

THE NATIONAL CHILDREN'S STUDY

Institute of Medicine Workshop

Steering Committee Briefing Document

October 16, 2012

This document is intended to inform planning discussions for the December 11, 2012 CNSTAT-IOM workshop on the National Children's Study Main Study design.

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I. Executive Summary

The National Children's Study is a congressionally mandated longitudinal birth cohort study intended to examine the effects of environmental exposures on the growth, development and well-being of children. Utilizing its early experience in the field, the Study evolved in the past few years from an activity designed largely by expert consensus into an integrated series of activities shaped primarily by data, evidence, and participant and community input. Data collection began in January 2009. By July 2009, the observed data differed from the expected data to such a degree that pilot Study design and implementation were changed. The initial Study plan was adjusted on the basis of both this early field experience and a previous Institute of Medicine review published in September 2008 (summarized in [Appendix A](#)).

The initial plan for sequential activation of about 100 locations across the United States into a single study changed to a design with a separate pilot (or "Vanguard Study") to assess quality of scientific output, logistics, and operations and a "Main Study" to examine exposure-outcome relationships. The initial door-to-door recruitment approach proved suboptimal with regard to time and cost, necessitating testing of additional recruitment strategies. Three alternative recruitment strategies were field tested that differed as to initial point of contact with potential participants- direct outreach, household-based through an NCS contractor, and provider-based through a licensed health care practitioner. Following approximately one year in the field, the recruitment approach using health care providers as the point of entry proved the most 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 to simplify geographic eligibility.

The Vanguard Study is also: implementing a new generation of informatics platforms ([Appendix B](#)); continuing the consolidation of data collection activities into regional operations centers; integrating the systematic development of health measurements into these regional operations centers; and planning for the Main Study visits, using a universal core questionnaire and supplemental modules, for only subgroups of the study population, triggered by events and exposures.

The NCS would like input on the following areas of significant change during the 2012 Institute of Medicine Workshop:

- The goals of the study

- The sampling design
- The recruitment strategy
- The study visit schedule
- The study visit structure

These topics are summarized in more detail in [“Section V. Proposed Main Study Design”](#) below. The following materials were prepared to provide background information and context for the preparation of meeting materials and selection of presenters and discussants for the December 11, 2012 meeting.

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. 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 this national longitudinal study, named the National Children’s Study (NCS or the Study), to :

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.

In 2006, after considering several options, NCS leadership decided on a geographically based probability sample. The sampling frame for the 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 was estimated to take four years through door-to-door contact with National Children’s Study contract staff.

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 ([Appendix A](#)).

Subsequently, the NCS established a study plan with intent to initiate data collection in a limited number of locations as a pilot. Later, 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 substantial divergence between observed and expected results. The data did not support the assumptions upon which the Vanguard Study was built, particularly regarding the efficiency of the household based recruitment approach. Projections and modeling indicated that, to reach the target enrollment of 100,000 children, this recruitment approach would take almost a decade at costs substantially higher than anticipated. Consequently, the NCS program staff began a systematic effort to examine alternative recruitment strategies.

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 set 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 several years in advance of the Main Study. The purpose of the Vanguard Study is to inform the Main Study.

The NCS Main Study will enroll about 100,000 children, and will also run for 21 years from enrollment. The launch of the Main Study is planned for when the Vanguard Study has documented 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 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 funding through 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 owned and managed by the federal government, and thus can be shared across the research community. Contracts are awarded for the standard five-year periods of performance and are openly competed before the end of the contract expiration. The National Children's Study awards contracts for recruitment and enrollment, data and specimen collection, data analysis, data and specimen archiving, and for multiple support functions.

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 provide Study oversight. A chartered National Advisory Committee and a Federal Consortium of participating Departments and Agencies provided formal advice regarding the study. 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 explore systematically 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, where contact is 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 determine systematically the effect of how initial contact between the public and the Study influenced recruitment. Each of these three recruitment strategies was implemented in 10 locations for a total of 30 locations. Coupled with the seven Study locations in the Initial Vanguard Study, data collection occurred at a total of 37 locations within the first two 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 how frequently 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. Based on data from the initial household enumeration recruitment phase at seven locations, approximately 15 percent of women enrolled in a preconception cohort transitioned to a pregnant state within a nine-month period.

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 (here, 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 rate of recruitment in the ARS showed a peak at about 20 weeks after initiation, followed by a decrease that had a marked slowdown by week 32 (Figure 1). Active recruitment for the three arms formally ended in November 2011, and passive recruitment (including self-referrals and women who were enrolled in a preconception cohort and subsequently became pregnant) ended in early 2012.

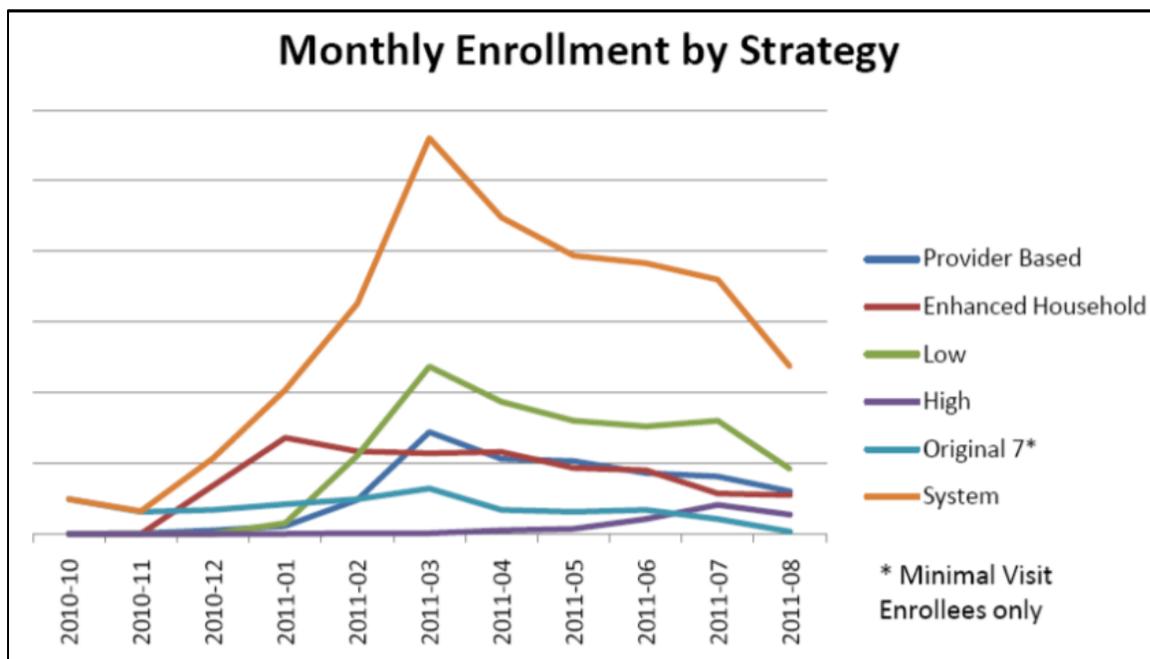


Figure 1: Enrollment Kinetics in Alternate Recruitment Substudy

Given that the ARS aimed to characterize recruitment strategies that are effective in identifying, recruiting, and enrolling eligible participants into a population-based cohort study, sufficient data were collected and analyzed to design next steps. The preliminary results indicated that the efficiency of enrollment differed among each recruitment strategy, with the provider-based approach the most efficient (Table 2).

Table 2: Comparative Recruitment Efficiency in Alternate Recruitment Substudy

	Provider Based	Enhanced Household	Direct Outreach
Number of locations x Weeks in field	701	747	719
Mean number of women enrolled per week	1.5	2.1	3.1
Mean number of women screened per woman enrolled	2.9	13.8	8.6

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 implemented using several tools such as 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. Multiple communications methods were used to accomplish this goal, including a weekly newsletter, weekly system-wide teleconferences, periodic in-person system-wide meetings, an NCS research festival, and multiple other communications for specific situations.

The frequency of face-to-face meetings with contractors was increased to 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 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 other specialized activities, the NCS established as a Formative Research project the development and validation of tools and instruments 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, assessment of concordance between stress biomarkers during pregnancy and self-reported stress, and questionnaires to assess the effects of various roles of fathers during pregnancy and early childhood on children's well-being and development.

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, between those meetings they 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 began in January 2010 to meet 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. Proposed Main Study Design

Goals and Outcomes

The primary objective of the National Children's Study is to examine relationships among exposures and outcomes that affect children's health and development. These factors include environmental exposures (with a broad definition of environment) and biological/genetic context. 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. The study objectives stated in the Children's Health Act of 2000 are presented, along with the respective design considerations, in Table 3.

Table 3: 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 exposures, education, socioeconomic status, etc.)

Exposures and Outcomes

A non-exhaustive list of examples of exposures of interest includes:

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

A non-exhaustive list of examples of outcomes of interest includes:

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

Both public health impact (based on severity as well as prevalence) on the overall population of children and scientific opportunity will inform the prioritization of mechanisms to be investigated. Examples of conditions of interest are shown in Table 4.

Table 4: 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)	1,000-3,000
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 4 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

The primary outcome of “children’s health,” as framed in the Children’s Health Act of 2000, is complex and measuring it poses several challenges. Since there is no universal and unambiguous definition of health, for study design estimation purposes we propose to prioritize a small number of model hypotheses built from a list of exposures and outcomes 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 many other hypotheses, including those that may not be envisioned at this time. The exposures we propose as surrogates for additional exposures are:

Analysis of

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

In samples of

- household dust
- blood
- urine
- questionnaires on exposures including social environment

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

Using this approach, 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.

Sampling Design

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 will also enroll pregnant women, enrolling some proportion of the women as early in pregnancy as feasible and an additional cohort of women preconception. In addition, populations that might otherwise be underrepresented in the cohort on the basis of exposures, demographics, or other factors would 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 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. 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.

The power calculations displayed in Table 5 can be interpreted as follows, using cerebral palsy (CP) as an example: CP has a prevalence of about 0.2 percent in the general population, which is the rate to be expected in the National Children's Study; Table 5 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, the National Children's Study can reliably detect only those that have an impact on the occurrence of cerebral palsy ($OR \geq 5.0$). 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 controlling 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. Also, 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 5 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 5 are 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 5 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 5: 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	18	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	12	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 outcome is a community rather than an individual level characteristic.

To illustrate the increase in the magnitudes of detectable odds ratios for subgroup analyses, Table 6 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 2 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 2. Many subgroups of interest will comprise less than 20 percent of the population and will thus have larger detectable odds ratios.

Table 6: 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 outcome is a community rather than an individual level characteristic.

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.

To select a sampling approach for the Main Study, the NCS Program Office held a series of meetings in 2012 with various groups ([Appendix D](#)). – 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” here to describe a group of participants who share a common experience such as pregnancy 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 analytic, logistical, or cost 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-layer 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, 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 collection of samples or data related to geographically-based environmental exposures. Within the selected geographic areas (PSUs), hospitals and birth centers would be sampled 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.

The 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 eight weeks of pregnancy. Health care providers would be randomly selected from referral lists provided by the participating facilities. If the number of providers is relatively 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 one-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

Potential disadvantages of the prenatal cohort could be issues of differential cooperation and recruitment rates introducing bias to the probability sample (currently under examination in the Provider Based Sampling Substudy), as well as variability in the demographics of women with prenatal care, and the timing of that prenatal care.

The third-layer cohort would be preconception women, using a broader list of providers than the prenatal providers but 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 two 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. This cohort would allow 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

The disadvantages of this cohort are, as mentioned above, the bias towards women with access to health care, who are likely different from the general population with regard to other demographic characteristics.

The fourth-layer cohorts could be outside the cooperating institutions, and even outside the designated geographic area, and would target populations that are 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 and thus 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, factors such as variability among participants with regard to access to resources, cooperation, compliance, response consistency, and retention may affect data collection and analysis.

Questions and answers 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% of the total sample size. Cohorts three and four (the preconception and supplemental cohorts) combined would be up to 10% 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% of births occur in hospitals and birthing centers. The proportion of at home births is estimated to be about 0.6% overall, with some rural states such as Montana, Oregon, and Vermont around 2%.

- **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 straightforward. 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 (about 6,000) in the United States. However, birth data are generally available from about 80% 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% of hospitals in a defined geographic area.

- **How will the hospitals and birthing centers be selected and how many do you intend to select?**

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 unconvinced of the reliability of such sampling. By using a proportion of, perhaps, 40% 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 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. 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% 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. Additional efficiencies of the birth cohort are the hospital engagement for birth biospecimen collection, and the fact that participants represent a unified cohort, meaning that they will all have the potential to have the same data 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 prenatal pilot studies actually created several cohorts of women for analysis, each with different sets of data. In essence, what we have done is separate these different cohorts at the outset, so that the data collection is more uniform within a cohort, which will lead to better precision 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 first and second 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 two years each.

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

We would like to collect data on exposure around the periconceptual 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 in pregnancy 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.

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 who 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 participants 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 who is enrolled into the Study.
- The proportion of women who receive a pre-birth data collection visit who 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.

Study 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 weeks 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 six months until five 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 based upon experience from the Vanguard pilot phase, scientific opportunity, logistical factors, and resources available. Scheduling the majority of data collection within the first five years of life will address both the critical knowledge gaps as well as maximize data collection while retention of participants is highest.

Study 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 to specific participants or subpopulations 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. The module-based visit strategy should provide an opportunity to collect information about very specific exposures or outcomes, while decreasing burden on respondents as all the modules will not be offered to all participants.

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.

VI. Summary

Using knowledge gained in the Vanguard pilot phase, and input from several groups of consultants and experts ([Appendix D](#)) we feel the current proposals for the NCS Main Study Design systematically address the major points outlined in the 2008 IOM Report (summarized in [Appendix A](#)) 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 ([Appendix C](#)).

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 ([Appendix B](#)).

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 nationally over 98% of children are born. In addition, the Main Study design includes a supplemental recruitment initiative to address any specific 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. Moving to a provider-based sampling strategy for the Main Study will enhance the ability of the NCS to leverage available electronic medical records.

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 five to ten 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. For more information see [Appendix C](#).

VII. Conclusion

The potential and opportunities of the National Children's Study must continually be addressed and refined by a comprehensive systems approach to ensure high quality data collection, processing, analysis, dissemination, and access. The December 11, 2012 Institute of Medicine Workshop provides an opportunity to garner input from a broader audience on the changes considered for the Main Study, specifically the areas of:

- The goals of the study
- The sampling design
- The recruitment strategy
- The study visit schedule
- The study visit structure

These domains can be used to shape the agenda for this meeting, and details contained within this document can be used for further context for determining the presenters and discussants at the workshop. We look forward to the engagement with the steering committee over the course of the next two months for workshop planning.

Appendix A: Summary of 2008 IOM Report on the Initial Study

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

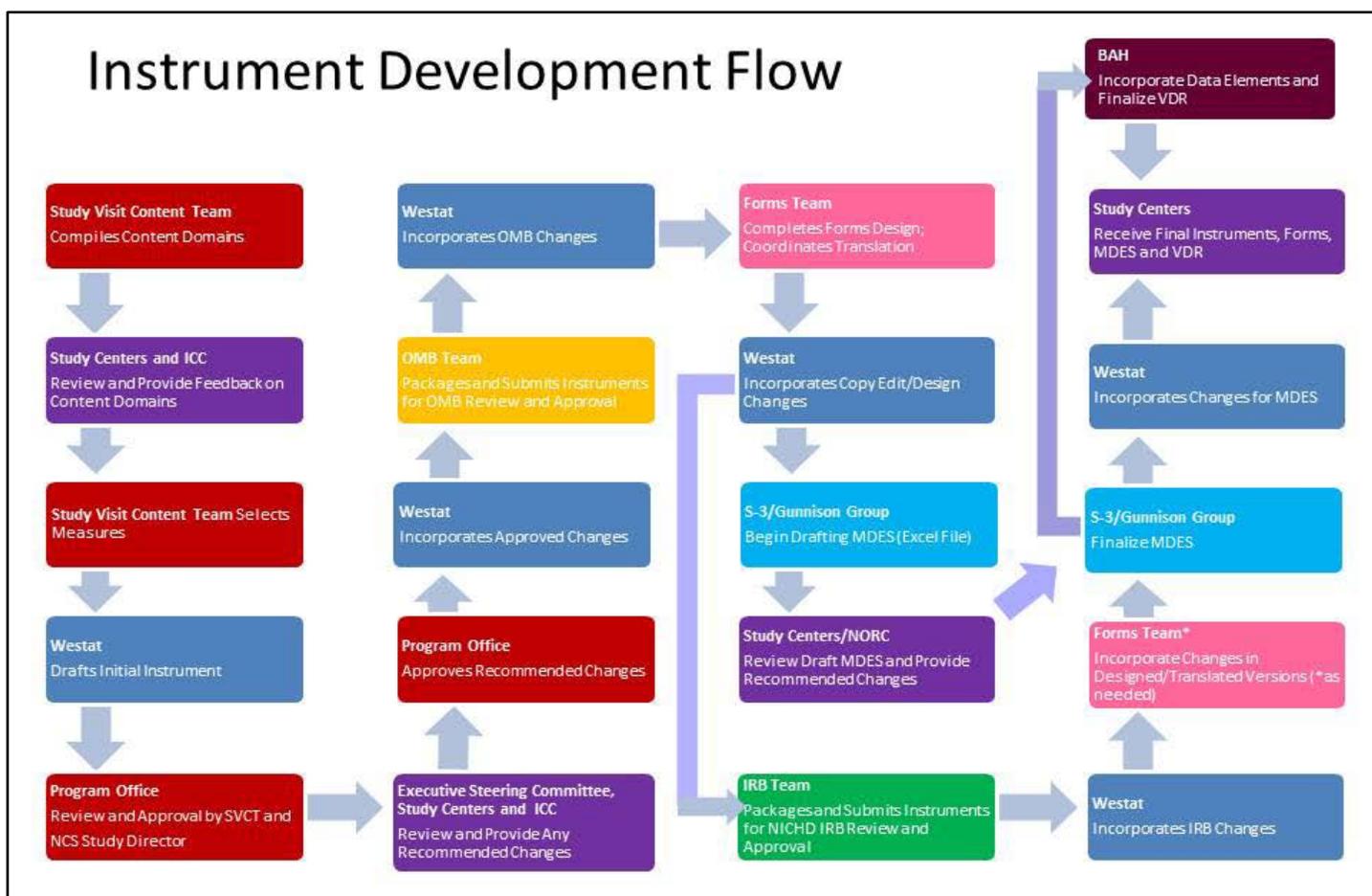
It is clear from our review that the NCS offers not only enormous potential, but also a large number of conceptual, methodological, and administrative challenges.”

Appendix B: 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 1.

Figure 1: 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.

Appendix C: Data

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 forty 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.

Appendix D: 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 (NCHS); the Census Bureau; the Bureau of Labor Statistics; the NIH, including the Division of Epidemiology, Statistics, and Prevention Research (DESPR) at the NICHD and the National Human Genome Research Institute (NHGRI); 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.