

REQUEST FOR OMB CLEARANCE

Recruitment Substudy for the National Children's Study, Phase 1

Part A only

A. Justification

A.1 Circumstances Making the Collection of Information Necessary

The National Children's Study rests on the principle that both health and susceptibility to disease are determined by dynamic processes that occur throughout life. Changes to these developmental processes can affect growth, viability, differentiation of major organ systems, and maturation, and specific health and disease trajectories. A range of determinants acting either in concert or synergistically may impact growth and development. These include the built and natural environments with their chemical and physical components, the social environment, individual behaviors, and biological factors, including genetics. Of particular importance are the earliest stages of human development, pregnancy and early childhood, when cell division, differentiation, and maturation are most rapid.

The National Children's Study (NCS) is the largest, long-term study of environmental and genetic influences on children's health ever conducted in the United States. By following 100,000 children from before birth to age 21, researchers hope to better understand how children's genes and their environments interact to affect their health and development. In the NCS, "environment" includes factors such as: air, water, and house dust; what children eat; how they are cared for; the safety of their neighborhoods; how often they see a doctor; and other factors. By tracking children's development through infancy, childhood, and early adulthood, the NCS hopes to determine the many factors that affect the developmental process, assessing root causes of both good health and disease. Findings from the NCS will benefit *all* Americans by providing researchers, health care providers, and public health officials with information from which to develop prevention and treatment strategies and health and safety guidelines.

Faced with the challenge of how to address the potential risks of many environmental factors that may be affecting the health and development of children, the President's Task Force on Health Risks and Safety Risks to Children concluded in 1999 that a large study to define the actual risks associated with broad environmental exposures is an essential first step. Following the recommendation of the task force, the U.S. Congress passed the Children's Health Act of 2000 which directed the National Institute of Child Health and Human Development (NICHD) to conduct a national longitudinal study of environmental influences (including physical, chemical, biological, and psychosocial influences) on children's health and development. The National Institute of Environmental Health Sciences (NIEHS), the Centers for Disease Control and Prevention (CDC), and the U.S. Environmental Protection Agency (EPA) joined the NICHD in planning the study.

The Children's Health Act of 2000 (Public Law 106-310, Sec. 1004 shown in Appendix C.1) specifies that the study should extend from the prenatal period to adulthood, following a sample of children through their developmental life stages. It should investigate the short-term and long-term influences of physical, chemical, biological, and psychosocial environmental exposures on children's health and development, including not only physical health, but behavioral, emotional, and educational outcomes as well. The study should elucidate both those factors that protect children from detrimental outcomes and those that put them at risk. The study population must be sufficiently diverse to address the existence and consequences of health disparities among children in the United States. The scientific rationale for this program of research has evolved as the National Children's Study.

The NCS Main Study plans to follow a sample of 100,000 children, born to women recruited from about 105 proposed study locations (generally corresponding to counties) within the US, from before birth to age 21 years. The Main Study defines "environment" broadly, such as air, water, dust, noise, stress and exposure to natural and manufactured products. By studying children through different phases of growth and development, researchers may be better able to understand the role these factors have on health and disease.

The National Children's Study is an observational research study. Participants will not be asked to change what they normally do, nor will they or their child be asked to take any medicines or drugs. Initially, researchers will collect information on women's pregnancies, including their diets, environments, chemical exposures, and emotional stress. When their children are born, and periodically thereafter, researchers will ask questions about the family and their environment, and collect biologic samples and environmental samples like air, water, and dust from their environments. Researchers will meet with families in both their homes and in clinical settings, and data also will be collected via telephone or mail-in questionnaires.

To conduct the detailed preparation needed for a study of this size and complexity, the NCS was designed to include a preliminary pilot study known as the Vanguard Study. The purpose of the Vanguard Study is to assess the feasibility (technical performance and reliability), acceptability (impact on study participants and study infrastructure), and cost (level of effort, personnel, resources, and money) of the recruitment strategy, study logistics and operations, and study visit assessments that are to be used in the NCS Main Study. The Vanguard Study begins prior to the NCS Main Study and will run in parallel with the Main Study. At every phase of the NCS, the multiple methodological studies conducted during the Vanguard phase will inform the implementation and analysis plan for the Main Study.

Before birth and throughout the children's lives, both the Main Study and the Vanguard Study will collect health-related information, administer health questionnaires, collect biological and environmental samples and make other assessments identifying children's chemical, physical, psychosocial, and biological exposures, as well as their genetics. However, of primary interest to the Vanguard Study are operational and performance data. In contrast, the goal of the Main Study is obtaining analytic data to evaluate exposure-response relationships.

A.2 Purpose and Use of the Information Collection

The Initial Vanguard Study protocol was designed to enroll approximately 1,750 pregnant women through seven study locations after 12 months of data collection. Two of the locations began recruitment in January 2009 and the remaining 5 in April 2009. As of May 2010, however, approximately 900 pregnant women have been enrolled, leading to questions about the assumptions underlying the Initial Vanguard Study recruitment model. The seven Initial Vanguard sites use a household enumeration and screening strategy to identify eligible women for recruitment into the study. Although household enumeration is often considered a gold standard for maximizing coverage, in that all dwelling units are identified and enumerated, for the NCS Initial Vanguard Study this method has not yielded the target number of births in the time frame projected from initial models. Consequently, additional methodological research is needed to evaluate the feasibility, acceptability, and cost of alternate recruitment strategies for enrollment of pregnant women into the NCS. This research will be conducted through the NCS Recruitment Substudy. The Recruitment Substudy will assess three alternate recruitment strategies – (1) a provider-based recruitment strategy; (2) an enhanced version of a household enumeration strategy; and (3) a two-tier recruitment strategy involving high-intensity and low-intensity data collection efforts.

NCS Recruitment Substudy: Sample

The same overall sampling frame will be used for all three alternate recruitment strategies, facilitating comparison. Primary sampling units (PSUs) were selected for the Main Study based on historical birth data. From these PSUs (typically, counties or groups of counties) secondary sampling units (SSUs) were selected, also based on historical birth data. These SSUs comprise clusters of census blocks.

A primary sampling unit corresponds to a study location. Study locations, already currently under contract to the NCS, were selected to participate in an alternate recruitment strategy based on study center interest and expertise.¹ Consideration was also given to geographic and demographic diversity of the locations in assigning study locations to an alternate recruitment strategy. Although no attempt was made, for the purpose of the Vanguard Study, to select study locations that would permit generalizations to the U.S. target population as a whole, sources of potential bias will be systematically examined. See Part B for more details on the proposed sample for the Recruitment Substudy.

NCS Recruitment Substudy: Methods

This Recruitment Substudy will systematically evaluate three alternate recruitment strategies: 1) Provider-Based Recruitment; 2) Enhanced Household-Based Recruitment; and 3) Two-Tiered “High-Intensity/Low-Intensity” approach. Each recruitment approach would occur in 10 study

¹ As such, results from recruitment approaches may be seen as “best case scenarios” in some circumstances and will be evaluated accordingly.

locations, for a total of 30 study locations implementing alternate recruitment strategies. Recruitment strategies will be assessed and compared on the basis of feasibility (including success in recruiting and retaining sufficient numbers of participants), acceptability (including the extent of selection bias in recruitment, effect on respondent burden, and impact on study infrastructure), and cost. Ultimately, these comparisons will inform the recruitment approach or approaches to be taken for the NCS Main Study. Each recruitment strategy will be provided with approximately equally resources, and will be associated with a specific communications theme appropriate for its mode of participant enrollment.

Provider-Based Strategy

In the Provider-Based Recruitment strategy, potential participants will be personally introduced to the study through the existing health care system. First, prenatal care providers serving women living in selected secondary sampling units will be identified by study centers. Care providers will include, but are not limited to, general practitioner offices, pediatrician offices, obstetrician/gynecological offices, and health clinics. Second, study centers will provide information about the NCS to create interest among identified providers and encourage them to help identify potential participants. Third, secure and HIPAA-compliant methods will be used to identify women who may be geographically eligible through provider records or contacts. In the provider-based recruitment model, enrollment may occur in the provider setting or through referral off-site. In all cases, however, informed consent will be administered by study staff (not providers). Health care providers will not be employees of the study nor engaged in the informed consent process or data collection.

Enhanced Household Strategy

In the Enhanced Household Recruitment strategy, potential participants residing in secondary sampling units will be personally introduced to the study through an advance letter by direct mail, followed by household canvassing. First, potential participants will be approached at the household doorstep to share further information about the study and enumerate a household. Second, study staff will ask age-eligible women to take part in further eligibility (pregnancy) screening. Third, study staff will invite eligible women to consent to participate in the study.

The Initial Vanguard Study used a household enumeration approach to identify age- and geographically-eligible pregnant women. The Enhanced Household Recruitment strategy will improve the ability to identify pregnant women by deploying staff trained in best practices to assist household enumeration and screening, among the most labor-intensive aspects of the study. To ensure highly skilled enumerators, staff with specific experience and training in enumeration will be employed. The most highly qualified of these professional enumerators may also be used to train enumerators at the study locations. The strategy will also benefit from optimized approaches based on the experience of the Initial Vanguard Centers as well as other best practices from other studies.

Two-Tiered High-Low Intensity Strategy

The Two-Tiered High-Low Intensity Recruitment strategy relies on a larger secondary sampling unit to increase the rate of identification of pregnant potential respondents. In the Two-Tiered Recruitment Strategy, secondary sampling units are enlarged to roughly three times the population as the secondary sampling units in the Provider-Based or Household Recruitment strategies.

Age- and geographically-eligible women will be asked to self-refer to participate in this data collection, designed to be of lower intensity than the Provider-Based and Enhanced Household strategies. Self-referral will be supported by direct mail and simultaneously-focused marketing campaigns. Then, after a period of time during which rapport has been developed between low intensity participants and the study, a geographically-defined subsample of low intensity participants will be asked to engage in a higher intensity data collection effort.

A tertiary sampling unit, roughly corresponding to the size of the secondary sampling unit in the Provider-Based and Enhanced Household approaches, will serve as the geographic basis of eligibility into a higher intensity data collection. Women participating in the lower intensity effort that reside in the tertiary sampling unit (itself embedded in the SSU) will be invited to join the higher intensity data collection. The higher intensity data collection corresponds in intensity to the Provider-Based and Enhanced Household strategies. Low intensity participants invited to join the high intensity effort also have the option of remaining in the low intensity effort, or, dropping out of the study. Low intensity participants not residing in the tertiary sampling units will not be eligible for the high intensity data collection. Instead, we will continue to invite these participants to respond to low intensity data collection efforts approximately every six months.

NCS Recruitment Substudy: Key Measures

The guiding research goal for the Recruitment Substudy is characterization of recruitment strategies, and components of recruitment strategies, that are effective in identifying, recruiting, and enrolling eligible participants into a population-based cohort study. We will measure progress toward this goal by examining the feasibility, acceptability, and cost of each recruitment strategy.

Feasibility

The primary outcome measure of the Recruitment Substudy is feasibility. Feasibility will be measured largely through recruitment and retention rates among the three proposed recruitment strategies.

Key rates associated with recruitment include:

- The number of women identified for contact by the study, per month
- The number of women successfully contacted by the study, per month
- The number of women determined to be eligible for the study, per month
- The number of women who have heard about the study, per month

- The number of eligible women consented into the study, per month

Key proportions associated with retention include:

- The proportion of age- and geographically-eligible women, initially contacted when not pregnant, who join the study when subsequently becoming pregnant
- The proportion of consented women who participate in at least one data collection study visit
- The proportion of women consented during pregnancy who participate in all data collection visits through the birth of a child
- The proportion of women who receive an ante-partum data collection visit and who also receive a birth visit

Acceptability

The secondary outcome measure of the Recruitment Substudy is acceptability. Acceptability will be measured by selection bias in characteristics of enrolled participants, enrollment burden, and the impact of enrollment methods on study infrastructure.

Key comparisons associated with selection bias in participant characteristics include:

- The distribution of women enrolled prior to pregnancy (preconception), during pregnancy, or peripartum
- For pregnant women, the distribution of gestational age at enrollment and at the first study visit
- The monthly enrollment rate of infants among consented women with due date within that month

Additionally, unit nonresponse will be examined, comparing the profile of recruited participants, retained participants, and those who declined participation, by recruitment strategy. For each strategy, characteristics of recruited and retained participants will be evaluated relative to a reference population to inform understanding of potential sample bias.

Planned comparisons include:

- Race/Ethnicity
- Age (date of birth)
- Marital status
- Primary language of household
- Employment status and education level
- Urbanicity
- Study center organizational structure and types of partners
- Community engagement strategies employed

Key measures associated with respondent burden and study infrastructure include:

- The respondent burden realized to achieve enrollment for each recruitment strategy
- The impact each source of entry (such as provider referral, household enumeration, community outreach events, self-referral, and others) has on study infrastructure (such

as staffing qualifications required to conduct a given strategy, office space, planning requirements, and need for specialized equipment or materials such as enumeration tablets),

- The impact each method of community engagement and outreach has on study infrastructure

Additionally, we will ask study centers to compile qualitative information about challenges to enumeration, recruitment and consent that are encountered during the conduct of the study. These reports will be delivered bi-weekly in a standardized format, to facilitate both field management oversight and systematic evaluation of study progress.

Cost

The third outcome measure of the Recruitment Substudy is cost. Cost will be measured empirically. Examples of the type of data to be collected include:

- The cost of recruiting and enrolling a woman into the study, by timing of entry (for example, preconception, early pregnancy). Costs will be determined by tracking staff time, supplies and equipment.
- The cost of media and community outreach per recruited and enrolled woman by outreach methods employed particular to each of the three recruitment strategies. Cost will be determined by media invoices, staff time and materials.

Recruitment Substudy: Supplemental Measures

Additional research questions will be asked particular to each alternate recruitment strategy to inform its potential implementation in the NCS Main Study. These “strategy-specific” questions are described below.

Provider-Based Strategy

It is anticipated that the Provider-Based Recruitment strategy may more efficiently identify age and geographically eligible pregnant women through the strategy’s connection with the health care system, which may be considered a familiar and trusted environment to potential participants. However, possible bias in participant demographic and pregnancy characteristics may be a potential issue. Therefore, in addition to the evaluation questions applicable to all three recruitment strategies, evaluation questions specific to the Provider-Based strategy include:

- What are the most efficient and effective ways to identify providers?
- What percentage of identified providers participate in the study?
- What techniques are most useful for engaging providers?
- Among participating providers, which strategies are most useful for identifying geographically-eligible women?
- How are provider strategies for identifying geographically-eligible women related to rates of recruitment?

Enhanced Household Strategy

Although household enumeration may maximize coverage and thus be less subject to respondent bias, it is a particularly labor intensive approach. Therefore, in addition to the evaluation questions applicable to all three recruitment strategies, evaluation questions specific to the Enhanced Household Recruitment strategy include:

- What are the most efficient and effective ways to reach households in the selected segments?
- What techniques are most effective for engaging household members at the doorstep (enumeration, screening, and enrollment)?

Two-Tier High-Low Intensity Strategy

The major goals of the two-tier strategy include generating data to gauge the desired size of the secondary sampling units necessary to yield enrollment targets, and developing information needed to better estimate bias between women who chose to participate in the low intensity data collection and the high intensity data collection. Therefore, in addition to the evaluation questions applicable to all three recruitment strategies, evaluation questions specific to the Two-Tier High-Low Recruitment strategy include:

- What is the optimal size of the secondary sampling unit to identify sufficient numbers of age-eligible (pregnant) women to meet study goals?
- What is the level of data collection intensity which optimizes the data collected at an acceptable response rate?
- Among women who are offered a high intensity effort but decline, what percentage will choose to remain in the low intensity effort (rather than dropping out altogether)?
- How do demographic and health characteristics of women who join the high intensity effort differ from those of women who are eligible but decline?

A.3 Use of Information Technology and Burden Reduction

Information technology solutions will be used, as appropriate, to limit respondent burden. This may include incorporation of previous information into the interview process, computer-assisted telephone interviewing, and information management solutions to ensure that the proper study components are administered at the appropriate times. Forms and questionnaires that are given to participants will be developed in user-friendly formats to reduce the time they take to complete.

A.4 Efforts to Identify Duplication and Use of Similar Information

Before the planning and initiation of the NCS was launched, an inventory and review of longitudinal studies was conducted. The review examined whether the study goals could be addressed without embarking on an entirely new study. The systematic review of all available

longitudinal cohort studies found no study capable of answering the questions and concerns that led to the proposed National Children's Study regarding potential long-term effects in children from environmental exposures.

In addition, a systematic review was conducted to assess the information available to inform the experience of the Initial Vanguard Study with respect to recruitment and retention. The review found that there was insufficient information to enable the NCS to determine the feasibility, acceptability, and cost of alternate recruitment strategies for enrollment of pregnant women into the NCS. The literature on recruitment and retention strategies in epidemiological and clinical research did not include sufficient research on recruitment into studies that were comparable to the NCS in size, length, longitudinal design, scope of coverage, diversity of participants, and types of information requested. Nonetheless, lessons from other studies were identified and incorporated into the Recruitment Substudy design.

Recruitment and retention practices, outcomes, and "lessons learned" were reviewed from the following studies (among others): the National Health Interview Survey; the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; the Early Childhood Longitudinal Studies (Kindergarten and Birth Cohorts); the Health Outcomes and Measure of the Environment Study; the Sister Study; the Family and Child Experiences Study; the Fragile Families and Child Well-being Study; the Survey of Income and Program Participation; and the National Health and Nutrition Examination Survey. The recruitment yields in these studies, the feasibility and cost data, and the differences in yields by respondent characteristics varied considerably. Consequently, reviewing this information has not been sufficient to build a model to determine the feasibility, acceptability and cost of different recruitment strategies for the NCS Main Study, and a Recruitment Substudy is necessary to obtain this information.

A.5 Impact on Small Business and Other Small Entities

The potential impact of the Recruitment Substudy on small businesses will include largely health care providers such as physicians, nurses, and others. Local NCS staff will work with physicians and other medical care providers or facilities to provide information about the study to their patients. With the consent of the participant, key medical diagnostic and treatment information on study participants will also be requested of medical providers. Where requested, the study will reimburse providers for any expenses incurred as part of filling requests for information.

A.6 Consequences of Collecting the Information Less Frequently

The schedule for collection of longitudinal data from NCS participants has been planned to coincide with important time periods for environmental exposures and developmental milestones for children. Women will be followed in the preconception period to maximize the chances that women will be identified and enrolled in the earliest stages of pregnancy, so that early maternal and fetal exposures can be measured. Understanding how these contacts with

the households and participants affect response rates and retention rates, as well as data quality, will be essential to inform the methodology for the Main Study.

A.7 Special Circumstances Relating to the Guidelines of 5 CFR 1320.5

There are no special circumstances that would cause this information collection to be conducted in a manner inconsistent with 5 CFR 1320.5.

A.8 Comments in Response to the Federal Register Notice and Efforts to Consult Outside Agency

Comments in Response to the Federal Register Notice

The 60 day Federal Register Notice regarding the NCS was published on pages 14165-14168 of the Federal Register on March 22, 2010.

One comment was received in response to the Federal Register Notice. That comment is reproduced below in its entirety:

THIS AND OTHER FEDERAL AGENCIES HAVE DONE ENDLESS STUDIES LIKE THIS ONE AND DIDNT EVEN BOTHER TO LOOK THEM UP AND STUDY THEM. THEY JUST LIKE TO DO MORE AND MORE AND MORE LIKE THIS ONE PROPOSED. THIS SPENDING OF AMERICAN TAX DOLLARS FOR NOTHING NEEDS TO STOP. THERE IS NEVER ANY PRODUCTIVITY FROM THESE STUDIES. THESE ARE SIMPLY MAKE WORK JOBS FOR POLITICIANS RELATIVES. SHUT THE WHOLE THING DOWN AND DOWNSIZE THIS AGENCY. THIS AGENCY CAN BE COM BINED WITH CDC AND OTHER HEALTH AENCIES. IT IS TIME TO STOP THIS SPENDING OF TRILLIONS OF DOLLARS TO GAIN ABSOLUTELY NO INCREASE IN HEALTH. AMERICA IS GOING DOWNHILL ON HEALTH AND RANKS ABOUT 50TH IN THE WORLD THESE DAYS, COURTESY OF NIH, CDC, US DEPT OF HEALTH, ETC -ON WHICH WE SPEND TRILLIONS OF DOLLARS.

Response to the comment: The National Children's Study was mandated by Congress through the Children's Health Act of 2000 (Public Law 106-310), which states:

- (a) PURPOSE.—It is the purpose of this section to authorize the National Institute of Child Health and Human Development* to conduct a national longitudinal study of environmental influences (including physical, chemical, biological, and psychosocial) on children's health and development.*
- (b) IN GENERAL.—The Director of the National Institute of Child Health and Human Development* shall establish a consortium of representatives from appropriate Federal agencies (including the Centers for Disease Control and Prevention, the Environmental Protection Agency) to—*
 - (1) plan, develop, and implement a prospective cohort study, from birth to adulthood, to*

- evaluate the effects of both chronic and intermittent exposures on child health and human development; and*
- (2) investigate basic mechanisms of developmental disorders and environmental factors, both risk and protective, that influence health and developmental processes.*
- (c) REQUIREMENT.—The study under subsection (b) shall—*
- (1) incorporate behavioral, emotional, educational, and contextual consequences to enable a complete assessment of the physical, chemical, biological, and psychosocial environmental influences on children's well-being;*
- (2) gather data on environmental influences and outcomes on diverse populations of children, which may include the consideration of prenatal exposures; and*
- (3) consider health disparities among children, which may include the consideration of prenatal exposures.*

Efforts to Consult Outside Agencies:

Strategic advice and oversight is also provided by independent advisors through several groups as described below. Some of these committees are independent of the NCS; other committees comprise both NCS Program Office, study center staff, and independent advisors.

The Steering Committee provides first-level scientific guidance to the National Children's Study. It is the arbiter of issues referred to it by the Program Office, the Principal Investigators, and the Executive Steering Committee. It is empowered to make protocol modifications that do not change the direction or cost of the study, subject to confirmation by the Program Office. The full Steering Committee meets face-to-face twice a year. Interim meetings by conference call are scheduled as needed.

The National Children's Study Federal Advisory Committee (NCSAC), constituted under the Federal Advisory Committee Act, meets quarterly to provide strategic advice and recommendations to the Director of the National Institutes of Health, the Director of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, and the Director of the National Children's Study regarding critical aspects of the study. There are currently three designated NCSAC subcommittees: Scientific Review, Ethics, and Community Engagement. The National Children's Study Federal Advisory Committee meets quarterly. These meetings are open to the public.

The Interagency Coordinating Committee represents the lead agencies for the study and meets monthly to oversee broad study issues and ensures interagency collaboration.

The representatives assure that at a high level, the mission and goals of the National Children's Study are maintained over time and that they reflect the scientific priorities of the study's four lead agencies. The committee is made up of staff from the U.S. Department of Health and Human Services (including the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and the National Institute of Environmental Health Sciences, of the National Institutes of Health, and the Centers for Disease Control and Prevention), and the U.S. Environmental Protection Agency.

The Independent Study Monitoring and Oversight Committee (iSMOC) monitors National Children’s Study data and the safety of study participants. The responsibilities of the iSMOC are to:

- Monitor human subject safety through review and evaluation of accumulated study data
- Review study conduct and progress
- Make recommendations concerning continuation or modification of the study.

During the study, the iSMOC will review data regarding procedure-related adverse events; unanticipated problems involving risks to subjects or others; adherence to the protocol; factors that might affect the study outcomes or compromise the data (for example, protocol violations, losses to follow-up, breach of subject confidentiality); and barriers to study progress or completion (such as slow enrollment, new data or findings, other milestones, change in resources, rate of endpoint accumulation). The iSMOC will recommend appropriateness of notification and referral of individual participants for significant abnormal findings on testing of stored samples. The committee consists of 5 to 10 individuals not associated with the study. Committee membership reflects the disciplines and clinical specialties necessary to interpret study data and to evaluate subject safety.

The Data Access and Confidentiality Committee (DACC) is a federal interagency committee that establishes policies regarding data access and confidentiality for the National Children’s Study. DACC is responsible for establishing policies related to who has access to study data, which data may be accessed, and when data may be accessed, including after the study’s completion. DACC reviews manuscripts and presentations to assess and reduce the risk of disclosure, that is, the direct or indirect identification of study participants and their families. Because DACC also serves communication and coordination roles among data-collection task groups to address and find solutions for data security issues, its members are kept apprised of protocol implementation. Each of the lead federal agencies in addition to NICHD—the National Institute of Environmental Health Sciences (NIEHS), the Centers for Disease Control and Prevention (CDC), and the Environmental Protection Agency (EPA)—has selected a representative to serve on DACC.

A.9 Explanation of Any Payment or Gifts to Respondents

To maximize response rates, many research studies, particularly those involving medical procedures, offer incentives for participants. For example, the National Health and Nutrition Examination Survey (NHANES) has offered their participants incentives since the 1970’s. Incentives are effective in increasing response rates for in-person surveys and can help increase response rates especially for minorities and low-income households. Incentives are particularly important for research studies involving the inconvenience of biologic specimen collection, or any other research activities involving clinical measures.

Recruitment and retention will be a significant challenge for the NCS in light of the long-term commitment required of participants (that is, 21 plus years), the invasive nature of some of the data collection elements (for example, saliva, blood, urine, vaginal swabs, hair, toenail clippings, environmental samples, and physical measures of height, weight, and skin fold), and the length of time required for certain data collection visits.

To recognize the time and effort participants expend to provide information for the Recruitment Substudy, the NCS will provide to participants an incentive after the completion of each in-person data collection event. Monetary or non-monetary incentives not exceeding \$25 will be offered. Reimbursement will also be provided for any expenses incurred in research participation such as travel to and from the research centers, parking, etc. Small “gifts of appreciation” for continued participation will periodically be provided to participants. These may include items of small monetary value (for example, t-shirts, tote bags, etc.), and are intended as tokens of appreciation. In addition, incentives are planned to encourage health care providers and community leaders to provide responses to evaluation questions that will identify issues that are important for the study.

The amount of incentives proposed by the NCS Program Office reflect the following criteria: (a) the time and effort required of the participant for the particular visit or task; (b) the inconvenience to the participant – for example, whether the particular visit or task involves travelling to another location or takes place in the home; and (c) the invasiveness or sensitivity of the information requested. Higher incentives and greater recognition are necessary to induce participation in activities that require more time and effort, are more invasive, involve more sensitive information, and are less convenient.

In the proposed Recruitment Substudy, data collection for the pre-conception through birth visits will be limited to completion of survey questionnaires which will take 30-60 minutes to complete. This is a smaller time and burden commitment than is expected in the Initial Vanguard Study. Participants will receive a remuneration equivalent to \$25 for completion of study questionnaires. This is comparable to the amounts given to Initial Vanguard Study participants for completing self-administered questionnaires of comparable duration.

Table A.1. NCS Incentives, by Study Activity and Impact on Participants, Stage 1

| Data Collection Activity Characteristics | Initial NCS Vanguard Study | NCS Recruitment Substudy |
|---|--------------------------------------|---------------------------------|
| Time for encounter | 3 hours | 0.5 to 1 hour |
| Sensitivity of questions | Sensitive, including sexual activity | Few sensitive questions |
| Physical measures | Yes | No |
| Environmental specimens | Yes | No |
| Biospecimens | Yes | No |
| Participant observation | Yes | No |

| | | |
|---|--|---|
| Monetary incentive, per visit | \$100* | \$25 |
| Non-monetary incentives (tote bags, post its, key chains, etc.) | <u>In addition to the monetary incentive</u> , non-monetary incentives valued at \$25 or less may be offered to participants | <u>As an alternative to the monetary incentive</u> , NCS logo gifts valued at \$25 or less may be offered to the participants in lieu of cash or local incentives not exceeding \$25 in value and deemed non-coercive by local IRBs |

NOTE: *For Preconception, First Trimester Mother Interview, and Third Trimester Mother Interview Visits.

A.10 Assurance of Confidentiality Provided to Respondents

The Recruitment Substudy will follow the same procedures and standards of confidentiality applicable to the NCS Initial Vanguard Study. Study data collected will be safeguarded closely and that actions will be taken to protect participant confidentiality. Participants will be informed about the Certificate of Confidentiality granted to NCS to protect data from involuntary disclosure.

The study centers, under contract to conduct the NCS, will have policies and procedures regarding confidentiality and protection of study data which will be reviewed and monitored by the NCS Program Office.

In addition to their own confidentiality procedures and policies, study centers will implement all federally required study-related confidentiality and data security procedures. All NCS Project Office staff, NCS study center staff, and other NCS contracting staff with access to NCS data must receive data confidentiality and security training provided by the NCS Program Office or its agent. These include completion of the NIH Computer Security Awareness Training, completion of a Human Subjects Protection Training, and signing an Assurance of Confidentiality or similar pledge that NCS data will only be used for the intended scientific purpose. All NCS Staff are required to complete security background checks consistent with Office of Personnel Management requirements. Only those cleared for Security Level D or higher will be eligible to request NCS data access.

To further assure confidentiality of participant data, the study will employ rigorous methods to provide security for personal identifying information. Each study center and the NCS Program Office Data Warehouse will be required to submit an NCS Security Plan and Assessment that complies with the Federal Information Security Management Act (FISMA) . This Security Plan will include a) certification and accreditation of proposed data capture and case management software; b) configuration of those systems on study equipment; c) full disk encryption and two-factor authentication of study computers housing NCS data; and d) security assessment of the physical computing environment. After study center complete the self-assessment of their

security plans, the NICHD Chief Information Officer will review all study center security plans to determine study center's authority to operate. Frequent and regular monitoring visits will assist in compliance with these terms.

Privacy Impact Assessments will be conducted prospectively and recurrently as needed.

Specific NCS data and materials to be collected, disclosure review, and data access are described in detail in the Data Access and Confidentiality Committee Manual. Principles and policies are available at <http://www.nationalchildrensstudy.gov/about/organization/dacc/Pages/PolicyManualandDataUseAgreements.aspx>; the manual is available to the public upon request. Specifically, all NCS data files will undergo disclosure review for personally identifiable information, using procedures consistent with or exceeding those named in Working Paper 22 of the Federal Committee on Statistical Methodology, and steps will be taken to appropriately manage disclosure risk. For example, genome-wide scans conducted on NCS specimens will be considered personally identifiable information and treated as such. Some biologic analyses (for example, HIV status, exposure to specific toxicants), results of some mental health screening tests, and reports of abuse are also considered sensitive.

A.11 Justification for Sensitive Questions

There are a number of questions contained in NCS questionnaires that could be considered sensitive. As part of the informed consent process, women will be informed that their participation in NCS is voluntary and that they may refuse to answer any question. All study questionnaires being proposed for the Recruitment Substudy have been or will be reviewed by Human Subjects Review Boards at NICHD and participating institutions.

During household enumeration, household reporters will be asked if any women in the household are pregnant. During pregnancy screening, women will be asked about their plans for pregnancy. These questions are necessary to determine eligibility for enrollment in NCS. Using in-person and telephone interview, other potentially sensitive questions will be asked, such as alcohol and tobacco use, pregnancy plans, and income. Each of these questions is necessary to assess potential eligibility into the study and to address key potential environmental exposures for children before and after birth.

A.12 Estimates of Hour Burden, Including Annualized Hourly Costs

Table A.2. Estimated Hour Burden and Cost for Recruitment Substudy Respondents—Stage 1 (July 2010 to December 2010)

| Recruitment Strategy | Activity | Type of Respondent | Number of Respondents | Responses Per Respondent | Hours Per Response | Annual Hour Burden |
|---|--|--------------------|--|--------------------------|--------------------|--------------------|
| Provider-based: 10 Study Locations | | | Projected for Stage 1 (July 2010-December 2010) | | | |
| | Screening Activities | | | | | |
| | Address Look-Up | Age-Eligible Women | 7,500 | 1 | 0.1 | 750 |
| | Pregnancy Screening | Age-Eligible Women | 1,500 | 1 | 0.42 | 630 |
| | Preconception Activities | | | | | |
| | Pre-Pregnancy Interview | Age-Eligible Women | 123 | 1 | 0.75 | 92 |
| | Pregnancy Probability Group Follow Up Script | Age-Eligible Women | 123 | 6 | 0.1 | 74 |
| | Pregnancy Activities | | | | | |
| | Women's Informed Consent Form | Pregnant Women | 1,500 | 1 | 0.67 | 1,005 |
| | Pregnancy Visit 1 Interview | Pregnant Women | 572 | 1 | 1 | 572 |
| | Pregnancy Visit 2 Interview | Pregnant Women | 572 | 1 | 0.75 | 429 |
| | Birth-Related Activities | | | | | |
| | Birth Visit Interview | Mother/Baby | 299 | 1 | 0.4 | 120 |
| | Total -Stage 1 | | 12,188 | | | 3,671 |
| Enhanced Household: 10 Study Locations | | | Projected for Stage 1 (July 2010-December 2010) | | | |
| | Screening Activities | | | | | |
| | Household Enumeration Script | HH reporters | 120,000 | 1 | 0.33 | 39,600 |
| | Pregnancy Screening | Age-Eligible Women | 51,198 | 1 | 0.42 | 21,503 |
| | Neighbor Report | Neighbors | 12,000 | 1 | 0.05 | 600 |
| | Preconception Activities | | | | | |
| | Pre-Pregnancy Interview | Age-Eligible Women | 211 | 1 | 0.75 | 158 |
| | Pregnancy Probability Group Follow Up Script | Age-Eligible Women | 211 | 6 | 0.1 | 127 |
| | Pregnancy Activities | | | | | |
| | Women's Informed Consent Form | Pregnant Women | 2,586 | 1 | 0.67 | 1,733 |
| | Pregnancy Visit 1 Interview | Pregnant Women | 986 | 1 | 1 | 986 |
| | Pregnancy Visit 2 Interview | Pregnant Women | 986 | 1 | 0.75 | 740 |
| | Birth-Related Activities | | | | | |
| | Birth Visit Interview | Mother/Baby | 516 | 1 | 0.4 | 206 |
| | Total -Stage 1 | | 188,695 | | | 65,653 |
| Two Tier (Low): 10 Study Locations Across Both Tiers | | | Projected for Stage 1 (July 2010-December 2010) | | | |
| Recruitment Strategy | Activity | Type of Respondent | Number of Respondents | Responses Per Respondent | Hours Per Response | Annual Hour Burden |

| | | | | | | |
|--|--|--------------------|--|---|------|---------|
| | Screening Activities | | | | | |
| | Low-intensity CATI Preg. Screener | Age-Eligible Women | 48,000 | 1 | 0.35 | 16,800 |
| | Low Intensity Consent Script | Age-Eligible Women | 28,800 | 1 | 0.33 | 9,504 |
| | Preconception Activities | | | | | |
| | Low-intensity CATI Questionnaire | Age-Eligible Women | 10,057 | 1 | 0.5 | 5,028 |
| | Pregnancy Probability Group Follow Up Script | Age-Eligible Women | 10,057 | 6 | 0.1 | 6,034 |
| | Pregnancy Activities | | | | | |
| | Low-intensity CATI Questionnaire | Pregnant Women | 518 | 1 | 0.5 | 259 |
| | Birth-Related Activities | | | | | |
| | Low-intensity CATI Questionnaire | Mother/Baby | 166 | 1 | 0.5 | 83 |
| | Total -Stage 1 | | 97,598 | | | 37,709 |
| Two Tier (High): 10 Study Locations Across Both Tiers | | | Projected for Stage 1 (July 2010-December 2010) | | | |
| | Screening Activities | | | | | |
| | Pregnancy Screening | Age-Eligible Women | 15,840 | 1 | 0.42 | 6,653 |
| | Preconception Activities | | | | | |
| | Pre-Pregnancy Interview | Age-Eligible Women | 761 | 1 | 0.75 | 571 |
| | Pregnancy Probability Group Follow Up Script | Age-Eligible Women | 761 | 6 | 0.1 | 456 |
| | Pregnancy Activities | | | | | |
| | Women's Informed Consent Form | Pregnant Women | 9,504 | 1 | 0.67 | 6,368 |
| | Pregnancy Visit 1 Interview | Pregnant Women | 3,552 | 1 | 1 | 3,552 |
| | Pregnancy Visit 2 Interview | Pregnant Women | 3,552 | 1 | 0.75 | 2,664 |
| | Birth-Related Activities | | | | | |
| | Birth Visit Interview | Mother/Baby | 1,857 | 1 | 0.4 | 743 |
| | Total -Stage 1 | | 35,826 | | | 21,006 |
| Grand Total, Recruitment Substudy | | | 334,308 | | | 128,039 |

A.13 Provide an Estimate of the Total Annual Cost Burden to Respondents or Recordkeepers Resulting from the Collection of Information

NCS participants will be reimbursed for any expenses resulting from their participation in NCS. This may include transportation costs to and from study visits or activities, and babysitting or elder care expenses. There are no other known costs to study participants.

A.14 Annualized Cost to the Federal Government

Based on the proposed study budget, the estimated overall cost to the federal government for the Recruitment Substudy of the National Children's Study during the period of this submission is \$__110__ million.

A.15 Explanation for Program Changes or Adjustments

This request for revision proposes the addition of a Recruitment Substudy to the Initial Vanguard Study to better inform the implementation of the Main Study.

Additionally, we request that eligibility of women in the Initial Vanguard Study be extended to include women who resided in the geographically-eligible locations at recruitment, but who subsequently moved residence outside of a geographically-eligible location prior to the sample child's birth. We estimate that this extension of the eligibility criteria pertains to very few women, but it would be advantageous to the study by maintaining good will with participants and supporting analysis on instrument functionality. Since the Initial Vanguard Study is not designed to yield national rates, expanding inclusion criteria in this small way would not impair the ability of the study to meet its objectives.

A.16 Plans for Tabulation and Publication and Project Time Schedule

Stage I of the Recruitment Substudy is planned to begin in July. Data on recruitment, retention, feasibility, acceptability and cost will be reported by each location on a biweekly basis to the NCS Program Office in standard form. Field updates will also be delivered by the locations on a biweekly basis in standard form. These data deliverables and field reports will be aggregated and analyzed by the NCS Program Office on a flow basis to evaluate Recruitment Substudy progress. (Anticipated measures are shown in Table A.3 below.) Stage 2 of the Recruitment Substudy (anticipated for January 2011 and not proposed in this revision) will evaluate potential sources of and magnitude of bias and evaluate item functioning. When sufficient numbers of participants have been recruited so that the evaluation measures have reached a steady state within each strategy, recruitment will cease and the analysis will be completed for the Recruitment Substudy.

Table A.3: Measures to be Computed for the Recruitment Substudy, with Timetable

| Alternate Recruitment Schema Evaluation Matrix | | | |
|--|--|-------------------------------|-----------------------------|
| Key Evaluation Question | | Data Source/ Questionnaire | Frequency of data reporting |
| FEASIBILITY | | | |
| 1 | How effective is the recruitment strategy per location and per schema? | | |
| | a. Number of women to be contacted for screening per month | N/A | Biweekly |
| | b. Number eligible women contacted by study per month | N/A | Biweekly |
| | | N/A | Biweekly |
| | c. Number eligible women consented per month | Consent | Biweekly |
| | d. Distribution of women enrolled while preconception, during pregnancy, or at birth | Pregnancy Screener | Biweekly |
| | | Birth Visit | Biweekly |
| Consent | | Biweekly | |
| e. Distribution of gestational ages at | Pregnancy Screener | Biweekly | |

| | | | |
|--|--|--|----------|
| | consent and first study visit | Consent | Biweekly |
| | | Study Visit questionnaires | Biweekly |
| | f. Monthly enrollment rate of babies among all eligible women with due date in that month | Pregnancy Screener | Biweekly |
| | | Consent | Biweekly |
| | | Birth Visit | Biweekly |
| | g. Birth visits (full & partial complete) among women receiving at least one pre-birth study visit | Study Visit questionnaires | Biweekly |
| 2 | Is the population recruited representative of the target population? | | |
| | a. Race | Pregnancy Screener | Biweekly |
| | b. Ethnicity | Pregnancy Screener | Biweekly |
| | c. Age (DOB) | Pregnancy Screener | Biweekly |
| | d. Marital Status | Pregnancy Screener | Biweekly |
| | e. Primary language | Pregnancy Screener | Biweekly |
| | f. Employment | Pregnancy Screener | Biweekly |
| | g. Education | Pregnancy Screener | Biweekly |
| | h. Parity | Pregnancy Screener | Biweekly |
| | i. Gravidity | Pregnancy Screener | Biweekly |
| 3 | How effectively do outreach and media campaigns reach eligible women? | | |
| | a. What was primary source for entry? | | Biweekly |
| | b. What were the number of and types of ways women heard about NCS? | Pregnancy Screener | Biweekly |
| | c. Principal media sources including print, broadcast, internet, social media | To be addressed through formative research* | Biweekly |
| | ACCEPTABILITY | | |
| 4 | How does retention vary by recruitment strategy? | | |
| | a. Number retained to first visit vs. total consented | Study Visit questionnaires | Biweekly |
| | | Consent | Biweekly |
| | | Follow-up calls | Biweekly |
| | b. Retention across all study visits | Study Visit questionnaires | Biweekly |
| | | Consent | Biweekly |
| | | Follow-up calls | Biweekly |
| | c. Percent "movers" | Consent | Biweekly |
| | | Follow-up calls | Biweekly |
| | 5 | Are the reasons for participation and nonparticipation comparable across the three recruitment strategies? | |
| a. Evaluate reasons given for nonparticipation | | To be addressed through formative research* | Monthly |
| b. Evaluate reasons given for participation in the study | | To be addressed through formative research* | Monthly |
| c. Respondent reactions to study assessments | | Study Visit | Monthly |

| | | | |
|--|---|--------------------------------|-----------|
| | | questionnaires | |
| COST | | | |
| 6 | What is the cost per recruited participant? | | |
| | a. Total number of consented participants | Consent | Bimonthly |
| | b. Total study cost | Study Center Invoice | Monthly |
| | c. Calculated cost per consented participant | See Note | |
| 7 | How do local travel costs vary across recruitment schema? | | |
| | a. For each PSU_ID, sum weekly STAFF_MILES from Weekly Staff Expense Table | Study Center will furnish data | Monthly |
| 8 | How do total charged administrative and field staff hours vary across recruitment schema? | | |
| | a. Administrative hours | Study Center will furnish data | Monthly |
| | b. Field staff hours | Study Center will furnish data | Monthly |
| 9 | How does total charged time for scientific staff vary across recruitment schema? (Cost of scientific staff as function of recruitment schema) | Study Center Invoice | Monthly |
| 10 | What were the dates, costs, and geographic targeting of outreach and media campaigns? (Need to capture the media outreach process for each schema type) | Study Center will furnish data | Monthly |
| 11 | What is the cost per delivered message in media campaigns (exact or appropriate)? (Need to capture the media outreach process for each schema type) | Study Center will furnish data | Monthly |
| | a. What is the size of the targeted population of the media campaign? | | Monthly |
| | b. What is the yield of responses from media campaign? | | Monthly |
| 12 | What is the cost in time for community outreach efforts (both contractor and volunteer labor and incentives)? (Cost of contractors and volunteers used in community outreach efforts) | Study Center will furnish data | Monthly |
| 13 | What is the cost for instrument development and IMS infrastructure? | Study Center will furnish data | Monthly |
| *Note: All analysis will be done by PSU and by recruitment schema, using reports submitted by the study centers. | | | |

A.17 Display of Expiration Date of OMB Approval

The NCS is not seeking an exemption from displaying the expiration date of OMB approval.

A.18 Exception for Item 19, "Certification for Paperwork Reduction Act Submissions"

The NCS is not requesting any exceptions.