other relevant groups. Any additional data collection proposed may require appropriate IRB and OMB approvals, as applicable. NCS Data Access and Confidentiality Policies apply.

8. Operations Research

The NCS is particularly interested in improving field operations using a systems approach to optimize all processes. It is our goal to maximize efficiencies related, but not limited, to the following areas: (1) Sample design, including the optimal number of Study Locations for efficient recruitment and tracking of Study participants and families; (2) Location of data collection efforts, comparing self-administration, home visit collection, and health care facility or clinic collected data and environmental and biological specimens for quality, consistency, information content and cost; (3) Logistical tracking, monitoring, and costs associated with production, distribution, and storage of Study materials and equipment; (4) Study Center staffing models; (5) Use of standards related to data acquisition, terminology, form generation and data table and database design and construction; (6) Data transmission, processing, retrieval, reporting, distribution, and archiving; and (7) Determination of cost and energy effective methods for Study operations.

Submissions may propose partnerships with other Study Centers and subcontractors including commercial entities.

SUBMISSION INSTRUCTIONS

Collaboration is encouraged among NCS Study Centers and Study Locations conducting field operations for recruitment as well as those not conducting field operations but with ideas for implementation of new technologies, methodologies, and instruments. Collaboration is encouraged because these are complex issues requiring detailed investigations to evaluate performance and document efficiency and acceptability.

Any proposed data collection could be subject to Institutional Review Board (IRB) review and Office of Management and Budget (OMB) clearance as appropriate and applicable. All communications developed for NCS participants or the general public must adhere to the tenets of Plain Language (www.plainlanguage.gov). Similarly, all training programs and associated materials should incorporate best practices for adult learning.

To be considered for selection, each interested NCS Study Center should prepare a Letter of Intent that describes their interest in participating in a development activity or study.

Please submit a separate letter for each proposed activity and prioritize the submissions. For example, a Center proposing to conduct two activities would submit two Letters of Intent, each with a stated priority. To aid the routing of these Letters of Intents, each letter should be submitted as a separate electronic document in a common format (.PDF, .RTF, .DOC, .DOCX) with a filename that includes information regarding the submitting Study Center's primary institution and the proposed activity. For instance, the XYZ Study Center submitting a visit assessment for neurodevelopment might use a filename such as Visit_Assessment_Neurodevelopment_Institution.pdf. No additional cover letters or materials should be submitted for consideration at this time.

Each letter is limited to five pages in length. Describe your proposed scientific approach to the task(s), highlighting key socio-demographic considerations and the geographic locations of interest. The utility and relevance of each proposed method or activity to the larger NCS should be described, along with the significance of any specified subgroups. Candidates should provide information on relevant evaluation criteria, data collection methodology, analytic plans, and organizational experience. At this time, please just respond to the stated scope of work. No formal budget, schedule or deliverables should be submitted at this time; however, descriptions of cost effective implementation plans that include estimates of the general number and types of personnel, estimated levels of effort, and timelines to start and complete the proposed projects are encouraged.

All Letters of Intent must be submitted by e-mail to the NCS@mail.nih.gov mailbox no later than 8:00 p.m. Eastern Standard Time on Friday, March 12, 2010. Successful candidates will be selected on the scientific, logistic, and operational quality of the proposal with consideration for factors such as geography and demographics. Letters of Intent will be evaluated by the Program Office and selected Study Centers will be contacted by Monday, March 29, 2010 for further information. Work on selected projects may begin in April 2010 and deliverables are expected throughout federal fiscal years 2010 and 2011 (FY2010-FY2011).

Time and resources for preparation of the Letter of Intent are not billable to the National Children's Study as this is a voluntary effort and not a required task issued under any existing contract. Any questions should be addressed in writing to NCS@mail.nih.gov.