National Children's Study
Response to the National Academy of Sciences Review of the National Children's Study Research Plan

Introduction and Summary

On May 22, 2008, the National Academy of Sciences (NAS) released its review of the National Children's Study Research Plan. This independent review was requested by the National Children's Study (the Study) and by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Institutional Review Board. The purpose of the NAS review was to ensure that the Study is scientifically sound and is designed to yield the greatest possible research benefits.

The Study is very pleased with the NAS review and feels that it clearly met the objectives for performing it. We were especially pleased with affirmation that the Study should be carried out and that the general approaches were found to be appropriate (size, representative sample, and priority exposures and outcomes included). Though some of the noted weaknesses and recommendations are either already being addressed or would require substantial additional resources to implement, a number of the recommendations point to ways that the Study can be improved. We welcome these recommendations and where possible will be incorporating them into the Study.

We think that the NAS panel performed a thorough and balanced review that offers valuable support and improvements to the Study, and we thank the panel for their hard work. The NAS panel consisted of members from the Committee on National Statistics; the Board on Children, Youth and Families; and the Board on Population Health and Public Health Practice.

Background

The Study's Research Plan is the initial description of the rationale, background, and substantive framework of the developing Study, designed for peer review and public comment. The two-volume document outlines the Study's sampling scheme, the general scientific hypotheses that underlie the core of the Study, and lays out a general plan for how those questions will be addressed by the Study. Additional portions of the document elaborate the Study's approach to consent and ethical issues, data use policies, and human subjects protections. The Research Plan addresses each of the above topics in an intermediate level of detail that allows for evaluation of the Study's overall approach but does not provide the level of operational detail in a final protocol for field implementation. For instance, the Research Plan does not include specific data collection instruments or consent document wording. Electronic copies of the Research Plan can be found at:
http://www.nationalchildrensstudy.gov/research/studydesign/researchplan/Pages/default.aspx.

In June 2007, the initial version of the Research Plan was submitted for independent external review to an expert panel convened under the auspices of the National Academy of Sciences. The charge to the panel was to "…assess the scientific rigor of the National Children's Study and

the extent to which it is being carried out…to maximize the scientific yield of the study." The panel produced a review document, with a public release date of May 22, 2008.

During the 11-month review period, it was imperative that the Study continue to evolve and that data collection measures for the initial pilot phase of the Study be developed.

It is important to note that the NAS panel reviewed the broad, higher-level Research Plan, and not the data collection instruments and other detailed information that form the operational protocol for the Vanguard Pilot phase and beyond. The Research Plan outlines the rationale, design, and methodological approaches that form the longitudinal framework of the Study; the Vanguard Pilot protocol consists of information specifically related to the initial data collection during the first 3 years of the pilot phase of this large long-term study. Thus, there is not always concordance between the NAS recommendations and the Vanguard protocol currently prepared for the Vanguard Pilot phase.

Study Response to the NAS Review

General Comments

The review highlights strengths of the Study and areas for improvement. The NAS panel described the Study's goals and design as being responsive to its authorizing legislation, the Children's Health Act of 2000. The panel concluded that the Study's large, nationally representative sample design was a major strength, as was the Study's ability to measure multiple exposures and outcomes from before birth through adolescence. The panel agreed that the Study's selection of core exposures and outcomes represented appropriate topics for research.

The NAS panel recognized the difficulties of conducting a large nationally representative sample in a country that lacks a comprehensive national health database. Similarly, the panel acknowledged that the Study must operate within strict budgetary limits. Still, the panel noted a number of challenges in maximizing the Study's full and optimal potential and listed 33 specific recommendations for consideration. The largest number of these recommendations have already been implemented or are in the process of being implemented; for others the Study agrees with the need for the recommendation but could not do so without significant additional resources; for still others the approaches were considered but alternative approaches were judged to be more appropriate; and for the remainder we agree reconsideration should be given, and the Study is in the process of determining how best to institute those changes. It should be noted, however, that though each of the recommendations has been placed in a single category, many of them could logically be placed in more than one. For instance, the collection of paternal data (recommendation 3-10) is already included in the protocol to much of the extent proposed in the NAS review but not to the full extent due to resource limitations.

The various recommendations are listed below by number and title according to the above response by the Study. In addition, for reference to the NAS review, each recommendation with discussion of the specific Study response is listed in order as presented in the NAS report.

Recommendations Already Implemented or in the Process of Implementation

Since the time of submission of the Research Plan for NAS review, the Study continued to evolve, particularly for the initial pilot phase of the Study. Because of this, the Study is already implementing the majority of the recommendations. These are:

Recommendation number	Recommendation summary
2-4	Use Vanguard Centers as pilots
3-1	A broader set of maternal health conditions
3-2	Detailed protocols on all pregnancy outcomes
3-4	Focus on prenatal and early life risk factors for asthma
3-5	Incorporate social and psychological factors in childhood obesity
3-7	Refine protocols on reproductive development outcomes
3-9	Consider personal air sampling in subsample
3-11	Reconsider measures of housing and neighborhood conditions
3-12	Reconsider psychosocial measures in terms of high quality and analytic utility
3-14	Assure the timing of biological sample measurement is appropriate
3-15	Use validated approach to genetic analyses
3-16	Store biological samples until more cost-effective studies are possible
3-18	Facilitate linkage to secondary data sources by geocoding residences
4-2	Field test the proposed household listing approach
4-5	Maintain strict standards for quality assurance of data collection
4-6	Plan to monitor progress in reaching sample size
4-8	Assure rapid dissemination of data and provide analytic support
5-1	Define the criteria for giving information to participants
5-3	Engage communities in the Study

Recommendations Suitable for the Study but Not Possible with Current Resources

The Study completely agrees with some of the recommendations, but they would not be possible to implement because they would require significant additional resources beyond the scope of the projected costs. They are:

2-2	More frequent data collections from Study participants and more extensive data collections from other sources (such as health care records)
3-10	Increase data collection on fathers including chemical exposure
3-17	Add measures of access to and quality of services
4-7	Maintain an ongoing methods development program

Recommendations Considered but Alternate Approach Chosen

For the recommendations listed below, the recommended approach had been considered during Study development but was not adopted because the approach presented in the plan was concluded to be more appropriate for the Study. These decisions were based on extensive input from a number of experts involved in the planning process.

3-8	Add specific measures relating to immigrant legal status
3-13	Dedicate funds and use the structure of the Study to support development of new instruments for key psychosocial measures
4-1	Have reserve segment samples as an option to meet recruitment goals
4-3	Consider use of exposure data in defining primary sampling unit (PSU)-specific sampling strata
4-4	Consolidate data collection into small number of survey organizations

Recommendations Requiring Further Work or Future Consideration

Finally, there are recommendations we agree deserve reconsideration and for which the Study is developing an approach. They are:

2-1	Give priority attention to health disparities
2-3	A clearer conceptual framework
3-3	A clearer rationale for neurodevelopment and behavior disorders
3-6	Consider replacing traumatic brain injury hypothesis to assure adequate injury identification and to link with related factors and treatments
5-2	Equal accessibility to data by Study and non-Study investigators

Recommendations by NAS Chapter

Chapter 2: Study Goals, Conceptual Framework, and Core Hypotheses

2-1: Insufficient attention to racial, ethnic, and other disparities

The NAS review acknowledges that the Study will gather a great deal of information relevant to understanding racial, ethnic, or socioeconomic disparities in child health and development. However, the research design is criticized as not being "informed by a concern with understanding the basis" for such disparities. The review also points out that attention is not given to how individuals from different groups interact with health systems or to how psychosocial experiences vary among population groups.

Although not specifically described in the Research Plan, the Vanguard Pilot data collection instruments were designed to collect data relevant to health disparities. For many of the Study's hypotheses, race, ethnicity, and socioeconomic status are important confounders or effect modifiers. Such variables will be collected from all Study participants, including both parents, at multiple times before and during childhood. These data will not only be used in analytic

explorations of exposure-health outcome relationships but also will enable the assessment of health disparities for all health and development outcomes.

To further understand and unravel the components of race, ethnicity, or socioeconomic status that may contribute to or mitigate health disparities, the data collection also includes information such as household composition, country of origin and ancestry, immigrant status, language spoken at home, neighborhood characteristics, use of social services, financial and food security, and perceived discrimination. These component variables are necessary to better understand the mechanisms by which these social, economic, cultural, and neighborhood factors interact with one another in leading to or in reducing disparities among different subgroups.

In the perinatal period, the role played by race/ethnicity and socioeconomic status in mediating the exposure-outcome relationship is not a straightforward, synergistic one. For example, while both African American and Hispanic population groups are more likely to be at socioeconomic disadvantage than non-Hispanic whites, the prevalence of preterm birth is significantly higher for African American women but not for Hispanic women when compared to non-Hispanic white women. In the Vanguard Pilot protocol, the questionnaire, environmental, and biologic data collected will enable the understanding of mechanisms underlying these complex population-level differences in pregnancy and infancy outcomes. For instance, racial and ethnic differences in exposures to maternal stress, infection, and chemical contaminants can all be explored in relation to preterm birth and may help improve understanding of current disparities.

An area highlighted in the NAS review not covered well in the existing data collection protocols is the "availability, use, and quality of medical, educational, and other services for study participants…." While information on the use of prenatal and child health care during infancy is included in the data collection protocols, the current protocols do not include ascertainment of availability of or potential barriers to care. These issues are now under development; relevant data collection instruments will be added to subsequent versions of the protocol. The Study will also seek the development of adjunct studies, particularly in relation to perceptions and inclination to access to health services that, when combined with the core study, can inform these issues further. A working group consisting of experts from the Study Centers and Program Office and Coordinating Center representatives is being reconstituted to advance these efforts.

Health Disparities Actions:

- Reestablish Health Disparities Working Group to focus and refine health disparities assessments, as highlighted in the Children's Health Act
- Ensure enhancement of data collection pertinent to use of, barriers to, and beliefs about health services and behaviors
- Continue practice outlined in protocol of including extensive demographic, exposure, and outcome data to enable analysis of causes and mediators of health disparities.

2-2: More frequent in-person measures and collection of medical records

In addition to increasing the frequency of participant contact, of particular interest to the NAS panel is the abstraction of medical records (and, relevant to subsequent Study protocols to be submitted to OMB, collection of school and other records). Embedded in this recommendation is

the recognition that addition of participant contacts or other data collections has significant budget implications; additional participant burden is not considered in this recommendation.

This recommendation underscores a primary challenge faced by the Study throughout the course of its development—the tug-of-war inherent in balancing the breadth and depth of data collection necessary to fulfill the multidimensional goals of the Study and the concurrent maintenance of reasonable participant burden and cost. The schedule of visits in the current OMB protocol submission includes five contacts during pregnancy—one at home, two in a clinical setting, and two phone calls. Two visits at birth, one focusing on the mother and one on the infant, are followed by four contacts during infancy (birth–12 months)—two at home and two by telephone. In addition, the data collection protocol includes abstraction of the prenatal, labor and delivery, and neonatal records. Increasing the number of contacts over this period to enable more frequent assessment of infant development would be ideal from a scientific standpoint. However, within the broader, long-term context of the Study, the proposed increased assessment may not be practical considering the additional burden on both the Study and the participants and cannot be supported by current budget projections.

The frequency of data collection decreases following infancy. The protocol currently under review by OMB contains phone contacts at 18 and 24 months. The Study's initial schedule of visits included an in-person child visit at 24 months; this was subsequently replaced with the phone contact due to budgetary constraints. The Study recognizes the importance of frequent follow-up, to measure both changes in exposures and to assess developmental and other outcomes. The Study is currently reexamining the potential for remote data collections, including self-collection of some environmental and biologic samples. The addition of in-person assessments during the second year of life is now limited by budgetary considerations, as the NAS review acknowledges.

Another route to increased frequency of visits is the initiation of adjunct study protocols carried out among subsamples of the Study. Adjunct studies are not included as part of the initial Vanguard Pilot protocol, so they are not referred to in the OMB submission. An example of the role adjunct studies may play in filling gaps, however, is a recently submitted draft adjunct study proposing the in-person assessment of cognitive and language development between 12 and 36 months of age in up to one-fifth of the Study population. If successful, this proposal would address an important area noted in the NAS review.

The routine abstraction of medical records has the potential to add significant clinical detail to the Study data without increasing participant burden, though at substantial cost given the fragmented U.S. health system. For example, the projected costs for abstraction of vaccine-specific information alone, as suggested by the National Vaccine Safety Council, are approximately $30 million.

The Study currently includes routine record abstraction through the birth of the infant. During infancy and throughout prenatal care, the Vanguard Pilot protocol also includes collection of clinical data through structured "medical provider" logs provided to the Study participants. If this technique proves successful in the Pilot, it will represent substantial cost savings compared to obtaining clinical information through the abstraction of records from a multitude of providers.

Also under development for the Study is an electronic "Personal Health Record." As the use of electronic medical records become more prevalent and, hopefully, more standardized, the Study will be in position to take full advantage of clinical data.

Frequency of Data Collection Actions:

- Continue pursuit of remote, self-collected, and other low-burden data collection methods as interval collections between scheduled home, clinic, and phone contacts
- Continue development of a possible electronic Personal Health Record suitable for use among Study participants
- Continue tracking of electronic medical record progress for potential incorporation into routine data collection.

2-3: Full development of conceptual model of child health and development

The NAS review states that, though the Study's Research Plan invokes a dynamic, life-course model, it does not specify a particular model. The review references the "life-course" approach as elaborated by Ben-Shlomo and Kuh, and, specifically, the application of this general model to a broader conception of child health and development as elucidated in the NRC and IOM report, *Children's Health, The Nation's Wealth*. This model articulates three "domains" that combine to define child health: health conditions, functioning, and health potential.

The conceptual models used as the basis of the Study's protocol development were not well-articulated in the Research Plan. As the review notes, the ecological and life-course perspectives positing that development occurs in the context of biologic, social, and environmental change over time underpin much of the overall Research Plan (for example, page A2-140 of the Research Plan) but are not specifically elaborated. In the debriefing meeting with the panel's chair, the apparent conflict between basing the Study on a "healthy development" model of health and well-being versus a more traditional "deficit model" of disease was discussed.

While the longitudinal models of health, development, and well-being are of central importance to the Study, the focus on child outcomes such as preterm birth, asthma, diabetes, obesity, unintentional injuries, and autism is also critical. The individual and societal toll claimed by many of the conditions targeted in the Study is substantial. A study the size and scope of the Study is necessary to understand the causes of those diseases and enable the amelioration of their individual and societal costs. Thus, while a conceptual model of life-course development and well-being is a foundation of the Study (though not well-articulated in the Research Plan), the Study's focus on specific diseases and conditions remains an important attribute and is directly responsive to the President's Task force and the Children's Health Act.

The data collection instruments included in the initial Vanguard Pilot protocol are designed according to the above approaches. The large amount of prospective prenatal data will form the underpinning for subsequent evaluations of "developmental origins" of health and disease. The relatively intensive follow-up in the first year of life corresponds to the life-course model's identification of key transition periods in which data collection is important. Collection of maternal and child biospecimens and home environmental samples before and after birth will

allow for the subsequent application of bioecologic analyses as the Study children develop and grow.

Given the large sample size and the prevalence of the outcomes stated above, the Study will capture more data on healthy development and typically developing children, as articulated in the *Children's Health, The Nation's Wealth* model, than any other study to date. The conceptualization and measurement of "health potential," as described in the *Children's Health* model, is less well-developed in general; efforts are ongoing to better incorporate these concepts in the Vanguard Pilot data collection protocol.

Conceptual Model Actions:

- Reestablish a working group on child development to help ensure that the protocol elements currently under review allow for appropriate incorporation of the life-course model of health and disease, following the *Children's Health, The Nation's Wealth* model referenced in the NAS review
- Continue ongoing efforts to both conceptualize and then operationalize assessments of "health potential"
- Ensure that development of future data collection protocols continue to adhere to this approach and to more clearly express it in future Study design documents.

2-4: The importance of a sufficient pilot phase

Described by the panel's chair as a "major recommendation," the NAS review stressed the importance of an adequate pilot phase for thorough testing of the Study's operations and data collection instruments. The review suggested increasing the time between the Vanguard Pilot study and the initiation of the initial "main study" sites, now referred to as the Wave 1 sites.

The importance of a vigorous pilot phase is undeniable for the Study. Areas in need of testing and iterative development include methods of community engagement, the household recruitment methods, specific data collection instruments, and the operations that tie all the field work together. An initial pilot study developed under an EPA contract would have preceded the Study Vanguard Centers by 12–24 months. The initial mission of that study was to test the household recruitment and enrollment procedures because a household-based pregnancy sample has never been attempted on the scale of the Study. Following enrollment, testing of the planned procedures and data collection instruments was planned. The study was eventually withdrawn by EPA after the submission spent more than one year in OMB without receiving a decision.

Following withdrawal of the initial pilot cohort, the Vanguard Pilot assumed greater import. Since the Research Plan underwent review, the start date for the Wave 1 sites has been delayed by 6 months, thus extending the Vanguard Pilot period. Additional delays may occur as a result of budget or OMB actions without intentional action on the part of the Study Program Office. However, if those delays do not occur, initiation of data collection at the Wave 1 sites will be adjusted as necessary to ensure an adequate opportunity to test the Study protocol.

A primary purpose of this Vanguard Pilot submission is evaluation of the household-based sampling plans. The future success of the Study will be dependent on the initial recruitment and

maintenance of a valid sample. Some testing of protocol components (such as the video consent) will occur under this submission. After establishment of this Vanguard Pilot cohort, subsequent portions of the protocol will allow for more testing of specific data collection instruments.

A generic clearance was also submitted to OMB to enable formative testing during the initial Vanguard Pilot phase. Studies performed under that clearance are intended to supplement the Pilot activities of the initial Vanguard cohort. Planned studies will allow testing of different community engagement activities critical to recruitment, alternative data collection techniques to minimize cost and respondent burden, and varied data collection instruments.

Necessity for Adequate Pilot Study Actions:

- The necessity of an adequate pilot phase is essential and fully recognized
- Take all necessary steps to ensure an adequate pilot study, including additional delay of main Study protocol at the Vanguard and Wave 1 Study sites.
- Use studies under the proposed OMB generic clearance to test approaches to community engagement, data collection methodologies, etc.

Chapter 3: Priority Outcome and Exposure Measures

The 18 recommendations in Chapter 3 of the NAS review relate to the exposure and outcome measures outlined in the Research Plan. As mentioned previously, the Research Plan described the overall Study in broad detail and was not designed to provide specific detail for the early part of the Study covered in the current Vanguard Pilot protocol. Many of the recommendations concentrate on topics primarily addressed in subsequent protocol submissions. In addition, the advent of the new Study Centers has provided a new and large pool of expertise to enhance the development of the future data collection instruments. Thus, though each recommendation will be addressed, some are of limited relevance to the Vanguard Pilot protocol currently under OMB review.

Pregnancy Outcomes

3-1: Less focus on maternal hypothyroidism and more on a broader set of conditions

The NAS review suggests that the Study protocol focuses on a relationship of potentially limited scope (hypothyroidism and adverse pregnancy outcome) to the exclusion of other exposures that may have broader impact on pregnancy outcome and subsequent development. The potential importance of a wide range of psychosocial, chemical, and biologic exposures on pregnancy outcome is undeniable. The maternal hypothyroid hypothesis was developed as a specific example of the influence an environmentally mediated maternal condition may have on pregnancy outcome and child development.

Data collection relevant to numerous additional potential exposures is included in the protocol. For instance, the initial Vanguard Pilot protocol includes instruments applicable to each of the specific issues elaborated in the review—maternal depression, stress, and periodontal disease. Maternal depression will be addressed several times during pregnancy and after birth by using the Center for Epidemiological Studies Depression Scale. Assessment of maternal stress includes

administration of a Perceived Stress scale at several time periods during pregnancy as well as collection of maternal saliva for cortisol. Periodontal disease will be assessed through questions developed by the Periodontal Epidemiology group; initial plans considered inclusion of a periodontal examination during pregnancy, but the associated cost and burden make them infeasible for the entire Study cohort. Periodontal exams during pregnancy may be appropriate as an adjunct study on a subset of the population.

3-2: Include all pregnancy outcomes, including pregnancy losses

The review stresses the importance of ascertainment of all pregnancy outcomes, not only those resulting in a live birth. The identification of women early in pregnancy is a hallmark of the Study, making it an important vehicle for studying pregnancy loss. The current Vanguard Pilot protocol contains prospective questions to ascertain pregnancy status and possible loss during pregnancy. If a loss is identified, permission to review associated medical records will be sought. A proposal for more detailed data collection, including questions to be asked of the mother and specific medical record and autopsy abstraction forms, is currently under development by investigators from the Study Centers.

Pregnancy Outcome Actions:
- All pregnancy outcomes are included in the current data collection protocols.
- Continue development of detailed pregnancy loss protocols and further refinement of other pregnancy outcomes including identification of birth defects.

Neurodevelopment, Behavior, and Child Health and Development

3-3: Development of clear rationale for relevant outcome and exposure measures

The NAS panel voiced a number of concerns regarding the assessment of neurodevelopment and child behavior within the Study. The concerns generally fall within one of two broad categories:
- Lack of an overall model or plan for determining the domains and constructs most relevant to the Study
- Questionable choice of specific instruments for measurement of those domains, especially a focus on "screening" as opposed to more rigorous diagnostic assessments.

The lack of a well-articulated longitudinal plan for determining the developmental and behavioral domains of most interest to the Study is recognized. The basis for many of the decisions on the measurement domains included in the Vanguard Pilot protocol stemmed from a national workshop sponsored by the Study in 2004. The purpose of the workshop and resulting white papers was to:
- Determine key measures within the neurobehavioral domains relevant to the Study
- Recognize the longitudinal nature of the study assessments
- Identify critical timing of exposures relevant to the Study.

Though much of the material in the Research Plan and the actual measurement instruments included in the initial Vanguard Pilot protocol resulted from those activities, the underlying conceptual model driving those decisions deserves additional elucidation. To that end, working

groups from the Study Centers will refine the longitudinal domains and critical periods of measurement of adult psychosocial status and child development.

Independent of the model(s) driving the definition of measurement domains, the review questions specific instruments listed in the Research Plan. The panel expressed a general discomfort with the reliance on screening assessments, parental report of diagnosed conditions, and reported provider diagnoses as a basis for identification of children with specific neurodevelopmental or behavioral disorders. Initial plans for the Study considered following all positive screening tests with more definitive clinical diagnoses performed under Study auspices. However, prohibitive costs and operational constraints limit the ability of this geographically diverse population-based study to perform standardized clinical diagnostic tests.

One possible solution to this problem suggested by the NAS panel is to reduce the scope of the Study to a small number of targeted disorders, and to minimize the use of general screening and developmental assessments. This would satisfy the diagnostic concerns but would greatly narrow the scope of the Study and would not be consistent with the Study's charge as described in the Children's Health Act.

The chosen approach is to rely on screening and assessment measures that have been vetted for reliability and validity in other large-scale non-clinical studies, such as the Study of Early Child Care and Youth Development and Early Childhood Longitudinal Study (ECLS). Follow-up adjunct studies designed to provide further assessment of children with positive screens will continue the diagnostic process. Collaboration has already started to fill these gaps. One example is the interest of the NIH Autism Consortium in longitudinal assessment of Study children with positive Modified Checklist for Autism in Toddlers screens. In situations where adjunct studies are not practical, parental report and selective abstraction of specific medical records, as funding allows, are included in the protocol. Several national surveys have developed parent-reported items, including the National Health Interview Survey and the ECLS.

A number of the specific measures outlined in the Research Plan and included in the initial Vanguard Pilot protocol were described by the NAS panel as being "ad hoc" and "not well informed." Though the lack of their fit within a well-elucidated framework is recognized, the choice of specific measures was carefully based on a number of factors relevant to the context of the Study. As mentioned above, they are generally measures that have been successfully employed in large-scale non-clinical studies with known psychometric properties. Additionally, they are of appropriate burden to fit within a multidimensional study that must collect data on a number of fronts.

Some of the suggestions advanced in the review may be considered the "gold standard" for a particular domain but do not fit within the Study. For example, the Strange Situation measurement of attachment is a lab- or clinic-based procedure performed at 12–18 months of age. The Study has only a home visit (necessary for environmental assessment) and phone contacts during that period; the Strange Situation is not valid during the home visit as the home setting is definitely not "strange." Although the panel recommended Achenbach's Child Behavior Checklist, this instrument cannot be used before 18 months of age, and thus the Brief Infant Toddler Social Emotional Assessment is included in the protocol at 12 months. In

addition, the Child Behavior Checklist (CBCL) is a long instrument (approximately 100 questions); a shortened version was used in the ECLS-B, but its psychometric properties relative to those of the full CBCL have not been rigorously tested. Testing of this and other abbreviated instruments is an example of how formative research projects may be used to develop efficient data collection instruments for use later in the Study.

Finally, a number of instruments mentioned in the review are applicable later in childhood than the time period addressed by the current Vanguard Pilot protocol. These recommendations will receive full consideration during the ongoing and subsequent deliberations of the Psychosocial and Developmental working groups.

Neurodevelopmental and Behavioral Actions:

- Refine conceptual model(s) for assessment of neurobehavior and development by the newly formed working groups comprising members of the Study Centers, Program Office, and Coordinating Center
- Reexamine specific measures included in the early data collection protocol to ensure they conform to the models and address concerns raised in the review
- Conduct formative developmental studies to develop shortened versions of existing instruments for later in childhood and utilize those versions, where psychometrically sound, to minimize burden and allow enhancement of under-represented domains.

Asthma

3-4: Focus on prenatal and early life risk factors for asthma

The NAS panel's comments on the asthma hypotheses and proposed data collection methods were generally positive. Concerns primarily focused on assuring adequate collection of information early in the Study that may be related to subsequent incidence of childhood asthma. The specific areas mentioned in the review not specifically enumerated in the Study hypotheses (for example, maternal diet, food allergies) are included in the Vanguard Pilot data collection instruments. Information collected via the pregnancy and infancy questionnaires coupled with collection of household dust samples at the home visits will ensure ascertainment of common allergens as well as potential exposure to pesticides and other chemicals of potential interest mentioned in the review.

Asthma Actions:

- Use Vanguard Pilot phase to assess ability of current protocol to adequately assess the prenatal and early life exposures potentially related to risk of subsequent asthma. In particular, protocols for dust sample collection, although common in targeted environmental studies, have not been widely used within a multipurpose study like the Study.
- Continue efforts to link indoor measurements at the times of the home visits to questionnaire and local air pollutant data to allow estimation of indoor concentrations and exposures during other time periods.

Obesity and Growth

3-5: Broaden approach to incorporate psychosocial factors in addition to "biogenetic" factors

The review suggests the Study develop an expanded view of the antecedents of obesity; the current hypotheses target somewhat narrow biologic exposures such as the *in utero* environment and early life diet. The likely importance of multiple contextual factors, such as community neighborhood social and physical environments, parental beliefs and behaviors, and later peer interactions, acting in combination with more traditional biologic factors is acknowledged. Many of these characteristics are incorporated in other Study hypotheses (for example, family influences on child health and development; impact of neighborhood and communities on child health and development) though not specifically focused on obesity in the Research Plan.

Data collection during pregnancy and infancy includes Study participant-reported neighborhood assessments, television and other media use, parental and infant diet (though difficulties in accurate dietary measurement are acknowledged), and health and activity practices, all of which address important areas highlighted in the NAS review. Objective observation of the neighborhood physical environment will also be part of the early data collection and is further discussed in the response to Recommendation 3-11. Subsequent linking of external data sources to Study data will allow for analysis of additional pertinent factors such as household accessibility to grocery stores. The combination of these factors with the biologic factors outlined in the specific obesity and growth hypotheses should provide ample data to "elucidate the web" of factors that interact to result in childhood obesity and its sequelae.

Other concerns raised by the panel refer to measurement of obesity in the parents and the child. The current protocol relies on basic anthropometric measures for both the adults and the infant. Though more complex measurements (such as bioelectric impedance assessment [BIA] and bone ultrasound) were considered, they are not operationally practical for this population and study design. For instance, BIA measurement is not reliable during pregnancy due to fluid changes. As the children age, additional measures of "body habitus" will be considered for incorporation into future protocols.

Obesity and Growth Actions:

- Ensure collection of relevant contextual data is included in protocols beyond 18 months
- Undertake small studies to assess various methods of parental and child diet
- Continue evaluation of methods to assess obesity as the Study's children age.

Injury

3-6: Reevaluate and possibly replace current traumatic brain injury hypothesis

The inclusion of injury as a core Study outcome was considered important by the NAS panel, given the high pediatric morbidity and mortality associated with unintentional injuries. However, although the recognition of repeated mild traumatic brain injury as an important research topic was applauded in the review, the panel was concerned both by the difficulty in ascertaining this

outcome and by the focus only on this specific injury type. In particular, the review mentioned interest in "environmental causes of childhood injuries" (without further elucidation of "environmental") and in the potentially modifying effect of clinical treatment on long-term injury outcome.

The original hypothesis was developed because of emerging evidence of the potential public health importance of repetitive head injury. In addition, the reporting methodologies used to assess the presence of mild head injury will also capture more common and less subtle injuries such as falls, burns/scalds and motor vehicle crashes. Although the challenges in identifying and diagnosing mild brain injury are recognized, more definitive examination of that hypothesis is possible through potential adjunct studies that may be able to use more targeted measures (such as neuroimaging, as mentioned in the review) than the core protocol.

Examination of the potential modifying effects of clinical treatment on long-term injury sequelae will, of necessity, occur later in the Study. For this protocol submission, it is important that both injuries and their treatment, if any, are documented.

Injury Actions:

- Use results of pilot study, particularly the medical provider logs, to assess reporting of all injuries, not just head injury
- Ensure appropriate identification of injuries and treatment, as ability to incorporate medical record information into data collection increases
- Reestablish a working group to address the study of genetic, biologic, behavioral, and environmental contributions to injuries.

Reproductive Development

3-7: Refine and develop protocols for reproductive development outcomes, particularly those measured at birth

The NAS review raises concerns about measurement of the reproductive outcomes that may be associated with exposure to hormonally-active agents (HAAs). The immediacy of pregnancy outcomes is well-recognized and has been considered in the Vanguard protocol data collection. Congenital defects of the reproductive system (and other birth defects) will be ascertained from medical records and interviews with parents; in-depth standardized physical examination of every child at birth is not feasible given the geographically dispersed sample. Anthropometric measures will be obtained in all mothers (and fathers, where possible) beginning at the first home visit, and in children before birth via ultrasound, at birth, and at subsequent ages. These data will be used to determine developmental trajectories for growth and development as well as to control for genetic determinants of body size.

Additional outcome measures of concern for HAAs, including polycystic ovary syndrome, endometriosis, and onset of puberty in both boys and girls, will be ascertained at the appropriate ages based on contemporary methods. At the least, Tanner stages will be evaluated, possibly through self-examination, in both boys and girls. Hormonal profiles will be measured from samples collected during pregnancy, at birth, and at multiple ages in children.

Data will be collected on exposures to HAAs in the environment and diet, as well as any pharmaceuticals with endocrine activity. Various populations are expected to be associated with different levels of exposure; for example, farming communities may have higher levels of pesticide exposure that may vary depending on the crop and seasonality, and inner-city poor children and racial/ethnic minorities in substandard housing may be expected to have higher levels of lead exposure. The results of the Vanguard Center pilots will aid significantly in helping to identify potential population exposure differences. Using the Vanguard results, targeted subsampling of populations or areas in the main study with expected greater exposure may aid in defining exposures in those populations while reducing the costs in situations where a majority of samples may be below detection limits. In addition, community-based measures will be used where possible, reducing the costs of individual measures where, for example, air sampling or community water sampling may suffice.

Reproductive Development Actions:

- Use experience of Vanguard phase to assess ability to identify early outcomes, such as birth defects, potentially related to hormonally-active agent exposure
- Continue development of later reproductive outcomes, such as self-reported Tanner stage as being tested in the National Health and Nutrition Examination Survey (NHANES).

Demographic measures

3-8: Add to measures on immigration and legal status to "well-planned" battery of demographic data

The interviews included in the initial Vanguard Pilot protocol include questions concerning the country of birth of the child's parents and, if not born in the United States, how long they have lived in this country. Nativity and country of origin of the child's grandparents is also ascertained. Information on languages spoken in the home is asked after the birth of the child. However, questions about "legal status" of the parents are not asked. Input from a number of the Vanguard Centers firmly indicates that the inclusion of those questions, especially in a federally sponsored study, would severely hamper recruitment and retention of those difficult to reach population subgroups.

Demographic Measures Action:

- Include current battery of demographic data including nativity and language. "Legal status" will not be included due to the serious impact on Study participation and cooperation.

Chemical Exposure Measures

3-9: Consider personal air sampling in subsample

The NAS panel suggested the addition of collecting personal air samples from a subpopulation of Study women and children. Though not specifically stated in the review, the intent seems to be to use personal exposure data as a validation tool for the household and neighborhood air assessments and to provide data for more accurate modeling of individual exposures. The Study

has developed statistical approaches for "validation" substudies to evaluate and adjust for these sources of "measurement error" and to evaluate temporal variability relative to the timing of exposure measures. The use of a personal air sampler by at least a portion of Study mothers was initially considered for inclusion in the Vanguard Pilot protocol. However, the physical burden and costs associated with the current technology precluded use of this method for any reasonably-sized subsample of the Study. However, the Study eagerly awaits upcoming advances in personal-level air sample technology, for instance those being developed as part of the National Institute of Environmental Health Sciences (NIEHS) Exposure Biology Program, for inclusion in future iterations of the Study protocol. As they become available, these technologies may be applicable either to mothers in subsequent waves of data collection or to children in both the Vanguard wave and subsequent waves.

In addition to personal air sampling, the review mentions collection of meconium and deciduous teeth as examples of other biologic specimens that may estimate a variety of chemical exposures. The current Vanguard Pilot protocol under review by OMB includes provisions for meconium collection and storage. The collection of primary teeth will certainly be considered for portions of the protocol addressing data collection among children of appropriate age.

3-10: Measure paternal chemical exposure and collect additional paternal information

This recommendation centered around the potential importance of paternal environmental exposure on subsequent child health and suggested the ascertainment of paternal chemical exposures and other information similar to that collected for the mother. Though perhaps not evident in the Research Plan, the assessment of paternal factors is an integral part of the Study's data collection protocol. During pregnancy, questionnaire, biospecimen, and physical examination measures will be sought from the biologic father. These data will enable the assessment of similar information collected from the mother including demographic characteristics, chemical exposures, family and medical history, mental health, and cognition. After the birth of the child and through infancy, the Study continues data collection from either the biologic father or, in relevant situations, another primary caretaker, at the same intervals as from the mother and child.

Chemical Exposure Actions:

- Continue interaction with NIEHS, the Environmental Protection Agency (EPA) and other programs to monitor development of personal air samplers suitable for use in pregnancy and early childhood and evaluate potential use of portable air samplers in small validation studies
- Consider whether additional biologic or environmental sample collections, or other measures, are needed to characterize exposures to persistent and non-persistent organic compounds
- Use Vanguard Pilot phase to assess ability of the Study to enroll and collect data from fathers.

Physical Exposure Measures

3-11: Reconsider measures of housing and neighborhood conditions

NAS panel concerns regarding the collection of household and community physical environment data include both the relevance of specific measures and the assurance that the timing of specific assessments correspond to critical or sensitive periods of child development. Development of a protocol that collects data relevant to the many factors of interest to the Study, including chemical exposures, social and community interaction, and land use and availability of space for outdoor physical activity, has been challenging. In addition, such an instrument or instruments should be applicable to the broad range of urban, suburban, and rural locations encompassed by the Study.

In concert with the Study Program Office, experts from several of the Vanguard Centers, the Coordinating Center, and outside experts recently held a workshop to discuss this topic. Areas of discussion included the necessary melding of the physical and social assessments (most existing instruments focus on one or the other domain) and the timing and source of data collection.

The current Vanguard Pilot protocol contains a small number of questions regarding the household and neighborhood physical environment and the community social environment. Many of the specific items listed as of questionable importance in the NAS review (such as garage location) are not included in the current questionnaires. Based on the results of the above-mentioned workshop, an observational data collection instrument is being designed and will be tested in several of the Vanguard locations. The instrument involves observation by the Study staff as they complete the household visit and does not contribute to participant burden. In addition, a working team to assure appropriate longitudinal assessment of these factors, as mentioned in the NAS review, is being established.

Physical Exposure Measure Actions:

- Continue development and testing of integrated physical and social observational instrument by Vanguard Centers
- Establish Study Center working team to assure appropriate longitudinal assessment of household and neighborhood factors.

Psychosocial Exposure Measures

3-12, 13: Reconsideration of measures to assure high-quality data and development of new instruments

The general tenor of the comments in this section of the review, though not explicitly stated, is that the Research Plan suggests a sacrifice of depth of data collection in specific areas for breadth of coverage of numerous domains. In addition, even with the attention to a broad array of factors, some important areas (for example, transitions among family structures) have been overlooked. The difficulty of addressing these concerns within the participant burden and cost constraints of the Study is acknowledged by the panel. To overcome these limitations, the panel suggests a refocus on a smaller number of "domains of interest in terms of outcomes" and a "careful elucidation of the choices made with specific reference to goals, hypotheses and relevant outcome measures." The panel also strongly suggested using methods development studies to develop and test instruments designed to efficiently measure those key constructs.

Refinement and further development of the healthy development conceptual model for the Study (described in response to recommendation 2-3) will help determine the outcomes and domains of most importance to the Study. As these domains and outcomes are more clearly elucidated, with the assistance of the reconstituted Psychosocial Working Group, relevant measures will be reevaluated. Further, review of the relevant measures included in the initial portion of the Vanguard Pilot protocol has already begun. The specific comments and suggestions made by the panel (for example, potential replacement of the planned videotaping of maternal-child interaction at 6 months with measures of attachment later in infancy) require consideration within the context of the entire Study (for example, a home visit rather than a clinic visit at 12 months). Many of those comments will be relevant for future protocols, as the Study's Pilot cohort ages.

The use of the Vanguard Pilot to compare instruments (for example, comparison of in-field psychometrics of short and long forms of the Bayley III) is an underlying rationale for having a Vanguard phase. Whether the Study is in a position to develop brand new instruments, as suggested by the panel, will require additional consideration.

Psychosocial Exposure Action:

- Reevaluate psychosocial exposure measures within the Study framework, considering the conceptual models specified earlier in this document, with the Psychosocial Working Group.

Biologic Exposure Measures

3-14: Review timing of exposure measures to assure appropriate relationship with relevant outcomes

The main concerns expressed by the panel address the timing of assessment of biologic measures. The review includes some comments regarding specific measures relevant to the initial Vanguard Pilot protocol, particularly ascertainment of child infections and maternal glucose metabolism.

Ascertainment of infections early in childhood is difficult. Information can be obtained from reports of health provider visits or directly from records associated with those visits. However, not all infections result in interaction with the health system. So, in addition to collecting information from the child health provider log every 3 months, maternal report of infection-related symptoms will be ascertained at the 6 and 12 month visits. Serologic markers from archived biologic samples will enable longitudinal assessment of infectious exposures.

The assessment of maternal glucose metabolism during early pregnancy has proven more problematic, within the context of the Study, than initially thought. An early home visit is necessary given the importance of environmental sample collection. At the time the Research Plan was written, the processing requirements for measurement of glucose and insulin seemed to preclude inclusion of those analytes on specimens obtained during a home visit. In addition, procurement of fasting blood samples at the initial home visit seemed infeasible. However, measurement of glucose and insulin from those samples may be possible. In addition, record

abstraction from the prenatal records, including serum glucose and glucose tolerance test results, will add to the Study-specific measurements, including the time-averaged HgbA1c measures.

The timing of the Study participant contacts during the initial portion of the Vanguard Pilot protocol was determined by a number of factors related to assessment of child health and development, including the ascertainment of biologic exposures. Optimizing each assessment in a multidimensional study such as the Study is impossible. Results from the pilot phase will help determine whether the schedule of contacts can be further optimized.

Biologic Exposure Actions:

- Reevaluate timing of maternal glucose measurements and assessment of childhood infection obtained during pilot phase by expert working group
- Continue incorporation of medical record data and other information as possible in future protocol submissions.

Genetic Measures

3-15, 16: Revise approach to genetic analyses; collect longitudinal samples and store until more cost-effective studies are possible

The NAS panel expressed some concern regarding the Study's approach to genetic analyses as outlined in the Research Plan. One identified weakness is the proposed use of the candidate gene analyses for some areas, rather than genome-wide association studies. An approach suggested by the panel to overcome their concerns (recommendation 3-16), is the collection and storage of the biospecimens for future analysis, when more cost-effective analytic tools are available. This "biobanking" approach is the strategy that has been adopted by the Study. It will allow for the incorporation of contemporary understanding of rapidly changing areas such as epigenomics and "transcriptomics" and the development of the analytic methods needed to explore those areas. Importantly, this strategy allows for investigation of temporal relationships between exposure and gene expression at different life stages, a key component in the elucidation of gene-environment relationships.

While suggesting that now, and in the future, genome-wide studies may be more fruitful than candidate gene approaches, the panel also raises concerns regarding the scattershot use of such methodology and the potential for the elaboration and "dissemination of false information (including false positive results…)." Their recommendation for internal and external validation of genetic association studies has superficial attractiveness, but what is meant by "validation" requires more explanation. The Study's process for determining appropriate use of biologic specimens and environmental samples, including genetic association studies, for individual analyses will require review and approval by a Sample Oversight Group. This group will comprise the requisite scientific personnel to ensure that proposed analyses are well-founded and will minimize the potential for spurious associations.

Several questions raised by the panel may benefit from further explication. The review mentions the lack of parental blood suitable for gene-expression studies. However, the current protocol does contain such material collection from both the mother and the biologic father during

pregnancy. The statement that only a single cord blood sample is available for expression studies is somewhat confusing, since the availability of cord blood is a unique event for any individual. Blood collected from the child over the course of the Study can be used for gene expression studies, providing a rare ability to examine changes in expression over the life course and in relation to a variety of exposures.

A final concern raised by the panel is that the most commonly collected tissue in the Study, blood, may not be the appropriate one for gene-expression studies relevant to many of the Study priority outcomes, such as the neurobehavioral outcomes. The overall design of the Study limits the degree to which other human tissue may be obtained for analysis. However, appropriate adjunct studies may be used to address some relevant areas. For instance, in the current Vanguard Pilot protocol, the protocol for placental collection does not allow for proteomic analyses because a minority of the sites has the ability to collect samples in that fashion. However, enhanced collection enabling the immediate processing of tissue samples in liquid nitrogen or RNAse inhibitor may be possible at some of the tertiary care facilities in the Study and could be included as an adjunct study. The Study is also working with other institutes within NIH to consider possible adjunct studies, such as neuroimaging, that may substitute for tissue analyses.

Genetic Measures Actions:

- Assure ongoing development of plans for collection and analysis of genetic material to stay abreast of rapidly changing field. A Genetics/Epigenetics and Genomics/Epigenomics Working Group is being established for this purpose.
- Continue plans for storage of specimens for subsequent analyses in nested case-control studies, as in Recommendation 3-16.
- Use adjunct studies for collection and analysis of tissues other than blood that may be useful for targeted gene-expression studies.

Missing Exposures

3-17: Add measures of access to and quality of services

As mentioned in the response to recommendation 2-1, efforts to enhance the Study's collection of data relevant to access to health care are ongoing and include reestablishment of a Working Group given that task. The current protocol does include collection of data about source of care and expected payment mechanism (health insurance). However, as mentioned in the response to recommendation 2-2, given the fragmentation of health information in the United States, obtaining provider information to assess quality of health services is not feasible without substantial additional resources.

Collection of information related to child care is included at each postnatal contact (phone and in-person) included in the Vanguard Pilot protocol. Subsequent data collection as the child ages will include data collection on schooling and use of educational services; those protocols will be developed.

3-18: Facilitate linkage to secondary data sources by geocoding residences

The NAS review recognizes the major benefits that can accrue to the Study by linking secondary data sources to the Study-collected data. These data may include U.S. Census demographic and socioeconomic data, EPA environmental data, crime information, weather data, information related to state or local rules and policies, and a host of additional types of information. The panel suggests geocoding of the participants' households to maximize the linkage capability. Concurrently, the panel also recognizes the ramifications to participant confidentiality incurred by making detailed geographic data available to the research community.

The current protocol includes GPS measures of the participants' residences. In addition, similar measures of child care and, in the future, school locations are under consideration. The privacy and confidentiality concerns are well-recognized by the Study and include not only the geographic data but a wide array of information collected during the Study. In short, the Study held an expert workshop on data access and confidentiality, has drafted extensive data security and confidentiality plans currently under program review, and will convene an ongoing Data Access and Confidentiality Committee to assure maintenance of the maximal protection for Study participants while maximizing opportunities for research. Procedures for data access will be guided by established standards used in other national studies collecting sensitive and personally identifiable information. These and related concerns are also raised by the NAS panel in their comments associated with recommendations 4-8 and 5-2 and are further considered in those sections.

Missing Exposures Actions:

- Enhance collection of health care access and utilization measures as discussed in recommendation 2-1
- Continue plans to obtain GPS measurements of participant residences to enable linkage to secondary data sources
- Continue identifying extant databases with potential to link to Study data.

Chapter 4: Study Design, Data Collection, and Analysis

Sampling Design

4-1 Allow flexibility in number of screened households in each PSU to ensure enrollment target (1,000 births) is reached

Though the NAS panel lauds the Study's household-based sampling design, the review raises concerns that the estimated "household-to-enrolled-to-birth ratio" may be too low and may result in a smaller than desired study population. One solution offered by the panel was to increase the number of secondary sampling units (segments) in each PSU, and subsample within each of the segments, keeping a portion in reserve to be released if initial recruitment goals are not met. Another solution not offered by the panel is to extend the enrollment period, should recruitment fall short of the targets after completion of the initial enrollment period. After consideration of both possible solutions, the Study design team determined that extension of the enrollment period better fit the requirements of the Study. Factors going into that decision included: the

phased nature of the enrollment via the several waves of location start-up, the need for intensive targeted community engagement, and field operational factors.

The panel also suggested using the Vanguard Pilot phase of the Study to evaluate the various components of enumeration, recruitment, and enrollment to improve sampling estimates in the subsequent waves of the main study. The Study's sampling design was the result of a long, thoughtful evolutionary process culminating in an expert workshop held in March 2004. The ultimate recommendation of the distinguished members of that panel was to attempt a household-based sample. However, because such a process had never been attempted on the scale of the Study, the panel also recommended a "carefully planned and implemented" pilot study to examine the various recruitment parameters, thus paralleling the NAS panel's recommendation. As mentioned in the reply to recommendation 2-4, such a study was planned but attempts to field it were unsuccessful. In the absence of that initial pilot, the importance of the Vanguard Pilot phase in testing the sampling approach is magnified; evaluation of the sampling, recruitment, and enrollment plan is a key feature of the Vanguard Pilot.

4-2: Field test the described household listing approach

The plan for household enumeration described in the Research Plan entailed use of U.S. Postal Service or related address lists as the basis for enumeration rather than the more time and resource-intensive hand listing often performed for household-based population surveys. The review expressed concerns regarding the accuracy of such lists and suggested the approach be considered "experimental" and be fully evaluated.

The approach to listing and enumeration for the Vanguard Pilot study is in full accordance with the NAS recommendations. During the Vanguard Pilot phase, segments will be listed by hand, following the "gold-standard" of household-based sampling. In addition, some segments will also undergo more resource-efficient variations on listing and enumeration, including use of available lists and combined listing and enumeration. The results of the various approaches will be compared and will determine the listing approach used for the main study.

4-3: Consider use of exposure data in defining PSU-specific sampling strata

After discussion of the potential benefits of oversampling certain subgroups (for example, defined by race or chemical exposures) the NAS panel endorsed the equal probability sample design adopted by the Study as optimal, given the multidimensional nature of the Study. Selection of the Study sample is a two-stage process—selection of the PSUs, performed by the National Center for Health Statistics primarily based on data available from birth certificates, followed by secondary selection of segments within each PSU. The definition of strata from which those segments are selected is primarily the responsibility of the local Study Center, with input from the Coordinating Center and the Program Office. These strata are based on population or geographic characteristics specific to each PSU. Environmental exposure data can be included in those strata definitions; at least one Study Center has done so and is currently undertaking a sensitivity analysis to determine the extent that inclusion of those data changed the strata definitions compared to those created using demographic and health system characteristics.

The Study is a multipurpose study with many potential exposures of interest, including environmental chemicals. Defining secondary sampling units based solely on environmental exposures theoretically may limit diversity of other exposures, just as exclusive use of socioeconomic variables to define secondary strata may theoretically limit the range of environmental exposures. In reality, however, the geographic diversity of the entire Study sample both between and within PSUs should assure adequate variability of wide range of exposures, without undue focus on any specific exposure type. In addition, from a practical perspective, detailed chemical exposure data are not available at a segment level throughout the country, thus limiting the universality of that approach.

Sampling Design Actions:

- Use extension of enrollment period to ensure recruitment targets are met
- Closely evaluate household enrollment throughout Vanguard Pilot phase to enable necessary changes to procedures both during that phase and for the main study design
- Field test the alternative listing approaches described in the Research Plan during the initial Vanguard Pilot phase to determine adequacy for main study
- Continue to allow local Study Center input into definition of secondary sampling strata to allow consideration of exposures of local importance.

Data Collection

4-4: Consolidate data collection into small number of survey organizations instead of decentralized Study Center approach

The NAS panel had a number of comments and concerns regarding the quality of data collected over the complex course of the Study. The concerns included quality control, response rates, and participant burden. To address these concerns, the panel recommended the Study "consider ways in which the **survey data collection** [bold added] could be consolidated into a smaller number of highly qualified survey organizations."

The NAS panel suggests that emulating the simplified data collection approach of "large health-related surveys" may result in higher quality data than will working with the 30–40 Study Centers envisioned as the prime data collectors. The complexity of the Study is well-recognized and appreciated and derives from the population-based sample and the breadth and depth of data to be collected from the Study's participants. The nature of these complex data distinguishes the Study from the conventional surveys and drives the different approach to data collection. Though the Study participants are derived primarily from a probability-based household sampling scheme, the Study encompasses much more than the traditional household survey. In addition to questionnaires administered during home visits, the data collection protocol includes collection of environmental samples, biospecimens, and physical measures in the home; interaction with the local health system for collection of primary data (for example, antenatal ultrasounds during the initial phase); clinic visits for physical and other assessments; and potential collection of medical and other local records.

As the NAS review acknowledges, the Study Center approach maximizes the contribution of scientists to the development of the data collection protocols, thus addressing many of the

concerns raised earlier in the NAS review. This has occurred to some degree in the development of the Vanguard Pilot protocol and will increase during the life of the pilot phase and throughout the main study.

The NAS review suggests response rates may be maximized by use of a single survey organization. However, given the longitudinal nature of the Study and ongoing interaction of the participants with Study personnel, a strong local presence with vigorous community interaction and engagement is necessary to ensure the highest participation. The involvement of local Study consortia (many of which include national survey organizations such as NORC, Battelle, or RTI), most of whom are already ingrained within the communities, is likely to result in higher response rates, a key concern of the NAS panel, than will data collection from a remote survey organization.

As the review notes, strong oversight of the data collection procedures and rapid and continuous review of data completeness and quality is necessary to ensure the decentralized data collection model will be successful. Data quality and assurance plans have been developed to ensure this occurs both at the local level and by the central Coordinating Center. The survey organization Westat is currently under contract as the Study Coordinating Center and is responsible for assuring standardized training and data collection procedures and for implementing the data quality and assurance program. Thus, there is a strong central presence underlying the seemingly decentralized field operations. The Vanguard Pilot phase is crucial for testing all these procedures throughout the course of the Study. In addition, a relatively small cadre of Project Officers within the Study Program Office monitor the work of each the Study Centers. The Project Officers meet formally on a weekly basis and meet informally much more frequently, thus providing additional central oversight.

In summary, the Study is more complex than a "conventional health survey" and requires a different structure. The combination of local Study Centers and a strong central Coordinating Center provides the optimal mix of scientific expertise, local presence and experience, and standardization and oversight necessary to ensure maximum participation and data quality.

4-5: Maintain strict standards for data quality and have remedial plans ready

As mentioned above, a data quality and assurance protocol has been developed with the Coordinating Center. The general outline of the plan is presented in Chapter 15 of the Research Plan with some detail presented for the individual components. This program addresses the training of local fieldworkers and staff, monitoring of individual-level and site-level data completeness and quality, and, of prime interest to the NAS panel, site-specific enrollment and retention rates. Monitoring is continuous and essentially real-time. Data are to be transmitted to the Coordinating Center from each Study location on a daily basis; reports will be created with varying frequencies (generally daily (for example, enumeration and pregnancy screening) to monthly (ultrasound technician specific reports), depending on the procedure under question, and monitored by the Coordinating Center in concert with the Program Office Quality Assurance officer. Retraining and certification protocols are being developed.

It is important to note that although not mentioned in the Research Plan, the Coordinating Center is equipped to take over all or part of data collection at any location where the local site fails to adhere to the Study's data quality requirements. As mentioned in the comments to recommendation 4-4, the initial Vanguard Pilot phase is critical to the evaluation of these policies and procedures and will guide necessary changes.

4-6: Plan to monitor progress in reaching sample size; rely on experience of Vanguard Centers and use Vanguard phase to test different procedures

The majority of comments and concerns underlying this recommendation echo those behind recommendations 4-1, 4-2, and to some extent 4-5. As mentioned above, a key purpose of the initial Vanguard Pilot protocol is to test and monitor the recruitment, early retention, and data collection procedures of the Study. Results from this phase of the Study will be used to adjust procedures for the main study waves. The testing of less resource-intensive listing techniques was discussed in the response to recommendation 4-2. Another example of a specific method proposed for testing during the initial Vanguard Pilot phase is the use of an interactive video consent tool compared to the traditional paper consent form. The interactive tool was designed to enhance participant understanding of the Study; evaluation of the success of the video consent on increasing participant understanding and its effect on recruitment and early retention has been incorporated into the Vanguard Pilot protocol.

4-7: Maintain an ongoing methods development program for procedures such as sample retention and for testing reliability and validity of survey questions

In addition to the quality assurance monitoring discussed above, the NAS panel also recommended an ongoing program to test separate components of the protocol. Some of this testing is inherent in the Vanguard Pilot protocol; two examples are mentioned in the response to recommendation 4-6. Another example is the cognitive testing of interview instruments performed by the Coordinating Center. The Study recognizes the need for ongoing methods development studies and has a generic clearance package under review by OMB to enable these studies. The focus of the initial studies to be performed after clearance has been obtained is evaluation of the influence different Community Engagement techniques at the Vanguard Centers have on recruitment and early retention. Subsequent studies will be able to focus on evaluating different data collection tools.

Though the importance of ongoing methods development studies is well-recognized, the ability to maintain a full slate of such studies within the context of the Study will depend on future funding. The Coordinating Center and each Vanguard and Study Center currently have funding for initial methods development. As mentioned, these first studies must focus on maximizing enrollment via the household sampling, given the novelty of this approach and the lack of prior testing. Future funding will determine the ability to maintain a vibrant methods development program as recommended by the NAS panel.

Data Collection Actions:

- Ensure strong central oversight of decentralized data collection activities by the Study Program Office and the Coordinating Center

- Use initial Vanguard Pilot phase to evaluate policies and procedures for monitoring of household recruitment and early retention
- Use Vanguard Pilot phase to evaluate quality assurance practices and modify as needed
- Encourage ongoing methods development studies under umbrella of OMB generic clearance package, to the extent funding permits.

Data Analysis and Dissemination

4-8: Assure rapid dissemination of data and support for future analysis of those data

To maximize the utility of the Study, the NAS panel highlighted the need for rapid dissemination of well-documented analytic files as well as provision of technical support for use of those files. The review also acknowledges the existence of "formidable challenges" to the assurance of participant confidentiality and implicitly recognizes the inherent tension between those two goals. Achieving a reasonable balance between data access and maintenance of participant confidentiality is of critical importance to the Study; the necessity to promote and foster analyses of Study data to ensure the broadest possible benefit of the collected data is well-recognized.

The NAS panel suggested creation of a network of data centers similar to those used by the U.S. Census as one method to enhance data dissemination. Other models, such as restricted data licenses or remote data access, have also been considered. Given the complex and sensitive nature of this issue, a panel on data access and confidentiality, comprising federal and academic experts, was convened in the autumn of 2007. Among the recommendations of this group was the establishment of an ongoing data access committee to develop an appropriate data access plan. The Study is in the process of convening such a committee to help establish the specifics of a reasonable and well-balanced data access and confidentiality plan.

Creation and support of publicly available analytic datasets falls under the purview of the Coordinating Center. Their tasks include creation of sample weights, maintenance of the analytic files, and study documentation. An appropriate disclosure review plan will be developed, informed by the deliberations of the Data Access and Confidentiality Committee. Data released to eligible researchers will be reviewed prior to release to ensure that confidentiality protections are sufficient. Thus, as the recommendation suggests, appropriate documentation and support for proper analysis of publicly available data is included in the study design and is necessary to maximize the completion of useful and valid research.

Data Analysis and Dissemination Actions:
- Continue the Study's commitment to establishing data access to the general research community as quickly as possible, while assuring appropriate confidentiality safeguards.
- Establish a Data Access and Confidentiality Committee to develop a data access plan designed to achieve a fair balance between maximizing scientific analysis and protecting participant confidentiality.

Chapter 5: Ethical Procedures and Community Engagement

Criteria for Giving Information to Participants

5-1: Define the criteria for deciding what information will be given to participants

In this section of the review, the NAS panel identified the topic that perhaps has garnered the most discussion over the course of the Study's development. Within the Study community—comprising various federal agencies, a chartered Federal Advisory Committee, academic researchers, community representatives—there is a diversity of opinion on the benefits and liabilities of reporting collected information back to the participants. This is a complex issue in any setting and is made more complex by the large variety of data being collected and because analysis of the vast majority of biologic and environmental samples will occur years after their collection.

Several groups have taken on the task of developing appropriate reporting policies. The most active are the Ethics Subcommittee of the Study's Federal Advisory Committee and the Study Steering Committee (composed of the Study Center principal investigators; representatives from NICHD, EPA, and the Centers for Disease Control and Prevention (CDC); the Coordinating Center; and community representatives).

Some data with clear clinical relevance will be routinely returned to Study participants. These data include blood pressure and anthropometric measurements, for which well-established reporting guidelines, such as those used in NHANES, can be followed. However, for many potential analyses of biologic or environmental samples, the use of common concepts such as "clinically relevant" and "actionable" to define policies have limited application to the Study due to the unknown relevance of many exposures (for example, "actionable" levels of many chemicals, such as pesticides, are unknown). It is important to note that most of the planned analyses in the Study utilize a nested case control approach with delayed analysis of biologic specimens and environmental samples, further complicating the determination of "clinical relevance."

All proposals for delayed analysis of stored specimens and samples will be reviewed by a Sample Oversight Committee to assure they are consistent with the mission of the Study. As suggested by the NAS panel, the current policy of the Study is to have reporting decisions reviewed on a case-by-case basis by a Data and Safety Monitoring Board. Criteria for such decisions and the specific responsibilities for the Sample Oversight Committee and the Data and Safety Monitoring Board are being developed and center on the concepts discussed above. This will remain an important issue throughout the course of the Study and will receive ongoing attention by both the Advisory Committee and the Steering Committee.

Criteria for Giving Information to Participants Actions:

- Continue development of process to determine reporting of appropriate findings to Study participants, paying particular attention to the delay between collection and analysis of many samples

- Establish the Sample Oversight Committee and Data and Safety Monitoring Board to provide guidance regarding provision of information to participants.

Protection and Release of Information

5-2: Data should be equally accessible to Study and non-Study investigators, with strict confidentiality safeguards

This section of the NAS review follows from the data dissemination discussion that culminated in recommendation 4-8. Two distinct but related concerns expressed by the panel are the "three-tiered approach to data access" referenced in the Research Plan and the implication that "Study" researchers would enjoy more privileged data access than their "non-Study" counterparts.

As mentioned in the response to recommendation 4-8, the Study's approach to data dissemination and access has evolved and become more nuanced since the Research Plan was developed. The convening of the external expert Data Access and Confidentiality Committee was the first step in developing the eventual data access policy. The deliberations of the standing committee on that topic, comprising both outside experts and Study representatives, will result in a policy that will receive ongoing review and scrutiny as time and technology advances. The general principle underlying the Study's approach to data access is that the data will be made available as rapidly and as widely as possible according to federal guidelines and with adequate provisions to ensure data integrity and security. As stated above, the interest of all parties is best served by promoting and fostering analyses of Study data to ensure the broadest possible benefit from its collection.

Of specific concern to the NAS panel is that Study investigators will receive priority access to the Study's data. In strong terms, the panel spoke against using priority data access as "recompense" for the "sweat equity" expended by the investigators, noting that "…the study centers competed on their ability to collect the data, not their ability to analyze it…the process of collecting data will give sites a significant advantage in carrying out timely analyses of them."

The relative access to data for Study and non-Study scientists has been the subject of substantial discussion; many of the same issues raised by the NAS panel, including the above-stated arguments, have been aired in those conversations. As mentioned, the precise data access policies are still under development. However, the underlying premises as stated above remain—maximize productivity of the Study data while maintaining confidentiality. Regardless of the procedures for data access, investigators with a direct relationship to the Study will be subject to the same privacy and confidentiality constraints as investigators without a direct Study relationship. Within confidentiality guidelines, data will be made accessible as soon as possible. It is important to state, however, that data will not be released until undergoing rigorous validity testing. Rapid release of faulty data is much more deleterious to the public good than a more controlled release of high-quality data.

Finally, public release of the data generated from this initial Vanguard Pilot is not anticipated. The collection of these data is designed to inform the procedures and instruments to be used in the main study waves and will not be incorporated into the final national probability sample.

While the Vanguard Pilot data will receive vigorous use within the Study, the sample size does not enable analysis of the research topics set forth in the Study's hypotheses.

Protection and Release of Information Action:

- Establish a Data Access and Confidentiality Committee to develop a data access plan designed to achieve a fair balance between maximizing scientific analysis and protecting participant confidentiality.

Community Engagement

5-3: Engage communities in implementation, analysis, data interpretation activities that go beyond recruitment

Based on the Study's Research Plan, the NAS panel expressed concerns regarding the extent of community involvement in the Study. Though engagement of the community to assure optimal recruitment was recognized, the panel indicated opportunity for more in-depth involvement within the context of the Study. In retrospect, the Research Plan, compiled as a document for peer review, did not specifically enumerate the extent to which local communities are involved in the Study and will continue to be so through the life of the Study.

A Community Outreach and Engagement Committee, comprising community representatives from each of the Vanguard Centers, has been active since shortly after their initial contracts were let. This group meets by phone on a biweekly basis to address a wide range of community issues, not solely those related to initial recruitment.

As the NAS review notes, each Study Center must, as a contract deliverable, develop a community needs plan and assessment for each Study location. These plans include a wide range of activities including community input in segment boundary definitions and selection of stratification variables (as noted above), meetings with community advisory boards and other community groups, and community input in development of specific study materials. As part of the contractual process, each site must form a Community Advisory Board to provide advice on the implementation of the Study at that site. In addition, the overall Steering Committee and the Executive Steering Committee contain community representatives who contribute to discussions concerning the data collection protocols, other operational considerations, and broad ethics discussions.

Finally, formative studies and other community based data collections are planned to gather community input and to enhance strategies for local community involvement in the Study through focus groups, small surveys, and other mechanisms at individual sites. Experiences at the Vanguard locations can then be transferred, to the extent possible, to the other Study locations.

Community Engagement Actions:

- Continue vigorous community engagement activities in the Vanguard locations and the subsequent main study locations.

Summary List of Study Actions to Specific NAS Recommendations

General Action in Response to the NAS Review:

- Revitalize and refocus scientific work groups to address the specific issues enumerated by the NAS panel.

Health Disparities Actions:

- Reestablish Health Disparities Working Group to focus and refine health disparities assessments, as highlighted in the Children's Health Act
- Ensure enhancement of data collection pertinent to use of, barriers to, and beliefs about health services and behaviors
- Continue practice outlined in protocol of including extensive demographic, exposure, and outcome data to enable analysis of causes and mediator of health disparities.

Frequency of Data Collection Actions:

- Continue pursuit of remote, self-collected, and other low-burden data collection methods as interval collections between scheduled home, clinic, and phone contacts
- Continue development of possible electronic Personal Health Record suitable for use among Study participants
- Continue tracking of electronic medical record progress for potential incorporation into routine data collection.

Conceptual Model Actions:

- Reestablish a working group on child development to help ensure the protocol elements currently under review allow for appropriate incorporation of the life-course model of health and disease following the *Children's Health, The Nation's Wealth* model referenced in the NAS review
- Continue ongoing efforts to both conceptualize and then operationalize assessments of "health potential"
- Ensure that development of future data collection protocols continue to adhere to this approach and to more clearly express it in future study design documents.

Necessity for Adequate Pilot Study Actions:

- The necessity of an adequate pilot phase is fully recognized
- Take all necessary steps to ensure an adequate pilot study, including additional delay of main study protocol at the Vanguard and Wave 1 Study sites.
- Use studies under a proposed OMB generic clearance to test approaches to community engagement, data collection methodologies, etc.

Pregnancy Outcome Actions:

- All pregnancy outcomes are included in the current data collection protocols
- Continue development of detailed pregnancy loss protocols and further refinement of other pregnancy outcomes including identification of birth defects.

Neurodevelopmental and Behavioral Actions:

- Refine conceptual model(s) for assessment of neurobehavior and development by the newly formed working groups comprising members of the Study Centers, Program Office, and Coordinating Center
- Reexamine specific measures included in the early data collection protocol to ensure they conform to the models and address concerns raised in the review
- Conduct formative developmental studies to develop shortened versions of existing instruments for later in childhood and utilize those versions, where psychometrically sound, to minimize burden and allow enhancement of under-represented domains.

Asthma Actions:

- Use Vanguard Pilot phase to assess ability of current protocol to adequately assess the prenatal and early life exposures potentially related to risk of subsequent asthma. In particular, protocols for dust sample collection, while common in targeted environmental studies, have not been widely used within a multipurpose study like the Study.
- Continue efforts to link indoor measurements at the times of the home visits to questionnaire and local air pollutant data to allow estimation of indoor concentrations and exposures during other time periods.

Obesity and Growth Actions:

- Ensure collection of relevant contextual data is included in protocols beyond 18 months
- Undertake small studies to assess various methods of parental and child diet
- Continue evaluation of methods to assess obesity as the Study's children age.

Injury Actions:

- Use results of pilot study, particularly the medical provider logs, to assess reporting of all injuries, not just head injury
- As ability to incorporate medical record information into data collection increases, ensure appropriate identification of injuries and treatment
- Reestablish a working group to address the study of genetic, biologic, behavioral, and environmental contributions to injuries.

Reproductive Development Actions:

- Use experience of Vanguard phase to assess ability to identify early outcomes, such as birth defects, potentially related to hormonally-active agent exposure
- Continue development of later reproductive outcomes, such as self-reported Tanner stage as being tested in NHANES.

Demographic Measures Action:

- Include current battery of demographic data including nativity and language. "Legal status" will not be included due to the serious impact on participation and cooperation

Chemical Exposure Actions:

- Continue interaction with NIEHS, EPA and other programs to monitor development of personal air samplers suitable for use in pregnancy and early childhood and evaluate potential use of portable air samplers in small validation studies

- Consider whether additional biologic or environmental sample collections, or other measures, are needed to characterize exposures to persistent and non-persistent organic compounds
- Use Vanguard Pilot phase to assess ability of the Study to enroll and collect data from fathers.

Physical Measure Actions:
- Continue development and testing of integrated physical and social observational instrument by Vanguard Centers
- Establish Study Center working team to assure appropriate longitudinal assessment of household and neighborhood factors.

Psychosocial Exposure Action:
- With the Psychosocial Working Group, reevaluate psychosocial exposure measures within the Study framework, considering the conceptual models specified earlier in this document.

Biologic Exposure Actions:
- Reevaluate timing of maternal glucose measurements and assessment of childhood infection obtained during pilot phase by expert working group
- Continue incorporation of medical record data and other information as possible in future protocol submissions.

Genetic Measures Actions:
- Assure ongoing development of plans for collection and analysis of genetic material to stay abreast of rapidly changing field. A Genetics/Epigenetics and Genomics/Epigenomics Working Group is being established for this purpose.
- Continue plans for storage of specimens for subsequent analyses in nested case-control studies, as in recommendation 3-16.
- Use adjunct studies for collection and analysis of tissues other than blood that may be useful for targeted gene-expression studies.

Missing Exposures Actions:
- Enhance collection of health care access and utilization measures as discussed in recommendation 2-1
- Continue plans to obtain GPS measurements of participant residences to enable linkage to secondary data sources
- Continue identifying extant databases with potential to link to Study data.

Sampling Design Actions:
- Use extension of enrollment period to assure recruitment targets are met
- Closely evaluate household enrollment throughout Vanguard Pilot phase to enable necessary changes to procedures both during that phase and for the main study design
- Field test the alternative listing approaches described in the Research Plan during the initial Vanguard Pilot phase to determine adequacy for main study
- Continue to allow local Study Center input into definition of secondary sampling strata to allow consideration of exposures of local importance.

Data Collection Actions:

- Ensure strong central oversight of decentralized data collection activities by the Study Program Office and the Coordinating Center
- Use initial Vanguard Pilot phase to evaluate policies and procedures for monitoring of household recruitment and early retention
- Use Vanguard Pilot to evaluate quality assurance practices and modify as needed
- Encourage ongoing methods development studies under umbrella of OMB generic clearance package, to the extent funding permits.

Data Analysis and Dissemination Actions:

- Continue the Study's commitment to establishing data access to the general research community as quickly as possible, while assuring appropriate confidentiality safeguards.
- Establish a Data Access and Confidentiality Committee to develop a data access plan designed to achieve a fair balance between maximizing scientific analysis and protecting participant confidentiality.

Criteria for Giving Information to Participants Actions:

- Continue development of process to determine reporting of appropriate findings to Study participants, paying particular attention to the delay between collection and analysis of many samples
- Establish the Sample Oversight Committee and Data and Safety Monitoring Board to provide guidance regarding provision of information to participants.

Protection and Release of Information Action:

- Establish a Data Access and Confidentiality Committee to develop a data access plan designed to achieve a fair balance between maximizing scientific analysis and protecting participant confidentiality.

Community Engagement Action:

- Continue vigorous community engagement activities in the Vanguard locations and the subsequent main Study locations.