THE NATIONAL CHILDREN'S STUDY
Briefing Document

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DRAFT

This document is intended to structure discussions about the National Children's Study Main Study design and the Vanguard Study Provider-Based Sampling feasibility substudy for the National Children's Study Advisory Committee meeting on October 24, 2012.

Table of Contents

I. Executive Summary 3
II. Background on the National Children's Study 4
III. Current NCS Structure 12
IV. NCS Vanguard/Alternate Recruitment Studies 13
V. Provider- Based Sampling Feasibility Study 18
VI. Other Design Considerations 29
Visit Development 29
Informed Consent 30
Informatics Models 33
VII. Proposed Main Study Design Plans 34
Goals and Outcomes 34
Target Population 37
Study Sample Size 38
Recruitment and Retention Strategy 41
Sampling Frame 42
Visit Schedule 49
Visit Structure 50
Data Collection Strategy 50
Data Archiving and Sharing 50
VIII. Summary 51

I. Executive Summary

The National Children's Study (the NCS or the Study) is a Congressionally mandated portfolio of activities that includes a longitudinal birth cohort study intended to examine the effects of environmental exposures on the growth, development, and well-being of children. The Study underwent several changes in the past few years evolving from an activity driven by consensus of expert opinion into a series of integrated activities that are driven by data, evidence based, and participant and community informed. The initial Study plan was reviewed by the Institute of Medicine and adjusted on the basis of reported strengths and weaknesses. Data collection began in January 2009 in a pilot phase, and by July 2009, the observed data differed from the expected data to such a degree that the pilot Study design and implementation were changed.

The initial plan for a sequential series of activation of about 100 locations across the United States into a single study became a separate pilot (or "Vanguard Study") to study logistics and operations and a "Main Study" to examine exposure-outcome relationships. The initial recruitment approach was not resource effective with regard to time or cost, necessitating the development and testing of additional recruitment strategies. Three alternative recruitment strategies were field tested based on initial point of contact with potential participants- Direct Outreach, Household based through an NCS contractor, and Provider based through a licensed health care practitioner. The recruitment approach, using health care providers as the point of entry, was the most resource effective. Currently, the Study is testing a further refinement of the provider- based recruitment strategy using hospitals and birthing centers in addition to clinics and offices, in a sample frame adjusted from the initial sampling frame. The NCS plans to utilize data from the ongoing provider- based sample recruitment substudy as a bridging study to the proposed Main Study design.

Other changes to the Study include:

- The implementation of a collaborative improvement process for quality control, consistency, and to stimulate innovation;
- Establishment of a network to develop and validate objective, quantitative, inexpensive and rapid assessments of health across the human developmental spectrum;
- Expansion of a formative research program to address components of the Congressional mandate that cannot be adequately addressed in a longitudinal birth cohort study;

- Development, testing and implementation of modern informatics platforms that are open architecture, conform to international data standards, modular and interoperable;
- Establishment of federal security standards compliant data transmission and archive process;
- Implementation of a cooperative federated model for Institutional Review Board clearance and review;
- Development of operational toolkits to engage underrepresented populations; establishment of a national board of community advisors;
- Development of new tools to customize the sharing of information with participants;
- Development of innovative data based hybrid model for the sampling frame for the Main Study.

The Vanguard Study is also implementing a new generation of informatics platforms, continuing the consolidation of data collection activities into regional operations centers, integrating the systematic development of health measurements into the regional operations centers, and embarking on a new generation of Study visits using a core questionnaire with supplemental modules triggered by events and exposures.

The proposed Main Study design, developed through a data driven, evidence based, and participant and community informed process, systematically addresses the major comments from the 2008 Institute of Medicine review of the NCS Scientific Plan.

II. Background on the National Children's Study

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

1. The Children's Health Act of 2000 (Sec. 1004) states that the Director of the NICHD shall establish a consortium of representatives from appropriate Federal agencies to: "Plan, develop, and

implement a prospective cohort study, from birth to adulthood, to evaluate the effects of both chronic and intermittent exposures on child health and human development."

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

The law requires three research imperatives justifying the collection of information:

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

From 2000 to 2006, the NICHD funded the work of the National Children's Study by engaging more than 20 working groups comprising experts from around the country to develop different components of the initial Study design. The initial plan was based on enrolling 100,000 pregnant women through an adjusted national probability sample based on area.

The selection of a sampling frame for the National Children's Study historically reflected a wide range of options. In 2006, after considering several options, NCS leadership decided on a geographically based probability sample. The sampling frame for the Vanguard Study was initially based on a weighted probability selection of about 100 of the approximately 3,000 counties in the United States, using counties as the Primary Sampling Units (PSUs). The counties were then divided into Secondary Sampling Units, or segments, that were normalized to have about 250 live births per year. Some sparsely populated areas required clusters of counties. Recruitment of participants was restricted to women residing within the selected Secondary Sampling Units. Over time, subsequent adjustments were made to the sampling process to address additional criteria, such as increasing demographic and geographic diversity.
As planned, recruitment would occur through door-to-door contact with National Children's Study contract staff over an estimated four year period.

The initial visit schedule was based on a total of three prenatal visits with one in the home and the other two in a clinical setting. Each child would have a total of 9 visits over 21 years beginning with a birth visit

in a clinical setting. Home visits were scheduled at 6 months and 12 months, 8 years and 16 years. Clinic visits were scheduled for 3, 5, 12, and 20 years.

A panel of the Institute of Medicine (IOM) reviewed the Research Plan for the National Children's Study following discussions at three meetings that took place on September 21, 2007, November 8, 2007, and January 24, 2008. The IOM report was released on September 12, 2008. Five strengths and nine weaknesses were noted. For accuracy in communication, the relevant text from the IOM report is quoted verbatim.

*" **STRENGTHS***

*1. **Responsiveness to the Children's Health Act of 2000***

The stated goals for the NCS, and the design of the NCS for achieving those goals, broadly reflect the stipulations of the Children's Health Act.

*2. **The large number of births to be included***

100,000 births would provide enough statistical power to examine many hypothesized relations that cannot be investigated with smaller samples.

*3. **The longitudinal design stretching from before birth until age 21***

A data set that contains data gathered prospectively over the entire course of pregnancy, childhood, adolescence, and early adulthood will enable many new life-cycle relations between exposures and outcomes to be investigated. Data gathered prospectively (or with relatively short retrospective periods) should be more precise than data that are based on long periods of recall. A particularly attractive feature of the study is the effort to recruit births before conception and during very early periods of gestation, when certain environmental exposures may prove to be critically important.

*4. **The many variables to be generated on both outcomes and exposures***

The enormous array of social, psychological, biological, chemical, and physical measures that will be generated under present plans will permit investigation of relationships that have not previously been studied. Some of these relationships are included among the study's hypotheses, but fortuitous and unanticipated findings can also be expected. At the same time, the large number of variables increases the risk of establishing "false positives," that is, relationships that appear to be statistically significant but have in fact been generated by chance. In addition to the variables generated by the study itself, many ancillary variables on characteristics of participants' communities from readily available sources, such as the decennial census, surveys, and

administrative records, can be appended to the data set to augment the analytical usefulness of the study.

5. ***The well-designed national probability sample***

The births selected for the NCS will be identified from a probability sample of households chosen with standard and well-justified sampling techniques. The use of established random selection methods at each sampling stage will ensure that the NCS samples of households, eligible women of childbearing age, and births are national probability samples. We endorse the study's decision to use probability sampling without oversampling any groups. Statistical power could have been increased for any particular investigation by implementing a different sampling design. But modifying the sampling scheme to better address any particular relationship would often have reduced the power for investigating other relationships. The possibility of adding more precisely targeted studies—when resources and respondent burden permit—has been appropriately built into the research design. Nevertheless, it is important to note that the sample size and sampling scheme of the study represent a compromise and are not designed to address any single hypothesis."

"WEAKNESSES AND SHORTCOMINGS

1. ***Absence of an adequate pilot phase***

A principal shortcoming of the NCS, as planned, is the absence of a pilot phase. The study design is extremely complex in terms of identifying subjects, enlisting their enrollment and continued participation, administering the very large number of survey and clinical instruments, and managing huge databases generated by disparate organizations. In addition, we raise many questions about the instruments that have been chosen and about the timing of their application. We think that, if the study is to achieve its promise, experimentation is needed with respect to methods to increase response rates and data instruments. Many of the concerns that we raise about the research plan could be addressed in a pilot phase. Data-gathering will begin at the seven centers designated by NICHD as Vanguard Centers a year earlier than elsewhere. The data that will be generated in Vanguard Center sites are expected to become part of the final data set, meaning that experimentation is likely to be kept to a minimum. Moreover, the lead time between the start of data collection at the sites in the Vanguard Centers and elsewhere appears too short to take full advantage of the lessons that will be learned. The absence of a pilot phase is a serious shortcoming that could be at least partially addressed by increasing the delay between data-gathering in the

Vanguard sites and elsewhere and by treating the Vanguard sites in a more experimental fashion. A delay for the enrollment phase of the study would also allow time to consider more fully the appropriate conceptual framework and specification of hypotheses and measures for the study.

2. ***Decentralization of data collection***

Data collection will be the direct responsibility of 35-40 different study centers. While the study centers will be supervised by government officials and the coordinating center, they will individually contract with outside agencies for data collection. This unusually decentralized data collection strategy reduces the chances that data will be of uniformly high quality over the life of the study and sharply increases the burden of supervision. More centralized and conventional models, such as that employed by the large National Longitudinal Study of Adolescent Health, appear more likely to produce high-quality data. Given that the decentralized approach could not readily be altered at this stage because contracts already have been signed, it will be incumbent upon the government to ensure that staff and other resources are sufficient to closely monitor data collection activities and take prompt remedial steps as necessary. A detailed and specific contractual plan is essential for this purpose.

3. ***Inadequacy of plans to maximize response rates and retention rates***

The success of the study will depend critically on the initial survey response rates and the subsequent rates of sample attrition. The NCS research plan does not explicitly address the best methods and procedures for achieving the ambitious baseline response rates that are targeted. The importance of efforts to increase initial response rates by dealing rapidly with underperforming sites cannot be overstated. Maintaining the representativeness of the sample over time is key to the quality of the results. Little is said in the research plan about how the study expects to maximize retention of sample cases. The risk of sample attrition is especially great in a study such as the NCS that targets children and young adults, the most mobile segments of the population. Typically, the largest loss to follow-up occurs in the early stages of a longitudinal study. Ascertaining the best methods to increase initial response rates and to reduce attrition rates is a matter of great urgency for project management.

4. ***Weakness of conceptual model***

The research plan does not define the basic concepts of health and development. While mentioning them, it frequently defaults to a deficit model that focuses on disease and impairment and the risk factors that contribute to them, rather than on the factors that encourage healthy development. Late additions to the set of hypotheses that are addressed to healthy development are not well

specified. Consequently, there is an imbalance of hypotheses, with specific hypotheses about disease conditions and vague hypotheses about social environments and children's intellectual and social development. The same imbalance appears in the measures selected. Little attention has been paid to outcomes in later childhood and adolescence that might have encouraged attention to additional or alternative exposures.

5. ***Weakness of certain data instruments***

The success of the study depends critically on the quality of the data instruments to be employed for assessment of environmental exposures and child outcomes. Our review revealed gaps, uncertainties, and insufficient rationales for a substantial number of instruments. Among the measures that appear most appropriate are those related to asthma and to biological exposures such as allergens and maternal physical activity. The list of proposed variables about which we have raised questions includes: birth defects, pregnancy outcomes (including fetal death), child mental health disorders, maternal depression, brain injuries, reproductive development outcomes, nonpersistent organic chemicals, pesticides, childhood infections, and the social environment in the home. The set of psychosocial measures selected appears particularly problematic. We hope that the issues we have raised about these measures will encourage a reconsideration and fresh articulation of the bases on which they were chosen, including the introduction of additional measures as substitutes or supplements when appropriate. We also suggest that efforts to assess the validity and reliability of the most problematic measures be made by the Vanguard Centers for their sites. Even when suitable measures have been selected, the timing of their deployment—as proposed in the research plan—will leave large gaps in the measured trajectories of child health and development. These gaps, particularly with respect to in-person home or clinic visits, will make it difficult to identify critical periods of exposure to various environmental agents. The period that will be most successfully studied is that of pregnancy, birth, and the first year of life because that is the period of most intense observation. At older ages, we urge more frequent measurement of key variables, at least for a subsample of the NCS participants.

6. Insufficient attention to racial, ethnic, and other disparities

The Children's Health Act asks the study to "consider health disparities among children," a phrase that typically directs attention to racial and ethnic disparities and can also include language, socioeconomic, and geographic area disparities. While the study will gather a great deal of information that is relevant to understanding such disparities, the research design was not informed by a concern with understanding their basis. The absence of virtually any hypotheses

about racial and ethnic disparities is striking. In particular, there is no attention to generating data on how individuals from different groups may interact with health systems, a factor whose importance has been suggested in many previous studies, nor on psychosocial experiences that differentiate among population groups.

7. ***Failure to adequately integrate data from medical records***

The use of health services is an important variable intervening between exposure and outcome. Given a particular exposure to environmental conditions, the quality of the medical services that are employed can make a large difference in outcomes. High-quality information about the use of medical services would also help to address major questions in health policy. These would include, as just noted, the potential sources of racial and ethnic disparities in health outcomes. Data on the use of health services will be derived almost exclusively from retrospective reports of parents, which are often unreliable. While they may be expensive to collect and mobilize and are themselves imperfect, records from physicians and hospitals would provide an extremely valuable and sometimes indispensable supplement to parents' reports. Medical records could also play an important and often central role in clarifying diagnoses and identifying patterns of child development. We urge that greater attention be paid to incorporating such data.

8. ***Failure to plan adequately for disclosure of risk to participants***

As soon as data collection begins, the NCS will face questions about the circumstances under which information about a child's health and development, as well as his or her exposure to toxic agents, should be conveyed to participants. The study plans to provide information on conditions that are "clinically relevant and actionable," but this is not a conventional concept and needs to be defined and made operational. There is insufficient detail in the research plan about how decisions will be made about what to disclose. Some of the decisions—for example, regarding transmitting information about fetal defects encountered through ultrasounds—are urgent to make. Clearer plans must also be developed regarding what parents and children need to be told about emerging research findings.

9. ***Failure to plan for rapid dissemination of data***

We think that the present plan is unwise in reserving a period of time for researchers associated with the data collection phase of the study to have exclusive access to its data for analytic purposes. Such a practice slows the advance of science and violates increasingly widespread norms, including those prominent within the National Institutes of Health itself. We urge wide and rapid dissemination of the data produced by the study. The data will be used for many analytic purposes

that cannot presently be anticipated. The NCS is a national study paid for by public dollars, and we think that the data and results should be made accessible to the entire research community (with appropriate protections to preserve confidentiality) as soon as practicable. Achieving rapid data dissemination will require early and elaborate organizational and budgetary planning.

CONCLUDING OBSERVATION

It is clear from our review that the NCS offers not only enormous potential, but also a large number of conceptual, methodological, and administrative challenges."

The NCS established a study plan with intent to initiate data collection in a limited number of locations as a pilot. Subsequently, additional Study locations would be activated about a year after the pilot in three or more "waves" over a period of several years.

In January 2009, the NCS began data collection in the pilot phase, named the Vanguard Study, at two locations, and in April 2009, added another five for a total of seven active locations. The Initial Vanguard Study protocol was designed to enroll approximately 1,750 pregnant women after 12 months of data collection using household enumeration and screening to identify eligible women for recruitment.

By late July 2009, as the first births in the Study occurred, the early recruitment data indicated a divergence between observed and expected results. The assumptions, upon which the Vanguard Study was built, particularly regarding the efficiency of the household based recruitment approach, were not supported by the data. Projections and modeling indicated that recruitment to reach the target enrollment of 100,000 children would take almost a decade and the costs would be substantially higher than anticipated. Consequently the NCS program staff began a systematic effort to examine alternatives.

The basis for decision making was shifted from building expert consensus to an approach that is data driven, evidence based, and participant and community informed. The Vanguard Study was reorganized with a new protocol designed to examine the feasibility, acceptability, and costs of recruitment, retention, study logistics, and operations. Here, feasibility means the technical performance and characteristics; acceptability means the impact on participants and the Study staff and infrastructure; and cost refers to level of effort, personnel, time, money, and other resources.

III. Current NCS Structure

The National Children's Study has become an integrated system of activities. The current major components are the NCS Vanguard Study, the NCS Main Study, the NCS Substudies, and Formative Research. The NCS Vanguard Study is the pilot phase for methods and logistics development. The Vanguard Study has its own cohort of about 5,000 children and will proceed for 21 years in parallel but always in advance of the Main Study. The purpose of the Vanguard Study is to inform the Main Study, but not to merge with it.

The NCS Main Study is the exposure response phase, will enroll about 100,000 children, and also runs for 21 years from commencement. The launch of the Main Study is delayed until the Vanguard Study can document an efficient and cost effective scalable recruitment strategy. Requests for Proposals to carry out the Main Study are currently targeted for 2013, with recruitment currently targeted to begin in 2014 and continuing for about 3 years. The NCS Substudies are studies within either the Vanguard, or eventually the Main Study, that use a subset of the larger population. Formative Research is short-term limited studies, often for methods development, that occur external to the Vanguard Study in either laboratories or using other cohorts to support and inform the Vanguard and Main Studies.

A Concept of Operations document based on the planned data life cycle is available on the National Children's Study Web site (http://www.nationalchildrensstudy.gov) at http://www.nationalchildrensstudy.gov/about/overview/Pages/NCS_concept_of_operations_04_28_11.pdf.

The National Children's Study is run by a dedicated Program Office at the NICHD with oversight and budget funding provided by the Office of the Director, National Institutes of Health. The Study issues contracts to provide the federal government flexibility in deploying resources as data becomes available and the Study evolves. In addition, contracts ensure that the data collected are not simply the property of multiple awardees as would be the case for grants where the recipients own the data, but rather that the data are managed by the federal government, and thus can be shared across the research community. Contracts are awarded for the standard 5 year periods of performance and are openly competed before the end of the contract expiration. The National Children's Study awards contracts for data collection, data analysis, data and specimen archiving, and for multiple support functions.

Oversight is provided by the Office of Management and Budget, the Department of Health and Human Services, the Office of the Director, National Institutes of Health (NIH), and an independent Study Monitoring and Oversight Committee. Advice is formally provided by a chartered National Advisory Committee and by a Federal Consortium of participating Departments and Agencies. Additional input comes from structured interactions with contractors and through multiple stakeholders and other interested parties.

IV. NCS Vanguard/Alternate Recruitment Studies

Vanguard Study Alternate Recruitment Substudy Phases 1 and 2

Based on data analysis from the Initial Vanguard Study in seven locations and following an extensive consultation process, the NCS designed an approach termed the Alternate Recruitment Substudy (ARS) to systematically explore three additional recruitment strategies based on how members of the public were informed of and recruited into the Study:

- Provider-based, where participants learn about the Study and are referred through health care providers (broad definition of provider, including pediatricians, obstetricians, public health nurses, midwives, etc.)
- Direct outreach, where participants learn directly about the Study through media and community outreach and are invited to self refer and enroll
- Enhanced Household-Based Recruitment with contact through NCS field contractor staff going door to door in selected neighborhoods augmented by additional outreach activities and health care provider referrals

The primary research goal of the ARS was to characterize recruitment strategies that could be used to identify, recruit, and enroll eligible participants into a population-based cohort study. A secondary goal of the ARS was to systematically determine the effect of how initial contact between the public and the Study influenced recruitment. Each of these 3 recruitment strategies was implemented in 10 locations for a total of 30 locations. Coupled with the 7 Study locations in the Initial Vanguard Study, data collection occurred at a total of 37 locations in the first 2 years of the NCS Vanguard Study.

Women who were not pregnant in the screening phase of each recruitment arm were followed as a preconception cohort to determine whether they became pregnant and eligible to enroll in the Study. In an effort to improve recruitment efficiency from the preconception cohort, probabilities of becoming

pregnant were assigned to each woman based on their self-reported intention to become pregnant. During the initial household enumeration recruitment phase at 7 locations, an estimated 15 percent of women transitioned from the preconception cohort to a pregnant state within a 9 month period. Despite the use of a probability algorithm to enrich for women likely to become pregnant, there appeared to be no enrichment above expected baseline of conversion from preconception to pregnant cohort.

Phase 1 of the ARS involved the administration of questionnaires at each Study visit and began in July 2010 when the NCS obtained clearance from the Office of Management and Budget, Office of Information and Regulatory Affairs. Phase 2 of the ARS added a questionnaire targeted to fathers and introduced biospecimen and environmental sample collections. Twenty-two of the 37 study locations began biospecimen and environmental sample collection during the fourth quarter of 2011.

Preliminary Results from the ARS

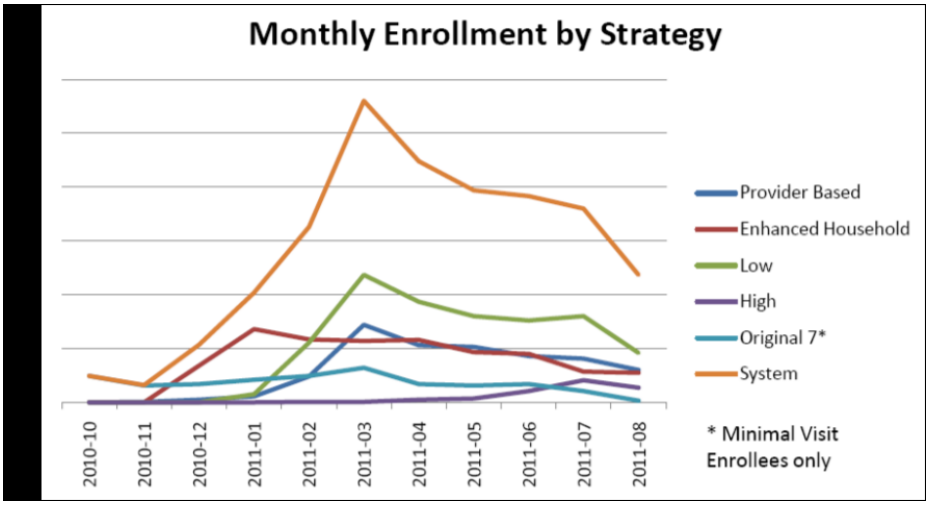
The preliminary results indicate that each recruitment strategy differs in efficiency (the number of women contacted compared to the number enrolled) and that each strategy has different biases. Overall, the Provider-Based Recruitment strategy was the most efficient with about three women contacted for each woman enrolled and the highest proportion of enrolled women who were pregnant. Details can be seen in Table 1. Note that in all tables and figures, values are rounded per NCS policy for public display of aggregate data. Consequently, due to the rounding, calculations shown in the tables may not be internally consistent.

Table 1: Overall Summary of NCS Recruitment Substudy as of June 14, 2012

Selected Measures from the Alternate Recruitment Substudy	Provider-Based Recruitment	Enhanced Household-Based Recruitment	Direct to Public
A. Women eligible for contact	3,600	27,750	19,350
B. Women Contacted for Pregnancy Screen (% of eligible)	3,200 (89%)	22,050 (79%)	19,300 (99%)
C. Women Completing Screen (% of contacted)	2,100 (66%)	20,400 (93%)	15,850 (82%)
D. Women Pregnant or Trying (% of screened)	1,600 (76%)	2,600 (13%)	2,800 (18%)
E. Women Enrolled (% of pregnant or trying)	1,250 (78%)	1,600 (63%)	2,250 (80%)
F. Babies Enrolled	850	750	900
Women contacted/women enrolled	2.9	13.8	8.6
Proportion of enrollees pregnant at the time of enrollment	89%	52%	50%

For Provider-Based Recruitment, potential participant residence addresses were pre-screened using an Address Lookup Tool to identify the women possibly eligible based on residence in a Secondary Sampling Unit (SSU, or segments within a PSU). The Address Lookup Tool provides only an approximate indication of whether a woman resides within an NCS SSU. About 66 percent of the women contacted for the Pregnancy Screener completed the pregnancy screen. The 34 percent difference between women contacted and women who completed the Pregnancy Screener was primarily due to additional women classified as ineligible for participation based on having an address outside an SSU. Initial analysis of the kinetics of rate of recruitment in the Alternate Recruitment Substudy showed a peak at about 20 weeks after initiation, followed by a decrease that had a marked slowdown by week 32. Active recruitment for the three arms formally ended in November 2011, and passive recruitment, that included self-referrals and women who were enrolled in a preconception cohort and subsequently became pregnant, ended in early 2012.

Figure 1- Enrollment Kinetics in Alternate Recruitment Substudy



Other Activities

Among the operational goals of the National Children's Study Vanguard Study is the integration of a systems approach to all activities, which was initiated by the development of a Concept of Operations for the Data Life Cycle, and construction of system maps to document the interrelationships among activities.

An additional goal is to build a learning community. To accomplish that goal multiple modalities of communications were deployed including a weekly newsletter, weekly system wide teleconferences, periodic in person system wide meetings, an NCS research festival, and multiple situational communications.

The number of face-to-face meetings with contractors were increased to occur weekly for support contractors and every six months for the entire NCS system. The system wide meetings were broadened to include staff from local Study Centers in addition to local Principal Investigators and Co-Investigators. To facilitate input, a collaborative web based information portal was established, dedicated e-mail accounts and a Help Desk for field operations were implemented, and a training consortium to build on field experience and expertise began operations.

In addition, the NCS piloted the Collaborative Improvement Network concept that has been successfully applied to health care delivery, but never before to a large scale research project. Following an initial phase as a Formative Research Project, the Collaborative Improvement Network process is now extended

to include retention activities, informatics transitions, and is integrated into the operations of data collection and analysis.

The measurement of health, which is necessary to achieve the goals of the NCS, is challenging due to a general lack of instruments and assessments that measure health in a positive, quantitative, and objective manner across the human developmental spectrum. Linking with, and leveraging the efforts of, trans NIH initiatives, such as the NIH Toolbox for neurologic assessments, the Patient Reported Outcomes Measurement Information System (PROMIS) initiative, and with other specialized activities, the NCS established as a Formative Research project the development and validation of tools and instruments that can be used to assess health and health potential. The results were initial development of a conceptual framework and typology and validation of dozens of instruments for use in younger children.

The Formative Research component of the NCS expanded to address the section of the Children's Health Act to "Investigate basic mechanisms of development disorders and environmental factors, both risk and protective, that influence health and development that influence health and developmental processes." Among the many projects were development and testing of new environmental assays, development of a toolkit to engage underrepresented populations such as American Indians, development of tools to customize the sharing of genetic and other information, molecular studies on placental function and handling of environmental exposures, stress markers during pregnancy, and the various roles of fathers during pregnancy and early childhood.

To enhance the level of feedback and input from community participants, the NCS Program Office established a panel of national community advisors. While each Study location has a local Community Advisory Board, that body is selected by and reports to the local field contractor. The NCS Program Office sought direct input that was not dependent upon filtering by field contractors. The national community advisors meet twice a year in person and in between those meetings, have scheduled teleconferences to provide input into Study design, outreach, proposed Study visit structure, and perceived burden.

To enhance transparency and facilitate public discussion, the NCS Federal Advisory Committee met quarterly instead of every six months. In addition, the NCS Program Office worked with the Advisory Committee to adjust format and content of the meetings to facilitate discussion.

V. Provider- Based Sampling Feasibility Study

To better understand the potential efficiencies and processes of a prenatal care provider-based model and relate it to the proposed Main Study approach, the NCS proposes a new recruitment approach within the Vanguard Study, designed to eliminate the recruitment limitation of requiring participants to reside within small geographic Secondary Sampling Units (SSUs), and instead, base the eligibility on residing within the larger Primary Sampling Unit (PSU) and receiving care from a designated provider. Designated providers will be either office and clinics or hospitals and birthing centers. The Study goal is to enroll about half the participants from prenatal providers at offices and clinics and half from hospitals and birthing centers.

The main goals of the Provider-Based Sampling Feasibility Study are:

1. To learn how to develop a list frame of providers. The specific details on the sources used for the lists of providers and how each Study Center involved in Provider-Based Sampling compiles this information will be used to provide information on the list frame development process.
2. To examine the efficiencies of recruiting pregnant women at the first prenatal visit, including the mean gestational age of enrollees. This will help the NCS calibrate expectations for Main Study recruitment activities and the likelihood of collecting data on early prenatal exposures.
3. To generate data on costs associated with developing sampling frames of providers, gaining cooperation of providers, identification and enrollment of participants, and implementation of Study Visits.
4. To establish participation rates of providers, including willingness to provide information requested by the Provider-Based Sampling Frame Questionnaire, and, if selected, to serve as an NCS recruitment location.
5. To compare the efficiency, demographics, quantity and quality of environmental exposure information, and retention of populations of women recruited perinatally with women recruited early in pregnancy.

In addition, we propose using either the birth visit or the initial prenatal visit as a screening tool to allow for a uniform probability of selection of participants, and in the case of using the initial prenatal visit, to decrease the mean gestational age at recruitment for pregnant women when compared to the earlier NCS Vanguard Study Provider-Based Recruitment arm. In this pilot, a prenatal Provider can be an individual (physician, midwife, nurse practitioner, or physician assistant), an office-based practice or a

facility, such as hospitals and birthing centers. We intend to assign office or clinic-based practices that will enroll pregnant women in a prenatal cohort and hospitals and birthing centers that will enroll women during the perinatal period to separate strata.

Three additional Study locations, Harris County, Texas, Jefferson County, Kentucky, and Worcester County, Massachusetts, have been selected to pilot this approach in their respective PSUs. Based on data from the ARS, the NCS believes that three PSUs is the appropriate sample size needed to determine if the provider-based sampling approach is feasible and efficient.

Recruiting Study Participants in the PBS

Recruitment of Study participants at the selected provider locations will in general follow the Vanguard Study protocol and procedures. Potential participants are screened on age eligibility, residence in the sampled PSU (county), confirmed pregnancy, and appearance for either an initial prenatal visit (Pregnancy Visit 1) using the Provider-Based Sampling Eligibility Screener or for a birth at a hospital. In some locations, medical records may be pre-screened to identify participants meeting these eligibility criteria. Post-enrollment, PBS participants recruited in offices and clinics will be administered the previously-approved Pregnancy Visit 1 instrument if appropriate and receive all subsequent Study Visits already in use in the ARS (excluding the Father Interview). Unlike earlier arms of the NCS Vanguard (Pilot) Study, PBS participants will not be enrolled prior to pregnancy and will not participate in preconception activities.

The recruitment goal for this feasibility study will be about 250 births per PSU. Based on our experience from the Provider-Based Recruitment strategy of the ARS, about 80 percent of identified eligible women agreed to enroll in the NCS. Assuming an 80 percent enrollment rate and an estimated attrition rate of 20 percent (from pregnancy loss and participant attrition through birth), we estimate that about 200 eligible women will need to be invited to participate in each PSU for the office and clinic based enrollment and about 160 eligible women in order to achieve the desired number of 250 births per PSU in this feasibility study.

The target population is all pregnant or perinatal women of the age of majority residing in one of the three selected PSUs with a first prenatal care visit or birth visit during the recruitment period. This includes the birth visit for women who had no prenatal care.

The following groups are eligible for inclusion as participants in the Provider-Based Sampling Feasibility

Substudy:

- Pregnant or perinatal women of the age of majority (typically, age 18) or older residing in a selected NCS primary sampling unit
- Children born to enrolled women
- Adult caregivers for enrolled children who have legal responsibility to authorize needed care for an enrolled child

A pregnant woman who is seen on her first prenatal visit for her current pregnancy at a selected prenatal care provider, or who presents at a selected hospital or birthing center will be eligible for recruitment. In this pilot, a provider can be an individual (physician, midwife, nurse practitioner, or physician assistant), an office-based practice, or a facility, including hospitals and birthing centers. This will inform the Main Study in two ways: recruitment yields of women and provider sampling frame coverage.

We will sample women in three stages. We describe each stage in further detail below:

1. First Stage: Geographic-Based Primary Sampling Units
2. Second Stage: Provider-Based Secondary Sampling Units (SSU)
3. Third Stage: Sampling of women within a selected provider location

First Stage of Provider-Based Sampling: Primary Sampling Units

Three existing NCS counties (PSUs) were selected for implementation of the Provider-Based Sampling Feasibility Study. These counties, while geographically and demographically diverse, do not, and were not intended to, support generalizations to regions or to the broader U.S. target population. We anticipate that improvements in operational efficiency and adjustment of sampling criteria we can enroll the same number of women in the same time frame from three locations as we previously did with ten who comprised the Provider-Based Recruitment arm of the ARS.

Second Stage of Provider-Based Sampling: Prenatal Care and Birth Providers

The NCS ARS tested three recruitment strategies: Provider-Based Recruitment, Enhanced Household-Based Recruitment, and the Direct Outreach Recruitment. The underlying geographic multi-stage, sampling design was the same across the three recruitment strategies. Within each PSU, we selected a stratified random sample of geographic segments, called SSUs, each designed to yield the same number of annual births. Eligibility for enrollment in the NCS was restricted to women who resided within the geographic boundaries of the SSUs.

During the recruitment phase of the ARS, we identified operational limitations with overlaying Provider-Based Recruitment on top of the SSUs. These limitations included the need to approach nearly all providers to seek their cooperation in allowing their patients' addresses to be screened for geographic eligibility. Within provider offices, field contractors screened thousands of addresses to identify women living in households located in the relatively small SSUs. In PSUs with large numbers of health care providers, many of the providers had few patients that actually resided within one of the SSUs.

Provider-Based Sampling differs from this earlier approach in that geographic eligibility for women is based on residence in the PSU and not a SSU. This feasibility study informs the following questions:

1. Can a comprehensive list of prenatal care and birth providers who serve women residing in a selected county, inclusive of providers located both within and adjacent to the selected county, be constructed?
2. Can we associate a measure of size (MOS) with each of the providers on the list that accurately reflects the number of women who reside in the selected county receiving first prenatal care or birth services?
3. What percentage of providers selected from the list will agree to participate in the Study?
4. Can substitute providers be selected with similar characteristics (e.g., MOS, race/ethnic makeup, Medicaid usage) as original sample provider locations be identified as replacements for providers who decline participation?
5. Do the methods developed for sampling women at the selected provider locations work as operationally intended?
6. Do the three stages of sampling and subsequent recruitment methods yield the expected numbers of eligible women?
7. Does pre-screening of patients' geographic eligibility (county residence) by provider office staff affect expected enrollment yields?
8. Are there differences in the efficiencies in recruitment between prenatal care providers and birth providers?
9. Are there differences in the quality and quantity of prenatal exposure data collected retrospectively versus prospectively?
10. Are there differences in the demographics of women enrolled at prenatal care provider locations versus birth providers?
11. Are there differences in the feasibility of collecting perinatal samples retrospectively versus prospectively?

Construction of the Sampling Frame

In each selected PSU, we constructed a list frame of locations of prenatal care providers that will be known as the Sampling Frame. Hospitals and birthing centers will be included in the sampling frame in order to provide sample coverage for those women who do not receive prenatal care through a first visit with a selected provider. The resulting frame will have two strata - one for prenatal care providers and one for hospitals and birthing centers. We aim to have about the same number of women recruited from the two strata.

We considered various approaches to construction of this sampling frame and decided to include all provider locations that serve women residing in the PSU. As a result, some provider locations will be located outside of the PSU, but only women who reside in the PSU will be eligible for enrollment.

The three key steps in the construction of a PSU-specific sampling frame are:

1. Generating a list of all provider practice locations that provide prenatal and birthing services to women who reside in the sampled PSU.
2. Collecting information about the characteristics of each provider location guided by the use of sources such as publicly-available information, sources containing previously collected data, and the NCS Provider-Based Sampling Frame Questionnaire, which was developed for the NCS to gather this information.
3. Compute the MOS based on data from the Provider-Based Sampling Frame Questionnaire and other data sources.

Variability in population size, numbers of providers, and state and local institutions across the three PSUs necessitated tailored strategies for creating the sampling frames. Differing population sizes result in vastly different numbers of providers, and each PSU has variable availability of standardized data sources, such as birth certificate data, to construct the frame. The methods of sampling frame construction employed by each PSU are described in detail below and will allow the NCS to assess the feasibility, cost, and sample coverage of the different approaches, which constitute a likely mosaic of circumstances that we could expect in the Main Study. The sections below describe the efforts planned or underway at each of the three PBS locations to accomplish step 1-generating a list of provider locations.

Provider Location and Hospital or Birthing Center Frame

Each Study Center generates a list of provider locations that provide prenatal care services to women who reside in the sample county. The measure of size (MOS) and stratification data are collected from birth certificate data, from a provider based sampling frame questionnaire, or from other data sources for each provider location on the list. To define the final provider location sampling frame, provider locations with MOS below a threshold that is determined for each location are dropped.

Two populations are not covered by the provider sampling frame: women with no prenatal care and women with prenatal care only at locations not in the final provider location frame (the small MOS provider locations and provider locations missing from the original list). In order to give these women a chance for inclusion, a frame that includes the associated births will be constructed. To do so, a list of hospitals and birthing centers will be compiled. The list will include all hospitals and birthing centers where women who reside in the sample county go to have births. In order to support a more stable understanding of the sampling and operational processes associated with recruiting hospitals and birthing centers, reviewing and sampling from lists of births, and contacting and recruiting women sampled from birth records into the NCS, the stratum of hospitals and birthing centers will likely need to be oversampled.

The two strata, prenatal care providers and hospitals or birthing centers, can be compared in many ways including efficiency of recruitment, the feasibility to collect perinatal samples, quantity and quality of prenatal exposure data, demographics of enrolled populations, and retention rate.

Stratified Probability Sampling of the Provider Locations

Once we construct the Sampling Frame for each PSU, we will construct two strata, one for prenatal care providers and one for hospitals and birthing centers. We will select a subset of provider locations using a stratified Probability Proportional to Size (PPS) sampling design. The variables used for stratifying and sorting the provider practice locations will come from the Provider-Based Sampling Frame Questionnaire (e.g., method of payment, race, ethnicity, language spoken, age) and geocoding information or, for Harris County, TX, from birth records . The MOS for providers will be the estimated number of first prenatal care visits from women who reside in the sampled PSU. To avoid highly inefficient operational situations, we will likely determine a lower bound threshold for the MOS for a provider practice location below which the location would not be eligible for selection.

In some cases, provider practice location-level information for a multiple-location practice may be unavailable and only practice-level information will be reflected on a single record on the frame. If such a

practice is selected, we will employ an additional stage of sample selection to randomly select one (or more) of the practice locations.

The number of provider practice locations that will be included in the development of the subset determined by the stratification procedure will be selected depending on several factors, such as the total sample size, the expected number of women to be selected from each sample location, the number of locations on the frame, and the distribution of the MOS across all the locations on the frame. Since the number of locations and the distribution of the MOS across the locations will likely vary among the PSUs, the number of provider practice locations that will be included in the development of the subset determined by the stratification procedure will also vary among the PSUs.

Third Stage of Provider Based Sampling: Sampling of Women within a Selected Provider or Hospital and Birthing Center Location

Design Parameters

To avoid multiple chances of selection, we will sample women at their first prenatal visit to the provider locations on the sampling frame. In this context, we define the first prenatal visit as the first visit to a provider location listed in the sampling frame. Visits to provider locations not on the sampling frame are not classified as "first prenatal visits".

In each PSU, we expect that between 13 and 17 prenatal office or clinic based provider locations and 3 hospitals will be selected. The actual number of offices or clinics sampled in each PSU will be dependent on the distribution of the provider location MOS in each PSU's frame.

We considered several statistically valid methods for selection of eligible women within a selected provider office or clinic. Operational considerations at the provider office or clinic level and by the field contractor staff will need to be taken into account in determining plausible procedures. Our general approach is to aim for an equal probability sample of eligible women over the two stages of sampling within the PSU. The selection probability of a woman β in provider office or clinic α is given by:

$$P(\alpha\beta) = P(\alpha)P(\beta \mid \alpha)$$

where $P(\alpha)$ is the PPS selection probability for location α and $P(\beta \mid \alpha)$ is the rate for sampling women at that location. For an equal probability of selection for each woman, $P(\alpha\beta)$ is a constant, say f. Thus,

the sampling rate for that location is given by $P(\beta \mid \alpha) = f / P(\alpha)$. Application of this rate will yield an equal probability sample, but the sample size will vary by location depending on accuracy of the measures of size used in selecting the locations.

The procedures for the identification, screening, and enrollment of pregnant women can be accomplished several ways. Some possible methods are listed:

1. One in every four women on a continuously updated list of women kept by the office or clinic staff. Possibly, where every fourth line is identified as the sampled women;
2. One in every fourth day is selected for the office or clinic staff to maintain a list of all women coming on the selected days;
3. Every other week is selected for the office or clinic staff to maintain a list of all women coming in the selected weeks. Every other woman on the list is selected;
4. One in every fourth week is selected for the office or clinic staff to maintain a list of all women coming in the selected weeks;
5. One of the 4 months is selected for the office or clinic staff to maintain a list of all women coming in that month.

Different methods can be employed across the sampled providers within each location. The choice may be influenced by the particular provider location's logistics, operations, and staff willingness to support the Study. However, there can be some benefits derived from coordinating the sampling methods employed across the sampled provider locations in terms of making the overall process more efficient for the staff at the provider location. For example, if some of the provider locations employed a method based on time periods, the sampled time periods could be coordinated to selected non-overlapping time periods for the different locations to the extent possible, thus spreading the workload for the field contract staff as smoothly as possible over the enrollment period.

Hospital Engagement and Participant Recruitment Processes at the Birth Visit

Approaching Birth Centers and Hospitals

The current PBS design is intended to select providers based on their rates of service to eligible women. Hospital and birthing centers are represented to ensure coverage of women who receive no prenatal care or received care from a provider not included in the overall list frame. Therefore, selection of hospitals will occur to ensure adequate coverage of the sampled population. However, women who receive no

prenatal care are likely to be different than those who are treated earlier in pregnancy. In addition to any demographic differences between these groups, women first identified at or immediately after giving birth will require a different approach for enrollment than those identified earlier in pregnancy. Given these factors, the process of recruiting women at hospitals or birthing centers will be distinct from those recruited at other provider locations.

One critical difference is the timing of enrollment. The clinic/provider model assumes recruitment, enrollment, and administration of informed consent and the conduct of initial study assessments during pregnancy. The hospital/birthing center approach does not allow for prenatal assessments, and informed consent generally cannot be anticipated and administered until post-delivery. Some women have several visits to the hospital during the perinatal period and it is possible that such women may be offered enrollment prior to delivery. Once enrolled, however, there is no variation in the postnatal data collections of participants enrolled in clinics and office practices with those enrolled at hospitals and birthing centers.

Ensuring comprehensive identification of eligible women at hospitals will also require a different approach. To avoid a pregnant woman having more than one chance at enrollment, women who give birth at a facility will be screened through admission records or asked if they receive care from selected listed providers from the other stratum. Only women who did not receive care from the listed providers will be offered enrollment during the hospital visit. If the selection of each woman relies on hospital admission information and initial contact with her cannot occur until after delivery, we risk missing women who are unavailable at the hospital as the result of early discharge or birth complications. The NCS must take such situations into account to limit possible bias in the sample.

The NCS anticipates some variation in how participants are identified and recruited at hospitals and birthing centers based on institutional characteristics, such as size or affiliation, or demographic characteristics, such as urbanicity. Variation by field contractor is anticipated as resulting from differential staffing models, resources, and levels of effort assigned to the task.

Field contract staff will contact selected hospitals to understand their local procedures and determine how to best conduct Study activities within these constraints. Some examples are provided below.

(1) Selection of eligible women: Potential participants who meet eligibility criteria will be identified based on a systematic selection process, such as every nth delivery on a specific day of the week. Ongoing contact between field contractor and hospital staff will be required to review admission

logs to identify recent deliveries (e.g., within the past 24 hours). Some hospitals or birthing centers may have pre-admission records that could be accessed to identify eligible women prior to delivery.

(2) Possible specimen collection: If implemented during the PBS, field contractors will need to negotiate an agreement with selected hospitals and birthing centers to preserve critical birth samples for some set period of time after delivery.

(3) Contacting eligible women: Based on the determined selection routine, eligible women will be identified and contacted by field contractor staff prior to discharge from the hospital or birthing center. At this time, NCS staff will introduce the Study to the woman and her family (as applicable) and invite her to enroll.

(4) Administration of Informed Consent: Women will generally be enrolled/consented post-delivery. After answering any questions, an NCS staff member will administer the informed consent document. The consent documentation will include all activities completed at the hospital and birthing center. Detailed contact information on the participant will be collected to facilitate follow-up visits. Any woman who is not able to provide consent due to birth complications will be contacted once her health improves. The NCS will never attempt to consent women who are cognitively unable to provide an informed response.

Process Evaluation Specific to Hospital Engagement: How Are we Evaluating This?

Field contractors are asked to collect information that will allow the NCS to understand the process of and resources required to engage hospitals and birthing centers. Each metric will be examined by available stratification variables, such as urbanicity, size, academic affiliation, and others. Specifically, we seek to understand the level of effort and steps required to identify the key decision makers and gatekeepers and the various types of negotiations and agreements required by hospitals. We are also interested in what is required to engage nursing staff, admissions, or other critical hospital personnel who may restrict access to potential participants. Key metrics of interest are frame construction and the participation rates of hospitals and birthing centers. If the NCS submits and receives approval to collect birth specimens we will also track availability of enrolled women's birth specimens by hospitals.

Women Who Received no Prenatal Care

Any sampling that is taking place only at the prenatal care provider location could miss women who do not seek prenatal care prior to delivery. We suspect that some of these women may have unique

exposures and we would like to include them in the Main Study. Recruiting women at delivery who indicate that they have not sought prenatal care gives the NCS the opportunity to determine the willingness of these women to participate in the NCS. We intend to sample these through the hospital locations, then using a targeted approach, to identify women who indicate that they have not received prenatal care. The same instruments would be used for this cohort of women as for the rest of the women enrolled, beginning with the Birth Visit.

Sampling Women Not on the Prenatal Care Provider Sampling Frame

We propose to use the same sampling method as above for the prenatal care cohort, and again, use the hospitals to perform a targeted screen for women with prenatal care from providers not on the prenatal care provider list frame. This should not be confused with the list of selected providers; rather, this is an evaluation of the entire list frame of providers, as a measure of frame coverage. This would serve to inform the Main Study to ensure that we enumerate, determine a measure of size, and determine stratification characteristics of all providers including hospitals and birthing centers. The same instruments would be used on this cohort of women as the rest of the women enrolled, beginning with the Birth Visit.

Logistical Link to Main Study

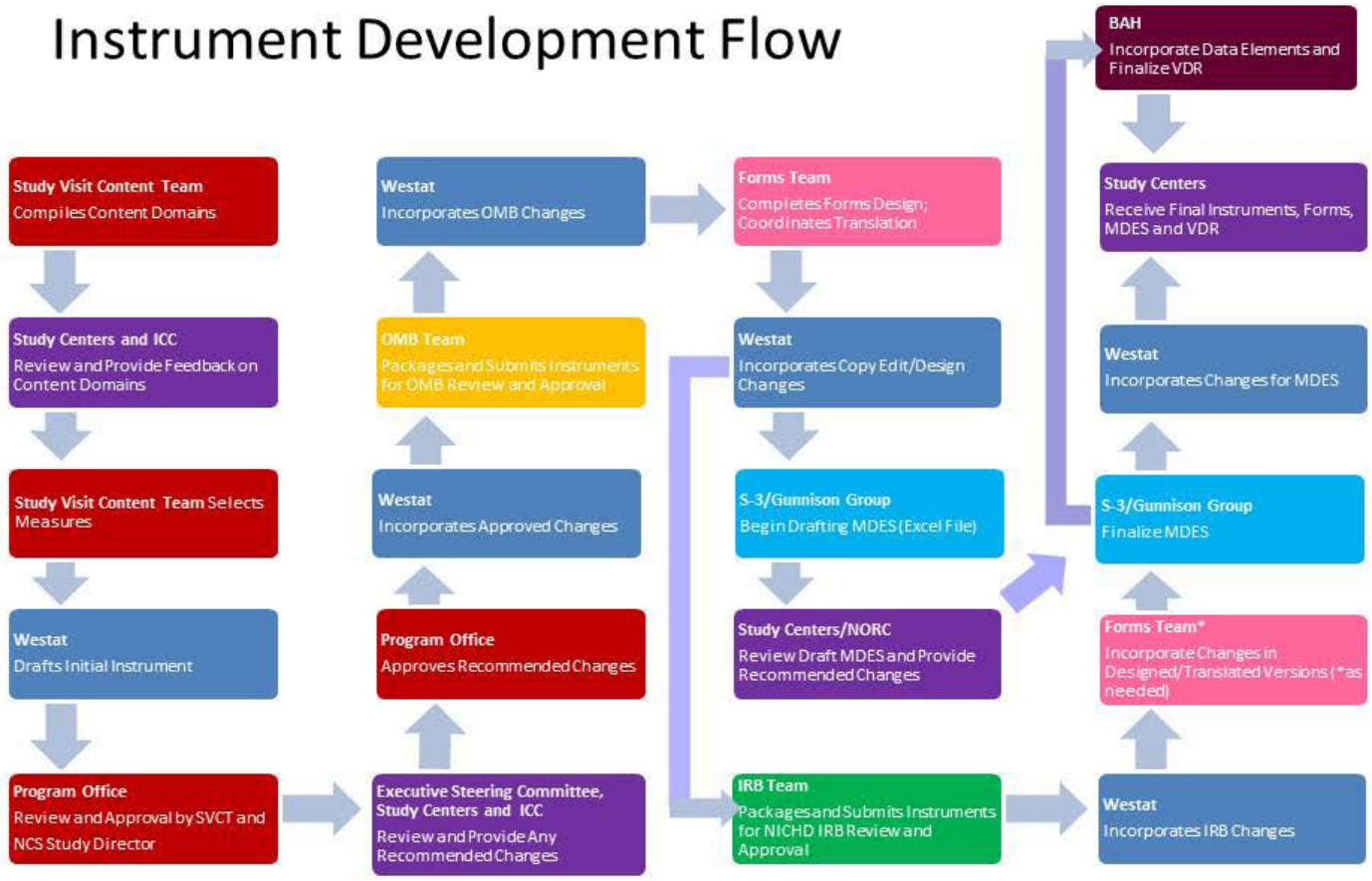
The NCS is proposing a Main Study design that relies on identification of eligible women at multiple locations, including hospitals or birthing centers, and prenatal care provider offices and clinics. To better inform the methods for the Main Study, the NCS seeks a broader understanding of both sampling and operational issues related to working with the full range of provider institutions to identify and enroll participants. To do so, we are documenting the amount of staff labor, other resources, and required length of time to enumerate, sample and recruit provider locations – including hospitals and birthing centers – and complete operational negotiations. Having accurate projections of these processes and their associated timelines will be critical in planning for the Main Study. Additionally, we will track provider, institution, and participant cooperation rates to help us understand what is required to engage hospitals and providers to recruit women into a cohort study, and what effort is required to recruit the women themselves. Understanding these cooperation rates will allow us to more accurately project the necessary resources and implementation approach for the Main Study.

VI. Other Design Considerations

Visit Development

Study Visit Development is managed by three coordinated teams—the Study Visit Content Team, the Instrument Development Team, and the Forms Development Team. The Study Visit Content Team also coordinates overall protocol development. Each team works in conjunction with support and field contractors to develop the concepts and then the specific elements of each Study visit. A summary of the workflow process for instrument and visit development is in Figure 3.

Figure 3: NCS Workflow Process for Instrument and Visit Development with integration of data elements



Informed Consent

Participants provide consent for their own involvement and permission for their children's participation in the NCS in stages. Participating mothers provide written consent for their own participation when they join the Study. Mothers (or other legally authorized representative (LAR)) provide their written permission for children's participation at two separate time points. First, the mother or LAR is asked to provide written permission for a child's participation from birth through 6 months (using either the *Parental Permission for Child's Participation (birth through 6 months with samples)* or the *Birth Visit Information Sheet (birth through 6 months no sample collection)*) parental permission forms. At the time of the administration of the 6-month data collection, the NCS administers the *Parental Permission for Child's Participation* (6 months through Age of Majority) to the mother or the child's LAR. This form requests written permission for the NCS to collect information and samples involving enrolled children from 6 months through the child's age of majority. The parental permission mentions that parents and guardians will be provided with descriptions of the data collection activities to be conducted during a particular visit at the start of each visit.

To date, the NCS has used a series of visit-specific Visit Information Sheets (VISs) for administration during in-person visits that involve questionnaire administration and/or sample collection. The VISs supplement the initial consent forms and process throughout the in-person Study visit schedule by informing the participants of the activities to be completed at the particular visit and reminding them that participation is voluntary and that they may skip questions and samples as they choose. Similarly, instruments that are administered by telephone include a very brief informational script with less detail than the written VIS, which reminds participants that their participation is voluntary and that they may skip questions as they choose.

We have merged the existing written VIS and short informational script into a single multi-mode introductory Visit Information Script (VISCR) that can be read to participants during both in-person Study visits and for all visits conducted via telephone. For visits that do not involve data collection activities, other than questionnaire administration, this script will represent the entirety of the VIS process. The use of a single script will benefit both participants and Study operations by providing: (1) consistent language for all participants for a given visit that includes only questionnaires and/or self-administered questionnaires (regardless of mode of administration); and (2) flexibility to the Study and participants by supporting administration of questionnaires both in-person or by telephone. For visits that include other data collection activities, such as biological and environmental sample collection and physical

measurements, we have drafted VIS language specific to each data collection activity. For postnatal visits that include non-questionnaire-based other data collection activities, such as biological and environmental sample collection and physical measurements, we have created VIS language describing the administration and possible risk specific to each data collection activity. Therefore, administration of postnatal visits involving sample collection and collection of anthropometric or physical measures will include a reading of the multi-mode introductory VISCR followed by reading and distribution of a hard copy sample collection visit information sheet describing the specific sample collection and other procedures that will take place during the visit (*Sample Collection VIS* Specifications). When applicable, a *Reconsideration Script* for data collections that can be captured at one of multiple visits, are administered as part of the VIS administration to recognize that participants may choose not to provide specimens during a particular specimen at a given visit, but may choose to provide the specimen at a subsequent visit. The language of the script can be administered to caregivers of enrolled children as well as adult participants.

From an operational perspective, instead of providing a template VIS for each postnatal visit, we are providing a VIS Specifications document which includes introductory and closing language and modular language describing each collection procedure and any associated risks. Field contractors collecting samples and/or physical measures can develop visit-specific VISs by drawing from the language in the specifications document for collection activities corresponding to the visit. The VIS process will appear unchanged to Study participants, as they will continue to receive a document explaining data collection activities planned for the current visit. This change to the VIS development process is an operational and technical one to account for the modular structure of visits, beginning with the 30-Month Interview.

This approach to VIS development reduces additional burden to participants by reducing redundancy across VISs and between the VIS and the consent, and reducing overall time for VIS administration across visits. This approach also simplifies field procedures and reduces potential for error and protocol deviations for data collectors, as there is uniformity of VIS administration across all postnatal visits. This consolidation of VIS language into a single document, from which visit-specific collection VIS may be tailored, will minimize the administrative burden associated with review of multiple modifications to a template VIS as data collection procedures are phased into the protocol. With this revised specifications document, as additional procedures and future visits are developed and added to the Study protocol, NCS oversight and regulatory bodies' review will only involve the single specifications document as opposed to multiple VISs.

The NCS has developed data collection forms associated with each unique specimen collection. These forms will capture any item nonresponse and any stated reasons. For example, the Biospecimen Child Blood Collection Instrument has a question that records the reason the participant chose not to participate in the collection. The SOP has a statement notifying the data collector to record a reason in this scenario. There are similar questions in each of the data collection instruments where the data collector must record the reason why the participant did not wish to participate.

To ensure the collection of standardized, quantitative information on Study processes, case management, and nonresponse, NCS IT systems also include multiple options to record negative (or positive) reactions from participants and field staff. These may occur and be recorded at any point within a Study Visit, from administration of consent and beyond.

All visits involving questionnaire administration begin with the reading of the Multi-Mode Visit Introductory Script (VISCR). For visits where specimens will be requested, there are written Visit information Sheets (VIS) describing the specimen collections requested of each participant at that visit.

The VIS associated with the referenced child visits includes a description of the proposed biospecimen collections (e.g. urine, saliva, blood). Any concerns or comments from the participant may be recorded in the Information Management System (IMS) tables associated with the VIS administration. The NCS has intentionally provided open-ended fields to allow for the collection of this information. If a participant chooses to decline a particular biospecimen collection, this information is captured in the IMS. When applicable, a Reconsideration Script for data collections that can be captured at one of multiple visits is administered as part of the VIS administration to recognize that participants may choose not to provide specimens during a particular visit, but may choose to provide the specimen at a subsequent visit.

In the case of a participant who previously provided written consent for willingness to participate in biological and environmental specimen collections but indicates that she/he is not willing to provide any further biological (or environmental) sample for subsequent visits, data collectors are required to (1) re-administer the appropriate written consent form so that participants can indicate in writing their new preference regarding specimen collection and (2) enter a new record noting the withdrawal of consent for these types of measures. The IMS tables associated with the Informed Consent process is one way the NCS can measure ongoing participant satisfaction and retention.

Field data collectors are required to document additional case management information. Specifically, all contacts with participants are to be recorded with the associated outcome or disposition. If the contact is associated with the administration of a Study Visit, additional information on the event and each instrument is required. Systems have been developed to allow data collectors to provide both coded and open-ended responses for all of these areas; allowing the NCS to systematically track participant refusals and stated concerns. If the outcome of a specific data collection visit is a refusal, data collectors are required to complete an additional form, not administered to the participant but to the data collector. This form – designed to immediately assess unit nonresponse – collects reasons for participant refusals and is one additional tool for the NCS to assess participant attrition.

Informatics Models

The NCS recognizes the valuable contribution informatics play in many aspects of research studies, particularly those with the complexity and longevity seen with the NCS. Our approach to informatics has been informed by several trends, including the use of open, modular and flexible architecture, the leveraging of standards-based terminologies and transmission specifications, interoperability, and established development communities. Overall, this approach fosters innovation while adapting to the ever-evolving field of informatics.

The Initial Vanguard Study utilized a centralized model of data management where NCS case management systems and data capture systems utilized the same approach across field contractors. This centralized approach is common in large scale data collection, even in multi-center studies. In the Initial Vanguard Study experience, it was determined that data capture systems and case management systems used successfully by other studies did not meet the particular needs of a study as complex and dynamic as the National Children's Study. Therefore, a new solution was sought. In particular the NCS sought a non-proprietary open source, modular, and interoperable solution.

The NCS Program Office used a facilitated decentralization model to support informatics in the Alternate Recruitment Substudy. Like in the Initial Vanguard Study, the NCS Program Office developed evaluation questions and plans; data fields, tables and relationships; formatting and transmission standards; a central data archive; and specifications and guidelines for data security, participant confidentiality, and regulatory compliance. Distinct from the centralized model, however, the facilitated decentralization model allowed field contractors to select case management systems, data acquisition platforms, and, as appropriate, data collection tools to acquire data whose specifications (including content, format, and

security requirements) have been established by the NCS Program Office. All data systems were certified and accredited per the Federal Information Security Management Act of 2002 (FISMA) and related regulatory compliance. This model aided in identifying the costs, acceptability, and feasibility of implementing and maintaining myriad systems and processes. Based on analysis of the experience, the NCS has recently begun a process of convergence whereby the number of IMS systems has been reduced to a limited number of solutions and the infrastructure management will leverage a secure, remote, and centrally-hosted ("Hub") model.

Information Management Systems are coordinated through the Chief Information Officer, NICHD. The Initial Vanguard Study utilized a centralized model of data management, including case management systems and data capture systems. Based on the first year of experience with the centralized model and identification of multiple technical and logistical challenges in planning scale-up, the NCS Program Office implemented a new approach to provide greater flexibility and encourage exploration and innovation to determine preferred methods for case management and data acquisition.

All NCS data systems are certified and accredited per the requirements of the FISMA and related regulations. All NCS data specifications are consistent with international medical research standards, such as those developed by the Clinical Data Interchange Standards Consortium (CDISC).

The NCS emphasis on interoperable modular architecture means that any component of a data system can accurately and efficiently communicate with other data systems, while adhering to international data standards. The approach is flexible to support innovation, accommodate evolving technology, and extend functionality. In addition, its components can be reused or adapted for other studies.

VII. Proposed Main Study Design Plans

Goals and Outcomes

The primary objective of the National Children's Study is to examine exposure- outcome relationships that affect children's health and development. These factors include genetic context and environmental exposures with a broad definition of environment. The National Children's Study is not a study in a conventional sense. It will primarily function as a high quality data collection platform for researchers to explore hypotheses, access biospecimens and environmental samples, and analyze data.

Table 2: The Main Study objectives as stated in the Children's Health Act of 2000 with design implications

Study Objectives	Sample and Study Design Implications
Evaluate the effects of both chronic and intermittent exposures on child health and human development	Visit schedule with an emphasis on documenting early exposures and events High retention of children is important to gather chronic and intermittent exposures
Investigate basic mechanisms of developmental disorders and environmental factors	Broad scope of data collection supplemented and informed by formative research program
Perform complete assessments of environmental influences on children's well-being	Broad scope of exposure and outcome data collection supplemented by personal health records
Gather data from diverse populations of children including prenatal exposures	Need to recruit diverse population groups and capture prenatal exposures
Consider health disparities among children	Ensure sampling of disadvantaged population groups (in terms of exposure, education, socioeconomic status, etc.)

EXPOSURES AND OUTCOMES

Examples of exposures of interest are exposures to industrial chemicals and byproducts in the air, water, soil, and commercial products: natural products in the air, water, soil, and commercial products: pharmaceuticals used for therapy and in the environment: radiation: and effects of proximity to manufacturing, transportation, and processing facilities. Additional exposures of interest are living with animals, insects, plants, media and electronic device exposure, noise, access to routine and specialty health care, learning opportunities that are structured and unstructured, diet and exercise, and family and social network dynamics in a cultural and geographic context.

Examples of outcomes of interest are premature birth, birth defects, growth and development, interpersonal relationships and bonding, inflammatory processes including allergies, asthma, and infections, genetic and epigenetic status, epilepsy and other neurologic disorders, cardiovascular screening and function, childhood cancer, multidisciplinary multidimensional aspects of sensory input, autism and other neurodevelopmental disorders, learning and behavior, and precursors and early signs of chronic diseases such as obesity, asthma, hypertension, and diabetes.

The priority of the mechanisms to be investigated will be informed by the public health impact (based on severity as well as prevalence) on the overall population of children and by scientific opportunity. Examples of conditions of interest are summarized in Table3.

Table 3: The prevalence estimates per 100,000 for selected childhood illnesses.

Condition	Estimated Prevalence per 100,000
Obese	17,000
Overweight	30,000
Premature Birth	12,500
Learning Disorders	5,000
Asthma	5,000
Birth Defects (aggregate)	3,000
Autism Spectrum Disorders (aggregate)	1,100
Schizophrenia	1,100
Congenital Heart Disease	800
Epilepsy	470
Childhood Cancers	320
Down Syndrome	125
Fragile X Syndrome	50

**Note that the legal federal threshold for a rare disease is a prevalence of about 64 per 100,000.*

The prevalence of many of the conditions in Table 3 is possibly underestimated due to disparities in health and access to health care limiting diagnosis. In addition, the prevalence presented represents only the level of each disease spectrum where formal evaluation and intervention are required. Children with less severe symptoms or with restricted access to health care may have health impacts from these conditions but not rise to a level captured by formal health care records.

Use of Model Hypotheses

A primary outcome of "children's health," as framed in the Children's Health Act of 2000, is complex and poses several challenges to measure. Without a single unambiguous definition of health, we propose for study design estimation purposes to prioritize a small number of model hypotheses built from a list of exposures and outcomes that can be assigned to build models to analyze the properties of a particular design. Each exposure can be assigned to each outcome in a matrix table to generate model hypotheses. If a design supports the model hypotheses, we argue that the design can support other hypotheses including

those that may not be envisioned at this time. The exposures we propose as surrogates for more specific exposures are:

Analysis of

- heavy metals
- pesticide residues
- semi-volatile organic compounds

In samples of

- household dust
- blood
- urine

The outcomes we propose as surrogate outcomes for additional outcomes are:

- linear growth rate and body mass index as a surrogate for general health
- a metabolic screen of serum total protein, blood urea nitrogen, cholesterol, iron, and calcium for nutrition and dietary exposure
- frequency and duration of health system encounters for respiratory illness for pulmonary health
- timing of standard neurodevelopmental landmarks and any deviation from adjusted trajectory for cognitive and social development

A model hypothesis for testing a design could thus be pesticide residues in household dust as the exposure and linear growth rate and body mass index as the outcome.

Target Population

A birth cohort of children born to mothers residing in the United States will be the primary target population. Prenatal exposures are of interest and significance so the National Children's Study, as the law proposes, will also enroll pregnant women with a goal to enroll some proportion of the women as early in pregnancy as feasible and an additional cohort of women preconception. In addition, populations that may be underrepresented in the cohort on the basis of exposures, demographics, or other factors may be supplemented through targeted recruitment.

Study Sample Size

A range of medically important outcomes will be used here to illustrate the ability of the National Children's Study to test exposure-outcome associations involved in a series of hypothetical hypotheses with power of 80 percent. These outcomes exhibit the range of prevalence that NCS outcomes are likely to have. While some outcomes are common, most are uncommon and some are rare. Many of these outcomes are relevant for a single hypothesis, but some are relevant for more than one. For example, several hypotheses address different possible predictors of some childhood conditions, including environmental factors, exposure to bacteria and microbial products, maternal stress during pregnancy, and diet. For each outcome, a set of different exposures is considered. In each case power has been calculated for exposure prevalence of 1 percent, 2.5 percent, 5 percent, 25 percent, and 50 percent (this range is based on hypotheses developed for the National Children's Study).

Based on a two-sided binomial sample size calculation for a condition of interest such as childhood malignancy with a national prevalence of 0.5 percent, an alpha of 0.05, and power of 0.80, our ability to detect small but potentially biologically meaningful changes in the prevalence of the outcome of interest such as an environmental exposure leading to an increase in the malignancy rate of 5 percent or more in the Study population requires a sample size of roughly 100,000 children at the time of analysis. The sample size estimate is not necessarily calibrated for conditions that appear at different developmental stages and is not adjusted for attrition over the life of the Study.

Using cerebral palsy (CP) as an example, the results on power displayed in Table 4 can be interpreted as follows: since CP has a prevalence of about 0.2 percent in the general population, that is, the rate to be expected in the National Children's Study. Table 4 gives the odds ratio (OR) that can be detected with 80 percent power for exposures or risk factors with a 5 percent significance level and a prevalence ranging from 1 percent to 50 percent. For rare exposures, only those that have a dramatic impact on the occurrence of cerebral palsy (OR $\geq$ 5.0), can be reliably detected in the National Children's Study. However, for more common exposures, such as those with 5 percent prevalence or greater, factors with more modest effects (OR < 2.6) can be detected with 80 percent power.

Two simplifications were made in these power calculations. First, the analyses consider only the simple bivariate relationships between the exposures and outcomes without addressing the need to control for confounders. The inclusion of confounders likely results in a reduction in the power for detecting the effects of exposures, but often the reduction will be modest. Second, all outcomes and exposures are

assumed to be dichotomous variables. This assumption is again made to simplify the table. In fact, most of the NCS outcomes and exposures will be continuous variables. As a result, the power estimates in the tables are likely to be conservative since dose-response analyses with continuous outcome or exposure variables would likely lead to greater power.

Table 4 displays the magnitude of the minimum odds ratios that can be detected with 80 percent power for the selected outcomes and the range of exposures for analyses. The sample sizes for Table X assumed to be the full sample for which data are available. As noted above, the sample available is reduced through attrition and, for some outcomes, by availability of special data required for analysis.

As Table 4 shows, the magnitude of the detectable odds ratio depends on the prevalence of both the outcome and the exposure. For a given outcome, the closer the prevalence of the exposed group is to 50 percent, the smaller the detectable odds ratio and the greater the power. Similarly, in general, the closer the prevalence of the outcome is to 50 percent, the smaller the detectable odds ratio; the detectable odds ratios are small when the exposure prevalence is reasonably high. All the ratios are less than two when the exposure prevalence is between 25 percent and 50 percent.

Table 4: Detectable odds ratio when analyzing a total NCS sample of 100,000 children.

Outcome	Age	Prevalence of outcome (%)	Prevalence of exposure				
			1%	3%	5%	25%	50%
Type I diabetes	18	0.2	5.71	3.72	2.86	1.93	1.89
Musculoskeletal defects	1	0.2	5.00	3.33	2.60	1.80	1.75
Cerebral palsy	1	0.2	5.00	3.33	2.60	1.80	1.75
Nervous system defects	1	0.3	4.09	2.82	2.25	1.62	1.58
Metabolic syndrome	18	0.4	4.03	2.78	2.23	1.61	1.56
Heart defects	1	0.6	3.03	2.21	1.84	1.42	1.38
Infant mortality*	1	0.7	6.01	3.87	2.95	1.97	1.94
Type II diabetes	18	1	2.75	2.05	1.73	1.36	1.32
Autism spectrum disorder	3	1	2.75	2.05	1.73	1.36	1.32
Major birth defects	1	3.5	1.76	1.47	1.33	1.16	1.14
Adolescent aggressive behavior	18	4	1.82	1.50	1.35	1.17	1.15
Chronic physical aggression (CPA)	10	4	1.76	1.47	1.33	1.16	1.14
IQ score less than 75	1	5	1.73	1.45	1.31	1.16	1.14
Asthma	4	7.5	1.53	1.33	1.23	1.11	1.10
Neurocognitive development	1	8	1.55	1.34	1.24	1.12	1.10
Depression	18	8.3	1.57	1.35	1.25	1.12	1.11
Asthma	7	8.5	1.51	1.32	1.22	1.11	1.10
Neurodevelopmental disabilities	18	10	1.52	1.32	1.22	1.11	1.10
Preterm birth < 37 weeks	0	12	1.41	1.26	1.18	1.09	1.08
Asthma	18	12.5	1.47	1.29	1.20	1.10	1.09
Adverse pregnancy outcomes	0	15	1.38	1.23	1.16	1.08	1.07
Developmental disabilities	18	17	1.41	1.25	1.18	1.09	1.08
Obesity	12	17.1	1.39	1.24	1.17	1.08	1.07
IQ score less than 100	18	50	1.32	1.20	1.14	1.07	1.06

* The exposure for this hypothesis is a community rather than an individual level characteristic.

To illustrate the increase in the magnitudes of detectable odds ratios for subgroup analyses, Table 5 presents results comparable to those in Table 5, but with the sample size reduced to a 20 percent subgroup. The results in this table could be applied to case-control studies, or other analyses based on subsets of the overall NCS sample. It is assumed that the geographic distribution of the subgroup is proportionate to the general population, which would generally be true in case-control studies and other subset analyses. The detectable odds ratio remains below two when the outcome prevalence is 3.5 percent or higher and the exposure prevalence is 5 percent or more, but for rarer outcomes and

exposures, it exceeds two. Many subgroups of interest will comprise less than 20 percent of the population and will thus have larger detectable odds ratios.

Table 5: Detectable odds ratio when analyzing a 20 percent subsample.

Outcome	Age	Prevalence of outcome (%)	Prevalence of exposure				
			1%	3%	5%	25%	50%
Infant mortality*	1	0.7	17.91	10.13	7.08	4.32	5.35
Type I diabetes	18	0.2	16.13	9.42	6.68	4.12	4.99
Musculoskeletal defects	1	0.2	13.44	7.96	5.69	3.50	3.93
Cerebral palsy	1	0.2	13.44	7.96	5.69	3.50	3.93
Nervous system defects	1	0.3	10.23	6.19	4.51	2.81	2.93
Metabolic syndrome	18	0.4	10.04	6.07	4.42	2.76	2.86
Autism spectrum disorder	4	1	5.87	3.78	2.89	1.94	1.90
Heart defects	1	0.6	6.73	4.26	3.22	2.11	2.08
Type II diabetes	18	1	5.87	3.78	2.89	1.94	1.90
Major birth defects	1	3.5	2.96	2.15	1.79	1.39	1.35
Adolescent aggressive behavior	18	4	3.13	2.24	1.85	1.42	1.38
Chronic physical aggression (CPA)	10	4	2.97	2.16	1.80	1.39	1.35
IQ score less than 75	18	5	2.89	2.10	1.76	1.37	1.33
Asthma	4	7.5	2.35	1.80	1.55	1.27	1.24
Neurocognitive development	12	8	2.40	1.83	1.57	1.28	1.25
Depression	18	8.3	2.46	1.85	1.59	1.29	1.25
Asthma	7	8.5	2.30	1.77	1.53	1.26	1.23
Neurodevelopmental disabilities	18	10	2.33	1.78	1.54	1.26	1.23
Asthma	18	12.5	2.21	1.71	1.49	1.24	1.21
Preterm birth < 37 weeks	0	12	2.04	1.62	1.43	1.21	1.18
Adverse pregnancy outcomes	0	15	1.95	1.56	1.39	1.19	1.17
Developmental disabilities	18	17	2.07	1.62	1.43	1.21	1.18
Obesity	12	17.1	2.00	1.59	1.40	1.20	1.17
IQ score less than 100	18	50	1.90	1.49	1.33	1.15	1.13

* The exposure for this hypothesis is a community rather than an individual level characteristic.

Recruitment and Retention Strategy

The primary recruitment mechanism will be through health care providers, with the birth cohort recruited through hospitals and birthing centers, and the pregnancy cohorts recruited through prenatal care providers that feed into the hospitals and birthing centers participating in the birth cohort.

A key goal for the NCS Main Study is to obtain information on the health and developmental outcomes of subjects as they move through childhood, adolescence, and early adulthood. To answer many of the

central scientific questions, it will be essential to retain a sample of sufficient size throughout the course of the Main Study. Determining expected rates of retention of participants through pregnancy to birth and beyond is a key part of the analytic plan for the Vanguard (Pilot) Study. Retention of participants from visit to visit will be carefully monitored.

Specifically, to plan retention strategies for the Main Study the NCS will use data from the Vanguard Study to monitor:

- The proportion of consented women who participate in at least one data collection Study visit.
- The proportion of women enrolled during pregnancy and participating in all data collection visits through the birth of a child that is enrolled into the Study.
- The proportion of women who receive a pre-birth data collection visit that also receive a successful birth visit.
- The proportion of women enrolled during pregnancy and participating in all data collection visits of an enrolled child.

Retention challenges and solutions will likely vary by the nature of the visit, the length of time between visits, and the participant's stage in the Study cycle. Information collected from field data collectors represents a critical source of data from which to evaluate the feasibility and acceptability of the NCS Vanguard Study. Our ability to utilize these data to inform subsequent decisions requires coordination of several operational efforts, including hiring, training, and monitoring of field staff and the development of instruments, study procedures, and case management documentation. For example, unit nonresponse – both initial and due to attrition – will be assessed systematically through the administration of the Nonrespondent Questionnaire. Additionally, our understanding of participant reactions to introducing the collection of biospecimens from infants will be informed by these multiple sources.

Sampling Frame

The sampling frame of the National Children's Study should incorporate a population with diverse racial, ethnic, socioeconomic, educational, cultural, and immigration statuses as well as a geographic gradient of exposures of various types and a range of access to health care services. Desired characteristics in a sampling frame are the ability to address the Study objectives, enroll the target population, collect exposures of interest, and monitor for outcomes of interest, while utilizing the resources available and anticipating the future.

In order to select a sampling approach for the Main Study, the NCS Program Office held a series of meetings in 2012 with various groups. – The first meeting with statisticians from other Federal agencies was held on March 22, 2012. Topics discussed included dual sampling frame methodologies and the feasibility of these methodologies for the NCS, use of research-ready health organizations (including the advantages and disadvantages of using these organizations as sampling units in the NCS), and discussion of other alternative sampling methods. Sampling approach discussions were held with the Federal Consortium (on April 17, 2012), at the public meeting of the Federal Advisory Committee (on April 24, 2012), and with a group consisting of all participating Contractor organizations (on May 26, 2012). A final open meeting was held with Federal and non-Federal statisticians on May 29, 2012. In addition, the NCS Program Office sought further insight through multiple bilateral meetings with professional societies, advocacy groups, and individual statisticians in person, teleconference, and e-mail exchanges. All of these exchanges were instrumental in reaching the proposed approach.

We are proposing a multi-layered cohort approach for the Main Study design. In order to maintain consistency in language and understanding we use the term cohort to describe a group of participants who share a common experience such as pregnancy or birth during a designated period and are enrolled in the Study within a defined time frame.

The rationale for using a layered cohort approach is our perception of differences among the characteristics of each cohort that have logistical, cost, or analytic implications and the difficulty of identifying and enrolling a single generalizable sample of women, spanning from preconception to birth, in a practical manner. We propose a set of layered cohorts that would comprise the NCS Main Study sample.

The first layered cohort would be a multi-stage probability sampled birth cohort. We would call this the core probability sample, as it would have the simplest recruitment strategy and probably the lowest cost compared with the other layered cohorts. This cohort would be comprised of women enrolled perinatally at hospitals or birth centers. The rationale is that the time of entry into the Study would be relatively uniform, and hospitals and birth centers are relatively easy to identify and enumerate for a sampling frame.

This multi-stage probability sample would start with a geographic frame, from which areas with approximately equal numbers of births would be probabilistically selected for the Study; these would be called Primary Sampling Units (PSUs). While it is possible to consider an alternative approach and

generate a nationwide list of hospitals and birth centers and select facilities from that list, we feel that limiting the list of hospitals and birth centers to selected geographic areas is more likely to generate a complete and accurate listing. We also favor using geographic areas as the Primary Sampling Units to better control for field work costs and coverage of geographically-based environmental exposures. The number, size, and locations of areas to form the geographic frame have yet to be determined.

Within the selected geographic areas (PSUs) selection of hospitals and birth centers would be from an enumerated list, with the probability of sampling proportionate to the number of births at the hospital or birth center. Women giving birth at the selected hospitals and birthing centers would be sampled systematically by an approach such as date or day of birth or 1 of n or some other method.

This cohort would have the following potential advantages:

- Probability based sample that could be generalized to live births in the U.S.
- Participants would be enrolled with approximately the same starting point
- High expected rate of participation among selected institutions
- High expected rate of enrollment of newborns
- Broad demographic profile because most births occur in hospitals or birthing centers
- Cost effective based on data from prior studies
- Enhanced feasibility of collection of birth samples (cord blood and placental tissue) as participating hospitals will be known in advance facilitating establishment of operational aspects of the collection

The major disadvantage is that any prenatal data would be retrospective and based on recall and chart review with little or no opportunity for collection of prenatal environmental or biological samples.

A second layer cohort would be pregnant women who seek health care from prenatal care providers who are on the hospital privilege lists at the same selected facilities used to enroll the birth cohort described above. The women could be enrolled at any stage of pregnancy, but the goal would be as early in pregnancy as possible to collect samples and document contemporaneous exposures with a target of 8 weeks of pregnancy. Health care providers would be randomly selected from hospital privilege lists provided by the participating facilities for provider lists above a threshold number yet to be determined. If the number of providers was small, then all providers would be contacted. All women who receive care from a selected provider would be eligible independent of domicile address. Pregnant women receiving

care from the cooperating providers would be sampled using a systematic approach of 1-in-n patients from a list, or a time interval sample.

This cohort would have the following potential advantages:

- Probability based sample that could be generalized
- Leverage infrastructure and cooperation of institutions
- Ability to collect prenatal samples and document exposures prospectively
- Ability to document fetal loss
- Option to combine data with first layered cohort

A third layer cohort would be preconception women using a broader list of providers than the prenatal providers from the same cooperating facilities as in the first two layered cohorts. The women would be followed for conversion to a pregnant state for up to 2 years. Once a woman becomes pregnant in this cohort, we intend to follow her and her child, if the pregnancy results in a live birth, using the same methods as the other two cohorts. The advantage of this cohort is the targeted ability to determine exposures during critical stages of early pregnancy, as well as exposures that may have occurred in the peri-conception period or those leading to infertility. These exposures, as well as early pregnancy outcomes such as fetal loss, may represent the tail end of a distribution that is truncated in the cohort of pregnant women. This cohort provides the opportunity to model such relationships, while making it logistically feasible to follow and recruit women. It is unlikely that this cohort is an unbiased sample, but would favor women with access to health care and other demographic characteristics. Thus these women would bypass the systematic selection process for the pregnancy cohort or the birth cohort. We are interested in exploring technical methods to relate the data in this cohort to the other cohorts.

This cohort would have the following potential advantages:

- Leverage infrastructure and cooperation of institutions
- Ability to collect preconception samples and document exposures prospectively increasing reliability of exposure assessment
- Ability to document time to pregnancy, infertility, and early fetal loss

Additional cohorts could be outside the cooperating institutions, and even outside the designated geographic area, and would target populations that may be underrepresented for any reason of scientific interest. An example of one of these cohorts would be a small sample of pregnant women residing in a community where fracking is taking place, where the scientific interest lies in the environmental

exposure, but the area or number of births may be so small that the probability of selection into any other cohort is low. These cohorts could be part of ancillary studies that would leverage the resources of the NCS. These targeted cohorts are not expected to be part of the larger probability samples described above, although probability based approaches may be used. These cohorts are intended to be analyzed independently of the core cohorts. We propose a scientific review process to screen proposals for targeted cohorts for alignment with the Study goals and prioritization with available resources.

As with all studies there may factors, such as variability among participants with regard to access to resources, cooperation, compliance, response consistency, and retention that may affect data collection and analysis.

Potential questions about the proposed sampling design

- **How large would each of the cohorts be?**
  Cohorts one and two (the birth and prenatal cohorts) would comprise 90 percent of the total sample size. Cohorts three and four (the preconception and supplemental cohorts) combined would be up to 10 percent of the total sample size of 100,000.
- **What proportion of all births in the United States occurs in hospitals and birthing centers?**
  Based on data from 2006, about 99 percent of births occur in hospitals and birthing centers. The proportion of at home births is estimated to be about 0.6 percent overall with some rural states such as Montana, Oregon, and Vermont around 2 percent
- **Why use an area frame to determine Primary Sampling Units? Why not a list of hospitals with birthing centers?**
  An area frame has two advantages. The first is that the number of hospitals with birthing centers within an area is limited, so assessing coverage and generating a list should be straight forward. The second is that, logistically, we would like to leverage geographic clustering to control the number of field offices and field personnel.
  A list of all hospitals and birthing centers can be generated from the universe of licensed hospitals in the United States (about 6,000). However, birth data is generally available from about 80 percent of hospitals from national databases with variability in detail and quality. We anticipate it would be feasible to obtain the relevant data, with consistent quality and completeness, from close to 100 percent of hospitals in a defined geographic area.
- **How will the hospitals and birthing centers be selected and how many do you intend to select them?**

We are considering several options and will make a determination in consultation with statistical sampling experts once we have other aspects of the design clarified.

- **Will using a birth cohort approach as the first layer bypass the expectation for assessing prenatal exposures?**

  For a cohort enrolled perinatally, the prenatal exposure data will not be prospectively collected and any prenatal biological samples will be serendipitous. Through cooperation with prenatal care providers we hope to generate a prenatal health history via medical chart abstraction, which can serve as a partial exposure history, but will not include the specific examination of environmental exposures of interest. Some environmental scientists argue that a local environment is relatively stable and that sampling can reflect chronic exposures that represent the environment several months earlier. However, we remain uncertain about the reliability of such sampling. By using a proportion of, perhaps, 40 percent of the overall Study population as a birth cohort we believe we can obtain a useful sample that can generate accurate generalizable data. Further, while we are missing the individual household exposures, we can still combine these data with general exposure data collected at the municipal or neighborhood level (water quality, air quality, known industrial pollution) to achieve additional retrospective exposure information.

- **How will you collect biological specimens, such as cord blood and placentas, when the women are identified at birth?**

  In most cases we expect to enroll women based on systematic sampling and would request that all protocol specified specimens be collected on all births at participating hospitals during the enrollment window. Those women that do not enroll and for which there is no other reason to retain the specimens would have the specimens discarded. For women that enroll, the Study would receive the specimens. Some hospitals routinely collect blood on pregnant women for type and cross and may collect placentas and cord blood on all births. We would plan to leverage those specimens from facilities that collect them.

- **How do you expect to enroll pregnant women, particularly women who are early (less than 12 weeks) in pregnancy?**

  We will use a list of prenatal care providers from the selected hospitals and birth centers as a first step and then, if the number is manageable and the staff cooperative, attempt to use all the providers. If the list is large we will take a random sample of the providers guided by a measure of size based on the number of annual deliveries. We would leverage the cooperation of the

hospital or birthing center participation to support participation of prenatal care providers. We will enroll women at any stage of pregnancy but would encourage early enrollment.

- **How will the pregnancy cohort be related to the birth cohort?**

  We plan that both cohorts will be probability samples and, through the use of the same geographic area and same facilities, we can align the two stages of the sampling strategy. The use of the prenatal care providers and selection of pregnant women add stages to the prenatal cohort sampling. We can analyze the demographic and health profiles of both cohorts to confirm the characteristics and detect possible bias in the population recruited compared to community data.

- **If you are enrolling both a birth cohort and a prenatal cohort at the same facility, will you not bias one or the other if they have to compete for the same pool of pregnant women? Would not the birth cohort favor women who did not seek prenatal care, which in general is less than 5 percent of all pregnancies?**

  The overall strategy is to use systematic methods and track when a woman is offered enrollment. One approach could be to enroll each cohort at different times with the expectation that the birth cohort may be easier to fill. Subsequently, the prenatal cohort would enroll. We are exploring various options and will do modeling to help guide a selection.

- **Would it not be easier to just enroll a prenatal cohort across a continuum of pregnancy lengths and not have a separate birth cohort?**

  We believe starting with a birth cohort would be more advantageous mainly because it is easier to build sampling frames of birth hospitals and birthing centers than to build sampling frames of prenatal care providers. An additional efficiency of the birth cohort is the hospital engagement for birth biospecimen collection. This hospital based recruitment would be leveraged for the prenatal cohort with recruitment limited to only the privilege lists of sampled hospitals, again, to make enumeration of the provider population simpler, and to use the relationship with the birth hospital to facilitate potential prenatal provider cooperation as well as biospecimen collection. Furthermore, we anticipate the costs of the birth cohort will be lower because it will be easier to recruit and we will not incur expenses for the prenatal visits. We can use the data from the prenatal cohort to calibrate the reliability of the retrospective recall and chart review approach for prenatal exposures that we will use for the birth cohort. As we have seen in our current recruitment substudies, having a large variation in entry points to the Study actually creates several cohorts of women for analysis, each with different sets of data. In essence, what we have

done is separate these cohorts at the outset, so that the data collection is more uniform within the cohort, which will lead to better sample sizes for analysis.

- **How will the preconception cohort be enrolled and how many preconception women do you target?**

  We plan to use the same hospitals and birthing centers as in the other two cohorts, but expand the staff listing to include all providers that provide healthcare to age eligible women. We would encourage broad outreach and enrollment. We estimate that for every woman enrolled that would become pregnant we would have to follow at least six women for about 2 years.

- **What is the rationale for the preconception cohort?**

  We would like to collect data on exposure around the periconceptional period which would have an impact on early fetal development, especially organogenesis, allowing for investigations on fertility, fetal loss, and malformation. We would also like to enroll women as early as feasible, and beginning with a preconception cohort may enrich for identifying women early in pregnancy.

- **What is the proposed business model?**

  Several options are under consideration, but one approach is to have recruitment and protocol directed data collection as separate sets of contracts. Recruitment contracts would be issued to hospitals, birthing centers, and health care providers with an additional contract for supplemental recruitment of underrepresented populations. Protocol directed data collection contracts would be issued to qualifying teams that would perform primary data collection services. Primary data collection could be supplemented and confirmed by structured data transfers from selected medical records from health care providers.

Visit Schedule

Both the Vanguard Study and the Main Study emphasize data collection early in pregnancy and early in child development because the largest knowledge gaps and, perhaps the most critical events, occur during those time periods. Consequently, pregnancy data collections for the cohort of pregnant women are scheduled twice, if possible, prior to about 20 week's gestation and once later in pregnancy. Data collections for children are scheduled at birth and then every three months for the first year and every 6 months until 5 years old for a total of 13 opportunities. Seven of the opportunities will be face to face encounters and include biospecimen and environmental sample collection. The other six are remote data collections, typically by telephone interview. Subsequent data collections have not been scheduled

but will be on average about every other year until 21 years old, for a total of eight additional opportunities. In sum, 21 data collection opportunities per child are planned, but that may change.

Visit Structure

Multiple modalities for data collection are under evaluation, with the current plan based on a core questionnaire model administered at every childhood visit plus supplemental modules to be administered based on events and conditions such as age, developmental stage, and other triggers such as specific exposures or hospitalizations. While the core questionnaire is intended for all participants, supplemental modules may be administered on a missing by design basis to leverage the large study population and extend resources. In addition, the visit schedule is flexible, in that children will not have assessments precisely at a given age but, instead, within a window of several weeks around a particular age to improve compliance and to capture data across a range of specific ages.

In addition to questionnaires, other modalities for data capture such as sounds, images, geographic movements, and mapping of social interactions and networks will be used. The core questionnaire and other questionnaires are essential, however, for calibrating the data from other modalities and for linking NCS data to other data sources.

Data Collection Strategy

Data collection will be implemented by limited number of NCS contractors who will have primary data collection responsibilities. The NCS Vanguard Study currently uses four contractors to collect data on a national sample estimated to be about 5,000 children in 40 locations. The NCS Main Study data collection contractors will likely be assigned geographic regions. The data collection contracts will be separate from the recruitment contracts, but the data collection contractors will be expected to work closely with the recruitment contractors to obtain data on NCS participants that is in personal health records. The NCS data collection will seek to extend data that is in the personal health record and maintain consistency across the NCS system. Electronic health records can be shared through existing mechanisms and non-electronic records can be selectively copied and abstracted.

Data Archiving and Sharing

A Concept of Operations document based on the planned data life cycle is available on the National Children's Study Web site at:

http://www.nationalchildrensstudy.gov/about/overview/Pages/NCS_concept_of_operations_04_28_11.pdf

The general framework is to make all data available for further study with access determined by a Data Access Board guided by the NCS Data Use Policy. Study data collection and archiving procedures are designed to maximize potential use of other data sources, particularly other federal databases. Specimens are considered data in a different form and are stored in a dedicated repository with a backup repository plan.

VIII. Summary

The proposals for the NCS Main Study Design address the major points outlined in the 2008 IOM Report as follows.

STRENGTHS

1. ***Responsiveness to the Children's Health Act of 2000***

The proposed Main Study design specifically addresses each component of the Children's Health Act of 2000.

2. ***The large number of births to be included***

The sample size of the Main Study will still be targeted at 100,000 live births into the Study.

3. ***The longitudinal design stretching from before birth until age 21***

Both the Vanguard and the Main Study will continue for 21 years.

4. ***The many variables to be generated on both outcomes and exposures***

The potential to collect data has increased over the past decade with new technologies and a more flexible visit structure to increase the number and precision of exposures and outcomes over the prior design.

5. ***The well-designed national probability sample***

The proposed sampling design enhances the generalizability of the sample over what was feasible using the prior design through a layered approach with the birth cohort component having the least bias of any feasible design. The birth cohort will anchor a probability based prenatal cohort. Additional cohorts will cover preconception exposures and underrepresented populations.

WEAKNESSES AND SHORTCOMINGS

1. ***Absence of an adequate pilot phase***

The National Children's Study now has a separate and robust pilot study in the Vanguard Study.

2. ***Decentralization of data collection***

Data collection is currently consolidated in the Vanguard Study into four regional operations centers. The Main Study data collection operations will be informed by the Vanguard experience and will likely utilize one set of contractors for recruitment and other contractors for data collection and support services.

3. ***Inadequacy of plans to maximize response rates and retention rates***

The Vanguard experience supports a provider-based recruitment and retention model. Specific retention strategies are proposed and tested through a Collaborative Improvement Network and tracing and follow up activities.

4. ***Weakness of conceptual model***

The proposed National Children's Study design places the definition of health and well-being, as stated in the Children's Health Act of 2000, as a core activity. A Health Measurements Network that began as a formative research project in the Vanguard Study developed a framework and typology. The work is now integrated into the Regional Operation Centers and is coordinated with other efforts at the National Institutes of Health and other international endeavors.

5. ***Weakness of certain data instruments***

The National Children's Study currently tests all instruments in the Vanguard Study for feasibility, acceptability, and cost. Through the formative research program and integrated Health Measurements Program the NCS invests in the systematic development of new instruments.

6. Insufficient attention to racial, ethnic, and other disparities

The Main Study design utilizes the broad lack of bias in hospitals and birthing centers, where about 98 percent or more of children are born. In addition, the Main Study design includes a supplemental recruitment initiative to specifically address any gaps in Study enrollment. Finally, the Study invested in formative research to develop methods and tools to engage specific populations such as American Indians.

7. ***Failure to adequately integrate data from medical records***

The National Children's Study collaborates with the NICHD, the National Cancer Institute Enterprise Vocabulary Services, the National Library of Medicine, and other federal agencies and standards development organizations and private sector vendors to align and harmonize terminology and data standards between health records and research data. The Study invests in developing its data infrastructure to align with and link with multiple data sources and emphasizing open architecture and interoperable informatics platforms.

8. ***Failure to plan adequately for disclosure of risk to participants***

The National Children's Study has held several public discussions as well as meetings with the independent Study Monitoring and Oversight Committee (iSMOC) to develop a plan for risk disclosure and data sharing with participants and communities. Consequently, the Study has a process in place to evaluate return of results and disclosure risks centered around the iSMOC.

The iSMOC monitors National Children's Study data and the safety of Study participants. The responsibilities of the iSMOC are to:

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

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

In addition, the Study invested in formative research to develop tools for ascertaining the level of data sharing that individuals are willing to engage in.

9. ***Failure to plan for rapid dissemination of data***

The National Children's Study developed a multi-level approach for data dissemination consisting of a Data Use Policy, Data Use Agreements, a Data Access Committee and the implementation of data standards to maximize the potential to use and leverage data. No period of exclusive data use for contractors exists. In addition, the Study developed an innovative model for trans Study publications consisting of a Publications Committee that prioritizes analyses and topics and Writing Teams that prepare the manuscripts. This model allows for coordinated and rapid dissemination of

findings in the medical literature and is a supplement to the data and specimen archives outlined in the National Children's Study Concept of Operations for the Data Life Cycle.

CONCLUDING OBSERVATION

The potential and opportunities of the National Children's Study must continually be addressed and developed by a comprehensive systems approach to ensure high quality data collection, processing, analysis, dissemination, and access.

Consultants on Statistical Aspects and Design

The sampling and data collection strategies have been presented to, and benefited from, comments received from staffs from several federal agencies, advisory committees, and scientific experts including: representatives from the National Center for Health Statistics; the Census Bureau; the Bureau of Labor Statistics; the NIH, including the Division of Epidemiology, Statistics, and Prevention Research at the NICHD and the National Human Genome Research Institute; the National Cancer Institute; the National Institute of Environmental Health Sciences; the NCS Federal Advisory Committee; NCS contractors; representatives from the Office of Management and Budget; professional organizations including the Population Association of America; and specific individuals including Mr. Warren Strauss of the Battelle Institute, Dr. Graham Kalton and David Hubble from Westat, Dr. Michael Elliott at the University of Michigan, and Dr. George Rhodes at the University of Medicine and Dentistry of New Jersey.