



DATE: July 18, 2014

TO: Dr. Margo Schwab
Office of Management and Budget
Office of Information and Regulatory Affairs

FROM: National Children's Study Program Office

SUBJECT: Request for Non-Substantive Change to National Children's Study, Vanguard (Pilot) Study (OMB Control #0925-0593, Expiration Date: June 30, 2017)
- Stage 2 Review of Request for Revision

CC: Ms. Seleda Perryman, Ms. Mikia Currie, Dr. Sarah Glavin, Ms. Jamelle Banks

The National Children's Study (NCS) received a Notice of Action from the Office of Management and Budget (OMB) on June 3, 2014 approving the continuation of NCS Vanguard Study data collection activities through the 60 month Study visit. The terms of clearance as noted on this action are as follows.

This package is being approved in stages due to breadth and complexity of the changes requested. The approval granted May 2014 ONLY covers the following elements: a) the continuation of already established data collection events (age-defined Study Visits or triggerbased collections) including all associated instruments protocols and consent documents, b) revision to the previously approved 30 month Study Visit, c) establishment of new Study Visits at 36 and 42 months. Although subsequent approval must be sought before implementing new Study Visits at ages 48, 54, and 60 months, adding biospecimen sampling to prior approved visits, conducting substudies and incentive tests, and initiating the sibling cohort, no additional public comment is required for the re-submission of the refined requests for these study components because public comment has already been sought and preliminary instruments were provided in the original submission. Additional discussion is also required to ensure that datasets are made available to non-NCS researchers in a manner consistent with the context in which they were approved.

Per these terms of clearance, the NCS now requests a non-substantive change from the Office of Information and Regulatory Affairs (OIRA) to reflect refinements made to previously approved Study visits. Details are provided below.

1. Revision to Study Visits at 48, 54 and 60 months

As indicated in the initial submission, data collection activities at 48, 54, and 60 months are required to assess enrolled children as they age through key developmental periods. These Study visits have been approved in concept as part of the full clearance but are not yet implemented. The 48, 54, and 60 month Study visits will be administered to eligible, enrolled participants previously recruited from 40 NCS Vanguard Study locations.

Each Study visit is comprised of multiple components and modules; some are used repeatedly across several Study visits, while others are specific to defined ages or developmental stages. Per the above terms of clearance, the NCS has streamlined and updated components as appropriate. Table 1 below describes modifications made to age-specific modules since the initial submission. A complete listing of all domains included in each questionnaire is provided in Table 3 below.

Table 1. Revisions to originally submitted 48, 54, and 60M Instruments

Questionnaire	Module Name	Revisions
48 Month Child	Physical Activity	Removed 1 item
48 Month Adult	Sleep Routine	Removed 2 items
48 Month Household	Occupational/Hobby Exposures	Shortened module to 3 items
54 Month Adult	Cultural Values	Removed module
60 Month Child	Physical Activity	Removed module
	Sun Exposure	Removed module
	Noise Exposure	Replaced original module with streamlined version used in 36 Month Child Questionnaire
60 Month Household	All Modules	Removed all questions in the questionnaire

NCS visits are developed to align with specific 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.¹ Broad categories describing these milestones include Social & Emotional; Language/Communication; Cognitive; and Movement/Physical Development.² The NCS also measures biological, environmental and social factors, categorized as General Health; Social Environment; and Physical Environment. These categories are mapped to specific instruments, assessments, and collections proposed for the 48, 54, and 60 Month Study visits. Table 2 provides this mapping for the sample collections, physical measures, and scored assessments associated with each Study visit. Collections or assessments that have not been implemented at younger ages are presented in italics.

Table 2. Sample Collections/Assessments and Associated Developmental Milestones of the 48, 54, and 60M Study visits

¹ 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>

² <http://www.cdc.gov/ncbddd/actearly/milestones/milestones-3yr.html>

Collection Type	Collection/Assessment	Target or Subject(s)	Milestone(s)	Study Visit(s)
Physical Measures	Anthropometry	Child	General Health	48M, 60M
	Blood Pressure	Child	General Health	48M, 60M
	NIH Toolbox Visual Acuity Test	Child	General Health	60M
	<i>Bioelectrical Impedance Analysis</i>	Child	General Health	48M, 60M
	<i>Lung Function</i>	Child	General Health	60M
	<i>NIH Toolbox Early Childhood Motor Battery</i>	Child	General Health; Movement/Physical Development	60M
	<i>Physical Activity Monitoring</i>	Child	General Health; Movement/Physical Development	48M, 60M
Biospecimens	Blood	Child; Adult	General Health; Physical Environment	60M
	Urine	Child; Adult	General Health; Physical Environment	60M
	Saliva	Child	General Health; Physical Environment	60M
	<i>Microbiome</i>	Child; Adult	General Health; Physical Environment	48M
	<i>Baby Teeth</i>	Child	General Health; Physical Environment	60M
Environmental Samples	Vacuum Bag Dust	Household	Physical Environment	48M, 60M
	Dust Wipe	Household	Physical Environment	48M, 60M
	Noise	Household	Physical Environment	60M
Scored Assessments	Ages & Stages Questionnaire-3™	Child	Social & Emotional; Language/Communication; Cognitive; Movement/Physical Development	48M, 60M
	SWAN Rating Scale for ADHD	Child	Social & Emotional; Language/Communication; Cognitive	60M
	<i>NIH Toolbox Cognition Battery</i>	Adult	Social & Emotional; Language/Communication; Cognitive	48M
	<i>NIH Toolbox Parent Proxy Emotion Battery</i>	Adult	Social & Emotional	48M
	Major Life Events	Adult	Social & Emotional; Social	60M

Collection Type	Collection/Assessment	Target or Subject(s)	Milestone(s)	Study Visit(s)
			Environment	
	<i>Autism Quotient Test</i>	Child	Social & Emotional; Social Environment; Language/Communication; Cognitive	54M
	NIH Toolbox Early Childhood Cognition Battery	Child	Language/Communication; Cognitive	60M

Table 3 provides similar information for the questionnaires administered at each Study visit. All domains and sections included in each questionnaire are noted, with any section not previously implemented at younger ages highlighted in italics.

Table 3. Questionnaire Domains and Associated Milestones from the 48, 54, and 60M Study visits

Questionnaire	Section Name	Target or Subject(s)	Milestone(s)	Study Visit(s)
Core	Child Care/Day Care Arrangements and Exposures	Child	Social Environment; Physical Environment	48M, 54M, 60M
	Viewing of Media/Reading Books	Child	Social & Emotional; Social Environment; Language/Communication; Cognitive; Movement/Physical Development	48M, 54M, 60M
	Program Participation/Receipt of Benefits	Child; Household	Social Environment	54M
	Health Insurance	Child	Social Environment	54M
	Health Care Utilization/Access	Child	General Health; Social Environment	48M, 54M, 60M
	General Health	Child; Adult	General Health; Social & Emotional	48M, 54M, 60M (Child); 48M, 60M (Adult)
	Medical Conditions - General	Child	General Health; Social & Emotional	48M, 60M
	Medical Conditions - Asthma & Eczema	Child	General Health	48M, 54M, 60M
	Well-Child Care/Vaccinations	Child	General Health	48M, 54M, 60M
	Emergency Room/Urgent Care Visits	Child	General Health	48M, 60M

Questionnaire	Section Name	Target or Subject(s)	Milestone(s)	Study Visit(s)
	Hospitalizations	Child	General Health	48M, 60M
	Medications	Child	General Health	48M, 54M, 60M
	Sleep Routine	Child	General Health; Social Environment; Social & Emotional	48M, 54M, 60M
	Concerns about Child's Development	Child	Language/Communication; Movement/Physical Development ; Social & Emotional	48M, 54M, 60M
	Employment	Adult	Social Environment	48M, 60M
	Occupation	Adult	Physical Environment; Social Environment	48M, 60M
	Education	Adult	Social Environment	48M, 60M
	Housing Characteristics	Household	Physical Environment; Social Environment	48M, 54M, 60M
	Neighborhood Characteristics	Household	Physical Environment; Social Environment	48M, 54M, 60M
	Pesticide Use	Household	Physical Environment	48M, 54M, 60M
	Smoking in Home	Household	Physical Environment; Social Environment	48M, 54M, 60M
	Pets	Household	Physical Environment; Social Environment	48M, 54M, 60M
	Income	Household	Social Environment	54M
Age-Specific	Parenting	Child	Social Environment; Social & Emotional	48M
	Physical Activity	Child	Movement/Physical Development; General Health; Social Environment; Physical Environment	48M
	Sun Exposure	Child	General Health; Social Environment; Physical Environment	48M
	Occupational/Hobby Exposures	Household	Physical Environment	48M
	<i>Sleep Routine</i>	Adult	General Health; Social Environment; Social & Emotional	48M
	Dietary Food Frequency	Child	General Health	54M
	<i>Health Behaviors</i>	Child	General Health; Social Environment; Physical Environment	54M

Questionnaire	Section Name	Target or Subject(s)	Milestone(s)	Study Visit(s)
	<i>Religious Affiliation</i>	Adult	Social Environment	54M
	<i>Parenting (Parental Modernity Scale)</i>	Adult	Social Environment; Social & Emotional	54M
	Noise Exposure	Child	Environmental Exposures; Social Environment; Social & Emotional	60M
	Race/Ethnicity	Child	Social Environment	60M
	<i>School Experiences</i>	Child	Social Environment; Social & Emotional; Physical Environment	60M
	Household Composition & Demographics	Adult	Social Environment	60M
Interviewer Completed	Interviewer Observations	Child; Adult; Household	Social Environment; Social & Emotional; Physical Environment	48M, 54M, 60M
	Indoor/Outdoor Dwelling Visual Observations	Household	Social Environment; Physical Environment	48M, 60M
Trigger-Based	Secondary Residence	Household	Social Environment; Physical Environment	48M, 54M, 60M

NCS Sub-Studies

Two NCS sub-studies were previously approved but are not yet implemented. This non-substantive change request seeks clearance to begin their administration starting at the 36 month Study visit.

Noise. Noise is recognized by the European Union and the World Health Organization as an important exposure to children (European Union, 2011; World Health Organization-Joint Research Centre of the Commission, 2011). 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 (Seidman and Standing, 2010). 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 (Schell et al., 2006; Evans et al., 2001; World Health Organization-Joint Research Centre of the Commission, 2011). Living in crowded and noisy environments is associated with health risks for children including an increase in stress (Ising & Kruppa, 2004). Studies of aircraft noise indicate a slight tendency towards a positive relationship between aircraft noise exposure and blood pressure in children, and studies on road-traffic noise show a more uniform trend in the direction of a positive relationship with systolic blood pressure in children (Paunović et al, 2011).

Sources of environmental noise are not well characterized but include noise such as transient noise intrusions from outdoors (e.g., airplanes, cars, trucks, construction, industry, or outdoor events) and sources indoors (e.g., television, music, appliances, and ventilation equipment). Some noises can arise

from either outdoors or indoors (e.g., sounds made by neighbors, talk, laughter, slamming doors, and noise from animals, such as barking dogs) (Omlin et al, 2011; European Union, 2011).

Typically, noise is assessed by recall questionnaire about exposure to noise or by measurement of a specific external source outside the home, such as an airport or highway. Both are inferior to a direct measurement of noise as proposed by the NCS. The NCS proposes to investigate the feasibility, acceptability, and cost to characterize noise in the homes of participants with a noise measurement device. This study will test the performance of the selected device to measure and record the intensity and duration of noise in the environment, the ability to identify sources of noise detected, assess participant tolerance and burden for this kind of measurement assessment, and determine the cost to deploy this kind of device. From this study, the NCS will learn the logistics required to set up an instrument to measure noise in homes, the duration of monitoring required to characterize noise in homes, and if the results of direct measurements are superior to conventional procedures.

Noise measurements will be conducted in the homes of approximately 200 NCS enrolled children, randomly selected, from one Regional Operations Center (ROC). (These children will not be the same as those children enrolled in the sub-study of physical activity). Noise measures will be collected at the 36 and 60 Month Study Visits for a total of 400 measurements. This number of measurements should provide a sufficient number of sampling events to determine the logistics to deploy the device, participant acceptance of the device in their home, and encounter different sources of noise.

The ability to efficiently and economically measure noise directly would produce better quality data while reducing participant burden than current measurement procedures (i.e., questionnaires).

Physical Activity. The NCS proposes a direct measurement of childhood physical activity at the 36, 48, and 60 Month Study Visits. We seek to identify 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 NCS will pilot the use of accelerometers at three data collection points with a subsample of approximately 200 NCS enrolled children in one ROC using a protocol developed and tested by the National Health and Nutrition Examination Survey (NHANES). (These children will not be the same as those children enrolled in the sub-study of noise). A total of 600 measurements will be taken. This number of measurements should provide a sufficient number of sampling events to determine the logistics to deploy the device, assess participant acceptance of the device, and assess differences in physical activity at different ages.

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 the performance and ability to evaluate accelerometer data in a cohort of young children and to gain experience with the rate of change in children's physical activities (and the ability to measure them) as they grow older. This collection will provide data on the benefits and limitations of the methodology, the informative value of accelerometer data to estimate children's physical activities, and an evaluation of the logistics associated with data capture, transmission, and analysis of accelerometer data. Multiple data collection times are required as the changes in data over time are currently unknown.

2. Revisions to Informed Consent Documents

The consent materials were revised in response to the comments provided by OMB. A number of revisions were made across the consent materials to:

- remove the use of the term “confidentiality;”
- to clarify and harmonize the periodicity of visits across all consent materials;
- to clarify the time points/ages at which children can be considered legal adults and provide their own consent versus the 21-year period that we hope to follow participants; and
- to provide more examples of sites on the body for planned skin swab collections.

These changes to the consent materials are noted in a summary table (Attachment 7) that lists individual comments and NCS responses. We also provided responses to six specific questions from OMB which touched on some of the areas specified above as well as issues regarding re-consent and the frequency of consent administration. A comprehensive response is available in Attachment 7.

In general, with regard to our approach to informed consent, the NCS views informed consent as a process rather than a single event. In the Vanguard Study, informed consent and assent are regarded as ongoing, cumulative processes rather than as single events. After administration of the initial informed consent form, the NCS ongoing consent process continues with the administration of the Multimode Visit Information Script (MMVIS, Attachment 13) and the Sample Collection Visit Information Sheet (SCVIS) requirements (Attachment 14). Participants' ongoing verbal consent or dissent for Study participation as well as for participation in specific assessments is obtained using these materials which are tailored to explain the activities around Study contacts and assessments. The MMVIS is read at all contacts (regardless of mode of visit administration) and the SCVISs are provided for the in-person visits including where assessments other than questionnaires are planned.

Because the NCS develops the content of contacts on a flow basis, the SCVISs are a critical part of the ongoing informed consent process. The MMVIS includes a reminder of the key points of the general information about Study participation conveyed during the initial consent process. In response to discussion with OMB, these key points have been made uniform across the MMVIS and the SCVIS as part of the changes made to the consent materials. The combination of the initial consent, which includes documentation of consent, and then the administration of MMVIS AND SCVIS materials for ongoing verbal consent for Study participation and the conduct of specific assessments, achieves a robust, informative, and minimally burdensome consent process.

List of Attachments (*includes only instruments/documents that were revised from the original submission*)

- Attach 1. 48 Month Adult Questionnaire
- Attach 2. 48 Month Child Questionnaire
- Attach 3. 48 Month Household Questionnaire
- Attach 4. 54 Month Adult Questionnaire
- Attach 5. 60 Month Child Questionnaire
- Attach 6. 60 Month Household Questionnaire
- Attach 7. IRB Response to OMB Consent Concerns
- Attach 8. Informed Consent Form - Pregnant Woman
- Attach 9. Informed Consent Form - Fathers and Parental Partners
- Attach 10. Informed Consent Form - Adult
- Attach 11. Parental Permission Child Participation- 6 Months to Age of Majority
- Attach 12. Parental Permission Child Participation- Birth to 6 Months of Age
- Attach 13. Multi-Mode Visit Information Script

- Attach 14. Sample Collection Visit Information Sheet Scripts
- Attach 15. HIPAA Authorization to Obtain Bodily Fluids and Tissues
- Attach 16. Authorization for Release of Birth Certificate
- Attach 17. Authorization for Release of Child Death Certificate
- Attach 18. Authorization for Release of Parent/Guardian Death Certificate
- Attach 19. Reconsideration Questionnaire Adult
- Attach 20. Reconsideration Questionnaire Child