REQUEST FOR OMB CLEARANCE

CONTINUATION OF NATIONAL CHILDREN'S STUDY VANGUARD (PILOT) STUDY DATA COLLECTION: STUDY VISITS THROUGH 60-MONTHS AND SIBLING BIRTH ENROLLMENT

PART A ONLY

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The National Children's Study (NCS) is submitting a complex request. The NCS and OMB have agreed on a staged approval. The first approval will cover the conceptual basis for full suite of new visits and design elements, however only some of new Information Collections (ICs) are ready to be fielded. As described below, NCS anticipates additional streamlining of the remaining components. Such changes will be submitted to OMB as non-substantive changes given that public notice has already been obtained on the full suite of new visits and design elements described in this package, and the draft ICs have been uploaded as part of the initial submission.

Specifically, the initial approval only covers fielding a subset of activities included in the full clearance package. They are:

- Establishment of new Study Visits at 36 and 42 months;
- Approval of revisions to the previously established 30 Month Study Visit;
- Alignment of NCS protocol across all Study Locations, including the conduct of previously approved biospecimen and environmental sample collections;
- Approval of Child- and Adult-focused questionnaires to be used if a death occurs; and
- Continuation of previously approved Study Visits (Birth through 24 Months).

Following an initial approval, the NCS will submit additional requests as non-substantive changes to finalize the following:

- Establishment of new Study Visits at 48, 54, and 60 Months;
- Enrollment of a new cohort of babies born to already enrolled mothers;
- Revision of previously established Study Visits (Pre-Pregnancy through 24 Months);
- Revision of informed consent documentation;
- Approval of a new instrument designed to measure participant engagement and motivation; and
- Conduct of methodological studies related to participant incentives.

The table below describes NCS plans for requesting clearance.

Study Visits are noted as either "Previously Established," "Revision to Previously Established," or "New." Included within each Study visit is a series of questionnaires; direct collection of samples, specimens and physical measurements; and scored assessments. Each measurement type is labeled as "Revised," "Previously Approved" (within the NCS), "New," or approved in an earlier stage of clearance. Detailed descriptions of specific measures and assessments contained within each Study visit are shown in Attachments 2 and 5.

Stage 1, highlighted in brown, requests the continuation of already established data collection events (age-defined Study Visits or trigger-based collections) and all associated instruments protocols and consent documents; revision to the previously approved 30 month Study Visit, and establishment of new Study Visits at 36 and 42 months.

Stage 2, highlighted in green, seeks approval for revisions to previously established data collection events (3 months – 24 months), and new Study Visits at ages 48, 54, and 60 months. The NCS also requests approval of revised Informed Consent documentation. Approvals granted under Stage 1 will also be continued under Stage 2.

Stage 3, highlighted in blue, requests continuation of protocols approved under Stages 1 and 2, and the introduction of a Sibling Birth Cohort. Study Visits, instrumentation and protocols related to the Sibling Birth Cohort are associated with revisions to previously established data collections (Pre-Pregnancy through Birth).

	Planned OMB Review Stage 1	Planned OMB Review Stage 2	Planned OMB Review Stage 3
Data Collection Events			
Pre-Pregnancy			**Revision to Previously Established Visit – Revised Instrumentation**
Questionnaires			Revised
Samples/Specimens/Measurements			Previously Approved in NCS
Scored Assessments			—
Pregnancy Visit 1			**Revision to Previously Established Visit – Revised Instrumentation**
Questionnaires			Revised
Samples/Specimens/Measurements			Previously Approved in NCS
Scored Assessments			Previously Approved in NCS
Pregnancy Visit 2			**Revision to Previously Established Visit – Revised Instrumentation**
Questionnaires			Revised
Samples/Specimens/Measurements			Previously Approved in NCS
Scored Assessments			—
Birth Visit			**Revision to Previously Established Visit – Revised Instrumentation**
Questionnaires			Revised
Samples/Specimens/Measurements			Previously Approved in NCS
Scored Assessments			—
3 Month Visit	Continue Previously Established Visit	**Revision to Previously**	Continue Stage 2 Approved Version

	Planned OMB Review Stage 1	Planned OMB Review Stage 2	Planned OMB Review Stage 3
	with Approved Instrumentation	**Established Visit – Revised and New Instrumentation**	(planned)
Questionnaires		Revised	
Samples/Specimens/Measurements		—	
Scored Assessments		New	
6 Month Visit	Continue Previously Established Visit with Approved Instrumentation	**Revision to Previously Established Visit – Revised and New Instrumentation**	Continue Stage 2 Approved Version (planned)
Core Questionnaires		Planned approval in Stage 1	
Age-Specific Questionnaires		Revised	
Samples/Specimens/Measurements		Previously Approved in NCS & New	
Scored Assessments		New	
9 Month Visit	Continue Previously Established Visit with Approved Instrumentation	**Revision to Previously Established Visit – Revised and New Instrumentation**	Continue Stage 2 Approved Version (planned)
Core Questionnaires		Planned approval in Stage 1	
Age-Specific Questionnaires		Revised & New	
Samples/Specimens/Measurements		—	
Scored Assessments		—	
12 Month Visit	Continue Previously Established Visit with Approved Instrumentation	**Revision to Previously Established Visit – Revised and New Instrumentation**	Continue Stage 2 Approved Version (planned)
Core Questionnaires		Planned approval in Stage 1	
Age-Specific Questionnaires		Revised & New	
Samples/Specimens/Measurements		Previously Approved in NCS	
Scored Assessments		New	
18 Month Visit	Continue Previously Established Visit with Approved Instrumentation	**Revision to Previously Established Visit – Revised and New Instrumentation**	Continue Stage 2 Approved Version (planned)
Core Questionnaires		Planned approval in Stage 1	
Age-Specific Questionnaires		Revised & New	

	Planned OMB Review Stage 1	Planned OMB Review Stage 2	Planned OMB Review Stage 3
Samples/Specimens/Measurements		—	
Scored Assessments		Previously Approved in NCS & New	
24 Month Visit	Continue Previously Established Visit with Approved Instrumentation	**Revision to Previously Established Visit – Revised and New Instrumentation**	Continue Stage 2 Approved Version (planned)
Core Questionnaires		Planned approval in Stage 1	
Age-Specific Questionnaires		Revised	
Samples/Specimens/Measurements		New	
Scored Assessments		Previously Approved in NCS	
30 Month Visit	**Previously Established Visit – Revised Instrumentation**	Continue Stage 1 Approved Version (planned)	Continue Stage 1 Approved Version (planned)
Core Questionnaires	Revised		
Age-Specific Questionnaires	Previously Approved in NCS		
Samples/Specimens/Measurements	—		
Scored Assessments	Previously Approved in NCS		
36 Month Visit	**New Visit**	Continue Stage 1 Approved Version (planned)	Continue Stage 1 Approved Version (planned)
Core Questionnaires	Revised		
Age-Specific Questionnaires	New		
Samples/Specimens/Measurements	New		
Scored Assessments	New		
42 Month Visit	**New Visit**	Continue Stage 1 Approved Version (planned)	Continue Stage 1 Approved Version (planned)
Core Questionnaires	Revised		
Age-Specific Questionnaires	New		
Samples/Specimens/Measurements	—		
Scored Assessments	New		
48 Month Visit		**New Visit**	Continue Stage 2 Approved Version (planned)
Core Questionnaires		Planned approval in Stage 1	
Age-Specific Questionnaires		New	
Samples/Specimens/Measurements		New	
Scored Assessments		New	
54 Month Visit		**New Visit**	Continue Stage 2 Approved Version (planned)
Core Questionnaires		Planned approval in Stage 1	
Age-Specific Questionnaires		New	
Samples/Specimens/Measurements		—	
Scored Assessments		New	

	Planned OMB Review Stage 1	Planned OMB Review Stage 2	Planned OMB Review Stage 3
60 Month Visit		**New Visit**	Continue Stage 2 Approved Version (planned)
Core Questionnaires		Planned approval in Stage 1	
Age-Specific Questionnaires		New	
Samples/Specimens/Measurements		New	
Scored Assessments		New	
Trigger-Based Events (New)	**New ICs**	Continue Stage 1 Approved Version (planned)	Continue Stage 1 Approved Version (planned)
Secondary Residence Questionnaire	New		
Parent-Caregiver Death Interview	New		
Child Death Interview	New		
Interviewer Observation Questionnaire	New		
Trigger-Based Events (Previously Established)	Continue Previously Established IC with Approved Instrumentation	Continue Stage 1 Approved Version (planned)	Continue Stage 1 Approved Version (planned)
Pregnancy Loss, Stillbirth & Neonatal Death			
Non-Interview Respondent Questionnaire			
Validation Interview			
Sibling Birth Cohort			**New ICs**
Screener			New
Retrospective Pregnancy Questionnaire			New
Informed Consent	Continue Previously Established IC with Approved Instrumentation	**Revision to Previously Approved Instrumentation**	Continue Stage 2 Approved Version (planned)
Methodological Experiments			**New ICs**

A. Justification

Overview

The National Children's Study (NCS) requests approval to continue Vanguard Study data collection activities. The NCS Vanguard (Pilot) Study (OMB #0925-0593) was approved by the Office of Information and Regulatory Affairs within the Office of Management and Budget with an expiration date of 8/31/2014. The purpose of the Vanguard Study is to assess the feasibility, acceptability, and cost of the recruitment strategy, study logistics and operations, and study visit assessments that will be used later in the NCS Main Study.

This Information Collection Request (ICR) serves as a formal request for renewal and revision to a currently approved study. The Vanguard Study has yielded valuable data and field experience related to participant recruitment, the conduct of Study assessments, and operational requirements associated with NCS infrastructure and field efforts. The objective of the proposed data collection is to obtain

further operational and performance data on processes and administration of new and revised Study visit measures. The ICR also covers other important requests, including initiating a new cohort to be enrolled and the initiation of methodological substudies.

A.1 Circumstances Making the Collection of Information Necessary

a. Legislative Mandate

The President's Task Force on Health Risks and Safety Risks to Children recommended in 1999 that a large study to define the actual risks associated with broad environmental exposures is the critical first step in addressing the potential risk factors that may affect the health and development of children in the United States (US). Following the recommendation of the task force, Congress passed the Children's Health Act of 2000 (Public Law 106-310) which authorized the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) to conduct a national longitudinal study of environmental influences on children's health and development. These environmental influences include physical, chemical, biological, and psychosocial aspects.

As stated, by law, the Children's Health Act of 2000 (Sec. 1004) states that the Director of the NICHD shall establish a consortium of representatives from appropriate Federal agencies to plan, develop, and implement a prospective cohort study, from birth to adulthood to fulfill two main purposes justifying the collection of information:

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."
2. "Investigate basic mechanisms of development disorders and environmental factors, both risk and protective, that influence health and development that influence health and developmental processes. "

The prospective cohort study, termed the National Children's Study [NCS], is expected to include three research imperatives justifying the collection of information (*italics added*):

A. "Incorporate behavioral, emotional, education, and contextual consequences *to enable a complete assessment* of the physical, chemical, biological and psychosocial environmental influences on children's well-being."
B. "Gather data on environmental influences and outcomes on *diverse population* for children, which may include the consideration of prenatal exposures."
C. "*Consider health disparities* among children which may include the consideration of prenatal exposures."

b. Purpose of Vanguard (Pilot) Study

The NCS Vanguard (Pilot) Study (OMB #0925-0593) was approved by the Office of Information and Regulatory Affairs within the Office of Management and Budget with an expiration date of 8/31/2014. The purpose of the Vanguard (Pilot) Study is to assess the feasibility, acceptability, and cost of the recruitment strategy, study logistics and operations, and study visit assessments that will be used in a second component, the NCS Main Study. "Feasibility" assessment refers to technical performance and reliability. "Acceptability" refers to the impact on the study participants and overall study infrastructure. "Cost" refers to the level of effort, personnel, resources, and money involved in a study development and implementation. Additional substudies and methodological research projects will inform future NCS

design and activities. The NCS Main Study will run in parallel with the NCS Vanguard (Pilot) Study. The Main Study design is being informed by the experience obtained in the NCS Vanguard Study, substudies and methodological research projects.

c. Purpose of this Submission

The National Children's Study requests approval to continue data collection activities for the Vanguard Study. No activities related to the Main Study are included. This Information Collection Request (ICR) serves as a formal request for renewal of the Vanguard Study clearance. It also covers several other important requests, including initiating a new cohort to be enrolled, revisions to the NCS protocol with both new and revised Study visits, and the initiation of methodological substudies.

Further detail can be found in A.2 (Purpose and Use of the Information Collection) and B.2 (Procedures for the Collection of Information).

d. History of the NCS Vanguard (Pilot) Study Data Collection Activities

Approval to conduct recruitment activities in seven NCS Vanguard Study locations was given by OMB/OIRA in September 2008. Data collection began in what became known as the Initial Vanguard phase using an area probability design normalized to an estimated 250 births per year and door to door recruitment. Subsequent approvals to test alternate recruitment strategies in additional Vanguard Study locations were granted in July 2010 and August 2012. To date, the NCS Vanguard Study has enrolled approximately 5,000 children in 40 Study locations.

A primary focus of the NCS pilot has been comparing alternative methods for identifying and recruiting participants. Multiple approaches were tested in conjunction with varying sampling strategies. Relying on an area probability design, the NCS tested several recruitment methods: a household-based approach; partnering with health care providers; and direct outreach. This phase, recruiting in an additional 30 Study locations, became known as the Alternate Recruitment Substudy (ARS). Based on the results of the approach using health care providers for recruitment, the NCS developed and implemented a modified approach in three additional Study locations to determine if further efficiencies could be gained by selecting a probability sample of providers as an alternative to the area probability design. This most recent phase became known as the Provider Based Sampling substudy.

The NCS continues to follow the children and families enrolled in the Vanguard Study, conducting Study visits in participants' homes and over the telephone. Data Collection visits may include the administration of questionnaires, neurodevelopmental assessments, physical measures, and the collection of biospecimens and environmental measures. In parallel with the earlier emphasis on recruitment approaches, the content of Study Visits varied by factors, such as geographic location, recruitment type, and operational considerations. The NCS Vanguard Study evolved to where the current priority is the alignment of Study visit content across participants to allow informed decisions regarding measures for consideration for the Main Study.

Operationally, the NCS Vanguard Study also evolved. Data collection was conducted under a decentralized model with data management occurring at each of the 40 Study locations. As of the fourth quarter of the 2013 calendar year, these functions were regionalized with four organizations each managing activities at ten locations. This new approach is intended to increase operational efficiencies, promote consistency, and improve data quality.

A.2 Purpose and Use of the Information Collection

The Vanguard Study continues to produce valuable data and field experience related to participant recruitment, the conduct of Study assessments, and operational requirements associated with NCS infrastructure and field efforts. The purpose of the proposed data collection is to obtain further operational and performance data on processes and administration Study visit measures.

A. Status of the NCS Vanguard Study

The NCS has enrolled approximately 5,000 children into the Vanguard Study. This cohort includes babies born across all recruitment periods (Initial Vanguard Study, Alternate Recruitment substudies, and Provider-Based Sampling substudy). An overview of Vanguard Study recruitment is available on the NCS public website as a Data Brief.[1] Detailed demographic information on the current cohort is also presented in Supporting Statement B (SSB) of this submission.

Re-consent of Enrolled Participants

As part of the transition from the use of local Study Centers to Regional Operations Centers (ROCs) for data collection, the NCS was required by the NICHD IRB to re-consent all participants that were monitored by local IRBs designated by the multiple field contractors and assign the NICHD IRB as the IRB of record. The re-consent was designed to again inform participants about the scope of the NCS and any new collections moving forward. This process does not negate any consent provided for earlier collections and is intended for prospective and not retrospective participation. As such, ROCs have been re-consenting participants in their Study Locations. This effort is close to completion with a re-consent rate of approximately 90 percent of all enrolled participants, including those with missing or limited contact information. Of participants that ROCs were able to successfully locate, the re-consent rate is approximately 98 percent.

All adult participants were administered the IRB and OMB approved version of the Informed Consent Form – New Adult or a parental permission form, as appropriate, all with information about sample collection and a signature page that indicates their choice about providing biospecimens and environmental samples. Participants in the Low-Intensity arm of the Direct Outreach strategy of the ARS were re-consented into the substudy and given six months to consider whether they would consent to being in the full NCS Vanguard Study, which would include Study visits that are conducted in-person as well as by phone. At the end of the six month period, these participants will be asked to provide consent to participate in the Study using the approved informed consent form or parental permission form appropriate for the participant type. As part of this ICR, the NCS provided modified informed consents and parental permission forms. These revisions were made to clarify and expand upon Study procedures. However, the NCS does not believe that these revisions necessitate or justify the burden of another re-consent process. Accordingly, the NCS is not planning to conduct an additional Study-wide re-consent process unless directed to do so by the NICHD IRB (In general, re-consent could be triggered in the future if the NCS Vanguard Phase protocol and/or informed consent materials have changed in ways that could affect participants' decisions about Study participation. The NICHD IRB determines whether re-consent or other notification of participants is required throughout the course of the Study.).

Subsequent re-consents will be targeted to newly identified respondents (on their own behalf or responding for the enrolled child). For example, re-consent will be required if a new respondent is

[1] http://www.nationalchildrensstudy.gov/newsandevents/databriefs/Pages/databrief_feb2014_no1.aspx

identified as the primary caregiver or legally authorized representative who provides consent for the child. Similarly, if approved to enroll subsequent births, selected NCS participants will be consented using the "Pregnant Woman" version. The NCS plans to continue the use of the "Reconsideration Script" during in-person Study Visits where samples and specimens are collected. Participants who previously declined to provide samples will be asked for their participation. If agreed, administration of the appropriate informed consent will be conducted. All Study Visits require the use of the Visit Information Sheet/Script to inform participants of what elements are included in specific visits and gain verbal, unrecorded permission to continue.

All proposed Informed Consent and parental permission documents are enumerated in SSB.

Attrition
As with any longitudinal study, attrition is a major concern of the NCS. Looking at participants enrolled during the Initial Vanguard and ARS phases, retention of women from enrollment to the Birth visit was 90 percent, and from enrollment to the 12 month visit was 74 percent. Please note that these data are from January 9, 2014 and do not include women enrolled in the Low-Intensity cohort of the Direct Outreach Strategy. Also note that some proportion of missed visits were the result of transitioning participants from local Study Centers to ROCs and the time required for data transfer. Detailed attrition information by demographic categories is presented in SSB.

B. Revisions to the NCS Vanguard Study Protocol

Vanguard Study Three-Year Plan
The NCS seeks approval to continue Vanguard Study data collection for the next three years. During this period, the NCS will conduct additional Study visits with enrolled children and their caregivers. The NCS also proposes enrolling up to 500 additional babies born to women whose children are already enrolled in the Study. As the NCS Vanguard Study cohort includes children from infancy to pre-school, this ICR includes revisions to established Study Visits and proposed new visits to accommodate the range of ages and developmental milestones.

This submission proposes establishing new Study Visits at the following ages:

- 36 month
- 42 month
- 48 month
- 54 month
- 60 month

The proposed Vanguard Study visit timeline reflects the need to pilot a "front-loaded" data collection schedule with the majority of visits occurring during the first five years of a child's life. Planned data collection is most intensive during early childhood because it is period of especially rapid change and a critical time for growth, development, and health.[2] In a span of a few years, humans change from helpless infants entirely dependent upon others to individuals who can move independently, exhibit complex problem solving and language skills, and interact with others in a positive and productive fashion.

[2] http://developingchild.harvard.edu/

Child growth and development is a dynamic and continuously changing process that nevertheless represents an orderly and predictable sequence of neurodevelopmental and physical growth. Extrinsic (caregiving style and personalities of parents and siblings, family economic status, cultural milieu) and intrinsic (genetic attributes, physical characteristics, state of wellness, temperament) influences exert themselves continuously upon this process, with resultant individual variation and unique developmental trajectories. These factors modulate the tempo and quality of developmental progress.

Developmental skills do not evolve in isolation but are interrelated. Development of normal social-emotional skills requires problem-solving, language, and fine motor skills. Fine motor development depends on developmental streams that include gross motor, cognitive, and visual perceptual skills. Conversely, infants are unlikely to be able to explore object details or practice manipulation of objects if they are concentrating on gross motor control to remain in a sitting position.

The ability to observe, measure, and follow over time these prodigious and exponential changes in motor function, language, cognitive, and social development requires frequent and thorough assessment. Early recognition of excursions from developmental norms requires identification and understanding of normal developmental patterns and their acceptable variations. Characterizing the sequence and rate of change of development is necessary to understand a child's total developmental progression while at the same time appreciating the patterns of development expected and achieved within individual developmental streams. The typical three year-old has a vocabulary of about 200 words, can pedal a tricycle, draw a person with two or three parts, and fears imaginary things. A typical six year-old has a vocabulary of about 10,000 words, can ride a bicycle, draw a 12- to 14-part person, and distinguishes fantasy from reality.

Ongoing collection of biospecimens and sources of potential environmental exposure also will be key during these years if the Main NCS Study data is to allow researchers to make causal inferences. Piloting these repeated measures in the smaller Vanguard Study will allow the NCS to make informed decisions about measures that warrant inclusion in the Main Study.

This NCS is always seeking to maximize the information collected while minimizing the burden on participants and families. As such, the NCS proposes to pilot the approach of alternating between in-person Study visits and telephone interviews, with comprehensive collections occurring at the 36, 48, and 60 month time frames. To promote participation, all visits during the Vanguard Study will be available in multiple modes to accommodate individual participants' schedules and preferences.

Detailed information on newly proposed visits and changes to established visits are provided below.

1. Alignment of NCS Vanguard Study Protocol across Enrolled Participants

As noted above, the NCS Vanguard Study has reached a stage where a critical examination of Study measures and associated operational logistics is needed. This is in contrast to our previous short-term focus on recruitment methodologies.

As a pilot, the NCS Vanguard Study affords a prime opportunity to fully test measures in advance of the Main Study and to assess individual data collection activities with respect to item nonresponse, timing and cost of training and administration, and outcomes. Therefore, to ensure sufficient data are collected to support the analysis of sub-groups, this protocol alignment will ensure that all enrolled participants will receive an identical protocol. While protocols will be defined for unique participant types (e.g., child, caregiver, or biological parent), all participants of a given type will be asked to

complete the same set of measures. This will hold true unless additional eligibility criteria exist such as age or gender of the participant or the measure is part of an experimental design where subsets of participants are assigned to specific treatment groups. Implementation will be through the use of core questionnaires and age-specific modules submitted with this ICR. Additional description is provided below.

The Vanguard Study will help the NCS assess factors that impact retention by eliminating any confounding issues related to visit content.

Standardization of Vanguard Study visits within participant types would occur for all Study visits newly established with this submission, as well as any revisions to existing Study visits. For revised Study visits, the protocol will be administered to participants eligible to complete the events. This change will only have an impact on upcoming Study visits. Participants who already completed a given Study visit will not be asked to take part in any collections that were not approved at the time they completed the visit.

The Vanguard Study is following enrolled children and caregivers recruited from 40 Study locations. However, current OMB approval only permits comprehensive data collection – including biospecimen and environmental sample collection – in 22 Study locations. Further, participants originally recruited into the Low-Intensity arm of the Direct Outreach Strategy were restricted to remote contacts only. To ensure that the NCS has the data needed to thoroughly examine all measures being considered for Main Study administration, all participants will receive the identical protocol. This is necessary to ensure that collection of all the data needed to thoroughly examine measures being considered for Main Study administration is complete. As a result of this alignment, all enrolled participants, regardless of their initial recruitment group, will be eligible to be administered the full NCS Study visit, including all questionnaires, assessments, physical measures, and collection of biospecimens and environmental samples. Participants will also no longer be restricted to specific modes or methods of data collection.

To ensure that all participants are fully informed about the scope of the Study and the content of specific Study visits, the NCS will administer the appropriate Visit Information Sheet at all Study visits (see Attachment 1, Informed Consent).

From an operational perspective the proposed data collection schedule – by promoting ongoing communication with participants - will also serve to minimize attrition, reduce the potential loss of important data, and decrease the numbers of cases needing substantial tracing and which may eventually be lost to follow-up. The proposed data collection schedule alternates between brief and more intensive Study visits every six months. This design allows us to balance the need for ongoing contact and information collection with management of participant burden and expectations. Additional information regarding NCS methods for maximizing engagement is detailed below.

2. Improving the Experience of NCS Vanguard Study Participants

The NCS is in the process of revising the structure of Study instrumentation and administration with the goal of improving participants' experience, reducing the length of in-person and telephone interviews, and offering greater flexibility for participating. Each improvement is designed to produce high response rates, greater retention over the long-term, and improvements in data quality and completeness. Revisions to instrument structure will be apparent in some but not all questionnaires and forms included in this submission. The NCS adopted a modular approach to the development of Study visits that continues and will become more standardized over time.

Beginning with this submission, whole instruments, or sections within instruments will be focused on a specific subject type or referent. This approach is intended to streamline the visit process going forward. For example, the Core questionnaire is now organized into three unique documents based on the referent (Child, Adult, Household). The Child Core questionnaire includes items with the child as the referent. Others are directed at the parent or primary caregiver's own experience and are asking the adult to report on themselves and not the specific enrolled child. Lastly, we ask questions that pertain to an entire household. These may be related to the physical structure of the living environment or about family-level demographics.

NCS Study visits often include questionnaires and assessments with differing referents and therefore require the participation of multiple respondents. Clearly defining the referent in advance allows data collectors to determine the required respondents and schedule Study visits in such a way as to reduce participant burden and promote flexibility. Operationally, this is critically important when managing cases with multiple caregivers and/or residences. Similarly, there are important questions that are routinely asked of NCS participants that could be administered in an alternate way that yields comparable outcomes but reduces overall burden. The choreography related to contacting and scheduling an upcoming NCS Study visit provides a useful illustration of how this process is operationalized under this ICR. When preparing to contact an enrolled NCS participant, the data collector will know the various respondent types required for specific Study instruments. Therefore, several critical steps can be completed during the scheduling contact: key respondents can be identified and/or confirmed; updated contact information on each can be collected; combined or individual appointments can be made with all required respondents; and the location(s) of home visits can be identified to accommodate situations where the enrolled child does not live full-time at a single residence. Choreographing these activities to occur during the scheduling contact will reduce the length of the actual visit and ensure that we have correctly identified the respondent needed to answer key questions. Components of a larger Study visit may now more easily be scheduled separately or conducted in varying modes. Instrumentation related to this specific process is detailed later in this section.

In keeping with existing NCS Vanguard Study procedures, the NCS requests that each visit (and associated instrumentation) be approved for multi-mode administration. To maintain high cooperation rates for Study visits, it is important to provide enrollees with multiple options to participate. Multi-mode data collection allows participants who are unable to schedule an in-person home visit to complete the majority of Study instruments associated with the visit either over the telephone, through mailed questionnaires, or via the web. The NCS recognizes that this may lead to increased item nonresponse for collections that require an in-person visit, but the retention of participants in the pilot phase is paramount. Similarly, there may be subgroups of participants who do not enjoy telephone interactions and prefer all visits to occur in person and the NCS requests the flexibility to accommodate such requests. The NCS will also benefit as understanding patterns of item and unit nonresponse and mode preferences over time will help us better refine our plans for the Main Study. Therefore, unless a measure or instrument requires a specific mode or method of administration (for example, in-person biospecimen collection), all instruments submitted as part of this ICR will be considered multi-mode.

NCS Study visit choreography continues to be refined to allow for greater flexibility and to reduce participant burden. Offering participants options is also key to maintaining response rates. For example, participant preferences are taken into account by allowing Study visits to be split across days and modes. Additionally, in-person visits at participants' homes may be designed to be administered by one or two data collectors. The addition of a second data collector allows for parallel data collection

with one administering questionnaires to a participant and the other collecting indoor or outdoor environmental samples. Administration time will vary based on how measures are administered, the mode of data collection, the number of data collectors, and participant response to individual question items.

The NCS is committed to limiting the actual time spent with a participant for the most comprehensive, in-person, home visit to no more than 4 hours with a target of two hours. This time includes any required administration of informed consent, all specimen and sample collection, and completion of interviewer-administered questionnaires. Prior to submission of any ICR, the NCS conducts timing tests of all instrumentation and procedures and refines Study visit choreography to ensure this standard is met. In this ICR, of the 18 proposed Study visits, two (36 and 60 month) may approach that limit over the three-year clearance period. Choreographed timings estimate the longest visits require between10 and 240 minutes to complete; with the variation dependent upon whether participants agree to sample collections, if new participants (for example, a new primary caregiver) require full administration of informed consent, or other case-specific issues.

While these two proposed Study visits are lengthy, previous Vanguard Study experience has demonstrated the willingness of participants to complete intensive data collection events. The NCS Vanguard Study protocol approved by OMB/OIRA on 8/31/2008 included pre-conception and pregnancy visits that were similar in scope and duration as what the NCS is now proposing. Study visits were conducted in-person at participants' homes, and included questionnaire administration, and extensive collection of biospecimens and environmental samples.

Between January 2009 and September 2010, participants who completed a pre-conception or prenatal Study Visit were asked to complete a "Participant Evaluation Questionnaire" to allow the NCS to better understand levels of engagement in the study. Out of the 1,532 women eligible to receive this instrument, the NCS received responses from 1,086 for a 71 percent response rate. A review of these data by demographic characteristics showed no statistically significant differences by age or marital status. Variation was seen across race, ethnicity, language and education. Specifically, white women were most likely to respond at 74 percent. Non-Hispanic women responded at 73 percent compared to 64 percent of Hispanic women. English speaking women responded at 72 percent compared to 61 percent of Spanish speaking women. Lastly, women with higher education were more likely to respond than others. When asked if the Study Visit was a positive experience, 97.4 percent reported it being either "somewhat positive" or "mostly positive."

These evaluation data show that the length of the pre-conceptional and pre-natal Study visits were not problematic among those who responded , with 65 percent of pregnant women and 90 percent of women trying to become pregnant reporting the length of the visit was "about right." Further combined analyses showed no evidence for nonresponse bias. Participants were asked about the length of the Study Visits and 71 percent of respondents noted that the length was "about right." The other response options included "a little too long" and "far too long." A review of demographic subgroups on the "about right length" estimate showed little or no deviation from the overall 71 percent. Specifically, the nonresponse (NR) adjusted estimates for this question are:

Demographic Dimension	Adjusted Overall Rate Estimate for "About Right Length" Accounting for Any Differential Nonresponse by Demographic Subgroup

Age	70.8%
Race	70.8%
Ethnicity	70.8%
Education	71.4%
Marital Status	71.0%
Language	71.0%

These results align with additional systematic and anecdotal sources of information. As part of ongoing quality improvement efforts the NCS established a set of collaborative improvement networks to examine methods and procedures and identify areas for refinement. One network, devoted to retention, examined the critical drivers that led to participant attrition, with the aim of identifying cases at risk before they are actually lost. Through an analysis of case management data, the group identified several factors that are most likely to be associated with participant loss. Predictive factors included mobility and the number of previous contact attempts required. There was no indication that the length of previous Study visits had any impact on subsequent participation levels. Lastly, field contractors received anecdotal feedback from participants when, to focus our resources on recruitment, the NCS switched to much shorter, less intensive interviews at the end of 2010. Some participants reported that they were happier with the lengthier collections as they felt they were making a greater contribution to the Study.

The NCS intends to analyze the impact of the proposed collections on unit and item nonresponse. Direct feedback will be solicited from participants regarding their experience in the Study which will further help refine future content development. Specifically, this ICR includes a revised "Participant Evaluation Questionnaire," now titled the "Participant Satisfaction SAQ," for administration at the 42 month Study Visit. Another new instrument – the "Participant Engagement and Motivation SAQ" is planned for the 48 Month Study Visit.

C. Establishment of New Study Visits

The NCS requests approval to establish and conduct new Study visits with Vanguard Study participants. Specifically, these new visits are designed to collect information on enrolled children ages 36 to 60 months. Visits will occur every 6 months, alternating between in-person and remote data collection. In-person visits will be administered when enrolled children are 36, 48, and 60 months of age. Remote data collection will occur at ages 42 and 54 months. This alternating schedule provides a balance for collection of biospecimens and environmental samples at key time points while still managing overall burden on participants.

The NCS seeks to collect detailed information on symptoms and experiences and not solely on known conditions. This strategy is to accommodate potential changes in diagnostic criteria over time, allowing end data users to assess health outcomes with more granular information, rather than reported diagnoses only. This holistic approach to information collection has been presented to NCS advisory groups and is the overarching paradigm being used by the NCS Health Measurement Network (HMN). The HMN is a collaborative effort across academic institutions and professional research organizations charged with the development and assessment of tools, instruments, methods, and assays that measure child health and well-being. All developed instruments and methods will be non-proprietary, portable, inexpensive, and easy for both administrator and participant to use. Once validated, these tools will be available to the larger research community free of charge.

The new visits included in this package (beginning with the 36 Month Study visit) are longer than the program's previous visits for three reasons: a) the initial set of visits was developed in the context of a focus on testing and comparing recruitment methodologies rather than study content; b) developmentally-appropriate diagnostic tools for the 36-60 month age group are somewhat longer; and c) multiple similar batteries are sometimes included in the same visit to provide data on which are likely to perform best in the NCS setting.

Proposed Study visits for the Vanguard Study include the following types of information collections (ICs): questionnaires, physical or anthropometric measurements, biospecimens, environmental samples, developmental assessments, and interviewer-completed questionnaires. The measures covered at each Study visit are provided in Attachment 2 ("New and Revised List of Instruments by Event") and item-level information is available in each specific instrument submitted with this ICR. Below are highlights of key components of the proposed Study visits, including collections and measures that are new to the NCS and have not been reviewed by OMB/OIRA or made available for public comment; measures that may be considered highly personal or sensitive; and measures refined to meet Departmental standards. Additional descriptions of all Study visits included in this ICR are provided in Attachment 4.

This ICR includes multiple collections using tools and assessments developed as part of the NIH Toolbox for the Assessment of Neurological and Behavioral Function (www.nihtoolbox.org). The development of the NIH Toolbox was led by Richard Gershon, Ph.D. at Northwestern University, and is designed to be a set of short assessments to measure emotional, cognitive, sensory, language, and motor function in children and adults ages 3 to 85 years. Intended inclusion of these assessments in the NCS was one of the drivers of this development effort. These assessments intend to evaluate function over time and across developmental stages; a necessary requirement for any longitudinal assessment. This submission represents the first opportunity to administer NIH Toolbox measures for inclusion in the 36-60 month Study visits. These measures are highlighted in the detail provided below.

1. Overview of the Thirty-Six (36) and Forty-Two (42) Month Study Visits

Each of the proposed NCS Study visits is intended to align with key periods in child development and assessments are intended to measure known developmental milestones. The scope of the assessments is based on the rate of development and the extent of the change during these time frames.[3] Broad categories describing these milestones include Social & Emotional; Language/Communication; Cognitive; and Movement/Physical Development.[4] The NCS is also measuring biological, environmental and social factors, categorized as General Health; Social Environment; and Physical Environment. These categories

[3] Developmental Milestones: Motor Development R. Jason Gerber, Timothy Wilks, and Christine Erdie-Lalena. Pediatrics in Review 2010; 31:267-277.
http://www.ncbi.nlm.nih.gov/pubmed/20595440

Developmental Milestones: Cognitive Development Timothy Wilks, R. Jason Gerber, and Christine Erdie-Lalena. Pediatrics in Review 2010; 31:364-367.
http://www.ncbi.nlm.nih.gov/pubmed/20810700

Gerber RJ, Wilks T, Erdie-Lalena C. Developmental milestones 3: social-emotional development. Pediatr Rev. 2011 Dec;32(12):533-6.
http://www.ncbi.nlm.nih.gov/pubmed/22135423

[4] http://www.cdc.gov/ncbddd/actearly/milestones/milestones-3yr.html

are mapped below to specific instruments, assessments and collections proposed for the 36 and 42 Month Study Visits.

Collection Type	Collection/Section Name	Target or Subject(s)	Milestone(s)	Study Visit(s)
Physical Measures	Anthropometry	Child	General Health	36M
	Blood Pressure	Child	General Health	36M
	NIH Toolbox Visual Acuity Test	Child	General Health	36M
Biospecimens	Blood	Child; Adult	General Health; Physical Environment	36M
	Urine	Child; Adult	General Health; Physical Environment	36M
	Saliva	Child; Adult	General Health; Physical Environment	36M
Environmental Samples	Vacuum Bag Dust	Household	Physical Environment	36M
	Dust Wipe	Household	Physical Environment	36M
Scored Assessments	Ages & Stages Questionnaire-3™	Child	Social & Emotional; Language/Communication; Cognitive; Movement/Physical Development	36M
	SWAN Rating Scale for ADHD	Child	Social & Emotional; Language/Communication; Cognitive	36M
	NIH Toolbox Early Childhood Cognition Battery	Child	Social & Emotional; Language/Communication; Cognitive	36M
	NIH Toolbox Emotion Battery	Adult	Social & Emotional;	42M
	Major Life Events	Adult	Social & Emotional; Social Environment	36M
Questionnaire - Core	Child Care/Day Care Arrangements	Child	Social Environment; Physical Environment	36M, 42M
	Viewing of Media/Reading	Child	Social & Emotional; Social Environment; Language/Communication; Cognitive; Movement/Physical Development	36M, 42M

Collection Type	Collection/Section Name	Target or Subject(s)	Milestone(s)	Study Visit(s)
	Program Participation/Receipt of Benefits	Child; Household	Social Environment	36M, 42M
	Health Insurance	Child	Social Environment	36M, 42M
	Health Care Utilization & Access	Child	General Health; Social Environment	36M, 42M
	General Health	Child; Adult	General Health; Social & Emotional	36M, 42M
	Medical Conditions – General	Child	General Health; Social & Emotional	36M, 42M
	Medical Conditions – Asthma & Eczema	Child	General Health	36M, 42M
	Well-Child Care/Vaccinations	Child	General Health	36M, 42M
	Emergency Room/Urgent Care Visits	Child	General Health	36M, 42M
	Hospitalizations	Child	General Health	36M, 42M
	Medications	Child	General Health	36M, 42M
	Sleep Routine	Child	General Health; Social Environment; Social & Emotional	36M, 42M
	Concerns about Child's Development	Child	Language/Communication; Movement/Physical Development ; Social & Emotional	36M, 42M
	Employment	Adult	Social Environment	36M, 42M
	Occupation	Adult	Physical Environment; Social Environment	36M, 42M
	Education	Adult	Social Environment	36M, 42M
	Housing Characteristics	Household	Physical Environment; Social Environment	36M, 42M
	Neighborhood Characteristics	Household	Physical Environment; Social Environment	36M, 42M
	Pesticide Use	Household	Physical Environment	36M, 42M
	Smoking in Home	Household	Physical Environment; Social Environment	36M, 42M
	Pets	Household	Physical Environment; Social Environment	36M, 42M
	Income	Household	Social Environment	36M, 42M
Questionnaire – Age Specific	Physical Activity	Child	Movement/Physical Development; General Health; Social Environment; Physical Environment	36M

Collection Type	Collection/Section Name	Target or Subject(s)	Milestone(s)	Study Visit(s)
	Noise Exposure	Child	Environmental Exposures; Social Environment; Social & Emotional	36M
	Toilet Training	Child	Movement/Physical Development; Cognitive; Social & Emotional	36M
	Sun Exposure	Child	General Health; Social Environment; Physical Environment	36M
	Race/Ethnicity	Child	Social Environment	36M
	Social Activities	Child	Social Environment; Social & Emotional; Cognitive	36M
	Risk & Safety Behaviors	Child	General Health; Social Environment; Physical Environment	36M
	Height	Adult	General Health	36M
	Weight	Adult	General Health	36M
	Alcohol, Tobacco, & Substance Abuse	Adult	Social Environment; General Health; Social & Emotional	36M
	Woman Abuse Screening Tool	Adult	Social Environment; Social & Emotional	36M
	Occupational/Hobby Exposures	Household	Physical Environment	36M
	Dietary Food Frequency	Child	General Health	42M
	Chronic Medical History	Adult	General Health; Social & Emotional	42M
	Family Medical History	Adult	General Health; Social & Emotional	42M
Interviewer Completed Questionnaires	Home Social Direct Observation	Child; Adult	Social Environment; Social & Emotional; Physical Environment	36M
	Indoor/Outdoor Dwelling Visual Observations	Household	Social Environment; Physical Environment	36M
Trigger-Based Questionnaires	Child Care Facility	Child	Physical Environment; Social & Emotional; Social Environment	36M
	Secondary Residence	Household	Social Environment; Physical Environment	36M, 42M

2. New Collections, Assessments, and Questionnaire Modules

The assessments and measures included in these subsections are all "new" to the NCS and have not been piloted in earlier phases. Once approved, these measures will be collected as part of at least one of the newly established Study Visits. Please note that several proposed assessments are collected at multiple Study Visits, including those previously established. Attachment 2 provides a tabular depiction of these collections as supporting documentation.

a. Additional Biospecimen Collection

Two new biospecimens are proposed for collection from NCS participants: microbiome swabs and deciduous teeth.

Microbiome Collection

Microbiome samples will be collected from all NCS children during the 6, 24, and 48 month Study visits and mothers during the birth, 6, 24, and 48 month Study visits. Current knowledge regarding the human microbial environment is limited and primarily based on data from adults. Understanding the source and evolution of the microbial environment in children and through the life course is a task only beginning to be addressed. Results of this collection will inform whether microbiome swabs will be incorporated into the Main Study.

The NCS microbiome collection methodology is modeled on the NIH Human Microbiome Project. The proposed measure was developed in consultation with Dr. Lita Proctor, National Human Genome Research Institute and project director for the Human Microbiome Project, and Dr. Kjirste Aagard-Tillery of the Baylor College of Medicine and principal investigator for an ongoing NCS formative research project on this collection. Final results of this project are not yet available; the NCS will make them available to OMB/OIRA when complete.

The NCS will pilot both interviewer and participant collection of the biospecimen. There are no additional eligibility criteria for participation in this collection and we anticipate high levels of cooperation (80 percent or higher) from participants in this collection in line with NCS experience collecting urine and vaginal swabs.

Swabs will be collected from children from the nasal, oral, and rectal cavities. Stool samples will be collected from children at the 24 month visit. A supplemental questionnaire will also be administered. In mothers, swabs will be collected during the birth visit from the oral, vaginal, and rectal cavities and then at 6, 24, and 48 months from the nasal, oral, and rectal cavities.

Shed Deciduous Teeth

Shed deciduous teeth will be collected from all NCS children at multiple time points beginning at the 60-month Study visit. Current knowledge and methods for identification and analysis of chemical exposures during fetal development is limited and is a critical focus of the National Children's Study.

Evidence suggests that chemical exposure during fetal development and the timing of such exposures may be evaluated through analysis of chemicals that have been incorporated into deciduous teeth, individual types of which have a set timetable of formation as part of fetal development. Therefore, analysis of deciduous teeth may provide an effective way to assess prenatal and potentially later chemical exposures. The collected data will be used to evaluate whether shed deciduous tooth collection is a measure that is technically feasible, acceptable to participants, and cost effective to justify incorporation into the Main Study.

The proposed measure was developed in consultation with Dr. David Caiman and Dr. Raymond Palmer of the University of Texas Health Science Center at San Antonio and Southwest Texas Oral Health Network. The NCS will utilize procedures and instruments developed by those researchers. This collection, and accompanying self-administered questionnaire, will be completed by the participant caregiver. Instructions on retrieval and shipment will be provided to participants during the 60-month Study visit with subsequent collections determined by schedule and frequency of individual tooth shedding. Postage-paid shipping materials will be provided to participants. Multiple collection points are required as teeth form at different times during fetal development and are shed at different times. Analysis of multiple teeth will provide information regarding the timing of different chemical exposures during fetal development. As with other NCS biospecimen collections, the NCS anticipates cooperation rates in excess of 80 percent.

Since the timing of individual tooth shedding will vary and cannot be aligned with NCS Study visits, the NCS requests approval to provide additional monetary incentives to participants. Incentives for biospecimen collection are needed to overcome perceived inconvenience, discomfort, or other negative experience associated with collection of biological samples. We propose to provide an additional $10 monetary incentive per shed deciduous tooth collected and shipped.

b. Environmental Sample Collection

NEW - Noise

The NCS proposes the addition of a new environmental collection as part of the NCS Vanguard Study; specifically to systematically measure noise levels at the enrolled child's home environment at the 36 and 60 month Study visits. As this is the initial attempt to evaluate this measure, the NCS will limit the collection to a random subset of Study locations. The sample size necessary is still being finalized, but for the purposes of this initial submission is estimated at approximately 600 NCS families. The proposed sample size is considered to be sufficient for this initial methodological test and was selected to ensure variation in participant location, family composition, and lifestyle activities that could affect instrument deployment and acceptance, and the results obtained.

Evidence has been accruing for over 30 years to indicate that young children are especially vulnerable to noise in their physical environment. Noise exposure has been associated with adverse health effects, manifested in the form of physiologic damage or psychological harm through a variety of mechanisms.[5] While increasing attention has been given to the health effects of noise in children, research is sparse and often the measure of exposure is limited to the proximity to a noise source.[6]

A primary source of noise exposure among young children is environmental noise, such as transient noise intrusions from the outdoors, (for example, airplanes, cars, trucks, construction, industry, or outdoor events) as well as indoor sources, (for example, television, music, appliances, and ventilation equipment). Some noises can arise from either outdoors or indoors (for example, sounds made by neighbors, talk, laughter, slamming doors, and noise from animals and barking dogs).[7] Despite this, the

[5] Seidman MD, Standring RT. 2010. Noise and quality of life. Int J Environ Res Public Health. Oct;7(10):3730-8. Epub 2010 Oct 19.

[6] Evans GW. 2006. Child development and the physical environment. Annual Review of Psychology, 57, 423-451.

focus of recent auditory effects studies in children has been on voluntary and not environmental exposures.

Noise may be an important exposure to children that can contribute to adverse health outcomes. While the principal health impact of loud noise is hearing loss, effects arising from lower noise levels may include hypertension, tachycardia, increased cortisol release, and increased physiologic stress.[8] [9] Recent studies have addressed non- auditory health effects of noise in children including reduced cognitive function, inability to concentrate, increased psychosocial activation, nervousness, and helplessness,[10] [11] but additional investigations are needed in young children to confirm and extend these findings over time.

Selected families will be asked to participate in this collection. With their consent, their homes will be equipped with a noise meter and measured for noise levels at various time intervals and data collectors will ask questions about the source and frequency of noise they encounter at home. To best integrate this pilot into the larger NCS protocol, data collection was scheduled to coincide with two proposed in-person visits and allow for variation in ages of the children.

The data will be used to evaluate the feasibility, acceptability, and cost required to deploy instruments, and to measure noise exposure in participants, including the placement of devices in homes, acceptance of the instruments by participants, and characterization of the location and duration of measurement.

c. Physical Measures

This ICR proposes to establish new NCS Vanguard Study visits to evaluate enrolled children between the ages of 36 and 60 months. These developmental windows allow the NCS to begin more comprehensive measurement of physical development and function. Below are five new NCS collections that fall within the physical measures domain. Each is important to test and evaluate in the NCS pilot to allow informed decisions to be made about the scalability and reliability of measures to consider for the Main Study. The first two measures discussed are proposed for only a subsample of enrolled NCS children, while the others will be administered to all participants as part of standard NCS data collection.

Bioelectrical impedance analysis (BIA)

The NCS proposes measuring body composition of children as part of the 48 and 60 month Study visits using bioelectrical impedance analysis (BIA). BIA is a non-invasive method for estimation of body

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[7] Omlin S, Bauer GF, Brink M. 2011. Effects of noise from non-traffic-related ambient sources on sleep: review of the literature of 1990-2010. Noise Health. Jul-Aug;13(53):299-309.

[8] Seidman MD, Standring RT. 2010. Noise and quality of life. Int J Environ Res Public Health. Oct;7(10):3730-8. Epub 2010 Oct 19.

[9] Ndrepepa A, Twardella D. 2011. Relationship between noise annoyance from road traffic noise and cardiovascular diseases: a meta-analysis. Noise Health. May-Jun;13(52):251-9.

[10] Schell LM, Gallo MV, Denham M, Ravenscroft J. 2006. Effects of pollution on human growth and development: an introduction. J Physiol Anthropol. Jan;25(1):103-12.

[11] World Health Organization-Joint Research Centre of the Commission. 2011. Report on "Burden of disease from environmental noise." http://www.euro.who.int/en/what-we-do/health-topics/environmental-health/noise.

composition including fat and fat-free mass. It is reported to yield more accurate measurements with less variability than those derived from skinfold measurements taken using calipers. An NIH Consensus Conference reported in 1994 that the amount of electric current used (< 1mAmp) is imperceptible, unlikely to stimulate the nervous system, and has not been reported to induce adverse events. The participant will be asked to step onto a scale-like device. The platform of the device has four sensors through which the imperceptible current passes. The impedance measurement is then used to calculate various measures of body composition, such as the percent of body fat and fat-free mass.

The software needed to produce these data has been developed for children as young as 5 years of age and at least one recent publication reported equations accurate in children as young as 2 years of age.[12] The sample size necessary for the NCS Vanguard Study is still being finalized, but for the purposes of this initial submission is estimated at approximately 200 NCS children. For comparison, conventional skinfold measurements using previously approved and implemented protocols will be collected.

This substudy is intended to evaluate the feasibility and acceptability of a two-electrode bioelectrical impedance body composition assessment in young children as part of a home study visit and evaluate its relationship to and potential to substitute for more conventional but more burdensome measurements of body composition. The selection of ages was determined to achieve the greatest possible age difference (between the first study visit age at which children reliably can be expected to stand independently for the measurement and the oldest available study visit age), to maximize ability to determine whether age related differences in feasibility and acceptability are observed. If successful, more accurate measurements of the physical antecedents of obesity will be available for inclusion in the NCS Vanguard and Main Studies.

Physical Activity (Accelerometer)

Beginning at the 36 month Study visit, the NCS will pilot a method to measure children's physical activity levels. The goal is to seek an objective, unbiased measure of physical activity of young children, as report of these measures by parents and caregivers are often subjective and potentially less informative than direct measures.

The sample size necessary for testing the accelerometers at three data collection points in the NCS Vanguard Study is still being finalized, but for the purposes of this initial submission is estimated at 600 NCS enrolled children using a protocol developed and tested by the National Health and Nutrition Examination Survey (NHANES). NHANES successfully measured physical activity in 3-4 year-old children with an 80% compliance rate. Additional data collection is needed in the NCS, because there is limited experience with measuring physical activity in young children and no longitudinal studies of physical activity measurement in young children to our knowledge. More study is needed to test accelerometer performance and ability to evaluate accelerometer data in a cohort of young children and the rate of change in children's physical activities (and the ability to measure it) as they grow older. This collection will help the NCS understand the feasibility to deploy these instruments in 3 year old children and to capture informative data about their physical activity; the acceptability of this measurement to participants in terms of compliance burden and to technicians in terms of burden associated with instrument deployment and retrieval; data transmission; and the cost of the instruments and the resources required to deploy and retrieve the instruments and to transmit the acquired data.

[12] Rush, E., Bristow, S., Plank, L., & Rowan, J. (2012). Bioimpedance Prediction of Fat-Free Mass from Dual-Energy X-Ray Absorptiometry in a Multi-Ethnic Group of 2-Year-Old Children. *European Journal of Clinical Nutrition:* 1-4.

While some research questions addressed here could be assessed independently within a single data collection period by collecting data at intervals over a longer period physical activity changes over time for specific age groups can be measured. These data may provide information about the changes in location and duration of physical activities at these locations. Likewise, factors that may influence opportunities for physical activity such as ethnicity, residential location, or household composition may be identified in this study.

Power analysis suggests that a 'complete' sample of 600 3-year-olds participating for 3 consecutive years (that is, for a total of 3 annual physical assessments done per child) would have 80% power or better to detect many of the effects of interest, where 'complete' means no children are lost to follow-up and no children have unusable accelerometer or GPS data. However, when we factor in an attrition rate of 10% loss per year and a non-compliance rate of 25% per year (for wearing both the accelerometer and GPS devices as instructed), the sample size would need to be more than doubled (that is, more than 1200 children) to be assured of 600 children with 3 annual assessments each. For logistic reasons (primarily to alleviate workload in the first year of study accrual), we propose to enroll 875 3-year-olds in the first year and follow them at 4 and 5 years old, and to enroll an additional 725 4-year-olds in the second year and follow them at 5 years old (hence a potential total of 1600 children monitored at ages 4 and 5). As there are approximately 5,000 children enrolled in the Vanguard phase, there should be sufficient children for the study analyses.

Participants will be asked to wear the waterproof Actigraph GT3X-plus physical activity monitor on their wrist continuously for a 7-day period and the GPS data logger on an elastic waistband for seven days when not bathing or sleeping. Participants will be fitted with monitors at the home study visits and parent/care providers will be given instructions regarding operation of the devices. After the 7-day period is over, participants will mail the monitors in the postage-paid envelope provided to their ROCs. Once the monitors have been returned, a check for $25 will be mailed to the participant as a token of appreciation for their time. The NCS believes the additional monetary incentive is required to get an adequate response and ensure sufficient data is collected from this small group of participants.

Pulmonary Function

The pulmonary function of NCS children will be assessed during the 60 month Study visit. This will allow collection of accurate information on the respiratory status of each child. Obstructive airway disease is an outcome of interest for the Study making accurate assessment of respiratory status critical. Additionally, as exposure data are collected on each child comparisons can be made to their lung function. Pulmonary function will be measured through spirometry, a simple, non-invasive method which has been found to be appropriate for children as young as 60 months.[13] This technique will measure the child's Peak Expiratory Flow (PEF) and Forced Expiratory Volume in one second (FEV1).

NIH Toolbox Early Childhood Motor Battery

Research findings suggest exposure to heavy metals and other industrial contaminants impairs children's motor skills. The NCS seeks to investigate the long-term impacts of early environmental exposures by testing a battery of direct child assessments related to motor skills. A component of the proposed NIH Toolbox is the Early Childhood Motor Battery at the 60 month Study visit. It is imperative to have direct assessments of motor skills to supplement indirect assessments of children's abilities rather than to rely exclusively on caregiver reports of children's outcomes. Administered to the NCS child by a trained data

[13] http://www.nhlbi.nih.gov/health/health-topics/topics/lft/types.html

collector, these measures directly assess strength, dexterity, endurance, and standing balance. Four specific tests are part of the battery including the Grip Strength Test, 9-Hole Pegboard Dexterity Test, 2-Minute Walk Endurance Test, and Standing Balance Test.

NIH Toolbox Visual Acuity Test

The NCS proposes assessing vision of the enrolled child at both 36 and 60 month Study visits. This assessment will allow the NCS to investigate the relationship between environmental exposures and physical outcomes. Using the NIH Toolbox Visual Acuity Test the NCS will directly assess vision by displaying items on a screen or flashcard for the child to identify.

d. Neurodevelopmental Measures

As part of this ICR, the NCS is proposing to measure cognitive and emotional function in children and adults. Several new tools are proposed and each is presented in detail below.

NIH Toolbox Early Childhood Cognition Battery

Exposure to heavy metals, such as lead, or other industrial contaminants is known to impair children's cognitive skills. It is imperative to have direct assessments of cognitive skills to supplement indirect assessments of children's abilities rather than to rely exclusively on caregiver reports of children's outcomes. Parents and other caregivers are likely to under or overestimate their children's true abilities, so direct assessment is key to maintaining data quality. The NCS proposes to collect such direct assessment on NCS children at two NCS Study visits, 36 and 60 months using the NIH Toolbox Early Childhood Cognition Battery. Four specific assessments of cognitive ability will be completed by the child independently using a computer, tablet, or other device. These include the Dimensional Change Card Sort Test, Flanker Inhibitory Control & Attention Test, Picture Sequence Memory Test, and Picture Vocabulary Test. These instruments measure attention, executive function, inhibitory control, working memory, and vocabulary. Multiple data collection opportunities will allow analysis of participant willingness to complete the assessments and ultimately to investigate long-term impacts of early environmental exposures.

NIH Toolbox Cognition Battery

Cognitive functioning of parents and caregivers will be assessed at the 48 month Study visit using the NIH Toolbox Cognition Battery. This tool allows for direct assessment of cognitive abilities such as attention, executive function, inhibitory control, working memory, reading, and vocabulary. Developed for administration to individuals ages 7 and above, this tool will allow the NCS to collect direct data on parents' abilities, and in turn, learn more about the child's social environment.

NIH Toolbox Parent Proxy Emotion Battery

Young children's emotional development is related to a broad range of later outcomes. For example, children who are "different" in some way or who suffer early abuse or are rejected in early childhood are more likely to be victims of bullying or to engage in delinquent behaviors later in life. It is important to assess the effects of young children's emotional development on later outcomes, for example social competence as a predictor of adjustment to and achievement in school, and to supplement outcome data we are collecting in other domains. The NCS will collect indirect measures of enrolled children's emotional development using the NIH Toolbox Parent Proxy Emotion Battery at the 48 month Study visit. The NIH Toolbox Parent Proxy Emotion Battery is a series of questionnaires the parent/caregiver completes about the child. This battery, recommended for parents/caregivers of children ages 3-12, includes measures of Positive Affect, General Life Satisfaction, Positive Peer Interaction, Social Withdrawal, Peer Rejection, Empathic Behaviors, Self-Efficacy, Perceived Stress, Fear, Sadness and

Anger. While it is important to include both indirect and direct assessments of children; parent proxy is needed at this age because young children cannot reliably self-report data on anger, fear, positive affect, peer interactions, etc.

NIH Toolbox Emotion Battery

Measurement of parental emotional function will occur as part of the Pregnancy Visit 1, 18, and 42 month Study visits using the NIH Toolbox Emotion Battery for Parent. This battery, designed for ages 8-85, includes measures of Psychological Well-Being, Social Relationships, Stress and Self-Efficacy, and Negative Affect. The Psychological Well-Being domain includes questions about pleasure, positive affect, life satisfaction, and meaning and purpose. The Social Relationships domain includes questions about emotional support, empathetic behaviors, friendships, instrumental support, loneliness, perceived hostility, and perceived rejection. The Stress and Self-Efficacy domain includes questions about perceived stress, self-efficacy, and coping strategies. The Negative Affect domain includes questions about anger, fear, sadness, and apathy. Each domain will provide important context to understand the home environment of children enrolled in the NCS. It will also allow for analytic opportunities to identify important correlations between parental emotional health and children's physical and developmental outcomes.

Autism Quotient Test for Children

Children enrolled in the NCS Vanguard Study will be assessed for autism during the 54 month Study visit using the Autism Quotient Test for Children (Cambridge University Behaviour and Personality Questionnaire for Children, developed by Simon Baron-Cohen). Given the increasing rates of autism, it is important to identify trends related to autism prevalence, and the NCS provides an opportunity to understand linkages between environmental exposures and autism. The Autism Quotient Test for Children is an indirect child assessment that is completed by the primary caregiver. It was selected for use in the NCS Vanguard Study after a comprehensive review of psychometric properties of prominent standardized questionnaires about autism. The Cambridge University measure offered the best balance of feasibility in the context of the NCS and it is non-proprietary. The NCS Vanguard Study will use this test to corroborate the identification of autism spectrum disorders. With the NCS environmental collections, researchers may determine possible linkages to early exposures.

Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Rating Scales (SWAN)

An indirect assessment of children for Attention Deficit Hyperactivity Disorder (ADHD) will be completed at the 36 and 60 month Study visits. We propose testing a short, self-administered assessment completed by a primary caregiver about the enrolled NCS child. It is important for the NCS to identify and understand any trends related to ADHD prevalence and any links between environmental exposures and this outcome. The Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Rating Scales (SWAN)[14] was evaluated and selected for inclusion in the Study. It is non-proprietary and scalable for the Main Study.

[14] Swanson, J. M., Schuck, S., Porter, M. M., Carlson, C., Hartman, C. A., Sergeant, J. A., Clevenger, W., Wasdell, M., McCleary, R., Lakes, K., & Wigal, T. Categorical and Dimensional Definitions and Evaluations of Symptoms of ADHS: History of the SNAP and the SWAN Rating Scales. *The International Journal of Educational and Psychological Assessment* April 2012, Vol. 10(1), 51-69.

e. Other Questionnaire Modules and Batteries

This section highlights additional new questionnaires or modules that are included in proposed NCS Study visits. These are highlighted for multiples reasons, including the need to adjust what the Study measures as children age or response to new to regulatory requirements.

Physical Environment of the Secondary Residence

The prevalence of children whose time is divided between multiple residences has increased over the past decades. This trend may be the result of the dissolution of a marriage or other relationship, or the use of home-based childcare with another family member. To effectively measure residential exposures of enrolled children, the NCS must first determine whether the child has a secondary residence and, if so, collect exposure information related to that residence. The process of identifying a secondary residence will be standardized and included in our revised Participant Verification and Tracing instrument (described in detail in Section A2B4 below). As secondary residences and the associated NCS respondent are identified, we will administer a newly developed questionnaire assessing the Physical Environment of the Secondary Residence. This instrument was designed to be consistent with the items collected on the primary residence during earlier Study visits and will be administered as we identify additional residence(s) for the enrolled child.

Women Abuse Screening Tool (WAST)

The in-person 36 month Study visit includes a short series of questions designs to assess domestic violence. The Women Abuse Screening Tool (WAST) is a validated tool, found to have high levels of internal consistency, construct validity, and discriminant validity.[15] Children's exposure to abusive settings is an important issue for the NCS to identify but with potential difficulties in so doing. For this reason we have selected a data collection tool that is brief and will be self-administered by the enrolled woman. Self-administration of sensitive questions is one tool proven to reduce nonresponse or intentional misrepresentation by participants. As is true for all of the measures in the NCS, participants can decline to respond to any individual item if they choose. NCS data collectors will not know any participant responses to these questions and therefore cannot respond if abuse is reported through this mechanism. All participants are provided with listings for social services and other local resources for support regardless of whether they are asked these questions.

Cultural Values and Context

The NCS proposes to test a short battery of items designed to assess and understand the cultural context of the enrolled child. Family and community-level characteristics, belief systems, and cultural models are an important element of a child's social environment as they influence, directly or indirectly, the experiences and exposures a child has by informing the behaviors of parents and other caregivers.

This brief 16-item instrument measuring parental values and cultural context was developed by the NCS to understand the role of culture in influencing parental health beliefs and behaviors and its relationship to, children's' health outcomes. Items were selected from a larger set of instruments and reduced to a brief questionnaire. Cognitive testing and pilot work with fewer than 10 respondents was conducted and revisions were made as appropriate (details are provided in SSB). Further testing of these items is required to determine whether they are appropriate for inclusion in the Main Study; the details of this additional testing are in the process of being developed.

[15]Brown JB, Lent B, Brett P, Sas G, Pederson L. Development of the woman abuse screening tool for use in family practice. Fam Med 1996;28:422–28.

Understanding Participants' Experience in the NCS

The NCS is committed to maintaining positive relationships with enrolled participants. This is crucial for any longitudinal study to maintain high response rates and data quality. To better understand participants' feelings towards the NCS and more generally motivation to be engaged in research, the NCS has developed two instruments included in this ICR. Each is intended to be self-administered by the participant. The first questionnaire, the Participant Engagement & Motivation Questionnaire, is planned for completion after the 48 month Study visit and designed to help document why participants agree to engage in research studies. Developed with our NCS bioethicist, this instrument is intended to understand participants' experiences in the NCS and their beliefs and concerns related to their expectations, motivations, and privacy. The secondary instrument – titled NCS Participant Satisfaction Questionnaire – is a much briefer subset of questions from the first instrument. Development of these instruments was accomplished through an extensive review of the literature for similar questionnaires and cognitive testing of the completed instruments. Beginning upon completion of the 42 month Study visit, the Participant Satisfaction Questionnaire will be mailed to participants at regular intervals. Request for inclusion of this instrument in post-60 month Study visits will be included in subsequent ICRs. Through the use of these instruments, the NCS aims to maintain positive relationships with participants and allow them to provide useful feedback about the Study, its procedures and perceived value to them, their families, and communities. Once approved, this questionnaire also will be provided to participants after completion of the 6-month Study visit.

School Attendance

Inclusion of measures related to school experience among NCS children is planned for the 60 month Study visit. These questions will provide important context for children's experiences and exposures. It will also allow the NCS to consider the collection of environmental samples from schools and surrounding areas in later visits. Any such collection would be included in a future ICR.

Adoption of Health and Human Services (HHS) Standards

The 60-month Study visit also includes measures a measure of disability required by HHS as part of data collection standards pursuant to section 4302 of the Affordable Care Act. Specifically, the law requires establishment and use of standards for measuring race, ethnicity, sex, primary language, and disability status. Inclusion of these standard measures (with the exception of the disability questions) was approved for use in earlier NCS Vanguard visits by OMB/OIRA on August 31, 2012.

The specific administration of these measures will vary by mode, with detailed response codes presented iteratively during telephone interviews. As described in SSB, the NCS will analyze these data to determine if any mode effects were introduced.

D. Highlighted Revisions to Previously Established Study Visits

The section describes changes or additions to instruments included in Study visits previously established through approved ICRs. This submission includes the full suite of NCS Study visits, from pre-pregnancy through pregnancy (including the Prenatal Father Questionnaire), birth, and post-natal visits from 3 to 30 months. All NCS Study visits are included for reasons highlighted in this ICR, such as the need to align protocols across all enrolled participants regardless of their avenue for recruitment, improvements to instrumentation and choreography to simplify visits and enhance participants' experience, and the initiation of a sibling birth cohort.

Revisions to existing instruments reflect correction of errors identified in the field related to skip patterns, interviewer or programmer instructions, response code lists, or misspellings. Others may

reflect the need to add single items that were missing in error from the previous versions, a reorganization of the instrument to reduce burden and facilitate response, or the addition of new modules considered important to evaluate in the Vanguard Study. Below are key revisions where questionnaires or sections have changed substantially. Smaller changes, such as updates to the Validation Questionnaire to accommodate additional Study visits, are not presented but instead are available for review in Attachment 2.

Additional Revisions to Core Questionnaire and Age-Specific Modules

As previously described, this ICR separates out instruments or sections within instruments by the specific subject type or referent. Core and Age-Specific Instruments are targeted to a child, an adult, or the household. Therefore the full Core Questionnaire is a composite of all three sub instruments. The Core Questionnaire includes standardized sets of items that are asked of NCS participants at either biannual or annual intervals. This module, previously approved by OMB/OIRA to be piloted at the 30-month Study visit, is designed for multi-mode administration and ensures consistent collection of key measures related to child health and development from ages 6 to 60 months. We have added two short series of items related to caregiver-report of symptoms of asthma and eczema (four and five questions, respectively). Items more appropriate to specific ages or developmental periods have been removed from the core and moved to an age-specific module. Both the core and any age-specific modules include minor additions designed to better align NCS data collection with birth cohort studies in other countries. While not highlighted in this section, all such additions are included in the instruments submitted for public review and comment.

As currently submitted, the child core questionnaire allows consistent collection of child care arrangements, viewing of media/reading books, program participation, health insurance, health care utilization, child's general health, medical conditions, medical visits (including well child care and vaccinations, emergency department visits and hospitalizations) medications, and sleep. For some topics, such as child care arrangements and health insurance, there is a screener question asking if there has been a change from the previous interview. If there are no changes, the respondent skips that series of questions. Some topics, where long term recall is likely to be problematic, are asked every 6 months. Examples include information about well child care visits and use of medications. Other topics, such as hospitalizations and medical conditions, are asked on a yearly basis. Other components of the core household questionnaire include housing characteristics, neighborhood characteristics, pesticide applications, household smoke, household income, and pets. The adult core includes yearly updates on general health, employment, occupation, and education.

Participant Verification & Tracing Interview

As part of our goal to improve the experience of NCS participants, the NCS developed a revised instrument titled Participant Verification & Tracing (PVT). This combined instrument will replace separate modules approved by OMB/OIRA on August 31, 2012. Historically, these questions were asked at different times within a NCS Study visit and were repeated at each encounter with a participant. Each section could be quite lengthy and added unnecessary time to each interview. Therefore, to reduce the overall time spent with participants during a Study visit these items have been restructured to be part of a scheduling contact. Questions have also been revised to be confirmatory and the administration developed to be conversational. This module will also ensure that the correct respondent and location for a given Study visit is identified up front to shorten the visit and maintain good will. This module is designed for completion by telephone, but the NCS requests multi-mode approval to allow maximum flexibility for participants.

Biospecimen Collection

The NCS is currently collecting biospecimens only from children at select Study visits. The NCS is considering testing the addition or reintroduction of biospecimen collections from the enrolled child's primary caregiver, including urine and blood. The addition of new biospecimen types for collection at existing Vanguard Study visits and the selection of biospecimen types for collection at new visits are intended to evaluate the feasibility, acceptability, and cost of the proposed new evaluations.

Time points for these potential collection events would be selected based on anticipated changes in the proposed measure at different ages, requirements for different collection procedures and methods at different ages, differing abilities to cooperate with collection procedures at different ages, and evaluation of alternative collection devices and methods for a given biospecimen type (for example, for cord blood collection, a CPD type cord blood bag versus a heparinized cord blood bag versus a CordStick collection device versus recovery of residual clinical samples; for child saliva collection, a foam pledget versus a polyolefin swab, Oragene versus Salimetrics salivary collection device, parent versus data collector child saliva collection; etc.).

Because children's psychomotor and mental development varies by age, it is preferable to evaluate different procedures for collection of the same biospecimen type at different ages (for example, bag urine in infants versus mid-stream catch urine in children; saliva swab in infants versus passive drool in children; etc.).

Paired adult and child collections of saliva, urine, and blood are being considered to evaluate the possibility of using adult specimens as a proxy for child exposures in the main study. If the NCS finds that exposures measured in child specimens are comparable to those collected from primary caregivers the NCS may consider reducing the frequency of collection of child exposures by eliminating those that are most problematic for participants.

Paired adult and child collections of skin and mucosal swabs are proposed to evaluate the human microbiome. These will be used to assess the composition of and/or changes over time in the microbial communities resident within the nose, mouth, adult vagina at birth, and rectum, with particular attention to comparison of microbiomes within maternal and child pairs. Child stool collection will be assessed to compare this biospecimen type and collection method for human microbiome evaluation with the rectal swab method.

Collections of shed deciduous child teeth (baby teeth) are proposed. These will be evaluated as a means to assess cumulative exposures to environmental chemicals and for comparison with spot measurements from other biological matrices (blood, urine, etc.).

Proportions and rates of completion for all of these measures will be examined with regard to consent for sample collection, consent for genetic analysis, and completion of sample collection. The impact of data collection setting or participant characteristics on feasibility or acceptability will be evaluated. Sample quality and suitability will be assessed, as will the operational quality and technical performance of NCS procedures for collection, transport, processing, storage, and analysis, together with the cost of the proposed measure. These analyses combined with the potential scientific value that a given evaluation may contribute to the NCS will be used to help define a schedule of evaluations that provides a maximum amount of high quality scientific information with a minimum amount of participant burden.

Assuring integrity and quality of biological samples is essential to generate valid data from measures for which NCS biological samples are intended. The Vanguard Study provides an opportunity to assess not only the feasibility but also the operational quality of sample collection, processing, shipping, storage, and analysis. On that basis, determinations may be made regarding necessary modifications to NCS procedures and inclusion or exclusion of selected sample types and analytes for the Main Study.

The approach being considered would evaluate whether a condition of homoscedasticity (homogeneity of variance) prevails in data generated from Vanguard Study samples handled according to NCS standard operating procedures when compared with relevant published normal reference data. Given the large number of potential analytes available for examination in NCS, the initial approach to selection of analytes for assessment of operational quality in the Vanguard Study focuses on those for which stability is known or suspected to be particularly susceptible to the influence of pre-analytic variables. For such analytes, given specified conditions and assumptions, sample sizes of several thousand combined collection/processing/analysis events per analyte may be required.

The table below details the specimens currently collected at each Study visit and the changes being considered. Estimates of the maximum number of participants eligible to provide specimens at specific Study Visits during the three-year clearance period are also provided. Note that these estimates do not account for any unit or item non-response related to individual Study visits, Study attrition, or operational constraints that limit participation. Pre-pregnancy and pregnancy projections are not included as they will be restricted to women enrolled in the proposed Sibling Birth Cohort (SBC). Detailed modeling on projections for that collection is ongoing with an expectation of up to 500 Birth visits from the SBC.

Note that the staged request for clearance is represented in this table. The stage number refers to the stage during which the NCS is requesting approval for a specific Study Visit. Superscripts note whether a specific biospecimens was ever approved prior to this request (for the same or an alternate Study visit), or part of an earlier requested stage for a different Study visit.

Proposed Biospecimen Collections		Approved Protocol		Request for Revision	Projected Estimate of Number of Visits 6/2014 – 6/2017
				Stage of IC Request	
		ARS	PBS	All NCS	
Pre-Pregnancy					
	Maternal Blood	X		3*	
	Maternal Urine	X		3*	
Pregnancy Visit 1					
	Maternal Blood	X		3*	
	Maternal Urine	X		3*	
Pregnancy Visit 2					
	Maternal Blood	X		3*	
	Maternal Urine	X		3*	
Birth Visit					SBC (300-500)

Proposed Biospecimen Collections		Approved Protocol		Request for Revision	Projected Estimate of Number of Visits 6/2014 – 6/2017
				Stage of IC Request	
		ARS	PBS	All NCS	
	Maternal Blood		X	3*	
	Maternal Urine		X	3*	
	Infant Blood Spot		X	3*	
	Cord Blood	X	X	3*	
	Placenta		X	3*	
	Breast Milk[16]			3*	
	Mother Microbiome			3^	
3 Month Visit					0 + SBC
	Breast Milk[16]	X		2*	
6 Month Visit					23 + SBC
	Child Urine	X		2*	
	Maternal Blood			2*	
	Maternal Urine			2*	
	Mother Microbiome			2	
	Child Microbiome			2	
12 Month Visit					527 + SBC
	Child Blood	X		2*	
	Child Urine	X		2*	
	Child Saliva	X		2*	
	Maternal Blood			2*	
	Maternal Urine			2*	
24 Month Visit					1,032 + SBC
	Mother Microbiome			2	
	Child Microbiome			2	
36 Month Visit					3,445 + SBC
	Child Blood			1*	
	Child Urine			1*	
	Child Saliva			1*	
	Maternal Blood			1*	
	Maternal Urine			1*	
	Maternal Saliva			1*	
48 Month Visit					4,483 + SBC
	Mother Microbiome			2	
	Child Microbiome			2	
60 Month Visit					4,397 + SBC

[16] Breast milk is collected at one month and at three months.

* Indicates that specific measure was approved as part of a previous Information Collection request.

^ Indicates that approval for specific measure is requested as part of an earlier Stage for a different Study visit.

Proposed Biospecimen Collections		Approved Protocol		Request for Revision	Projected Estimate of Number of Visits 6/2014 – 6/2017
				Stage of IC Request	
		ARS	PBS	All NCS	
	Child Blood			2*	
	Child Urine			2*	
	Child Saliva			2*	
	Child Teeth			2	
	Maternal Blood			2*	
	Maternal Urine			2*	
	Maternal Saliva			2*	

Environmental Sample Collections

The NCS is considering testing the revision of dust collection procedures and dwelling unit observations by the data collector. The NCS previously collected dust from participants' homes since the launch of the Vanguard Study using two methods: dust wipes (approved by OMB/OIRA on 9/22/2008) and the bulk collection using a vacuum bag (approved on 4/13/2011). The NCS now considering testing an additional collection using the vacuum bag method to the previously established 12 month Study visit.

Dust collection is a low-burden activity for participants. Data collectors ask participants to provide the NCS with a disposable vacuum cleaner bag. If this is not acceptable, dust is retrieved from the vacuum canister or removed from the bag and stored in another container. This change is being considered to better understand the availability of vacuum dust samples from participants and any differences that might exist due to the type of vacuum (canister, upright, cyclone) used by participants. The indoor and outdoor dwelling unit observation forms similarly are low or no burden to participants. Data collectors would ask permission to walk about the inside and outside of the home systematically and record characteristics specific to potential exposures.

Neurodevelopmental Assessments

The NCS is considering testing three neurodevelopmental assessments already in use to previously established Study visits. These additions would allow the NCS to determine whether we would be able to collect information longitudinally from parents or caregivers at key age-specific milestones, and further reflects our shift in focus from recruitment to evaluation of potential measures for the Main Study. Each brief assessment has been well received by NCS participants to date.

Measurement of infant temperament is being considered for the 3 month Study visit using the *Infant Behavior Questionnaire (IBQ-R)*. Parents would be asked to report the frequency of specific behaviors related to 14 areas of interest during a specified reference period. The *Ages & Stages-3*^{TM} questionnaires are under consideration for the 3, 6, and 12 month Study visits. These instruments are part of a series of age-specific self-administered questionnaires measuring child development. Children would be indirectly assessed on fine and gross motor skills, problem solving, communication, and social interaction. Lastly, as part of the 18 month Study visit the NCS proposes asking parents to complete a self-administered questionnaire developed to assess children's risk for autism spectrum disorder

between the ages of 16 to 30 months *(Modified Checklist for Autism in Toddlers (M-CHAT).™)* The M-CHAT would complement the proposed autism assessment at 54 months and provide data necessary to understand health trajectories.

Retrospective Pregnancy Questionnaire

Though hospital-based enrollment is an approved method of recruitment in the NCS Vanguard Study, women first identified at a hospital did not have the opportunity to complete NCS pregnancy visits. Therefore, the NCS lacks study-specific data on those pregnancies. To ensure that prenatal medical history on each enrolled child participant is recorded, the NCS developed a Retrospective Pregnancy Questionnaire for administration to enrolled women after the birth of the child enrolled in the Study. The development process is more fully described in SSB. This instrument may be completed during administration of the Birth, 3-month or 6-month Study visits on a schedule that is most appropriate for the individual participant. If approved, this instrument will only be administered to a small subset of the Vanguard Study cohort. Specifically, only women enrolled in the proposed Sibling Birth Cohort will be asked to complete it. While modeling to predict the number of likely pregnancies among already enrolled women, we anticipate no more than 500 babies will result from this effort.

Post-Natal Father Questionnaire

Women enrolled in the NCS during pregnancy were asked to identify the baby's father and provide permission for the NCS to contact him. If this information was provided, the NCS contacted the father in a subset of cases and attempted to complete an interview with him during the period of the pregnancy. Historically, not all fathers were eligible to complete a father-specific questionnaire. During the Initial Vanguard Study, pregnant women were asked to identify the father and provide permission for the NCS to contact and attempt to interview him. Within the ARS phase, only 15 of 30 Study Locations were allowed to conduct father interviews during the pregnancy period. (This was approved as part of the ARS Phase 2 ICR in April 2011). As a result, the NCS has only sparse data from the fathers of enrolled children recruited as part of the ARS. Currently, the NCS plans inclusion of all fathers at this time is critical to fill any gaps and ensure comprehensiveness. Furthermore, formal engagement of fathers in the data collection process is important for retention of families.

In this ICR, the NCS requests permission to conduct post-natal interviews with all fathers or secondary parents for whom we have permission to contact. This will allow the NCS to collect important demographic and contextual data to understand experiences of enrolled children. This instrument was developed to be appropriate for biological or non-biological, and residential or non-residential fathers. It utilizes gender neutral language so may also be administered to participants in same sex relationships where the domestic partner is considered to be a secondary parent. The Post-natal Father Questionnaire is planned for administration at the 9 or 18 month Study visits. Consistent with the goal of aligning instrumentation across all participants, this instrument will be offered to all fathers or secondary parents identified by the child's mother or legally authorized representative as the appropriate respondent.

The development of the Post-natal Father Questionnaire, including cognitive interviewing, is described more fully in SSB.

Understanding Health Disparities

To further understand health disparities, two new brief series of questions are being considered for possible inclusion in previously established visits. Specifically, the NCS is considering adding items to the Pregnancy Visit 1 and the 24 month Study visit. The first series consists of seven question items related

to participants' perceptions about their own racial identification and the relationship between their perceptions and self-reported health issues. The selected items are a subset of those asked as part of the Centers for Disease Control and Prevention's Behavioral Risk Factor Surveillance System Questionnaire (BRFSS).

The second series consists of eight questions related to the participant's country of origin, length of time in the United States (if not a native citizen) and residence status. The NCS recognizes that some of these questions may be considered sensitive by individuals who themselves or whose family members are undocumented. The NCS is considering whether collecting this information during the Vanguard Study would allow better understanding of such barriers and the levels of potential item nonresponse.

Participant Deaths

Two additional questionnaires included in this ICR are new to the NCS but are not associated with any specific Study visit. Each deals with the death of an NCS participant, either the enrolled child or an associated adult. The intent is to be able to adequately determine and track any death, collect some basic information from the family, and receive permission to collect official death certificates and medical records. These instruments build on the already-approved pregnancy loss and neonatal death instruments, allowing the NCS to collect important clinical information and to respond to regulatory and other oversight group requirements. Based on comments received from OMB/OIRA, the NCS revised these questionnaires to collect the minimum amount of information needed.

The death of a child or caregiver is a highly sensitive situation and the NCS developed protocols and data collector training programs to allow approaching families in a respectful and sensitive way. This is to allow families as much time and privacy as needed before attempting an interview. This interview may be conducted in one of several modalities based on the participant's preference.

In order to collect official death certificates from states, NCS must collect the decedent's Social Security Number. The NCS recognizes that this information is viewed as highly sensitive and would not request it if alternate methods to collect individual vital statistics data were available. Participants will be informed again about NCS efforts to protect against unauthorized disclosure, and the protections the NCS has in place to keep their information private. NCS data collectors and other staff are trained to safeguard all participant data, especially those that are highly confidential or disclosive. Few deaths are anticipated but each can provide an opportunity for learning.

E. Initiation of New Enrollment Cohort – Sibling Births

The NCS requests approval to expand the Vanguard Study through enrollment of babies born subsequently to women with children already enrolled in the Study. The NCS will refer to this as the Sibling Birth Cohort (SBC). NCS Main Study recruitment is planned over four years. Thus, women enrolled in the Main Study could experience more than one pregnancy during the recruitment period. Testing our ability to enroll additional births in the Vanguard Study is critical to our ability to best operationalize future recruitment activities. This potential addition to the NCS was also discussed with the NCS Advisory Committee and at a workshop held in January 2013 by the National Academies on the design of the NCS.[17] The potential inclusion of a sibling birth cohort was discussed at length and there was broad consensus for its inclusion. This ICR seeks clearance to fully pilot these activities. This experience is essential to determine what collections are scalable to the Main Study.

[17] http://sites.nationalacademies.org/xpedio/idcplg

Enrollment of subsequent pregnancies is desirable for several reasons. The existing relationship with the family may facilitate earlier notification of pregnancy. This, in turn, would allow collection of data, biologic specimens, and environmental samples early in pregnancy, during critical periods of development. The opportunity to follow new pregnancies would allow the collection of biospecimens, environmental samples, and standardized neurodevelopmental assessments on sufficient numbers of participants to understand what activities are feasible in specific settings, participants' willingness to complete requested measures, and whether measures are useful and scalable for inclusion the Main Study.

As most of the children enrolled in the Vanguard Study were born to women enrolled during pregnancy, some early exposure data already exists for each child. These include baseline specimens, samples, and questionnaire data available from prior study visits. The subsequent pregnancy can be used as a comparator for the initial pregnancy and provide valuable information on the ability to impute exposures and history. Lastly, inclusion of siblings permits an in-depth analysis of gene-environment interactions which likely underlie many outcomes of interest in the NCS Main Study. Babies enrolled during the SBC enrollment period would be considered participants in the NCS Vanguard Study and be followed through age 21, as per the approved protocol.

As part of the Request for Revision to the Vanguard Study to add 30 additional recruitment locations (approved on 7/23/2010) , the NCS reduced the scope and intensity of NCS Study visits and eliminated any biospecimen or environmental sample collection until a subsequent Request for Revision (approved on 4/13/2011). The timing of this request, variation in birth and enrollment patterns across Study locations, and the efforts to launch new measures led to insufficient numbers of participants for some infant collections. Enrolling a supplemental cohort of babies is intended to eliminate some critical information gaps.

Adding a Sibling Birth Cohort (SBC) would serve other important functions. It would allow the NCS to further refine operational methods and practices used when working with hospitals and health care providers, including providing additional data related to what is required to gain access to and cooperation from hospitals related to specimen collection and handling. Adding a SBC would allow the NCS to refine procedures for engaging hospitals and negotiating how specimens can be collected in a standardized way. It would also provide an opportunity to collect biospecimens from parents to determine whether parental specimens can serve as valid proxies for those taken from infants or children. If such proxy measures are valid, then it may be feasible to limit the types and frequency of sample collections from infants in the Main Study. Lastly, the SBC would help characterize the patterns of subsequent pregnancies across geographic regions and other participant characteristics, allowing for more precise planning of recruitment schedules for the Main Study.

A SBC would help address key questions. For example, can subsequent pregnancies be identified in the Study cohort? If so, at what gestational age are these pregnancies identified? At what gestational age does the first pregnancy visit occur? Is the first pregnancy visit earlier in pregnancy for subsequent pregnancies than in the rest of the Study cohort?

Additionally, are data collected as part of the mothers' prior enrollment in the study useful in providing baseline, pre-pregnancy information? And what is the completeness of data collection for subsequent pregnancies? How does this compare to completeness in the rest of the Study cohort?

The NCS proposes enrolling up to 500 sibling births. Currently enrolled women would be contacted for SBC follow-up. If a participant agrees, she would be screened to see if she is currently trying to become pregnant. All women who agree to be screened, regardless of intent to become pregnant, would be asked to contact the study should they become pregnant. Women would be provided with two home pregnancy test kits and asked to notify the NCS soon after learning of their pregnancy.

SBC participants would be administered the same protocol as approved for the NCS Vanguard Study, including the collection of environmental samples, biospecimens and physical measurements during pre-pregnancy and pre- and post-natal visits. Those who report that they are trying to conceive would be initially administered the protocols approved for preconception data collection. Others who self-report a pregnancy at a later time would receive pregnancy visit instrumentation and collections. The NCS recognizes that children in the same family may have different visit experiences. This would be managed with careful communication with participants and should not be an issue going forward as data collection is standardized and harmonized for all participants.

F. Initiation of Methodological Substudies

The NCS is considering two methodological experiments focused on the use of incentives as a tool to maintain participation in the NCS Vanguard Study and reduce data collection costs. The first experiment would test the impact of incentivizing participant self-scheduling of upcoming Study visits and the second would examine collection of participant tracing information between scheduled NCS visits. To better coordinate methodological testing across federal agencies, the NCS 66 will work with OMB/OIRA on the design of these experiments. Details of the proposed will be presented in subsequent change requests.

Maintaining ongoing cooperation from participants is critical to the NCS, and incentives represent one tool to promote high response rates. The Vanguard Study, as a pilot test, offers a unique opportunity to systematically assess incentive strategies prior to the implementation of the NCS Main Study. Specifically, the NCS is interested in understanding the optimal incentive types and amounts required to promote participant retention, yield high data quality, maintain sample composition, and reduce field costs.

The NCS conducted a thorough literature review to ensure the proposed information collection is necessary and potentially informative. While substantial information is available on cross-sectional surveys, our understanding of the effect of incentives in longitudinal studies is deficient.[18] The use of incentives is generally accepted, particularly when there is greater burden placed on respondents, such as in the case of longitudinal research.[19] While evidence in cross-sectional survey research shows that incentives are effective in boosting response rates, few experimental studies have directly assessed the effectiveness of incentives in longitudinal research. To date, the NCS has not systematically tested the impact of incentives on participation. The NCS incentive structure has been revised over time and participation in formative research projects offering incentives has not been systematic across NCS participants. The NCS Vanguard Study protocol approved in 2008 included a $100 monetary incentive for all in-person Study Visits, plus a non-monetary incentive valued up to $25. Once the NCS Vanguard

[18] Singer, E., Gebler, N., Raghunathan, T., Hoewyk, J.V., and McGonagle, K. (1999). The effect of incentives in interviewer-mediated surveys. *Journal of Official Statistics*, 15, 217-230.

[19] Laurie, H., and Lynn, P. "The use of respondent incentives on longitudinal surveys." In P. Lynn (Ed.) (2009). *Methodology of longitudinal surveys* (pp. 205-233). London: John Wiley and Sons.

Study transitioned to the ARS phase, incentive levels dropped to $25 as the survey administration portion of the interview was less burdensome. The ICR currently under review includes Study Visits similar in length and complexity to those approved in September 2008. These evolutions of the Study and the former decentralized nature of data collection and data management activities makes it difficult to draw any conclusions on the effect of incentives to date. The proposed incentive experiments are intended to maintain ongoing participation as well as inform decisions for planning the Main Study.

Thus, the NCS seeks to understand the effectiveness of varying the type and amount of incentives that participants receive. The proposed experiments have been designed to evaluate the impact of three factors on NCS cooperation rates, data quality, and data collection costs. The factors are: (1) the monetary incentive amount provided at each data collection event (or "wave"); (2) the timing of incentive delivery; and (3) the use of non-monetary incentives, either as a stand-alone incentive or in combination with a monetary incentive. The first experiment will test the impact of incentives on a procedural/operational issue, while the second will incentivize actual data collection to understand the associated data quality and cost issues. Given that the intensity of Study Visits have evolved, it is important to understand participants' willingness to engage at new levels. For efficiency, this test was embedded in the "early bird" design, maximizing the utility of the proposed experiment. The two proposed experiments will contribute to the scientific literature in this area and help close that knowledge gap. If these experiments prove to be effective in increasing survey response and data quality and decreasing field costs, the NCS may consider their implementation in the Main Study.

Planning for Future Methodological Research

The NCS supports ongoing methodological and formative research to support development of Vanguard and Main Study protocols. The NCS has been developing independent generic clearances under which to conduct domain-specific methodological research. Currently in place are the Biospecimen and Physical Measures, Neurodevelopmental, and Recruitment and Retention Clearances. The latter has been in place since 2008 and expires in September 2014. The NCS has opted not to request renewal of the Recruitment and Retention clearance as its scope is not necessarily aligned with current needs. In its place, the NCS will post a 60 day Federal Register Notice in support of a Survey Research Methods Generic Clearance. Additionally, another ICR focused on Environmental Methods is under development and should be submitted later this year.

For the long term, the NCS goal is to test new questionnaires and assessments through one of the above mentioned generic clearances. (As well as do the appropriate cognitive testing and other qualitative research as part of the development process.) As the timing for review and approval of these new clearances is unknown, the NCS requests additional burden hours for the conduct of such formative research as part of this ICR. Specifically, the NCS proposes maintaining a small level of burden within the Vanguard Study clearance to support methodological development until new mechanisms are in place. Please note that a substantially smaller number of burden hours are requested for this work. Previously approved burden for Methodological Research was 14,542 hours. The current request is only 2,835 hours to serve as a bridge until the new clearances are approved.

Proposed methodological research may examine the feasibility, acceptability, and cost of a series of Study protocols within a subset of Vanguard Study participants or external populations with similar eligibility characteristics. Examples of such protocols include data collection from persons not enrolled in the NCS Vanguard Study as a means of testing items for relevant populations efficiently in advance of the NCS Main Study. For example, smaller, in-depth data collection would be requested from children demographically similar to, but older than Vanguard Study children to test age-specific items, and from

persons who meet demographic but not geographic eligibility criteria for the NCS to test specific protocols and measures. At this time, the exact protocols and the size and specific subpopulations to be included have not been determined. As projects are developed each would be submitted for OMB/OIRA review and clearance as future requests for non-substantive change.

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 previously collected information into the interview process, computer-assisted telephone interviewing, and information management solutions that ensure proper study components are administered at the appropriate times. Forms and questionnaires given to participants will be developed in user-friendly formats to reduce the time they take to complete.

Title II of the E-Government Act of 2002 requires federal agencies to conduct privacy impact assessments (PIAs) before developing or procuring information technology (IT) systems that collect, maintain, or disseminate personally identifiable information (PII). In 2007, NIH released Manual Chapter 1745-1, "Privacy Impact Assessments," which reinforces the Department of Health and Human Services (HHS) requirement for PIA completion, and details NIH employee roles and responsibilities in support of this process.

PIAs provide a documented process, the purpose of which is to identify and protect employee and public citizens' Personally Identifiable Information (PII); and it ensures that the government has considered privacy safeguards necessary for the protection of PII passing through or being collected, maintained, passed through or disseminated in its systems. The NCS must effectively manage participant safety while preserving data integrity and availability to carry out NCS activities. To do so, privacy risks associated with NCS systems are documented by having field contractors complete PIAs and include risks in the system plan of action and milestones (POA&M). The NICHD Chief Information Officer (CIO) exercises appropriate oversight of contractors in carefully reviewing PIA information.

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

A key part of NCS protocol planning activities includes reviews of the scientific literature to determine what information, if any, has been collected on each domain of interest. Prior to any initial planning the NCS developed an inventory of longitudinal studies and conducted a comprehensive and systematic review. The review examined whether the study goals could be addressed without embarking on an entirely new study. This effort 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.

As the NCS Vanguard Study continues and new measures are introduced to reflect continuing development and growth of enrolled children, the NCS continues to conduct systematic domain-specific reviews and consult with scientific experts. The focus is not only to assess the utility of the measures themselves, but also to determine whether measures are able to be administered to a geographically dispersed sample, and if the methods of administration lead to unexpected patterns of response when compared with other national data collection efforts.

The piloting of measures in the NCS Vanguard Study would allow for informed and responsible decision making when planning the Main Study. This is true for both new assessments as well as those that have been revised based on data collected from NCS field efforts. Each requires additional testing to further

evaluate and determine their scalability and appropriateness for inclusion in the Main Study. The proposed addition of a Sibling Birth Cohort serves to illustrate this need. By following new pregnancies among already enrolled women we have an efficient way to refine our procedures and protocols, including but not limited to Study instrumentation, collection of samples and specimens from households and birthing centers, and testing of new non-proprietary assessments not previously available to the NCS.

A.5 Impact on Small Business and Other Small Entities

The NCS will not collect information from small businesses (for example, health care providers), because the recruitment portion of the Provider-Based Sampling Feasibility Study will be complete.
Health care providers, considered to be small business entities may be asked to provide information to the NCS. With the consent of participants, key medical diagnostic and treatment information on Study participants may be collected. 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 NCS Vanguard Study provides an opportunity to test and refine data collection activities and the required frequency of each collection to inform planning for the larger Main Study. Scientifically, the schedule of collection for each measure is designed to coincide with key developmental milestones for children and critical periods of potential environmental exposure. Multiple collections are required due to variation in exposures over time or when behaviors or beliefs may change as children age. Measuring these variations in the NCS Vanguard Study will allow analysis of the impact of repeated administrations on cooperation rates and provide critical data to plan for the most efficient Main Study data collection protocol.

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

a. Comments in Response to the Federal Register Notice

The 60 day Federal Register Notice regarding the Continuation of the National Children's Study Vanguard (Pilot) Study was published on pages 52548-52551 of the Federal Register on August 23, 2013.

Two written comments/requests were received. The first commenter initially requested additional information about the study, particularly the informed consent process and forms, which was provided. Comment 1 (below) was received in response to these additional materials. Overall, this commenter feels the study poses substantial informational risks to the subjects. The second commenter also requested additional information about the study, which was provided, and is opposed to the NCS in general, stating that it was too costly, and expressed concerns about the effects of federal programs. The NCS responded to both comments and they were publicly made available in the contents of the ICR submitted with the 30 day Federal Register Notice. All comments received and the responses to those comments are provided below:

Comment 1:

As currently planned, the National Children's Study would track the genetic, biological, and behavioral characteristics of tens of thousands of identified children through age 21. The revision proposed here would, among other things, start the tracking even before children are conceived. These information collections, including proposed revisions, would burden especially vulnerable subjects and would do so on an unprecedented scale, to an unprecedented extent, and in violation of law.

Because of burdens that would be imposed and because of major violations of existing law, these proposed revisions and much of the study as planned fail to satisfy the salient criteria for approval under the Paperwork Reduction Act, 44 U.S. C. sec. 3501, fail to satisfy human research protections requirements, 45 C.F.R. part 46, and failure to satisfy the Privacy Act, 5 U.S.C. sec. 552a.

THESE INFORMATION COLLECTIONS SHOULD BE DISAPPROVED, FOR FAILURE OF LEGAL SUFFICIENCY
These proposed revisions should be disapproved, and previous information collection approvals for the National Children's Study should be rescinded. The previous approvals do not satisfy approval criteria under the Paperwork Reduction Act and do not reflect understanding of the pertinent legal issues, sweep of these collections, or their implications for the future of these research subjects.

I write from the perspective of a lawyer and bioethicist. I have written on and taught ethics and law of human subjects research, have served on Institutional Review Boards (including that of the National Institute of Child Health and Human Development) for the protection of research subjects, and have represented abused and neglected children.

FAILURES TO MEET PAPERWORK REDUCTION ACT APPROVAL CRITERIA
This information collection revision and the entire project as planned violate existing law (the 44 U.S. C. sec. 3501(8) criterion for approval under the Paperwork Reduction Act) and fail (in violation of 44 U.S.C. sec. 3501(1)) to minimize burdens.

FAILURE TO ACCOUNT FOR BURDENS ON RESEARCH SUBJECTS
The National Children's Study information collection approval requests, past and present, assume that the only burden to be considered is the time spent answering researcher questions. Prior approval apparently was given on that assumption. But the National Children's Study planners themselves have recognized that these research activities as currently planned will expose research subjects to lifelong burdens of vulnerability to and effects of unwanted disclosures. National Children's Study, Data Access & Confidentiality: Concept of Operations, May 2013 <https://www.nationalchildrensstudy.gov/about/overview/Pages/NCS-CONOPS-Data-Access-and-Confidentiality.pdf>. That paper cautions that notwithstanding compartmenting and coding to hide identification, and notwithstanding a Department of Health and Human Services Certificate of Confidentiality under 42 U.S.C. sec. 241(d), the danger of unwanted disclosure is non-negligible and may be highly significant in light of federal information-sharing policies. In seeking information collection approval, the project planners in this connection appear not to have taken their own study into account.

These data could be used, lawfully or otherwise but without notice to the concerned study subject, to predict behavior and/or to evaluate for purposes of employment, credit, or security inquiries. See, e.g., Rachel Levinson-Waldman, What the Government Does with Americans' Data, Brennan Center for Justice, New York University School of Law, 2013 <http://www.brennancenter.org/sites/default/files/publications/What%20Govt%20Does%20with%20Data%20100813.pdf>; Susan Stellin, Security Check Now Starts Long Before You Fly, N.Y. Times, Oct. 22, 2013, at A1. Vulnerability to the consequences of unwanted and unrevealed disclosures is

exacerbated by federal policies favoring sharing of data-banked information. Neither the Privacy Act nor the Department of Health and Human Services' Certificate of Confidentiality bar disclosure to law enforcement agencies and to other agencies of government. Holders of information under the Department's Certificate of Confidentiality are allowed to disclose covered information voluntarily even while they cannot be compelled to disclose.

The study plan provides for acquisition of detailed medical and psycho-social data over so long a period that research subjects may never themselves realize how much of what kind of data has been compiled about them, how much of these data have been used for what purposes, and to whom these data have been disclosed and to what effect. However inchoate, these are far from minimal burdens and are far from ordinary.

FAILURES TO COMPLY WITH EXISTING LAW
FAILURES TO COMPLY WITH AUTHORIZING LEGISLATION
The National Children's Study is not exempted from any law or regulation. The extensive cohort study intended in the legislation was to be done in a way that would conform to human subjects protections and other applicable law. Study planners instead have opted to amass detailed, highly sensitive, personal medical and behavioral information on identified individuals and to do so without adequate protections for those individuals.

The Children's Health Act of 2000, Pub. L. No. 106-310, authorizing the National Children's Study, reaffirms Congressional intent "to ensure the adequate and appropriate protection of children in research" and requires regulatory review for that purpose, id. at sec. 1003, and specifically requires compliance with pediatric research protections for all research conducted or sponsored by the Department of Health and Human Services, id. at sec. 2701. The National Children's Study is not exempted from any law or regulation.

The proposed information collection and those already approved violate applicable human subjects protection regulations, 46 C.F.R. part 46. These regulations prohibit or stringently restrict some human subjects research, notably on very vulnerable persons, and strongly condition all human subjects research on several protective requirements—including but not limited to: Informed and fully voluntary consent by research subjects or their legally authorized representatives; right of and provision for withdrawal; assessment of burdens and benefits; fairness in selection of research subjects; confidentiality and protection of privacy; and provision for safety of research subjects.

FAILURES TO COMPLY WITH HUMAN RESEARCH PROTECTIONS REGULATIONS
No benefits; excessive burdens: Human research protections regulations require assessment of burdens and benefits. This study is expressly not for the benefit of the individuals to be studied, whether the children themselves or others in their family constellations who may be studied also—purposely or intentionally. The hope is that someday these data might be useful in medical science.

The burdens imposed are largely in the form of vulnerability to consequences of disclosures, accidental or otherwise, of decades of highly personal medical and behavioral data.

Violations of special protections for fetuses, neonates, and children: Research on a fetus is normally prohibited absent direct benefit to the fetus. 45 C.F.R. part 46, subpart B. In this situation there is no benefit, and societal benefit is speculative at best. The burden is not
biophysical but is rather the imposition of prolonged vulnerability to consequences of disclosure of

sensitive information. Neither does this research qualify under 45 C.F.R. part 46, subpart D, inasmuch as it involves greater than minimal risk and is unlikely to yield generalizable knowledge about the subject's disorder or condition. The extent and duration of data gathering are so great as to make the informational risk real and far more than minimal.

Questionable or no capacity to consent: One object of this information collection revision is to extend already legally questionable collections to cover not only actual, identified children but also to cover children in advance of their conception. Legal consent cannot be given by someone not empowered, as an actual parent might be, and an actual person to be bound under that consent does not exist.

Where actual children are involved, the study plan reflects no procedure to ascertain that persons who consent in the absence of parents are actually empowered to consent under relevant state law.

No consent from actual subjects: The study plan provides no clear procedure for children to be informed regularly of these data acquisitions, their right to withdraw, and procedures for them to withdraw.

Lack of candor and full disclosure in consent forms: Consent forms for the National Children's Study fail to say candidly that personal study data may be disclosed to law enforcement agencies and to other agencies of government. While saying that holders of study data cannot be compelled to disclose, these forms fail to make clear that holders of study data may disclose voluntarily.

These forms fail to make clear the substantial informational risks entailed in the National Children's Study.

PRIVACY ACT VIOLATION
The Privacy Act requires, at 5 U.S.C. sec. 552(e) et seq., that agencies shall inform each individual subject of rights and procedures relating to government gathering and storage of their personal information. The National Children's Study plan does not compy.

THE REVISED INFORMATION COLLECTION PROPOSAL SHOULD BE DISAPPROVED, AND PRIOR APPROVALS SHOULD BE RESCINDED.

National Children's Study plans should be reconsidered and revised so as to provide for reasonably promising research without running roughshod over individual rights and without posing substantial informational risks to subjects.

Response to comment 1:
The National Children's Study appreciates this comment and is committed to the ethical conduct of research.

In brief, this comment suggests that the NCS Vanguard Study should not have been approved by OMB/OIRA, that the NCS Vanguard Study is in violation of the terms of the HHS human subject protections regulation promulgated at 45 CFR 46 and that the Study violates the terms of the Privacy Act of 1974 at 5 U.S.C. § 552a.

First, this comment states that the NCS should not have been approved by OMB/OIRA as the commentator believes that OMB did not consider what he characterizes as the most serious burden

associated with the Study, the exposure of "research subjects to lifelong burdens of vulnerability to and effects of unwanted disclosures."

The NCS Vanguard Study has consistently provided information describing the development of the Study and describing the risks of the Study, including the potential for unintended privacy breaches and disclosure risks, as well as approaches for mitigating these risks to OIRA for clearance under the Paperwork Reduction ACT (PRA). The PRA is intended to "ensure the greatest possible public benefit from and maximize the utility of information created, collected, maintained, used, shared and disseminated by or for the Federal Government" and to "improve the quality and use of Federal information to strengthen decision making, accountability, and openness in Government and society."[20] All NCS requests for information collection have been submitted to, reviewed by and approved by OMB/OIRA in accordance with the intent of the PRA as described above and are available to the public at www.reginfo.gov under OMB number 0925-0593.

Second, this comment also states that the NCS violates sections of 45 CFR 46, the HHS regulation guiding the review and conduct of HHS funded research with human subjects. With regard to 45 CFR 46, the commentator believes that the research violates, "violations of special protections for fetuses, neonates, and children" as described in subparts B and D because he feels that the research is greater than minimal risk and offers "No benefits; excessive burdens."

The NCS informed consent form states that there is no direct benefit to participants from taking part in the research but that there are societal benefits from the knowledge to be gained from the Study. Observational studies inherently offer little or no direct benefit to participants and are conducted to advance scientific knowledge. The NCS experience to date has generated multiple contributions to the scientific literature and a search of Study related publications using the National Library of Medicine's PUBMED database can be accessed through the NCS website at the following url: http://www.nationalchildrensstudy.gov/research/researchpublications/pages/default.aspx

While IRBs can certainly disagree about the optimal wording of consent forms and what constitutes the interpretation of minimal risk; this comment is lacking in any explanation or criteria that could be used for determining that the Vanguard Study should *not* be considered as minimal risk research. The comment only states that collecting the kinds of health information that the NCS is designed to collect and maintaining this information for an extended period of time cannot be considered to be minimal risk research.

Minimal risk is defined as "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests" at 45 CFR 46.102 (i).[21] All NCS data collection activities are selected to meet the terms and intent of this definition.

The Study has in place multiple procedures to reduce the possibility of study related risks, such as unintentional violations of confidentiality and disclosure risks as well as possible risks related to Study procedures like blood draws. These risks are described in the OMB supporting statement, the NCS Vanguard Study informed consent forms, and Study instrumentation. For example, Sections A.3 and

[20]

[21] 45 CFR 46.102 (i) at http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html

A.10 of OMB Supporting Statement A describe the security procedures in place to protect confidentiality and protections for minimizing and limiting disclosure risk. The NCS consent form makes clear that the Study will do its best to protect confidentiality but cannot guarantee confidentiality.[22]

The NCS Vanguard protocol has undergone human subject protections review by the NIH NICHD IRB, institutional review boards (IRBs) at academic institutions, and by IRBs at collaborating hospitals and research organizations. Every IRB that has reviewed the Study has determined the NCS Vanguard Study to be minimal risk research and approved the protocol. When reviewing research, IRBs are required to consider the balance of risks and benefits. For an IRB to approve a research protocol, it must determine that risks are reasonable in relation to anticipated benefits. Approved research must strike an acceptable balance between possible risks (which can include physical harms, psychological harms, social or economic harms) and anticipated benefits (which can include individual benefits and or societal benefits). The Office of Human Research Protections (OHRP) provides the following guidance to IRBs when considering risks and benefits inherent to a research study, "In research where no direct benefits to the subject are anticipated, the IRB must evaluate whether the risks presented by procedures performed solely to obtain generalizable knowledge are ethically acceptable. There should be a limit to the risks society (through the government and research institutions) asks individuals to accept for the benefit of others, but IRBs should not be overprotective.[23]

Because NCS participants include not only adults, but vulnerable populations such as pregnant women and children, reviewing IRBs must find that the NCS Vanguard Study research protocol meets additional protections for these populations under 45 CFR 46 subpart B subsection 204 (which provides additional protections for pregnant woman and human fetuses) and under 45 CFR 46 subpart D (which provides additional protections for children in research). All of the reviewing IRBs have determined that the NCS Vanguard Study protocol meets these criteria and have approved the participation of children as research subjects in the NCS Vanguard Study protocol under 45 CFR 46.404 "Research not involving greater than minimal risk." Under this category, "the IRB finds that no greater than minimal risk to children is presented, only if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians."[24]

Additionally, the NCS Vanguard Study has in place an Independent Study Monitoring and Oversight Committee (iSMOC) that is charged with monitoring, "human subject safety through review and evaluation of accumulated study data."[25] The iSMOC reviews the NCS Vanguard Study under this charge on a semiannual basis and at each review to date has recommended that the NCS Vanguard Study continue.

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[22] The consent form includes the following language to this effect, "Although we are taking many steps to protect your information, there is always a chance that your information or identity or that of your family members could be disclosed. Such disclosures may also occur if you share information yourself or agree to have your research records released" and "We will get information about your health, your community, and your race and ethnicity. We will make files with this information available to approved researchers. In addition to the risks to individuals, the risks of providing information about racial or community groups are unknown. There is a possibility that specific Study findings will be associated with particular racial and ethnic groups."

[23] OHRP Institutional Review Board Guidebook, Chapter III at: http://www.hhs.gov/ohrp/archive/irb/irb_chapter3.htm

[24] http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html

[25] http://www.nationalchildrensstudy.gov/about/organization/advisorycommittee/Pages/Official-NCS-iSMOC-Charter-v1-93.pdf

Third, the commentator also states that there are numerous problems with the NCS Vanguard Study informed consent process. For instance, he believes that the NCS is asking women to provide permission for the participation of "children in advance of their conception." The NCS Vanguard Study has completed enrollment and data collection from the preconception cohort (that is non-pregnant women who met specific inclusion criteria) and the data collections and informed consent process for that cohort pertained only to the enrolled women not to children who were not yet conceived. Because data collection for this cohort is completed, no informed consent forms or other instrumentation for that cohort were submitted for PRA clearance.

With regard to informed consent, the commentator also indicates concern that, "Where actual children are involved, the study plan reflects no procedure to ascertain that persons who consent in the absence of parents are actually empowered to consent under relevant state law." While this level of granularity in the procedures of consent administration is not included in the materials submitted for PRA clearance, OHRP guidance is clear that in the absence of a parent, a guardian could provide permission for a child's participation and defines guardian to be "an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care."[26] Administrative procedures for identifying the guardian are described in NCS data collector training and instructional materials such as the informed consent manual of operations.

This comment states that "the study plan provides no clear procedure for children to be informed regularly of these data acquisitions." This is accurate in that the materials provided to OMB (which cover visits for up to 5 years of age) state that an assent process will be put in place but do not describe the assent process in detail. Assent was intentionally not detailed in this submission because we will not be administering an assent process to children 5 years of age and younger. The NCS assent process will include children 7 years of age and older, consequently, the assent process will be described in a subsequent OMB submission describing data collections procedures for visits conducted with this age group. The oldest children in the NCS cohort are currently 4 years of age.

Finally, the commentator feels that that the "Consent forms for the National Children's Study fail to say candidly that personal study data may be disclosed to law enforcement agencies and to other agencies of government. While saying that holders of study data cannot be compelled to disclose, these forms fail to make clear that holders of study data may disclose voluntarily." This last claim is inaccurate as the consent form contains a section dedicated to this topic, entitled, "When might the NCS Vanguard Study share my information?"[27] This section describes the circumstances under which participant's data might be shared

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[26] http://answers.hhs.gov/ohrp/questions/7198

[27] "When might the NCS Vanguard Study share my information?

- The NCS needs to share your information to do the research described by this informed consent form.
  - The Eunice Kennedy Shriver National Institute of Child Health and Human Development runs the National Children's Study.
  - We hire groups and organizations to do work for the Study such as collecting, storing, and analyzing data. These groups must be authorized by the Study to protect your information in ways described by Federal Privacy Regulations.
- The NCS may need to share your information to protect public health and safety.
  - If we learn that you or someone else is harming you, the child you take care of, or others around you, we may be required by law to report this to the police or a social services agency in your community."

Comment 2:
"this study is useless and wasteful. all it generates is a press release. please send a paper copy of all documents on this toue [sic] at XXXX. the costs of this study are enormous in gouging us taxpayers. where is the report on what you have found out to this date. that should be required before you get any authorization to go further. probably you accomplished zero. the budget for this committee should be zero. the people of america are not being helped by this committee. i have no respect for this agency's accomplishments. america has an epidemic of autism and colitis. nothing is being accomplished in the lab on these issues. we need people in the lab not sitting on their butts chatting about studies that never finish. this comment is for the public record. please acknowledge receipt [sic]."

Response to the comment 2:
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.

b. 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 include member of the NCS Program Office, contractors, and independent advisors.

Federal Consortium
The National Children's Study is led by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) of the National Institutes of Health (NIH) in collaboration with a consortium of federal government partners. Study partners include the National Institute of Environmental Health Sciences of the NIH, the Centers for Disease Control and Prevention, and the Environmental Protection Agency. These agencies, together with representatives from a multitude of additional government agencies interested in the National Children's Study, form the Federal Consortium. The primary purpose of the Federal Consortium is to provide a forum for representatives of these agencies interested in children's health, development, and environmental influences to share

ideas about the NCS's development, implementation, and potential benefits. Meetings provide opportunities to learn about the progress of the NCS and for the representatives to share their ideas about Study content, design, and implementation. The Federal Consortium meets at least twice per year.

Federal Advisory Committee

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. The NCSAC meets at least three times per year and meetings are open to the public.

Multi-Contractor Committee

The Multi-Contractor Committee consists of subject matter and data collection experts and community representatives and provides guidance to the National Children's Study. It is empowered to propose protocol modifications that do not change the direction or cost of the study, subject to confirmation by the Program Office. The Committee meets face-to-face twice a year. Interim meetings by conference call.

Data Monitoring Committee

A chartered 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, and make recommendations concerning continuation or modification of the study. The iSMOC reviews 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 recommends appropriateness of notification and referral of individual participants for significant abnormal findings on testing of stored samples. The committee consists of approximately 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 iSMOC meets twice per year.

NCS Scholars Program

The NCS initiated the National Children's Study Scholars Program to expand opportunities for involvement. This Program enables federal employees with subject matter expertise and experience in various fields to contribute in-kind to the development of this important and unique study. Depending on their specific area of focus, Scholars can work part time or full time, on site or remotely. All Scholars will work closely with the National Children's Study Program Office staff at NICHD to further the goals of the Study while supporting the missions of the federal agencies they serve.

NCS Health Measurement Network (HMN)

The HMN is a collaborative effort across academic institutions and professional research organizations charged with the development and assessment of tools, instruments, methods, and assays that measure child health and well-being. Organizationally, the HMN is focused on key domain areas with each team

having a roster of one lead and four to six subject matter experts. Current teams and associated expert leads are presented below.

Sensory Functioning: Rose Marie Rine, PhD (Marshall University)
Life Course Health Science: Ann Riley, PhD (Johns Hopkins University)
Physical Health & Systems: Russel Pate, PhD (University of South Carolina)
Motor Functioning: Jane Clark, PhD (University of Maryland)
Social/Emotional/Behavioral Health: Darren Dewalt, MD (University of North Carolina)
Cognitive Health: Phil Zelazo, PhD (University of Minnesota)
Statistics & Item Response Theory: Ron Hays, PhD (UCLA)
Environment: Rosalind Wright, MD, MPH (Mount Sinai School of Medicine)

A.9 Explanation of Any Payment or Gift to Respondents

Participants in the NCS Vanguard Study will receive monetary and non-monetary incentives for their time, effort, and any expenses incurred (for example, transportation costs). The NCS Vanguard Study will continue to provide incentive amounts that are consistent with the incentive schedule previously approved by the NICHD IRB and OMB/OIRA, with incentive amounts determined by the types of activities asked of participants. Specifically, individuals will receive $25 for participating in the interview portion of NCS Study visits. This may include questionnaires administered by a data collector in-person or over the telephone. It also includes and self-administered questionnaires.

Depending on the scope of each specific Study visit, the participant may be asked to provide or self-collect biospecimens or environmental samples. Incentives for biospecimen and other sample collection are needed to overcome perceived inconvenience, discomfort, or other negative experience associated with the collection. A monetary incentive of $25 is provided to each individual who provides any or all requested samples or specimens as part of a single Study visit. This amount covers all potential collections within a visit and is not a per-specimen incentive.

Small non-monetary incentives may be provided to participants as an additional token on gratitude for ongoing participation in the NCS. All such non-monetary incentives must be valued at $25 or less. These may include age-appropriate children's books or materials, key chains, tote bags, t-shirts, or other items found to be non-coercive by the IRB of record for the NCS. All non-monetary incentives and dollar values used in the NCS have been reviewed and approved by the NIH Office of Efficient Spending.

Lastly, there are participant-specific circumstances that require an incentive above and beyond those stated above. For example, the Study may require participants to travel to a health care provider to have blood drawn. Not all participants will have available transportation or are able to ensure any such costs. In such circumstances the NCS would seek approval via non-substantive change to modify the incentive structure.

Methodological or formative research conducted as part of the National Children's Study or activities completed outside of scheduled Study visits may have additional requirements for monetary and non-monetary incentives. These will be identified and detailed in the specific ICR in which approval is requested. Requests for approval to conduct methodological experiments on the use of incentives are included in this submission and details of the proposed incentive structure are provided in A2 above.

A.10 Assurance of Confidentiality Provided to Respondents

Although NIH does not have the statutory authority to promise confidentiality, it will do everything in its control to keep the information collected private to the extent permitted by law. Study data collected will be safeguarded closely and actions will be taken to maintain the privacy of the participants and protect the security of the information that they provide. Participants will be informed about the Certificate of Confidentiality (Attachment 3) granted to NCS to protect data from involuntary disclosure. NCS contractors (for example, ROCs and information management system (IMS) hubs) will have policies and procedures regarding protection of study data, which will be reviewed and monitored by the NCS Program Office. Each IMS will be capable of data capture, data management, quality control, and data delivery. The Program Office, ROCs, and support contractors will be connected through a secure network that will transmit encrypted data to ensure adequate privacy and protect against unauthorized access. The IMS will meet all HHS and other privacy and security requirements.

To further assure protection of participant data, the NCS will employ rigorous methods to provide security for PII. Each field contractor, support contractor and the NCS Program Office 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 field contractors and support contractors complete the self-assessment of their security plans, the NICHD Chief Information Officer (CIO) will review all study center security plans to determine the contractor's authority to operate. Frequent and regular monitoring visits will assist in compliance with these terms.

All NCS 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 Information Security and Privacy Awareness Training, completion of a Human Subjects Protection Training, signing an Assurance of Confidentiality, be party to a NCS data use agreement or an approved equivalent, and signing an Affidavit of Nondisclosure. NCS nonpublic-use data will only be used for the intended scientific purpose. NCS staff members are required to complete security background checks consistent with the Office of Personnel Management requirements.

Specific NCS data types, data users, the data lifecycle, disclosure review, and data access are described in detail in the NCS Data Access and Confidentiality Concept of Operations. The initial public draft is available at https://www.nationalchildrensstudy.gov/about/overview/Pages/NCS-CONOPS-Data-Access-and-Confidentiality.pdf. Specifically, all NCS data intended for a public audience will undergo disclosure review, using procedures consistent with those named in Statistical Working Paper 22 of the Federal Committee on Statistical Methodology, and steps will be taken to appropriately manage disclosure risk.

A.11 Justification for Sensitive Questions

This ICR includes some questionnaire items that may be considered sensitive or difficult for respondents to answer. Specific examples include questions related to domestic violence and the loss of a family member. Other topics, such as income, that are commonly asked in studies may also lead to potential discomfort. The NCS is aware of these issues and has taken steps to reduce participant concerns. As part of the informed consent process, all participants – mothers, fathers, and primary caregivers – are informed that their participation in NCS is voluntary and that they may refuse to answer any question. All proposed study questionnaires have been or will be reviewed by Human Subjects Review Boards at

NICHD and participating institutions. The NCS has requested approval for multi-mode administration of instruments, allowing flexibility for participants to respond in the method with which they feel most comfortable. Additionally, procedures have been developed to ask highly personal or sensitive questions as part of a self-administered instrument, allowing for maximum privacy of responses. Piloting these sensitive questions in the NCS Vanguard Study is necessary to allow informed decisions when considering items to include in the NCS Main Study.

A.12 Estimates of Hour Burden Including Annualized Hourly Costs

Estimates of annualized hour burden and annualized cost to respondents are laid out in Tables A.12.1 and A.12.1, respectively. The total number of estimated respondents is 35,625 annually. The total number of annual burden hours is 55,122. The estimated total annual respondent cost is $551,218. A comprehensive listing of all data collection activities and associated instrumentation is provided in Attachment 5.

By data collection activity, the number of estimated respondents varies based on the retention estimates between study visits. For all study visits, we are estimating 95% compliance from study visit to study visit.

The frequency of response varies by data collection activity. For instance, the Participant Verification & Tracing Interview is administered at every study visit starting at Pregnancy Visit 1; therefore, the frequency of response is 15, whereas the 36-Month Interview is administered only once.

The average burden per response was determined by timing instruments and applicable files (e.g., Multi-mode Visit Information Scripts) that impose burden and the average burden per response for sample and physical measure collections are estimates based on field experience.

In general, study visits range between approximately 10 to 240 minutes. Burden associated with biospecimen and environmental sample collection and physical measures collection differ based on what samples are collected (for instance, measuring pulmonary function at 60 months only takes 12 minutes per respondent, while activities associated with the collection of child blood, saliva, urine, and baby teeth at 60 months take 48 minutes).

Estimates of the total annual respondent cost for the collection of information use the appropriate wage rate categories. For individuals, the wage rate is $10.00 per hour.

The cost of contracting out or paying outside parties for information collection activities is included in A.14.

NOTE: Instruments or recruitment strategies in **bold** represent new collection.

A.12.1 Estimated Annualized Burden Hours

Table A.12.1 Estimates of Hour Burden for Vanguard (Pilot) Study Respondents, Study Visits through 60 Months of Age of the Child					
Data Collection Activity	**Type of Respondent**	**Estimated Number of Respondents**	**Estimated Number of Responses per Respondent**	**Average Burden Per Response (in hrs)**	**Estimated Total Annual Burden Hours**
Pregnancy Screening Activities					
Pregnancy Screener Sibling Birth Cohort SAQ *(9M to 60M)*	Biological Mother	1,122	10	3/60	561
Retrospective Pregnancy Interview *(Birth, 3M, 6M)*	Biological Mother	422	1	47/60	331
Continuous Activities					
Participant Verification & Tracing (PVT) Interview *(PV1 to 60M)*	Pregnant Woman, Father/Father Figure, Biological Mother, Primary Caregiver, Secondary Residence Caregiver	877	15	7/60	1,535
Validation Interview *(Pre-Pregnancy to 60M)*	Pregnant Woman, Father/Father Figure, Biological Mother, Primary Caregiver, Secondary Residence Caregiver	850	1	2/60	28
Participant Information Update - Incentive Substudy *(24M to 60M)*	Primary Caregiver	1,364	1	5/60	114
Event Driven Activities					
Pregnancy Loss, Stillbirth, & Neonatal Death Interview *(PV1, PV2, Birth)*	Pregnant Woman, Biological Mother	13	1	17/60	4
Parent-Caregiver Death Interview *(3M to 60M)*	Proxy	3	1	8/60	0.46
Child Death Interview *(3M to 60M)*	Primary Caregiver	4	1	8/60	0.58
Non-Interview Respondent Interview *(Pre-Pregnancy to 60M)*	Pre-Pregnant Woman, Pregnant Woman, Father/Father Figure, Biological Mother, Primary Caregiver	603	1	5/60	50
Secondary Residence Interview *(36M, 48M, 60M)*	Secondary Residence Caregiver	221	1	13/60	48
Preconception Activities					
Pre-Pregnancy Interview	Pre-Pregnant Woman	445	1	32/60	241
Adult-Focused Biospecimen Collection - Blood & Urine	Pre-Pregnant Woman	356	1	26/60	154
Pregnancy Probability Group Follow-up	Pre-Pregnant Woman	445	1	15/60	111
Pre-Natal Activities					
Pregnancy Visit 1 Interview	Pregnant Woman	333	1	86/60	481
Pregnancy Visit 2 Interview	Pregnant Woman	333	1	54/60	303
Adult-Focused Biospecimen Collection - Blood & Urine *(PV1, PV2)*	Pregnant Woman	267	2	26/60	231

Table A.12.1 Estimates of Hour Burden for Vanguard (Pilot) Study Respondents, Study Visits through 60 Months of Age of the Child					
Data Collection Activity	**Type of Respondent**	**Estimated Number of Respondents**	**Estimated Number of Responses per Respondent**	**Average Burden Per Response (in hrs)**	**Estimated Total Annual Burden Hours**
Environmental Sample Collection - Vacuum Bag Dust *(PV1)*	Primary Caregiver	283	1	3/60	14
Father Pre-Natal Interview *(PV1 or PV2)*	Father/Father Figure	317	1	64/60	338
Pregnancy Health Care Log *(PV1 or PV2)*	Biological Mother	333	1	5/60	28
Birth Activities					
Birth Interview	Biological Mother	317	1	40/60	214
Adult-Focused Biospecimen Collection - Blood, Urine, Cord Blood, Breast Milk, Placenta, & **Microbiome Swab**	Biological Mother	253	1	85/60	358
Child-Focused Biospecimen Collection - Infant Blood Spot	Child	253	1	3/60	13
Post-Natal Activities					
Infant & Child Health Care Log *(Birth to 60M)*	Primary Caregiver	2,067	1	5/60	172
3-Month Interview	Primary Caregiver	475	1	45/60	356
	Biological Mother	475	1	2/60	16
Adult-Focused Biospecimen Collection - Breast Milk, Blood, Urine, **Saliva, & Microbiome Swab** *(3M, 6M, 12M, 24M, 36M, 48M, 60M)*	Primary Caregiver	832	14	40/60	7,811
6-Month Interview	Primary Caregiver	475	1	49/60	386
Core Questionnaire - Child, Adult, & Household *(6M to 60M, except 9M)*	Primary Caregiver	1,107	9	34/60	5,646
Child-Focused Biospecimen Collection - Urine, Blood, Saliva, **Microbiome Swab, & Teeth** *(6M, 12M, 24M, 36M, 48M, 60M)*	Primary Caregiver	886	14	44/60	9,027
9-Month Interview	Primary Caregiver	554	1	14/60	127
Father Post-Natal Interview *(9M or 18M)*	Father/Father Figure	558	1	16/60	149
12-Month Interview	Primary Caregiver	554	1	52/60	478
Child-Focused Physical Measures - Anthropometry, Blood Pressure, **Vision Screening, Lung Function, & Motor Skills** *(6M, 12M, 24M, 36M, 48M, 60M)*	Child	1,217	2	9/60	365
	Primary Caregiver	935	13	41/60	8,375
Environmental Sample Collection - Vacuum Bag Dust, **Indoor and Outdoor Visual Observations, & Dust Wipes** *(12M, 36M, 48M, 60M)*	Primary Caregiver	1,085	13	8/60	1,775

Table A.12.1 Estimates of Hour Burden for Vanguard (Pilot) Study Respondents, Study Visits through 60 Months of Age of the Child					
Data Collection Activity	**Type of Respondent**	**Estimated Number of Respondents**	**Estimated Number of Responses per Respondent**	**Average Burden Per Response (in hrs)**	**Estimated Total Annual Burden Hours**
18-Month Interview	Primary Caregiver	562	1	51/60	475
24-Month Interview	Primary Caregiver	1,046	1	44/60	763
30-Month Interview	Primary Caregiver	1,286	1	61/60	1,302
36-Month Interview	Primary Caregiver	1,711	1	79/60	2,246
	Child	1,711	1	22/60	627
42-Month Interview	Primary Caregiver	1,364	1	43/60	972
	Biological Mother, Biological Father	1,364	1	15/60	341
48-Month Interview	Primary Caregiver	1,380	1	107/60	2,455
54-Month Interview	Primary Caregiver	1,431	1	34/60	804
60-Month Interview	Primary Caregiver	1,332	1	64/60	1,415
	Child	1,332	1	22/60	488
Subsample Studies					
Noise *(36M, 60M)*	Primary Caregiver	200	2	17/60	113
Bioelectrical Impedance Analysis (BIA) *(48M, 60M)*	Primary Caregiver	67	2	7/60	16
Physical Activity (Accelerometer) *(36M, 48M, 60M)*	Primary Caregiver	200	3	43/60	430
Total Vanguard (Pilot) Study					**52,286**
Total Formative Research					**2,835**
Grand Total Vanguard (Pilot) Study					**55,122**

A.12.2 Annualized Cost to Respondents

Table A.12.2 Estimated Annualized Cost for Vanguard (Pilot) Study Respondents, Study Visits through 60 Months of Age of the Child				
Data Collection Activity	**Type of Respondent**	**Estimated Total Annual Burden Hours**	**Hourly Wage Rate**	**Estimated Total Annual Respondent Cost**
Pregnancy Screening Activities				
Pregnancy Screener Sibling Birth Cohort SAQ *(9M to 60M)*	Biological Mother	561	$10.00	$5,612
Retrospective Pregnancy Interview *(Birth, 3M, 6M)*	Biological Mother	331	$10.00	$3,308
Continuous Activities				

Table A.12.2 Estimated Annualized Cost for Vanguard (Pilot) Study Respondents, Study Visits through 60 Months of Age of the Child				
Data Collection Activity	**Type of Respondent**	**Estimated Total Annual Burden Hours**	**Hourly Wage Rate**	**Estimated Total Annual Respondent Cost**
Participant Verification & Tracing (PVT) Interview *(PV1 to 60M)*	Pregnant Woman, Father/Father Figure, Biological Mother, Primary Caregiver, Secondary Residence Caregiver	1,535	$10.00	$15,347
Validation Interview *(Pre-Pregnancy to 60M)*	Pregnant Woman, Father/Father Figure, Biological Mother, Primary Caregiver, Secondary Residence Caregiver	28	$10.00	$283
Participant Information Update - Incentive Substudy *(24M to 60M)*	Primary Caregiver	114	$10.00	$1,137
Event Driven Activities				
Pregnancy Loss, Stillbirth, & Neonatal Death Interview *(PV1, PV2, Birth)*	Pregnant Woman, Biological Mother	4	$10.00	$37
Parent-Caregiver Death Interview *(3M to 60M)*	Proxy	0.46	$10.00	$5
Child Death Interview *(3M to 60M)*	Primary Caregiver	0.58	$10.00	$6
Non-Interview Respondent Interview *(Pre-Pregnancy to 60M)*	Pre-Pregnant Woman, Pregnant Woman, Father/Father Figure, Biological Mother, Primary Caregiver	50	$10.00	$503
Secondary Residence Interview *(36M, 48M, 60M)*	Secondary Residence Caregiver	48	$10.00	$480
Preconception Activities				
Pre-Pregnancy Interview	Pre-Pregnant Woman	241	$10.00	$2,410
Adult-Focused Biospecimen Collection - Blood & Urine	Pre-Pregnant Woman	154	$10.00	$1,543
Pregnancy Probability Group Follow-up	Pre-Pregnant Woman	111	$10.00	$1,113
Pre-Natal Activities				
Pregnancy Visit 1 Interview	Pregnant Woman	481	$10.00	$4,806
Pregnancy Visit 2 Interview	Pregnant Woman	303	$10.00	$3,028
Adult-Focused Biospecimen Collection - Blood & Urine *(PV1, PV2)*	Pregnant Woman	231	$10.00	$2,311
Environmental Sample Collection - Vacuum Bag Dust *(PV1)*	Primary Caregiver	14	$10.00	$142
Father Pre-Natal Interview *(PV1 or PV2)*	Father/Father Figure	338	$10.00	$3,378
Pregnancy Health Care Log *(PV1 or PV2)*	Biological Mother	28	$10.00	$278
Birth Activities				

Table A.12.2 Estimated Annualized Cost for Vanguard (Pilot) Study Respondents, Study Visits through 60 Months of Age of the Child				
Data Collection Activity	**Type of Respondent**	**Estimated Total Annual Burden Hours**	**Hourly Wage Rate**	**Estimated Total Annual Respondent Cost**
Birth Interview	Biological Mother	214	$10.00	$2,137
Adult-Focused Biospecimen Collection - Blood, Urine, Cord Blood, Breast Milk, Placenta, & **Microbiome Swab**	Biological Mother	358	$10.00	$3,584
Child-Focused Biospecimen Collection - Infant Blood Spot	Child	13	$10.00	$127
Post-Natal Activities				
Infant & Child Health Care Log *(Birth to 60M)*	Primary Caregiver	172	$10.00	$1,722
3-Month Interview	Primary Caregiver	356	$10.00	$3,563
	Biological Mother	16	$10.00	$158
Adult-Focused Biospecimen Collection - Breast Milk, Blood, Urine, **Saliva, & Microbiome Swab** *(3M, 6M, 12M, 24M, 36M, 48M, 60M)*	Primary Caregiver	7,811	$10.00	$78,114
6-Month Interview	Primary Caregiver	386	$10.00	$3,858
Core Questionnaire - Child, Adult, & Household *(6M to 60M, except 9M)*	Primary Caregiver	5,646	$10.00	$56,457
Child-Focused Biospecimen Collection - Urine, Blood, Saliva, **Microbiome Swab, & Teeth** *(6M, 12M, 24M, 36M, 48M, 60M)*	Primary Caregiver	9,027	$10.00	$90,266
9-Month Interview	Primary Caregiver	127	$10.00	$1,268
Father Post-Natal Interview *(9M or 18M)*	Father/Father Figure	149	$10.00	$1,489
12-Month Interview	Primary Caregiver	478	$10.00	$4,779
Child-Focused Physical Measures – Anthropometry, Blood Pressure, **Vision Screening, Lung Function, & Motor Skills** *(6M, 12M, 24M, 36M, 48M, 60M)*	Child	365	$10.00	$3,652
	Primary Caregiver	8,375	$10.00	$83,747
Environmental Sample Collection - Vacuum Bag Dust, **Indoor and Outdoor Visual Observations, & Dust Wipes** *(12M, 36M, 48M, 60M)*	Primary Caregiver	1,775	$10.00	$17,750
18-Month Interview	Primary Caregiver	475	$10.00	$4,755
24-Month Interview	Primary Caregiver	763	$10.00	$7,626
30-Month Interview	Primary Caregiver	1,302	$10.00	$13,016
36-Month Interview	Primary Caregiver	2,246	$10.00	$22,458
	Child	627	$10.00	$6,275
	Primary Caregiver	972	$10.00	$9,716
42-Month Interview	Biological Mother, Biological Father	341	$10.00	$3,411

Table A.12.2 Estimated Annualized Cost for Vanguard (Pilot) Study Respondents, Study Visits through 60 Months of Age of the Child				
Data Collection Activity	**Type of Respondent**	**Estimated Total Annual Burden Hours**	**Hourly Wage Rate**	**Estimated Total Annual Respondent Cost**
48-Month Interview	Primary Caregiver	2,455	$10.00	$24,548
54-Month Interview	Primary Caregiver	804	$10.00	$8,045
60-Month Interview	Primary Caregiver	1,415	$10.00	$14,148
	Child	488	$10.00	$4,884
Subsample Studies				
Noise *(36M, 60M)*	Primary Caregiver	113	$10.00	$1,133
Bioelectrical Impedance Analysis (BIA) *(48M, 60M)*	Primary Caregiver	16	$10.00	$156
Physical Activity (Accelerometer) *(36M, 48M, 60M)*	Primary Caregiver	430	$10.00	$4,300
Total Vanguard (Pilot) Study		**52,286**		**$522,864**
Total Formative Research		**2,835**		**$28,353**
Grand Total Vanguard (Pilot) Study		**55,122**		**$551,218**

A.13 Estimate of Other Total Annual Cost Burden to Respondents or Record keepers

NCS participants will be reimbursed for any expense resulting from their participation in the NCS, see section A.9. There are no additional costs associated with acquiring, installing, or utilizing technology and systems. In turn, there are no capital and start-up costs and there are no costs associated with operation and maintenance and purchase of services.

A.14 Annualized Cost to the Federal Government

The proposed information collection is estimated to cost about $20,479,000 per year over a three-year period. Note that this estimate assumes an average annual cost for each year. Actual costs will vary across years. The annualized cost to the federal government is based on budgetary data for task orders that include costs of information collection, design, development, tests, printing forms, mailing list compilation and maintenance, mailing or enumeration, editing, coding, tabulation, analysis and publication of results. Salary and travel costs associated with project development, implementation, and monitoring are incorporated into the annualized cost to the federal government.

A.15 Explanation of Program Changes or Adjustments

This section describes program changes that are largely the result of deliberate Federal government action. The only program change driven by statute is the proposed implementation of data collection standards pursuant to Section 4302 of the Affordable Care Act.

As noted in A.2, program changes/adjustments that affect burden include the initiation of a new enrollment cohort, the establishment of new Study visits, and revisions to already-established Study visits. The two proposed methodological substudies are designed to understand the impact of variable

incentives on participation in existing and proposed study visits. On their own, these substudies do not impose additional participant burden.

Currently, the NCS is approved for 22,911 annualized burden hours. With this ICR, the total annualized hour burden for the NCS Vanguard Study is approximately 55,122 hours, which is an increase in burden.

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

This ICR includes the introduction of new Study visits designed to assess NCS Vanguard Study children as they age. These visits – designed for children ages 36 to 60 months – may include questionnaire-based interviews as well as biological and environmental sample collections and other data collection activities. A number of new and revised data collection instruments are also proposed to be added to Study visits up to 30 month visits that have previously received clearance.

Key evaluation questions during this continued phase of the NCS Vanguard Study concern the logistical and operational feasibility of data collection procedures to assess and understand if each visit, components of individual visits, and individual data collection instruments, work to capture the desired information and can be scaled up for the Main Study. A number of critical evaluations to be performed are summarized in Table A16-1 below.

Table A16-1. Proposed NCS Vanguard Study Evaluations

Data Collection Level	Technical Performance	Cooperation/Response
I. Study Visit	- Visit completion rate (including number and percent of components completed) - Visit duration or time to complete	- Compliance rate - Attrition rate - Variations in these rates by demographic characteristics
	Comparison of the above evaluation metrics by mode of Study Visit administration (in-person, telephone, mail, and online)	
II. Study Visit components		
a. Biospecimen collection*	- Time to complete data collection component - Comparison to established national and/or gold standard measures - Data quality/suitability	- Data collection component completion rate - Unit response rate - Item response rate - Variations in these rates by demographic characteristics
b. Environmental sample collection*		
c. Physical measures		
d. Neurodevelopmental measures		
e. Other questionnaire topics		
	*Comparison of the above evaluation metrics by whether the specimen/sample collection is done by data-collector or participant, where applicable	
III. Individual data collection instrumentation under Level II component		
a. Biospecimen collection*	- Time to complete data collection component - Comparison to established national and/or gold standard measures - Data quality/suitability	- Data collection component completion rate - Unit response rate - Item response rate - Variations in these rates by demographic characteristics
b. Environmental sample collection*		
c. Physical measures		
d. Neurodevelopmental measures		

Table A16-1. Proposed NCS Vanguard Study Evaluations		
Data Collection Level	**Technical Performance**	**Cooperation/Response**
e. Other questionnaire topics		
	*Comparison of the above evaluation metrics by whether the specimen/sample collection is done by data-collector or participant, where applicable	

In addition to these key evaluation items, any specific assessments that are necessary and unique to individual instrumentation will be performed based on the criteria developed by individual domain teams. For example, the Participant Motivation Questionnaire, planned for administration after the 48 month visit, will be evaluated on individual response distributions to understand participant's experience in the Study and what motivates them to continue participation. Similarly, Participant Satisfaction Questionnaire responses will also be analyzed to help determine the acceptability of the various components of Study Visits. Data from these instruments may also be used when examining unit nonresponse overall.

The proposed *Sibling Birth Cohort* is designed to enroll births from NCS mothers' subsequent pregnancies with a primary goal of collecting data early in pregnancy, during critical periods of development. NCS Vanguard Study experience to date demonstrates the difficulty of enrolling women who are likely to become pregnant in the very near term and this new enrollment cohort enables us to test the feasibility of collecting pre- or peri-conception data with an efficient methodology that is not cost-prohibitive. The Sibling Birth Cohort will allow us to determine whether subsequent pregnancy data, along with the data already collected on the family environment from the NCS index child, can serve to provide peri-conceptional data. Table A16-2 describes our proposed evaluation in order to understand key feasibility questions.

Table A16-2. Proposed Evaluation of the NCS Sibling Birth Cohort Enrollment	
Key Evaluation Questions	**Evaluation Metrics/Description**
Can subsequent pregnancies be identified in the Study cohort?	Proportion of NCS mothers who become pregnant in X months following the birth of initial NCS child Proportion of NCS mothers with subsequent pregnancies who consent to enroll in Sibling Birth Cohort
How early in pregnancy can we identify subsequent pregnancies and conduct first pregnancy visit?	Distribution of and mean gestational age at which subsequent pregnancy is identified
	Distribution of and mean gestational age at which first pregnancy visit occur for this subsequent pregnancy
	Comparison of the mean gestational age at first pregnancy visit for this subsequent pregnancy vs. mean gestational age at first pregnancy visit for the index NCS pregnancy
What part of the mothers' prior data useful in providing baseline, pre-pregnancy information for the subsequent pregnancy?	Comparison on data items for changes (or no changes) over time between index pregnancy and subsequent pregnancy, adjusted for any residential or family composition changes, by domain areas – environmental exposure, health

Table A16-2. Proposed Evaluation of the NCS Sibling Birth Cohort Enrollment	
Key Evaluation Questions	**Evaluation Metrics/Description**
	behavior, parenting, stress, etc.
What is the completeness of data collection for subsequent pregnancies? And How does this compare to completeness in the rest of the Study cohort?	Data collection completion rates on subsequent pregnancy Study Visit(s) and its components Comparison of these rates to completion rates of Study Visits/components from index NCS pregnancy

The NCS will share our findings at various stakeholder meetings such as the NCS Federal Advisory Committee and Independent Safety and Monitoring Oversight Committee meetings. We will also disseminate the findings through manuscripts commissioned by the NCS Publication Committee when appropriate, strictly following the Agency's "Guidelines for Ensuring the Quality of Information Disseminated to the Public," and will include specific discussion of the limitation of the data collected for methodological purposes.

Table A16-3. NCS Vanguard Study Data Collection Timeline	
NCS Vanguard Study Activity	**Time Schedule**
Analysis of NCS Vanguard Study participant retention	ongoing
Launch of new and revised Vanguard Study measures	4-6 months after OMB approval
Launch of Sibling Birth Cohort enrollment effort	3 months after OMB approval
Begin analysis of new and revised measures	8-12 months after OMB approval

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 Exceptions to Certification for Paperwork Reduction Act Submissions

The NCS is not requesting any exceptions.