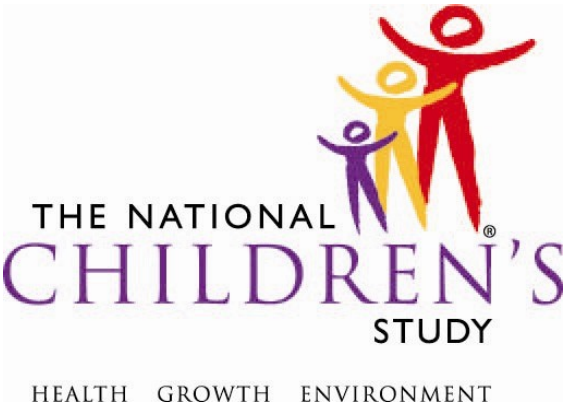

Supporting Statement A for

Pilot Study for the National Children's Study (NICHD)

OMB Re-Submission—August 29, 2008

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A. Justification

A.1 Circumstances Making the Collection of Information Necessary

Patterns of illness among children in the United States and other industrially developed nations have changed substantially during the past 100 years (Bloom & Dey, 2004). Before and during the first half of the last century, infectious disease posed the principal threat to child health and survival. Today, in contrast, the major illnesses and disorders that impair health, growth, and development are chronic conditions stemming from the complex interaction of environmental exposures and inherent genetic factors. Some label this the "new pediatric morbidity" (Haggerty, 1975). These conditions include: preterm births (Ananth, Joseph, Demissie, & Vintzileos, 2005); asthma (Mannino et al., 2002); injuries (Thornton, Craft, Dahlberg, Lynch, & Baer, 2002); childhood cancer (Linet, Ries, Smith, Tarone, & Devesa, 1999); neurodevelopmental disorders, such as learning disabilities, dyslexia, mental retardation, attention deficit/hyperactivity disorder, and autism (Boyle, Decoufle, & Yeargin-Allsopp, 1994; Newschaffer, Falb, & Gurney, 2005; Scahill & Schwab-Stone, 2000; Shaywitz, 1998); obesity and type 2 diabetes (SEARCH Writing Group, 2004); birth defects (Centers for Disease Control and Prevention, 2007; Decouflé, Boyle, Paulozzi, & Lary, 2001); and cardiac defects and disease (Towbin et al., 2006). Addressing the causes and contributors to these and similar chronic conditions is the major challenge to public health practitioners and pediatric researchers today, and constitutes the frontier that must be crossed if the health and well-being of children in developed countries is to move forward. The National Children's Study is designed to address these issues with robust science and the ability to generalize the data to the U.S. population.

The National Children's Study design rests on the principle that both health and susceptibility to disease are determined by dynamic processes that occur throughout life. Perturbations ("insults") that impact health may occur any time from the periconceptional period through adult life. These insults can affect viability, differentiation of major organic systems, somatic growth, and the development of functional processes including maturation of metabolic systems. 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.

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) 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 program of research designed to achieve these goals has evolved as the National Children's Study (NCS).

While there are many conditions of childhood that may greatly affect an individual or family, some also place a great burden on the U.S. population because of their prevalence, severity, and/or cost. For example, there are increasing concerns about the large (and perhaps growing) number of American children who have one or more major chronic health or developmental conditions. As many as 17 percent of children have a developmental disorder (Boyle et al., 1994), about 21 percent have a diagnosable mental or addictive disorder with at least minimum impairment (U.S. Department of Health and Human Services, 2000), and about 7 percent have asthma (Mannino et al., 1998). Through the extensive planning process of the NCS, the following areas emerged as the primary outcomes around which the study's core hypotheses have been generated: pregnancy outcomes; neurodevelopment and behavior; asthma; obesity and growth; injury; and reproductive development. Additionally, the NCS is committed to assessing predictors of healthy development. The data collection process will also allow the examination of a range of health outcomes that extend beyond those identified in this study.

The priority outcome areas were chosen not only because of their importance to public health, but also because their etiology and course can only be addressed through a research study of the scope and magnitude of the National Children's Study. Since many of the outcomes may arise as a consequence of in utero exposures, study of these outcomes and relevant exposures must begin before birth. Additionally, a variety of exposures likely contribute directly, indirectly, and interactively to these outcomes. A full understanding of their etiology requires a study covering a range of exposures. Genetics likely plays a role both in the origin and expression of numerous specific disorders, thus a complete study must include an exploration of direct genetic contributions and of gene-environment interactions. Furthermore, each outcome has a range of, sensitive periods for exposures, different ages of onset and changes in nature or severity over development. Only a longitudinal study can track these outcomes as they unfold during childhood and adolescence.

The NCS is designed as a longitudinal study that will enroll and follow a nationally representative sample of approximately 100,000 children born in the U.S. from before birth through their 21st birthday. The study will screen all households within selected areas of 105 Primary Sampling Units (PSUs) for age-eligible women, and then conduct further screening of these women to determine eligibility for enrollment into the pre-pregnancy or pregnancy phase of the study. For enrolled women, the data collection protocol includes obtaining interview data, physical measures, biologic samples, and environmental samples beginning in the months prior to conception or in early pregnancy.

A.2 Purpose and Use of the Information Collection

This request for OMB clearance is for a Pilot Study of NCS procedures and materials in the first seven study sites (Vanguard Centers). A cohort of babies born over a 12-month period (a "pilot cohort") in these Vanguard sites will serve as the testing group for all study procedures and materials developed over the study's planned 21-year follow-up period that subsequently will be used in the full study of 105 locations. This clearance submission covers the Pilot materials from enumeration and enrollment through the child's 2 year study contact.

Establishment of this Vanguard Pilot cohort will address many of the major operational recommendations elaborated in the National Academy of Sciences review of the NCS Research Plan

(http://www.nap.edu/catalog.php?record_id=12211). Major recommendations from this review included: assurance of an adequate Pilot period; evaluation of many aspects of the population-based household recruitment plan and subsequent sample retention; and assurance of high-quality data collection, including evaluation of the use of local Study Centers for data collection rather than a national survey organization.

A.2.1 Purpose and Format of Pilot Phase Data Collection

A primary purpose of this Vanguard Pilot Study is evaluation of the household-based sample selection plan. The future success of the NCS will be dependent on the initial recruitment and maintenance of a valid sample. Testing of specific protocol components (e.g., the video consent described later in this clearance package) also will occur during this Pilot phase. After establishment of this Vanguard Pilot cohort, subsequent portions of the Pilot protocol will allow for more testing of specific data collection instruments.

The Vanguard locations were selected randomly among the sampled 105 locations based on stratification into the four Census regions, metropolitan status, and the average number of births per year. From these strata, two certainty units were selected, four metropolitan but non-certainty units, and two non-metropolitan units such that two locations were located in each of the four U.S. Census regions. For these eight potential vanguard locations selected, seven Study Centers were selected under a contract mechanism upon consideration of the availability of funds and the quality of the proposals received.

The Vanguard locations currently are scheduled to begin enrolling women in January 2009, contingent upon requisite approvals, beginning with two Vanguard Centers followed three months later by the remaining five Centers. The first two Centers (Group 1) will provide initial information about the operational procedures and training through qualitative methods. In essence, the Group 1 Pilot locations, throughout the course of the study will provide the first opportunity to try data collection procedures and materials within an NCS setting, and serve as an initial source of qualitative evaluation data.

The initial phase of the Vanguard Pilot will allow preliminary insight into the feasibility of adhering to the NCS's complex data collection protocol. In compliance with the Study's authorizing language, the NCS protocol has been designed to cover a broad array of exposures and outcomes in substantial depth. While there is relevant field experience with each of the current protocol's components, their combination into a single large Study is unprecedented. The Vanguard Pilot will enable assessment of the individual components in the combined setting. Data on overall completion rates for each component, and item non-response or refusal within the components, will be obtained and analyzed. In addition, participant "satisfaction" data will assess their receptiveness to the various components. These data will be used to inform development of the final main study instruments. In addition, these Pilot data will be invaluable in assessing the usefulness of the various protocol components, should continuation of the current protocol be infeasible due to burden or cost constraints. In such a circumstance, decisions will have to be made based both on the content matter of the components in question as well as the effectiveness of a particular component within the context of the full NCS protocol. The Vanguard Pilot is necessary to provide that context.

Within 8 months of the start of the enrollment period (by September 2009), sufficient data on household listing and enumeration, eligibility screening, and enrollment of pregnant women should be available to assess the success of the household-based sample selection plan. Unless the results of this initial analysis indicate that the sampling and enrollment approach be dramatically revised, additional analyses of the Pilot data will guide potential revisions to the protocols as necessary within the next six month period. By early 2010, we plan to submit a new set of OMB materials for Wave 1 of the Main NCS Study, reflecting the changes based on the Vanguard Pilot evaluation. Enrollment for the Main Study will start within a

few months of OMB approval for that stage of the Study; the precise anticipated date for the start date of the Main Study will be based on the scope and complexity of changes from the Pilot design.

The current structure of the NCS involves collection of data by local Study Centers (generally consortia of local academic centers and health agencies, frequently in collaboration with national survey research firms) with general coordination through a single contract Coordinating Center (Westat), all overseen by the Federal NCS Program Office. Given the longitudinal nature of the NCS and ongoing interaction of the participants with Study personnel, a strong local presence with vigorous community interaction and engagement is critical in ensuring high participation and retention. Moreover, the NCS encompasses much more than the traditional household survey, including collection of biologic specimens from the study participants in the home and clinical settings, environmental samples from the home and neighborhood, and clinical data. The involvement of local Study Centers, most of whom are already ingrained within the communities, is likely to result in higher response rates than a data collection strategy led by a remote survey organization. The Vanguard Study Centers have developed initial community partnerships, will hire data collection staff from the community, and are well positioned to maintain continued contact with study participants and to communicate results to participants and the community. These are all identified as strategies important in making longitudinal studies successful (Eskenazi et al., 2005; Hardy 2003). Importantly, the Study Center approach maximizes the contribution of scientists to the development of the data collection protocols, thus addressing many of the concerns raised in the National Academy review. This has occurred in the development of the Vanguard Pilot protocol and will increase during the life of the Pilot phase and throughout the main NCS.

Strong oversight of the data collection procedures and rapid and continuous review of data completeness and quality is necessary to assure the success of the de-centralized data collection model. The Coordinating Center is responsible for assuring standardized training, data collection procedures, and for implementing the data quality and assurance program (described in more detail in Part B, Section 2.2). Thus, there is a strong central presence underlying the seemingly de-centralized field operations. The Vanguard Pilot phase is crucial for testing all these procedures throughout the course of the NCS.

A.2.2 Pilot Phase Evaluation Plan

The overall approach to evaluating and learning from the Vanguard Pilot relies on several tiers of evaluation reflecting the strategy used in building the NCS materials, instruments and specific measures. The tiers can be defined as:

- Tier 1: Evaluating the NCS enrollment plan in terms of meeting targeted enrollment goals specified in the study design
- Tier 2: Testing alternative data collection protocols for obtaining the targeted number of pregnant women and infants
- Tier 3: Evaluating specific data collection instruments and protocols
- Tier 4: Testing and evaluating refined instruments or protocols prior to incorporation into the Main Study

This tiered approach will continue throughout the twenty years of the Pilot as the enrolled infants grow and shift into the next stages of data collection. Each stage of data collection will include a feasibility assessment focusing on meeting retention goals (tier 1), testing of alternative data collection protocols as appropriate (tier 2), evaluation of specific measures or instruments (tier 3) and, as needed, additional testing and evaluation of refined measures, instruments or protocols prior to incorporating them into the Main Study (tier 4).

<u>Tier 1: Evaluating the enrollment protocols in terms of meeting enrollment goals</u>

The first tier focuses on evaluating the ability to recruit and enroll the required number of pregnant women and births with the current study design within the budgeted costs. Meeting the projected numbers of women and births is crucial to the statistical underpinnings of the study; the NCS needs to recruit, enroll and retain the targeted number of women and infants to address the Study's core hypotheses. This first component of the evaluation focuses on assessing whether the sample design coupled with the data collection methods and operational procedures as implemented in the Vanguard Pilot will identify, enroll and retain the projected number of women and infants for the Pilot. This first tier of evaluation also includes methods for identifying potential causes for any observed negative differential, focusing particularly on nonresponse and measurement error. Additional details regarding the evaluation criteria are presented in Part B, Section 2.3.

Tier 2: Testing alternative data collection protocols for obtaining targeted numbers

This tier of work compliments the previous tier in that the focus is testing potential alternative data collection protocols that lead to the identification of pregnant women, including methods for motivating their continued participation.

As noted in the previous section, the design of the NCS requires data collection methods that meet specific targets for numbers of enrolled pregnant women and infants. This is the core assumption defining the feasibility of the study. This tier includes three specific studies to be included in the initial Vanguard phase that address alternative approaches for recruiting and retaining the participation of pregnant women and their babies.

- Alternative Consent Methods: Comparing a traditional approach to an interactive video
- Automated self-response methods for pregnancy monitoring contacts
- The amount and delivery strategy for incentives

The Consent Methods study is fully developed and will be implemented starting with the Group 1 Vanguard sites. Please see the attached study plan for a full description of that testing as well as copies of the planned questionnaires for collecting the evaluative information.

The study assessing automated self-response methods for the pregnancy monitoring contacts includes several phases of development and testing. The first two phases focus on development of an Interactive Voice Response (IVR) instrument and a Web-based application for collecting the pregnancy status update information that respondents perceive as user-friendly, impose very little burden to respond, and include tools/methods for improving respondents recognition of and cooperation with the contact. These phases will take place under the NCS Generic clearance. The last phase reflects the testing of the IVR and Web-based application in the Vanguard Pilot to measure cooperation with these contacts, including accurate identification of pregnant women, within the NCS environment. The design of the final phase of testing will be further developed based on the results of the first two phases. The final phase of testing will occur as part of data collection in the Group 2 Vanguard locations.

Tier 3: Evaluating specific measures and instruments

The general plan for the NCS has been to use standard measures and techniques that have substantial scientific evidence supporting their analytic utility whenever possible. Relying on established measures allows concentration on testing and evaluation of the aspects of the Study not previously implemented in other survey, environmental or medical research projects. Thus this tier includes testing of methods and

instruments that have been developed specifically for the NCS as well as modifications to existing methods or instruments necessary for cost-effective implementation within the NCS.

The attached table lists the tests of alternative data collection protocols noted in Tier 2 as well as the specific evaluations of Tier 3 measures and instruments planned for inclusion in either the Vanguard Pilot, under the Generic Clearance, or not involving participant burden (i.e., specimen stability studies). As the data collection plans are developed for visits after infancy, the NCS anticipates continuing to add to this list.

Tier 4: Testing and evaluation activities leading to refinements for the Main Study

This tier of evaluation is perhaps more accurately thought of as further development and testing needed prior to incorporating methods modified from the Pilot into the Main Study. Outcomes from both the first and second tier of evaluation activities will define what testing occurs in this stage, if any, as well as the timeframe for the testing.

The relationship between the evaluative "tiers" and the Vanguard and subsequent Wave 1 study activities will vary depending on the purpose of the evaluation activities. For instance, assuming the Vanguard Centers begin household enumeration in January, 2009, the timing of Tier 1 and 2 studies (evaluation of factors related to establishment of the Study population) is expected to be:

- January – August 2009 – initiate household contacts and compile evaluative data as described; ongoing adjustments to procedures based on qualitative assessments of ongoing processes
- September – October 2009 – sufficient data available to assess initial enrollment procedures and make inter-Center comparisons. Use results of this and ongoing experience to adapt practices of under-performing Centers when necessary
- January – February 2010 – re-evaluation of amended enrollment procedures
- March 2010 – preparation and submission of initial Wave 1 OMB clearance package

Though this timeline suggests relatively discrete periods of evaluation and adaptation of practices, evaluative information will be compiled and examined on an ongoing basis. If there are obvious failings within a particular Center (or segment(s) within a Center) qualitative assessment and comparison with more successful Centers will help guide intermediate changes in enrollment-related procedures.

The timeline for evaluation of specific data collection instruments is dependent upon their place within the protocol. For example, evaluation of the completeness of prenatal medical care logs will likely follow a timeline similar to that described above. However, a similar examination of the completeness of the medical care logs of infants will not be possible until approximately mid-2010.

	Title and Objective	Accountability of burden hours?	Qualitative Testing only?	Analytical approach
EVALUATION OF SPECIFIC MEASURES OR INSTRUMENTS				
1.	**Listing and Enumeration Evaluation**: Evaluate an automated tool that links listing and enumeration as a combined activity. Key evaluative measures: completeness of listing using combined method versus traditional listing followed by household enumeration; level of effort to identify and correct operational issues such as duplicate listings or missed dwelling units.	Part of Pilot	Yes (too few cases/duplicates for statistical analysis)	The evaluation will include checking for duplicate listings in the electronic LE approach (and examining the enumeration dispositions of those duplicates), comparing the electronic and hard copy listings, and examining operational issues (usability of the tablets, ability of the LE data collectors to locate DUs for enumeration if they did not list the DU, etc.).
2.	**Validation of the Food Frequency Questionnaire (FFQ) during pregnancy and among Hispanic women; testing of modified reference period:** This study serves two objectives. First to validate the NCI FFQ with Hispanic women, and second to identify the reference period (past 1-month or past 3-months) that provides higher correlation estimates with the average of three 24HR dietary recalls for both Hispanic and Non-Hispanic women.	Generic Clearance	No	Comparison of nutrient specific correlation coefficients for the Hispanic and Non-Hispanic women relative to industry accepted correlations. Also compare the nutrient specific correlation coefficients for the 1 month and 3 month recall periods used in the FFQ again relative to industry accepted correlations.
3.	**Stability Testing of Biospecimens**: There are 3 parts to the stability testing - time from blood collection to centrifugation, short term refrigerated storage, and long term storage. Key evaluative measure: % change from the baseline measure with each aspect/stage of storage over time.	No burden hours / no respondents	No	Unit of analysis is the mean value or concentration in the blood; designed to detect a 10% decline in analyte concentration at each stage. Considering a random effects linear regression, but final analysis method TBD.
4.	**Stability Testing of Environmental agents**: There are 2 parts to the stability testing - short term freezer storage of pyrethroid	No burden hours/ no	No	Unit of analysis is the mean value or concentration of analyte

	wipe samples, and long term storage of other stored samples. Key evaluative measure: % change from the baseline measure with stage of storage over time.	respondents		in the sample; will be designed to detect a specified % decline in analyte concentration at each stage and over time. Final analysis method TBD.
5.	**Abbreviated Attachment Measure**: Two stage study, starting with secondary analyses of NICHD-SECCYD data to create a shorter version of the attachment Q-sort, which we will validate against the Strange Situation data also from NICHD-SECCYD. Key validation measure: Strength of relationship with Strange Situation data. Second stage is to implement the shorter version of the attachment Q-sort in the Pilot and assess both operational issues as well as internal reliability measures. Key evaluation measure: Internal reliability as well correlates with other variables collected as part of the Pilot.	Part of Pilot (Second stage only)	No	Minimum correlation of 0.3 for internal reliability measures and validity compared to other variables expected to correlate
6.	**Medical care logs:** Examination of completeness of the prenatal and infant medical care logs, as compared to medical records. Key evaluative measures: Completeness of recording of number and location of visits, assessment of "quality" of data recorded on the logs, using available medical records as the gold standard. Comparison of information recorded in logs to that reported during in-person and phone interviews. Interactions with health insurance, type of medical facility, and measures of participant SES to be explored.	Part of Pilot	No	Comparison of available medical records with medical care logs, with focus on locations with relatively easily accessible medical records to facilitate comparisons. Acceptable levels of correlation to be subsequently determined and based partially on difficulty in obtaining medical records. Data of specific interest on the infant log are those related to immunizations, including type and Lot number.
TESTING ALTERNATIVE DATA COLLECTION PROTOCOLS RELATED TO RESPONSE AND RETENTION				
1.	**Consent Evaluation**: Compare a traditional approach to an interactive video approach for obtaining consent. Key evaluative measure: difference in enrollment rates between women who receive the paper and pencil approach and women who receive	Part of Pilot	No	Minimal Detectable difference at 80% power = 10 percentage point difference in enrollment by method of consent

	the video approach.			
2.	**Testing of Self Response methods for pregnancy monitoring, phase I**: Usability testing, and some focus on cognitive aspects of response, with an IVR application and Web-based application for responding to the pregnancy follow-up contacts. Additionally, this test will also collect information about perceived privacy issues with either of the two modes. Key evaluative measures: various usability measures, perceived sensitivity of application for each mode, and privacy issues for each mode.	(Limited to 9 respondents for each application)	Yes	Analysis of debriefing data
3.	**Testing of Self Response methods for pregnancy monitoring, phase II**: Including more of the NCS context, recruited women will complete an in person Pregnancy screener and then about 8 weeks later receive a pregnancy follow-up contact in one of three conditions (IVR, web or choice of mode). Testing will assess effectiveness of different contact protocols by mode, as well as collect additional usability information. Key evaluative measures: cooperation rates and timeliness of response for each mode and by contact protocol; various usability measures.	Generic Clearance	Yes	Analysis of debriefing data, response rates and timeliness of response.
4.	**Testing of Self Response methods for pregnancy monitoring, phase III**: Continuing from the previous phases, this test will experimentally compare different methods for improving cooperation with these contacts. Key evaluative measures: cooperation rates, level-of-effort and timeliness for obtaining a complete.	Part of Pilot	No	Assuming two groups/protocols for contacts, minimal detectable difference of 5 percentage points at 80% power (within 1 month of close of Group 2 enrollment period)
5.	**Testing Incentive levels and protocols for in-person visits**: Several different approaches for testing incentives as part of the pilot are under consideration (described in Section A.9). The incentive manipulations will focus on amount and timing of delivery (as interaction terms). Key evaluative measures: cooperation and response at a particular visit, as well as retention in the study overtime.	Part of Pilot	No	TBD, depends on further development of study design.
6.	**Evaluation effect on enrollment and early retention of different methods of communication with Study particiants:** Different approaches for communicating with participants via newsletters, greeting and reminder cards, sharing of general	Part of Pilot	Yes	Examination of participant evaluation questionnaires in addition to ongoing analyses of data quality

study progress and results, will be compared, primarily between Centers. Key evaluative measures: participant satisfaction, data completion, early retention.		measures

The analyses of the Vanguard Pilot data in general and the various additional Pilot evaluations described above will answer many questions including the following:

- *Community engagement efforts*
  - Are women who report participating in any of the community engagement activities more likely to enroll in the study?
  - Of the women who enroll in the study, are those that reported participation in any community engagement activities more likely to continue with their participation?
  - Do medical providers encourage their patients to participate in the NCS?
  - How burdensome do medical providers perceive their role in the NCS?
  - Are hospitals participating in the NCS by providing the needed data at the birth visit? What proportion of birth visits result in a complete data collection? For those that are not complete, what data are missing?
- *Listing and enumeration recruitment results*
  - How does the actual ratio of age eligible women over the number of households listed and enumerated compare to the expected ratio?
  - How does the actual ratio of study eligible women over the number of age-eligible women compare to the expected ratio?
  - Of all addresses listed within and across sampled segments, what percentage result in a complete enumeration interview?
  - At the Vanguard Center and segment levels, what percent of all addresses are adds from listing? What percent of addresses get dropped during listing? What are the characteristics of addresses that get added/dropped?
  - Are there large geographic, demographic, or other differences in recruitment rates not explained by the community engagement activities described above?
- *Pregnancy screener response rates*
  - Of age eligible women asked to complete the screener, what percentage fully complete the screener (and thus can determine their pregnancy probability group)?
  - How does the actual distribution of pregnancy probability groups compare to the expected distribution? Does the distribution of pregnancy probability groups differ by Vanguard Centers?
- *Data collection and retention*
  - Are there any data collection components that are refused more often than others?
  - Do respondents understand instructions for SAQs and self-collected samples? Are SAQs completed properly? Are self-collected specimens collected properly?
  - Do reports of results, greeting cards, newsletters encourage participation and retention?
  - Based on the respondent satisfaction questionnaire, should specific study components be abbreviated, expanded, or re-worked?
  - Results of consent evaluation questionnaires completed by respondents. Does one consent format provide better response rates and understanding of Study goals and methods than the other (paper vs. video consent)? (See Section B.2.1 for an explanation of the consent evaluation.)

Estimated response rates for households and participants are included in Part B, Section 3.1. Data from the Pilot Study will provide actual response rates for households and participants in the seven Vanguard Center sites, which were selected to represent diverse populations and diverse areas (e.g. rural vs. urban). This information will guide refinement of response rate estimates and

sampling efforts for the Main Study. Information on the reasons for refusals and other forms of non-response (e.g. broken data collection appointments) will aid in revision of recruitment and retention approaches and materials.

Additionally, within the Pilot Cohort, the results of placing women in pregnancy probability groups must be analyzed. Assumptions have been made about which of a woman's characteristics best predicts future pregnancy, but the results of the application of the pregnancy algorithm must be analyzed in order to understand whether the algorithm produces the desired effect (i.e., approximately 20% of women will be enrolled in the preconception phase, and the majority of women will be enrolled during their first trimester).

A.3 Use of Information Technology and Burden Reduction

Computer-assisted interviewing (CAI) systems will be employed by the NCS Pilot for in-person and telephone data collection activities. Use of these technologies will reduce respondent burden by incorporating eligibility algorithms into the interview process. Complex skip patterns available only with such technology will enable data collectors and participants to quickly and accurately determine which questions are applicable for each interview and which women are eligible for the NCS protocols. In addition, for questions of a sensitive nature (e.g., questions asked of women of child-bearing age to determine if they are planning on becoming pregnant), an audio computer-assisted self interview (A-CASI) is planned. For telephone contacts with women between in-person visits, computer-assisted telephone interviews (CATI) or Interactive Voice Response (IVR) technologies are planned. Forms and questionnaires that are given to participants to complete will be developed in a format suitable for optical character recognition (OCR). These forms will be designed in user-friendly formats to reduce the amount of time necessary to complete them. As an overarching method of controlling all Study activities, an automated Information Management System (IMS), will be used. The IMS will determine and track study protocols so that burden to respondents is reduced by ensuring that the proper study components are administered at the appropriate times. The IMS will also track completion of all study activities, allowing for monitoring and calculation of response rates and cooperation rates for each study activity.

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

Before the planning and initiation of the NCS proceeded, an inventory and review of longitudinal studies was commissioned by the National Center for Health Statistics and undertaken by the Lewin Group (2000). The review examined existing resources to assess the possibility of addressing the study goals without embarking on an entirely new study and to identify possible duplication of efforts by the proposed longitudinal cohort study. Two databases were used to identify significant longitudinal studies: Medline and the listing of National Institutes of Health (NIH)-funded studies at the Community of Science, a network of scientists and research organizations on the Internet. From more than 37,000 citations, the search identified 154 studies that met the criteria of longitudinal (studies must collect data at a minimum of two points in time), longer than one year, prospective, observational (as opposed to interventional), general population (as opposed to disease specific), and meaningful sample size (generally 1,000 and greater) conducted in the United States.

A 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. Although the Lewin inventory identified 62 longitudinal studies of youth and their health outcomes, only five met the criteria of a predominantly U.S. sample, sample recruitment during pregnancy or early infancy, and sufficiently large sample size (greater than 10,000). Of these five, only one, the Early Childhood Longitudinal Study (ECLS-B) Birth Cohort met the above criteria and could possibly be adapted or used as a framework for a large longitudinal cohort study of environmental factors and children's health. The goal of the ECLS-B is to assess the health, growth, and developmental factors critical for school readiness and achievement. It identified a nationally representative sample of approximately 15,000 children at birth and is performing examination batteries at 9, 18, 30, and 48 months of age. Because the ECLS-B recruited participants at birth, the ability to prospectively measure outcomes and exposures before birth was not satisfied. In addition, the ECLS-B did not collect data for crucial chemical or biological exposures.

Prior and ongoing population-based studies of the National Center for Health Statistics were also considered as resources to address concerns about environmental effects in children. These included the National Health and Nutrition Examination Survey (NHANES), the National Survey of Family Growth (NSFG), the National Maternal and Infant Health Survey (NMIHS), the National Health Interview Survey (NHIS), and vital statistics. Of those surveys, only NHANES is done on a continuous or relatively frequent interval and collects physical measurements of the child, and collects some environmental measures and biomarkers. While NHANES serves extremely important surveillance and monitoring functions, it is not a cohort study and its cross-sectional design does not permit it to identify the kinds of exposure-outcome relations critical to the goals of the NCS. Nor does NHANES allow for the detailed assessment of prenatal exposures or outcomes.

A.5 Impact on Small Business and Other Small Entities

The potential impact of the NCS Pilot on small businesses will be limited to medical providers, hospitals, and possibly child care centers. 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.

Child care locations are important contributors to a child's overall environmental exposure because of the amount of time that children spend in those locations. It is planned that visits will be made to child care providers and day care centers to collect environmental samples starting with a sub-sample of the enrolled children who are in day care and at least 3 months of age. Reimbursement for any staff time involved in complying with study requests for information will be provided.

A.6 Consequences of Collecting the Information Less Frequently

As currently designed, the NCS will allow rigorous testing of the current study hypotheses. (Appendix C.2 provides a list of Study hypotheses topics.) 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. Appendix C.3.1 provides an overview table showing the planned schedule of visits. Because biologic and environmental samples and the extensive information collected from participant interviews,

exams, and other sources will be stored and available in the future, the NCS is designed to address a multitude of additional research questions, most of which have not yet conceived.

It is important to understand the consequences of the data collection methodology, including approaches used for household listing, enumeration and pregnancy screening, recruiting, collecting data and participant retention. For instance, the planned frequency of contacts for women being followed in the preconception period was developed 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 help inform the methodology for the Main Study.

A.7 Special Circumstances Relating to the Guidelines of 5 CRF 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

The 60-day Federal Register Notice regarding the NCS is published on pages 65049 through 65050 of Volume 72, Number 222 of the Federal Register on November 19, 2007.

Comment #1 (abridged) – "…I SEE NO REAL PURPOSE OF WHAT THIS STUDY WILL ACCOMPLISH. IT SEEMS LIKE JUST PAPER COLLECTION SO SOME BUREAUCRAT CAN SIT IN AN OFFICE AND STARE AT THE PAPER RESULTS. FOR THAT REASON, I OPPOSE THIS STUDY... THIS IS SCATTERSHOT SPENDING OF TAX DOLLARS. I THINK IT IS THE WRONG WAY TO GO. WE HAVE ENOUGH PAPER IN OUR SIN CITY WASHINGTON GOVT. WE NEED ACTION AND WE NEED RESULTS. THIS IS JUST MORE PAPER COLLECTION WITH NO REAL PURPOSE TO IT."

Response #1 – As written in Section A.1 of this supporting statement, PL 106-30, Sec. 1004 directs NICHD to undertake a study to address the influence of the environment on the health and development of children in the US. The NCS has been designed to fulfill that mandate.

There were no other public responses to the Federal Register Notice.

A.8.1 Efforts to Consult Outside Agency

Several committees and many individuals have been consulted on the NCS methodology, sampling and hypotheses, as well as specific instruments and samples to be collected, for the National Children's Study. The Study committees are described below. Members of each Committee and other individuals consulted about NCS are listed in Appendix C.5.

National Children's Study Federal Advisory Committee—The National Children's Study Federal Advisory Committee (NCS-FAC), constituted under the Federal Advisory Committee Act, provides advice and recommendations to the Director of the National Children's Study, the Director of the National Institute of Child Health and Human Development, and the Interagency

Coordinating Committee regarding critical aspects of the Study. A list of the members of the FAC can be found in Appendix C.5.1, and includes representatives from academia, industry, health care practice, and other professions. Early in the planning phase of the NCS, 22 Working Groups were convened under the auspices of the NCS-FAC, to enable the Study to receive input from literally hundreds of non-Federal scientists and other professionals.

Interagency Coordinating Committee—The Interagency Coordinating Committee (ICC) organizes and directs operations of the Study. This committee is made up of staff from two federal agencies: the U.S. Department of Health and Human Services (DHHS) and the U.S. Environmental Protection Agency (EPA). Within DHHS, staff is contributed from the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH). CDC contributes staff from the National Center on Birth Defects and Developmental Disabilities and the National Center for Health Statistics; NIH contributes staff from the National Institute of Child Health and Human Development and the National Institute of Environmental Health Sciences. EPA contributes staff from the National Center for Environmental Research, the National Health and Environmental Effects Research Laboratory, the Office of Children's Health Protection, and the National Exposure Research Laboratory. Members of the ICC are listed in Appendix C.5.2.

Steering Committee—The National Children's Study Steering Committee consists of members from each of the Vanguard Centers; the NCS Program Office, the Coordinating Center, the ICC, and invited community representatives. A list of Steering Committee members is included in Appendix C.5.3. This list will be expanded as additional Study Centers are added to represent additional study locations. Various working teams within the Steering Committee have convened and provided input into the study protocol and procedures (e.g, Sampling Team, Outreach and Engagement Team).

Others Consulted—A list of some of the many agencies and organizations that support the NCS can be found in Appendix C.5.4.

A.9 Explanation of Any Payment or Gifts to Respondents

In order to maximize response rates, many research studies, particularly those involving medical procedures, offer compensation for participants. For example, the National Health and Nutrition Examination Survey (NHANES) has offered their participants compensation since the 1970's. Incentives are effective in increasing response rates for in-person surveys (Creighton, King, & Martin, 2000) and can help increase response rates for minorities and low-income households (McGrath, n.d., Martinez-Ebers, 1997, Singer, & Bossarte, 2006, & Fredrickson et. al., 2005.) Compensation is 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. As recognition to participants for their time spent providing information for the study, the NCS is proposing a reimbursement of $100 after the completion of each in-person data collection visit conducted in the participant's home or in the study clinic. The initial in-person data collection visits (pre-conception and early pregnancy) are estimated to take about 3 hours. Compensation will also be provided for any expenses incurred in research participation such as travel to and from the research centers, parking, etc.

Reimbursement for child/elder care and/or transportation costs incurred in research participation will vary across the Vanguard Centers. For example, costs for child care will more than likely be higher in Queens, NY than they are in the counties in South Dakota and Minnesota covered by the BYPL Center. Transportation costs will also vary. In Queens, reimbursement may more often

be for subway, bus or taxi costs versus mileage/parking reimbursement for participants using their personal car in Orange County, California. Each Center will determine the usual and customary rate for child/elder care and transportation, and reimburse participants accordingly.

There is not a single plan for handling reimbursement of participants' expenses since this task will be handled by each local Vanguard Center. Institutions generally have mechanisms and requirements in place for requesting and tracking reimbursement of expenses. For example, some Centers may contract with taxi companies to provide transportation; other Centers may provide bus or subway passes, and others may choose to simply reimburse respondents for transportation costs. The method for handling transportation costs and reimbursement for participants will be determined by each Vanguard Center.

Reimbursing respondents for expenses has been approved by OMB for other NIH studies. For example, NHANES reimburses respondents for transportation costs to the Mobile Examination Center (MEC) and for child care while the participant is at the MEC. The transportation costs vary based on if the area is urban or rural and the distance required for respondents to travel from their home to the MEC.

Medical providers, hospitals, and day care centers which provide information for the NCS will be reimbursed at their usual and customary rates. This will include the costs of providing medical records, using their institution's staff to collect specimens for the study, responding to questionnaires, completing fetal ultrasounds, or providing access to facilities for purposes of collecting environmental samples. These costs are included in the current contracts with the Centers, and thus included in the Cost estimate.

Small "gifts of appreciation", with maximum value of $25, for continued participation will periodically be provided to participants. These may include items of small monetary value (e.g., t-shirts, tote bags, etc.), and are intended as tokens of appreciation. This Pilot test will provide some experience with the use of different types of incentives. In addition, small non-cash incentives are planned in order to encourage health care providers and community leaders to provide responses to evaluation questions that will identify issues that are important for the Pilot Study.

Several different approaches for testing incentives as part of the Vanguard Pilot are under consideration. This testing will supplement the data gathered in the first tier of evaluation. At this time, the following manipulations of incentives are being considered for testing in the second group of Vanguard Centers, comparing the impact on response at a particular visit, as well as retention in the study over time:

- The timing of when a visit incentive is provided (e.g., pre-paid or partially prepaid) and the amount of the visit incentive (e.g., $50, $75 versus the current $100). The amount and timing will be manipulated together, essentially testing the interaction of the timing and amount of the incentive, rather than a main effect of either alone in order to limit the number of groups and have adequate number of sample cases for analysis. For example, for the incentives provided for the T1 visit :
    - $50 all prepaid at the end of the visit in which the woman signs the consent materials
    - $25 prepaid at the end of the visit in which the woman signs the consent materials, and an additional $50 promised for the completion of the T1 visit
    - $100 promised for the completion of the T1 visit

- Whether a nominal incentive improves participation with the monitoring contacts over time, and specifically, whether a one-time incentive or a smaller, repeated incentive for a subset of contacts affects response

A detailed incentive plan can be found in Appendix C.6. The dollar values listed for both monetary and non-monetary incentives in the Incentive Plan indicate the maximum potential value for the Pilot phase since we will be testing different incentive amounts as part of the Pilot evaluation.

A.10 Assurance of Confidentiality Provided to Respondents

Study participants will be assured that the data collected will be safeguarded closely and that actions will be taken to protect confidentiality. To further protect participant confidentiality, NCS has obtained a Certificate of Confidentiality to protect data from involuntary disclosure (Appendix C.7).

The Vanguard Centers, under contract to conduct the NCS Pilot Study, have policies and procedures regarding confidentiality and protection of study data. In addition to their own confidentiality procedures and policies, they will implement all required study-related confidentiality and data security procedures. Westat, the NCS Coordinating Center (CC), along with its subcontractor, the University of Pennsylvania, which serves as the data center, also has clear policies and procedures regarding assurance of confidentiality and a pledge that all employees must sign. In addition, Westat provides all safeguards mandated by NICHD. All Study Center staff and the CC staff must adhere to the security requirements implemented by NICHD. These include completion of the NIH Computer Security Awareness Training, completion of a Human Subjects Protection Training, and signing a legally-binding Assurance of Confidentiality.

To further assure confidentiality of participant data, the study will employ rigorous methods including the use of unique identification numbers and a carefully designed computer Information Management System (IMS) that provide security for personal identifying information. For example, only unique identification numbers, without personal identifiers, will be used for all biologic specimens collected and all information derived from those specimens. Data that can be used to link the specimens collected from an individual to other data obtained from that individual will be protected by the IMS.

Specific data elements to be collected within the NCS have ramifications for confidentiality and will be addressed specifically in the Data Access and Confidentiality plan. Genome-wide scans conducted on NCS specimens will be considered personally identifiable information and treated as such. Some biologic analyses (e.g., HIV status, exposure to specific toxins), results of some mental heath screening tests, and reports of abuse are also considered sensitive.

The NCS protocol has received initial approval from the Human Subjects Review Boards at NICHD (contingent upon receiving the final Consent documents) and the Coordinating Center (Westat) (Appendix C.12). The protocol is also under review at each of the participating Vanguard Centers and, as needed, will receive review by local hospitals and other medical institutions.

A.11 Justification for Sensitive Questions

There are a number of questions contained in NCS questionnaires that could be considered sensitive by certain women. 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 pilot study 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. Only women with a high likelihood of pregnancy, or pregnant women whose due date is after a specified cutoff date in each PSU will be eligible to enroll. Therefore it is necessary to ask questions about behaviors related to likelihood of pregnancy (e.g. use of birth control if respondent is sexually active) Women will be provided the option of answering these questions using audio computer-assisted interviewing (A-CASI) techniques with headphones to listen to the questions being asked. She will enter her answers directly into the computer, and no one will be able to hear the questions or the responses.

Using in-person and telephone interview, other potentially sensitive questions will be asked. For the most sensitive questions asked during in-person visits (domestic violence, wantedness of pregnancy, use of medications not prescribed by a doctor, income), a computer assisted self-interview module will be developed and the participant will be offered the use of headphones for listening to the questions in private, if desired. All questions are directly related to the Study hypotheses. Participants' comfort with and willingness to answer these questions will be evaluated, based on experiences encountered during this Pilot Study.

A.12 Estimates of Hour Burden Including Annualized Hourly Costs

NICHD is requesting approval for the NCS Pilot Study at the seven Vanguard Centers. Data collection activities will include household enumeration, pregnancy screening, consent, in-person, telephone and self-collected questionnaires, physical measures, and collection of biospecimens and environmental samples from selected participants. Burden estimates including annualized hourly costs for the first three years of pilot data collection (for births in the Vanguard Center PSUs through June, 2010) are shown in Table A-1 and A-2. A detailed breakout of the burden estimates for each Study visit is shown in the Itemized Burden Estimate.

Table A-1: Estimated Annual Hour Burden based on three year totals

Types of Respondents (estimated hourly rate)	Estimated number of respondents	Estimated Number of Responses per Respondent	Average Burden Hours Per Response	Estimated total annual burden hours
Household activities ($12/hr)				
Household enumeration	76,911	0.33	0.08	2051
Eligibility screening	45,316	0.33	0.08	1208
Preconception activities ($12/hr)				
High probability women – with pre-pregnancy visit	380	1.7	0.93	577
High probability women – without pre-pregnancy visit	3737	0.67	0.08	199
Moderate prob, women	5,500	1	0.08	458
Low probability women	3,578	0.33	0.08	95
Pregnancy activities – women ($12/hr)	954	7	0.62	4134
Birth activities – mothers & children ($12/hr)	912	2	0.38	684
Postnatal activities – mothers & children ($12/hr)	893	4	0.81	2887
Fathers ($12/hr)	954	2	0.72	1370
Health care providers ($90/hr)	500	0.33	0.05	8
Community leaders ($75/hr)	500	0.33	0.05	8
Child care providers ($25/hr)	364	0.33	1.00	121
Total	79,229*	----------	----------	13,800

* Total number of respondents is less than the sum of the column since the mothers will be identified in the household enumeration and screening.

Table A-2: Estimated Cost Burden based on three year totals

Data Collection Activity	Years 1 - 3 (Jan. 2009 – Dec. 2011)		
	Total Number of Respondents	Total Hour Burden	Total Respondent Cost*
Screening Activities			
Household Enumeration	76,911	6,153	$73,836
Pregnancy Screening	45,316	3,625	$43,500
Neighbor Report	7,691	385	$4,620
Preconception Activities			
P1 Visit	380	1,140	$13,680
P1 SAQs and Self-Collections	380	380	$4,560
P1 Pickup Visit	380	190	$2,280
High Probability Phone Calls	8,194	1,311	$15,732
Moderate Prob. Phone Calls	5,500	1,320	$15,840
Low Probability Phone Calls	3,578	286	$3,432
Pregnancy Activities			
T1 Visit (mother)	954	2,862	$34,344
T1 Visit (father)	954	954	$11,448
T1 SAQs & Self-Collections	954	954	$11,448
T1 Pickup Visit	954	477	$5,724
1st Trimester Ultrasound (if needed)	477	716	$8,592
16-17 wk Phone Call	1106	554	$6,648
T3 Visit	920	2760	$33,120
T3 SAQs and Self-Collections	920	920	$11,040
T3 Pickup Visit	920	460	$5,520
36 wk Phone Call	865	432	$5,184
Birth-Related Activities			
B1 Visit	912	684	$8,208
B2 Visit	730	547	$6,564
B2 SAQs	730	547	$6,564
Post-Natal Activities			
1 mo. Visit	182	136	$1,632
1 mo. SAQs	182	92	$1,104
3 mo. Phone Call	893	513	$6,156
6 mo. Visit	875	2625	$31,500
6 mo. SAQs	875	875	$10,500

Table A-2: Estimated Cost Burden based on three year totals (cont'd)

Data Collection Activity	Years 1 - 3 (Jan. 2009 – Dec. 2011) – cont'd		
	Total Number of Respondents	Total Hour Burden	Total Respondent Cost*
Pregnancy Activities (cont'd)			
9 mo. Phone Call	857	428	$5,136
9 mo SAQs	857	428	$5,136
12 mo. Visit	745	2235	$26,820
12 mo. Dad Visit	745	745	$8,940
12 mo. SAQs	745	745	$8,940
12 mo. SAQs	745	745	$8,940
18 mo. Phone Call	724	362	$4,344
18 mo. SAQs	724	362	$4,344
24 mo. Phone Call	200	100	$1,200
24 mo. self-collected samples	200	100	$1,200
Community Activities			
Health Care Provider Questionnaire	500	25	$2,250
Community Leader Questionnaire	500	25	$1,875
Child Care Provider Activities			
Phone interview with provider	364	364	$9,100
Totals (Year 1 - 3):		41,424	$505,345
Annualized total estimates	----------	13,808	$168,448

* Respondent cost based on the estimated hourly rates for each respondent type listed in Table A-1

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. During pregnancy, participants will be asked to have ultrasounds during each trimester. The study will pay for these tests, and there will be no cost to the participant. There are no other known costs to study participants.

A.14 Annualized Cost to Federal Government

Based on the proposed study budget, the estimated overall cost to the Federal Government for pilot activities during the period of this three-year submission is $105 million. Thus, the annualized cost to the Federal Government is $35 million. The projected costs and budget for the Vanguard Pilot of the NCS have not changed since the first submission to OMB. The overall projected cost for the full Study remains at $3.2 billion to completion unadjusted for inflation.

However the field Vanguard Pilot will provide valuable information for more accurately projecting full study costs.

A.15 Explanation for Program Changes or Adjustments

There are no program changes or adjustments—this is a new data collection.

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

The timetable for the data collection for the NCS Pilot Study cohort is shown below in Table A-3.

Table A-3: Pilot Data Collection Timetable

January 2009	Enrollment of eligible women and first preconception and first trimester visits begin
July 2009-June 2010	Pilot cohort births
July 2009	1-mo. visits begin
October 2009	3-mo. phone calls begin
January 2010	6-mo. visits begin
March 2010	9-mo. phone calls begin
July 2010	12-mo. visits begin
January 2011	18-mo. visits begin
July 2011	24-mo. visits begin

There are no plans to merge data from the Pilot Study cohort with the data for participants in the Main Study. Data from the Pilot Study cohort will be analyzed primarily to determine the effectiveness and acceptability of study procedures and materials as described in Section A.2.

Data generated from this initial Vanguard Pilot will not be publicly released. The collection of these data is designed to inform the procedures and instruments to be used in the Main Study and will not be incorporated into the final national probability sample. While the Vanguard Pilot data will receive vigorous use within the NCS, the sample size does not enable analysis of the research topics set forth in the Study's hypotheses.

Some individual-level data with clear clinical relevance will be routinely returned to Study Participants. These data include blood pressure and anthropometric measurements, for which well-established reporting guidelines, such as those used in NHANES, will be followed. However, for many potential analyses of biologic or environmental samples, the use of common concepts such as "clinically relevant" and "actionable" to define policies have limited application in the NCS due to the unknown relevance of many exposures (e.g., "actionable" levels of many chemicals, such as pesticides, are unknown). Importantly, many of the planned analyses of the Vanguard Pilot specimens and samples will not occur immediately after collection, further complicating the determination of "clinical relevance".

Proposals for delayed analysis of stored specimens and samples will be reviewed by a Sample Oversight committee to assure they are consistent with the mission of the NCS Vanguard Pilot, such as stability testing of analytes. As suggested by the NAS Panel, the current policy of the

NCS is to have reporting decisions reviewed on a case-by-case basis by a Data Safety Monitoring Board. Criteria for such decisions, and the specific responsibilities and the Sample Oversight Committee and the Data Safety Monitoring Board are being developed and center on the concepts discussed above. This will remain an important issue throughout the course of the Study.

The NCS uses a clustered sample design that is important for a number of reasons, including the efficiency it brings to the data collection process for sampling births that are essentially rare events. The second stage of sampling is the selection of segments and canvassing the households in these segments to identify pregnant women. As a result, it is impossible to suppress the general nature of the segments from those in the sampled areas. For example, a person in the study may be able to infer that the people in the same block or apartment building are likely to be in the study, but there is no direct way for them to confirm this possibility. Those providing proxy information know that the household in question is within the segment, but they do not know whether the household has decided to participate in the study. Medical providers are the only others who might be able to determine the segment boundaries because they will be asked to help encourage eligible women (pregnant women living in the sampled segments) to participate in the study. Protocols for this referral procedure will vary by Vanguard Center and require approval by the NCS Program Office. Other individuals, including day care providers, are not to be informed about segment boundaries.

The Vanguard Center in each location has responsibility for controlling the release of information on the boundaries for the segments in the NCS. Three basic features must be considered when contemplating the release of information on the sampled segments within a site. The first is the need to share this information, the second is the level or specificity of information to be shared, and the third is the set of restrictions to be imposed on the person obtaining the information. The release of the information on the segments will only be permitted when this release meets a specific purpose that provides a critical benefit to the study. The release of the information on the segments will also be at the highest confidentiality level (least specificity) that satisfies the specific need. In addition, any agent who collects data or has access to data about a study subject must abide by the standard restrictions on federal government data collection activities. The sites must prepare a plan for release of information on segment boundaries and submit it to the NCS Program Office, who will approve the plan.

The NCS Data Access and Confidentiality Committee, the Disclosure Review Board, the NCS Publications Subcommittee, and the NCS Steering Committee (comprising the Principal Investigators from each Center) all have central roles in ensuring that study participants' data are appropriately protected. The Data Access and Confidentiality Plan (distributed under separate cover) describes the overall NCS confidentiality and security plan and the roles of each of those entities.

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." of OMB Form 83-I

NCS is not requesting any exceptions from OMB Form 83-I.