ATTACHMENT #1

THE NATIONAL CHILDREN'S STUDY PLAN

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I. PRECIS

A. Background

The Children's Health Act of 2000 authorized and directed the National Institute of Child Health and Human Development (NICHD) and a consortium of federal agencies to plan and conduct a longitudinal study of the impact of environmental exposures on children. The importance and timeliness of this study are based on many factors including past experiences demonstrating profound effects of environmental exposures on child health, such as exposures to lead in early childhood and alcohol during pregnancy; the special vulnerabilities of children to environmental exposures compared to adults; known ongoing exposures, such as prevalent levels of non-persistent pesticides or hours of media exposure per day in young children; and evidence for environmental contributions or causes to high impact conditions, such as autism, developmental disabilities, asthma and obesity. Further, science and technology have advanced to a point that it is now possible to examine the individual and combined effects of gene-environmental exposures, genetic variation, and multiple outcomes over life stages in the same individuals.

B. Goal and Aims

The goal of the National Children's Study (NCS) is to provide information that will ultimately lead to improvements in the health, development, and well being of children. The primary aim of the NCS is to investigate the separate and combined effects of environmental exposures (chemical, biological, physical, psychosocial) as well as gene-environment interactions on pregnancy outcomes, child health and development, and precursors of adult disease.

C. Methods

This longitudinal cohort study will follow a representative sample of approximately 100,000 children born in the United States. Children will be followed from before birth until 21 years of age.

C.1 Sampling and Recruitment

The NCS will employ a national probability sampling approach to select locations for conduct of the study. The sampling design utilizes a multistage clustered approach, with oversampling of certain populations to ensure adequate numbers of participants in target groups to allow valid inferences on exposure-outcome relations in these populations. Because the focus of the study includes assessment of the impact of exposures that occur early in pregnancy, pregnant women and their partners, and women of childbearing age comprise the initial target population for enrollment. At the time of enrollment, participants will be asked to provide written consent for participation in the study and will complete a short interview. Three distinct groups will be enrolled and followed: pregnant women and their partners, couples planning pregnancy, and women not planning but at risk of pregnancy.

C.2 Follow-up

Couples planning pregnancy will be visited up to four times in the 6 months following enrollment to assess pregnancy status, exposures, and to collect biological specimens. After this initial 6-month period, couples in this group who have not yet conceived, will follow the contact and data collection schedule of women at moderate risk of pregnancy. Following enrollment, women at moderate risk of pregnancy will be visited one time to collect interview data, and biological and environmental specimens. Following this visit, women in this group will be contacted every three months, by telephone, to assess risk of pregnancy status. Women at low risk of pregnancy will be interviewed yearly through the end of the enrollment period. It is anticipated that over the enrollment period, a woman's risk of pregnancy will not be stagnant. Data collection schedules will be modified based on the most current information on risk of pregnancy.

A minimum of 15 in-person study visits are planned from the first trimester of pregnancy through 21 years of age. Seven of these visits are in the home, seven are in a clinical setting and one is at the place of delivery of the infant. Additional home visits will occur with each change of permanent residence. Environmental samples will be collected at each home visit as well as from daycare and school settings (any location in which the child routinely spends at least 30 hours per week.) Additionally, remote data collections, e.g. telephone, computer, or mail-in questionnaires, will occur approximately every 3 months through age 5 years and yearly thereafter.

In person study visits are outlined in the table below:

AGE OF CHILD	LOCATION OF VISIT
Preconception	As outlined above
1st trimester	Home
2nd trimester	Clinic
3rd trimester	Clinic
Birth	Place of delivery
1 month	Home
6 months	Home
12 months	Home
18 months	Home
3 years	Clinic
5 years	Clinic
7 years	Home
9 years	Clinic
12 years	Clinic
16 years	Home
20 years	Clinic

Anticipated biologic specimens include blood, urine, hair, nail clippings, and saliva from mothers and children; blood, urine and hair from fathers; cord blood, placental tissue and meconium collected at/around the time of delivery; vaginal and cervical swabs, and breast milk from mothers; and semen from a sample of fathers. Anticipated environmental samples include air, dust, soil, paint, water, and food.

D. Expected Contributions of the Study

The NCS is in a unique position to answer many questions regarding effects of environmental exposures on the long-term health of children. The focus on exposures prior to and early in pregnancy is a unique feature of this study as is the breadth of planned exposure and outcome measurements. As technology continues to evolve, stored data specimens (biologic and environmental) will provide a valuable resource to answer important questions for future generations.

II. INTRODUCTION

A. Overview

The National Children's Study is a longitudinal cohort study that aims to examine the effects of environmental influences on the health and development of approximately 100,000 children. Environment is broadly defined to include biological, chemical, physical, social, psychological and behavioral influences on children's health and development. Priority outcomes include obesity, diabetes and physical development; psychological development; injuries; asthma; pregnancy-related outcomes; and mental health. Children will be followed from before birth until their 21st birthday. The goal of the study is to acquire information that will ultimately lead to improvement in the health and well being of children.

In the initial phase of this study, data will be collected in three to eight geographic areas in the United States, referred to as Vanguard Locations. Data collection in each Vanguard Location will be conducted by a single Study Center, referred to as a Vanguard Center. Vanguard Centers will be expected to follow a common Study protocol and will have primary responsibility for many aspects of the Study including, but not limited to, establishing community relationships and collection of data from Study participants and their environments. Additionally, the Vanguard Centers will pilot new Study procedures prior to incorporation of these procedures into the Study protocol. It is expected that additional contracts will be awarded to the remaining 30-50 Study Centers when full funding for this effort becomes available.

Importantly, a separate solicitation is being released for a single, competitively awarded NCS Coordinating Center (NCS-CC). The NCS-CC will perform the logistical and technical support to handle all of the data collected as part of the NCS and will assist the NICHD, as needed in coordinating efforts of the Study Centers. Additionally, the NCS-CC will provide training for all aspects of data collection and will be responsible for all data collections that do not require in-person contact with participants or their environment, e.g. conduct of telephone interviews, collection of self administered questionnaire or diary data, and collection of data from regional environmental monitoring systems.

B. Background

B.1 Description of Document

The purpose of this document is to describe the current study plan for the Vanguard Centers of the NCS. The Vanguard Centers will serve as the initial study centers for the NCS. It is anticipated that there will be 3-8 Vanguard Centers, depending on the availability of funds and the quality of proposals received. The intent of this document is to outline the Study Plan that will be utilized not only at the Vanguard Centers, but eventually also in the full complement of 30-50 Study Centers.

This document provides a broad outline of the Study including background and study rationale, the sampling scheme, schedule of visits, type and scope of data collections, and an overview of ethical issues. A more detailed Study protocol and operational manuals will be developed with the input of investigators from the Vanguard Centers and the NCS-CC.

Although the intent is to combine data collected through Vanguard Centers with data collected through Study Centers that are added later, several possibilities exist. If, through experience at the Vanguard Centers, it is learned that critical aspects of the protocol are infeasible, leading to major revisions in procedures, it may not be scientifically valid to combine initial data collected at Vanguard Centers with data collected in the full Study. Further, the addition of the full complement of Study Centers is dependent on receipt of full funding for the NCS.

B.2 Definitions

Steering Committee - The Steering Committee for the NCS will be the committee responsible for making recommendations to the NICHD Project Officer (PO) regarding Study design and data collections. The Project Officer must approve all recommendations, plans, or modifications prior to implementation. Initially, the Steering Committee will

include the PO and other members of the NCS Program Office, as well as members from the NCS- CC, the NCS Interagency Coordinating Committee (ICC), Principal Investigators from the Vanguard Centers, and possibly

representatives from other entities, such as contractors in charge of Information Technology (IT) or other specific aspects of the Study. The composition of the Steering Committee may change over the life of the project.

Draft Study Plan-document prepared by the NCS Program Office that outlines the general study design of the NCS.

Study Protocol-document to be developed by the NCS Steering Committee that specifies data collection for the NCS. The Study Protocol contains more detailed information than does the Draft Study Plan about Study design and data collections.

Manual of Operating Procedures (MOP)-document prepared by the NCS-CC in collaboration with investigators from the Vanguard Centers and the NCS-PO, that details all procedures to be used throughout the conduct of the Study. In addition to detailing what is collected in greater depth than the Study Protocol, it also details the multiple aspects of how specimens and information are gathered and submitted for processing and storage.

Primary Sampling Units (PSUs)- In a multi-stage probability sample these are the individual components into which the target population is divided for the first sampling stage. In the NCS, the PSUs roughly correspond to US counties.

Segments- In a multi-stage probability sample, PSUs are divided into smaller geographic areas called secondary sampling units or segments. In the NCS, the boundaries for these segments will correspond to "neighborhoods or communities" and will be defined by the NCS-CC with input from the individual Study Centers (see below).

Study Locations- In the full NCS, the counties that were selected as a result of the first stage of sampling are referred to as Study Locations.

Study Sites- In the full NCS, the segments selected as a result of the second stage of sampling, within an already selected Study Location, are referred to as the Study Sites. These Study Sites correspond roughly to neighborhoods, and will be the areas from which Study participants are recruited as well as the areas in which neighborhood data collections take place.

Study Centers—In the full NCS, the Study Centers are the organizations that are responsible for participant recruitment and data collection within a given Study Location.

Vanguard Locations— Eight Locations have been identified to potentially serve as the initial Study Locations for the NCS. These are referred to as the Vanguard Locations. Seven of the Vanguard Locations correspond to a single county; one Vanguard Location includes three adjacent counties.

Vanguard Sites—the selected segments (second stage of sampling) within a given Vanguard Location. These will be the initial places where study participant recruitment and data collection will occur.

Vanguard Centers - the organizations responsible for Study participant recruitment and data collection for the Vanguard Sites. The Vanguard Centers are the organizations to whom the contracts resulting from this solicitation will be awarded.

Interviews - structured query sessions conducted in person or by telephone between study participants and trained study personnel.

Questionnaires – a written or computer-based, self-administered form completed by the study participant. For the NCS, assistance for completion of questionnaires will be available by telephone if needed.

B.3 History

The Children's Health Act of 2000 (Public Law 106-310) lays the groundwork for this major national study of the impact of the environment on child health. The act authorized the NICHD "to conduct a national longitudinal study of environmental influences (including physical, chemical, biological, and psychosocial) on children's health and development." It directed NICHD to establish a consortium of representatives from appropriate Federal agencies to: " 1) plan, develop, and implement a prospective cohort study from birth to adulthood, to evaluate the effect of both chronic and intermittent exposures on child health and human development; and 2) investigate basic mechanisms of developmental disorders and environmental factors, both risk and protective, that influence health and developmental processes." The Institute is required to: "1) incorporate behavioral, emotional, educational, and contextual consequences to enable a complete assessment of the physical, chemical, biological and psychosocial environmental influences on children's well-being; 2) gather data on environmental influences and outcomes on diverse populations of children, which may include the consideration of prenatal exposures; and 3) consider health disparities among children which may include the consideration of prenatal exposures."

B.4 Significance and Scientific Rationale

Numerous examples of adverse effects of environmental exposures on the fetus and child attest to the special sensitivity of children to factors, substances and influences to which they are exposed. There appear to be unique windows of vulnerability during organogenesis, with early gestation being an especially vulnerable period. For neurological development the period of vulnerability persists throughout childhood and is particularly pronounced in the first two to three years. Further, immature mechanisms for elimination or detoxification of toxicants make children less able to rid themselves or effectively reduce the dose from a given exposure. Finally, developmental and behavioral characteristics of children often result in increased effective exposures in children versus adults exposed to the same environment. These include a higher surface area to body mass ratio, a higher respiratory minute ventilation rate, and increased consumption of drinking water and food per body weight. The NCS proposes to address the need to identify, and where possible quantify, the effects or absence of effects related to various environmental exposures in children. This information will form the basis of child health and environmental guidance and policy for many decades.

From an exposure perspective, a classic and well known example of an adverse environmental exposure is that of lead. By the mid 20th century, lead had become pervasive in our environment through paint, plumbing, gasoline additives and multiple other uses. Manifest toxicity in children was well known to pediatric and public health professionals. However, a series of reports beginning in the 1970's also linked measured lead exposure in children without obvious clinical toxicity, to long term cognitive and behavioral deficits. As the neuropsychological effects became evident at progressively lower levels of exposure, control and removal of lead from children's environments intensified, screening for lead exposure became routine and acceptable levels of exposure have progressively dropped. Other examples of exposures with known adverse effects are many, including exposure to other chemicals or biologics [exposure to alcohol or cytomegalovirus during pregnancy], physical exposures [ionizing radiation, prone sleeping in infancy], and psychosocial exposures [stress, poverty]. An even greater number of exposures have been postulated to result in adverse effects, but data are lacking to draw clear conclusions about either the presence or strength of an association. Examples of exposures that might fall in this grouping include effects of exposure to polybrominated flame retardants, pthalates, electromagnetic fields, or the effects of a variety of childcare arrangements.

Examined from another perspective, there is growing concern that a number of outcomes are the direct result of environmental exposures. Examples of conditions known to be caused or affected by environmental exposures are too numerous to list (e.g. air pollutants and exacerbations of asthma, mercury and Minamata Disease, low folate and risk of neural tube defects, lack of social efficacy and violence). This longitudinal study of children and families goes beyond easily recognized conditions to include those that are more subtle in expression, e.g. attention deficit/hyperactivity disorders, learning disabilities, behavioral disorders and depression. There is also a focus on conditions that appear to be increasing in our society e.g. asthma, obesity, certain birth defects (e.g. hypospadias), and developmental disabilities (e.g. autism and ADHD). Finally, recruitment of mothers early in pregnancy will enable examination of the impact of environmental exposures on important pregnancy and birth outcomes (e.g. preterm birth and low birth weight).

There is accumulating evidence from both animal and human research that many exposures result in a given adverse outcome only in genetically susceptible individuals (e.g. individuals with a particular polymorphism) or through alterations in gene expression. Evaluating the link between environmental exposures and developmental outcomes in humans is a major research challenge given the range of outcomes that may arise from one exposure, the synergistic effects of multiple exposures, and the range of factors that can result in one outcome. Recent advances in both technology and statistical modeling provide new opportunities to examine gene environment interactions and the synergistic effects of multiple exposures with multiple, complex outcomes. Only a study of the size and scope of the NCS is able to address these more complex interactions, and it is only by examining these interactions that we are likely to learn the answers to many of the most pressing questions surrounding child health and development. Further, it is likely that the extensive database established by this study will be used to study questions and relationships that have not yet been formulated with technology that has yet to be developed. This capacity for research and analyses beyond current aims of the study, constitutes a major contribution and impetus for undertaking this study.

III. GOALS, AIMS AND HYPOTHESES

A. Study Goal: The goal of the study is to learn information that will ultimately lead to improvement in the health, development, and well being of children.

B. Study Aim: The primary aim of the NCS is to investigate the separate and combined effects of environmental exposures (chemical, biological, physical, psychosocial) as well as gene-environment interactions on pregnancy outcomes, child health and development, and precursors of adult disease. More specific aims are:

1. To determine the presence or absence of effects, both harmful and helpful, related to the timing, frequency, magnitude, and duration of specific chemical, biological, physical, and psychosocial exposures in children's environments.

2. To determine possible environmental contributions to, or causes of, specific diseases and conditions of children, including but not limited to prematurity and other outcomes of pregnancy, neurological and developmental disorders, psychiatric and behavioral disorders, altered physical development and sexual maturation, obesity and insulin resistance, asthma, and injuries.

3. To determine the influence of environmental exposures and timing of exposure on the trajectory of healthy development in childhood, including but not limited to physical growth, cognitive performance, and social /emotional development.

4. To serve as a national resource for future studies of child health and development by providing a rich database and repository of environmental and biological samples and information that can be used to address future questions and hypotheses.

C. Sample Research Hypotheses:

The NCS requires many well-defined hypotheses to fulfill its aims and ascertain whether exposures to environmental factors affect the health and development of children, either adversely or positively, and whether certain health conditions of children result from environmental exposures. The uniqueness of this longitudinal study also enables assessment of the impact of multiple or recurrent exposures on varying health outcomes over time.

The NCS relied on the expertise and input of the Federal Advisory Committee (NCSAC), its Working Groups, an independent panel of experienced pediatric and environmental health researchers and the general public in developing priority topic areas for the Study. Within priority areas, many hypotheses were proposed by Working Groups and other entities, and then considered by the NCSAC, which made recommendations concerning their relevance and prioritization. A list of hypotheses that have been considered and used in planning the study can be found at http://nationalchildrensstudy.gov/research/hypotheses. It is expected that this list will grow as additional existing hypotheses are refined and, in the future, as new hypotheses emerge.

Initial development of the timing and type of exposure and outcome measures was guided by a series of hypotheses that pose questions of importance, require a study of this design and size, and can be addressed by the NCS. These hypotheses define relevant environmental exposures including physical, chemical, biologic, and psychosocial factors that affect one or several important outcomes including the outcome of pregnancy, child physical growth and development, injury, asthma, and psychological and emotional health. Many hypotheses also take into consideration the important impact of gene-environment interactions or the effect of access to health care services on health and well being.

It is also recognized that one of the greatest values of this study is the establishment of a databank of longitudinal measures and a repository of both environmental and biologic specimens that will allow future generations to address important questions of clinical and public health relevance. The avenues of investigation are too numerous to cite each and every possibility, but a number of specific study questions have been developed to assure that key measures are obtained and that the sample of participants and the study design are adequate for the questions to be addressed.

A brief list of some example hypotheses that can be addressed by the Study Protocol follows.

1. An intrauterine environment of insulin resistance and impaired glucose metabolism, measured during the first trimester of pregnancy, among women without diabetes before pregnancy, is associated with an increased risk of major congenital malformations, such as congenital heart defects.

2. Sub-optimal fetal growth due to abnormalities in the maternal-fetal environment, as measured by serial fetal ultrasound, followed by rapid somatic growth in the first several years of life, is associated with increased risk of central obesity, insulin resistance, and metabolic syndrome in adolescence.

3. Intrauterine exposure to infectious agents or to inflammatory mediators (potentially arising from infection of vaginal, cervical, uterine, or more distal sites such as periodontal tissue), early in pregnancy is associated with an increased risk of preterm birth. These same exposures may be independently related to the risk of autism in early childhood and schizophrenia in late adolescence.

4. Exposure to psychosocial stressors during vulnerable periods of pregnancy and early childhood can interact with genotype to influence neurobehavioral outcomes. For example, when exposed to stressful life events, individuals with a short allele of the 5-HTTLPR serotonin polymorphism will exhibit depressive symptoms while those with the same genotypes, but without serious negative life events, will not.

5. The development of asthma during childhood is influenced by the relative timing of exposure to respiratory viral infections and allergens in infancy. In particular, viral infection early in infancy prior to exposure to other respiratory allergens such as pollens or house dust mite antigen may increase the risk of asthma during childhood.

6. The development of asthma during childhood is influenced by exposure to air pollutants such as ozone and particulate matter. This relationship may operate through inflammation and oxidative stress, and thus may be influenced by polymorphisms in the GST (glutathione-S-transferase) family of genes.

7. Repeated, low-level exposure to nonpersistent pesticides, such as organophosphates, in-utero or postnatally increases risk of poor performance on neurobehavioral and cognitive examinations during infancy and later in childhood; this will be especially true for individuals with a genetically and phenotypically determined decrease in paraoxonase activity.

IV. STUDY DESIGN AND METHODS

A. Sampling Strategy

A.1 Overview of sampling

The NCS will include a sample of approximately 100,000 children born in the U.S. during the five calendar years 2007-2011. (Vanguard Centers will enroll from 2007-2011 and other Study Centers will enroll from 2008-2011). These births

will be identified and included in the study as early in the pregnancy as possible, with a target of enrolling at least 25% of pregnancies prior to conception and a cumulative total of 90% before the end of the first trimester of the pregnancy. A number of sampling designs were considered for the NCS [see Sample Design Options and other related documents available through the National Children's Study website: http://www.nationalchildrensstudy.gov/events/advisory_committee/other_work_062004.cfm] While it is recognized that there are advantages and disadvantages to each of the candidate approaches, after careful consideration, and upon the advice of the NCSAC, a national probability sample was chosen as the design that best fulfills the following goals:

- Collection of high quality measurement data to minimize measurement biases
- Avoidance of selection biases and other biases that could lead to invalid inferences concerning exposure/outcome relationships
- Capture of the diversity of the U.S. population such that both the range and diversity of exposures and outcomes are represented
- Ability to extrapolate results of the NCS to the U.S. population

For the NCS, a multistage, clustered sampling design is being utilized to facilitate collection of both individual and community-level data.

The NCS sample will be selected using a three-stage sampling design. The first stage was the selection of Study Locations from the full list of all US counties. Statisticians from the National Center for Health Statistics have drawn a sample of 96 Study Locations for implementation of the NCS (see Attachments A and B). In general Study Locations correspond to a single county; however, for counties with small numbers of annual births, a Study Location may combine adjacent counties. The probability of selection of a specific Study Location was based on the average number of births per year in that area. The second stage of the design consists of delineation and selection of area segments comprised of city or suburban blocks or combinations of blocks. These segments correspond roughly to neighborhoods. Those neighborhoods selected for the NCS are referred to as Study Sites and in the Vanguard Phase they are referred to as Vanguard Sites. The third stage of sample selection consists of selection of households and certain types of group quarters, such as dormitories, within the specified Study Sites. Each of these stages is described in greater detail below. If experience at the Vanguard Centers indicates that it is not feasible to conduct this Study using this sampling approach (such as unacceptably high non-response on key measures) the sampling strategy will be revised prior to the addition of new Centers.

A.2 Selection of Study Locations for the NCS

The process for selection of Study Locations was based on the need to achieve a representation of geographic areas with varying population densities in the target age group. Due to their large annual number of births, 13 counties were selected as self-representing units (also referred to as certainty units). These are units that were 'certain' to be selected into the probability sample. The remaining counties were placed into strata prior to selection. Strata were defined by metropolitan status (metro, non-metro), geography (9 Census Divisions), size (number of births), and percentage demographic characteristics (depending on the census region, characteristics were race, ethnicity, and percent low birth rate.) The non-self-representing counties (also referred to as non-certainty units) were selected with probabilities proportional to size, within the strata characterized above. This process resulted in a sample of 96 Study Locations intended to produce an NCS sample representative of US births. Of the 96 locations, 13 are self-representing metropolitan areas, 62 are non-certainty, metropolitan areas, and 21 are non-metropolitan areas. A map showing the selected Study Locations is included as Attachment A and a list of Study Locations is included as Attachment B. As noted in these documents, the 96 locations include 101 PSUs and 105 counties. Note that a properly drawn, probability-based sample of US counties, designed to represent US births, does not result in an evenly distributed sample of counties across the country. Such samples inevitably have clusters in some areas and voids in others, due to the distribution of the population across the U.S. and the random nature of the sample.

Although there was no oversampling of specific populations at this stage, it is anticipated that there will be opportunities to oversample specific populations during the second stage of sampling, as described below in section A.4. Further, it is anticipated that there will be opportunities for adjunct studies to address research questions related to specific populations

or exposures of interest. One currently planned adjunct study, for implementation in the full complement of Study Centers, is examination of health and developmental outcomes among children conceived as a result of assisted reproductive technologies.

A.3 Selection of Vanguard Locations

Geographic areas designated to potentially serve as the initial Vanguard Locations were randomly selected from the group of 96 Study Locations and are identified in Attachments A and B (download separately). This strategy allows the greatest flexibility in assuring that data collected in Vanguard Locations can be combined with data collected in Study Locations that are added later, and in this way contribute to the full sample.

The 96 Study Locations selected for inclusion in the NCS were grouped into strata, based on geography (4 U.S. Census Regions), and population density (certainty; non-certainty, metropolitan; and non-metropolitan). From these strata, a total of eight Study Locations (referred to as Vanguard Locations) were randomly selected with the following parameters: 1) two Vanguard Locations in each of the four US census regions (West, Midwest, South and Northeast) and 2) two certainty units; four metropolitan, non-certainty units; and two non-metropolitan units.

[NOTE: In this solicitation, offerors are asked to submit proposals that focus on <u>one</u> of the 8 Vanguard Locations. Based on the availability of funding, it is anticipated that 3-8 awards will be made. At least one award will be made in each of the categories of certainty; metropolitan, non-certainty; and non-metropolitan. This assertion is based on the availability of funds and receipt of at least one competitive offer in each category.]

A.4 Delineation Of Segments And Selection Of Study Sites

To assess community related environmental exposures, the NCS will collect a variety of community-based measurements, including environmental data (e.g. assays of regional or neighborhood air samples), social data (e.g. collective efficacy and neighborhood cohesion), physical characteristics (e.g. presence of open space, traffic density or patterns), and data from schools and other regional entities. Thus, there is interest in defining segments based on functional neighborhoods or communities rather than by the more traditional use of census boundaries (e.g. blocks, block groups, tracts). This task will require input from those closest to, and most knowledgeable about, the neighborhoods within the Study Location. During the initial phase of the NCS, the NCS-CC will work with investigators from the Vanguard Centers to define the segments within the Vanguard Locations. The specific segments that are chosen as the focus of data collection efforts, referred to as the Vanguard Sites, will be selected on a probability basis. In addition to defining meaningful boundaries for delineation of segments, the prevalence of exposures of interest within delineated segments will be estimated to allow oversampling based on defined parameters of interest. Income, ethnicity, population density, age of housing, and air quality are examples of parameters that could be used to characterize segments. These parameters could then be used in the selection of Vanguard Sites, with oversampling to ensure adequate representation of populations of interest in the final Study sample. This strategy also facilitates the Study's ability to maximize exposure gradients between segments within the Study Location.

To maintain the representative nature of the sample, the actual selection of the segments that will serve as the Vanguard Sites will be conducted by the NCS-CC. In addition to ensuring the within Study Location, random selection of study sites, this also provides a means to ensure that the entire sample contains adequate representation of known exposures of interest with adequate numbers within select subgroups to allow valid inferences.

A.5 Selection of Households

As described in further detail below, households within the Vanguard Sites will be screened to identify women eligible for enrollment in the study. It is likely that in some sites all households within the defined geographic area will be screened. In contrast, for the more populous sites a sample of households may be selected for the initial screening. This decision is

dependent on the anticipated number of eligible women and anticipated rates of participation within the Vanguard Site. For Sites in which a decision is made to screen a sample of households, the NCS-CC will design the sampling approach and select the individual households to be approached.

B. Recruitment of Study Participants

B.1 Recruitment Goals:

The final sample size of the NCS will include approximately 100,000 live born infants. Each of the 101 primary sampling units within the 96 study locations is expected to contribute approximately 250 births per year. This is true both for the Vanguard Locations and for Study Locations that are added later. (Note that for three locations in the full sample, there are multiple PSUs per study location. None of these Study Locations are included in the list of potential Vanguard Locations.) At Vanguard Locations, enrollment is over a five year period (2007-2011) while at Locations added later enrollment is over a four-year period. In all Study Locations, births will be identified and included in the study as early in the pregnancy as possible, with a target of enrolling at least 25% of pregnancies prior to conception and a cumulative total of 90% before the end of the first trimester of the pregnancy.

Depending on the number of contracts awarded there will be 3-8 Vanguard Centers, each overseeing data collection at a single Vanguard Location. Thus, the final combined sample size for all Vanguard Locations will be between 3,750 and 10,000 live born infants.

B.2 Household Recruitment

The primary method for recruitment is through a household sampling approach. However, to ensure adequate representation of the targeted population, provisions are made to supplement this approach with recruitment through sites of prenatal care and, if necessary, also at the time of delivery. This is described in further detail under sections IV.B.3 and IV.D.3.

In general, at the time of the household screening, two groups are targeted for enrollment; women who are in their first trimester of pregnancy and women at risk of pregnancy. The “at risk of pregnancy group” is further divided into high, moderate and low risk of pregnancy, as described in further detail below (Section IV.E.1).

B.3 Recruitment Through Other Mechanisms E.G. Prenatal Care Providers

In addition to enrollment through the household screening approach, a number of supplementary approaches will be utilized to ensure that the final sample is representative of births in the Vanguard Site. To accomplish this, Vanguard Centers will provide a mechanism to enroll study participants through prenatal care providers. They will also establish a mechanism that allows women in the targeted geographic area to contact the study to indicate their interest in participation. These mechanisms provide a means for women who were missed through the household screening, to be represented in the study. These might include non-responders to the initial screening or women who move into the targeted area during the enrollment period but after the initial screening has taken place. Similar to the household screening method, women will be eligible to participate if they live within the boundaries of a targeted Vanguard Site and meet other eligibility criteria (e.g. enrollment before the end of the first trimester of pregnancy). However, if initial experience shows that women who first present for prenatal care after the first trimester (about 15% of U.S. births in 2002) are underrepresented in the Study, this special population will be eligible for enrollment through the alternative enrollment mechanisms described above (i.e. through prenatal care providers or when they contact the study.) Additionally, if women who have no prenatal care (about 1% of U.S. births in 2002) are underrepresented, a mechanism will be established to enroll this group at the time of delivery.

C. Inclusion and Exclusion Criteria

C.1 Inclusion Criteria

The following groups of women will be eligible for inclusion in the study:

- Women who are in the first trimester of pregnancy at the time of the initial screening or initial contact with the study, regardless of maternal age
- Women who are ≥18 years of age and are planning pregnancy at the time of the initial screening or initial contact with the study
- Women who are at risk of pregnancy (as defined in section IV; E.1) but not planning pregnancy, who are ≥18 years of age and <40 years of age at the time of the initial screening or contact with the study

Additionally, to be eligible for inclusion in the study, women must be residents of the targeted Study Site at the time of enrollment.

C.2 Exclusion Criteria

- Pregnant women who indicate that they intend to move out of the segment boundaries prior to delivery
- Women planning pregnancy or at risk of pregnancy who plan to move out of the segment boundaries within one year of the date of screening
- Women planning pregnancy or at risk of pregnancy who are cognitively impaired or mentally ill, such that they are unable to fully understand requirements of the study
- Women who are surgically sterile or whose partners are surgically sterile
- Women who are not residents of the study segment at the time of delivery

D. Enrollment and Retention

D.1 Community Outreach and Engagement

The NCS places high value on community engagement but will not follow a strict community-based participatory research model, which is defined as a collaborative research approach that is designed to ensure and organize participation by communities affected by the issue being studied, representatives of organizations, and researchers, in all aspects of the research process and action. Because the core protocol includes collection of data from multiple sites across the U.S., to answer specific study questions that require a national sample, it is not possible to define core study questions and protocol development through input of local communities with their varied needs. However, principles of community-based research will be adhered to when feasible and appropriate.

To build trust, enhance the credibility of the study, and ensure community engagement on the local level, during the first year of the Study, investigators from Vanguard Centers will conduct community needs assessments to identify children's environmental health issues in the target community. These assessments will focus on community concerns regarding the core NCS protocol and additional concerns (e.g., health issues, etc.) that may be considered for inclusion in the core protocol at all sites, or as a specific special study focus in the particular site. Community activities will include identification of community resources and recruitment of community partners to facilitate engagement. Examples include advance contact with community leaders to gather information about the community, town meetings, and listening sessions. Key community members will be recruited and engaged in support of the study in activities such as acting as a spokesperson for the study, providing insight into local issues to enhance the relevance of the NCS for their community's health, and serving on a community advisory board. Previous studies have shown the importance of involving community members in the actual data collection for the study, or as liaisons to special populations such as the medically underserved, business leaders, and state and local officials. This approach will be utilized at the Vanguard Centers, to the extent possible.

Prior to the enrollment period, each Vanguard Center will increase the awareness of the study among community residents. Building on the community engagement efforts and involvement of community members described above, a variety of strategies will be used to announce the NCS enrollment period. Examples include press releases, appearances on local television and radio shows, and other methods to increase community excitement and interest in the NCS. Wherever possible, these activities will involve joint participation of study staff and community members. These press and public relations activities will be supported with the technical support of the NCS-CC and Program Office of the NCS and with the approval of the NCS Project Officer.

Throughout the enrollment period the Vanguard Centers will engage in ongoing efforts to involve and solicit input from the community. Each Center will establish a plan for community involvement and engagement. Examples of these components may include establishment of a community advisory board, partnership with key community entities, or incorporation of key community leaders in components of the Center structure. However, steps for community engagement will vary depending on the characteristics and experiences of the communities and the Centers, and it is expected that the most effective approaches will vary between Centers.

D.2 Screening of Households within Selected Segments (Vanguard Sites)

The area household sampling approach will be used to select a probability-based sample of pregnant women, women at risk of pregnancy, and couples seeking pregnancy. The NCS-CC will provide each Vanguard Center with a list of all residential housing units within the selected Vanguard Site (s). The NCS-CC will also send advance mailings to all households in the sample. Staff from the Vanguard Center will visit each listed household to conduct a short screening interview to determine the number of pregnant women and women of child-bearing age residing in the household. The screener will include data on basic demographic characteristics of persons in the household, current pregnancy status of age-eligible women, and, for non-pregnant age-eligible women, information that will allow determination of "risk of pregnancy" status. Women meeting eligibility criteria will be approached for enrollment in the study.

D.3 Recruitment through Prenatal Care

Recruitment through providers of prenatal care will be utilized to supplement the household screening approach. As noted above, this method is being utilized to capture those women missed in the initial screening rather than as a primary means of recruitment into the study. During the planning phase, Vanguard Centers will establish relationships with birth hospitals and providers of prenatal care who serve women in the targeted area. One approach for identifying providers of prenatal care is to obtain lists of obstetric staff and other birth attendants from area hospitals. (According to national data for 2002, over 99% of live births in the U.S. occurred in a hospital and 92% of these births were attended by a physician.) However, the most appropriate approach for identifying providers of prenatal care may vary by location. Other facilities, such as birthing centers, that handle a significant number of births in the Vanguard Site, should also be approached for participation in the study.

During the "start up" pre-enrollment phase of the Study, staff from Vanguard Centers will introduce the NCS to providers of prenatal care. Participating prenatal care providers will be provided with in person training and written materials to educate them about the NCS. In-person trainings will be provided by staff from the Vanguard Centers. Written materials will be prepared by the NCS-CC but Vanguard Centers will be responsible for delivering materials in-person at the time of the training sessions. It is anticipated that, at a minimum, providers of prenatal care will be asked to display information about the study in their offices and to provide women who are planning pregnancy or who are in their first trimester of pregnancy with a Study brochure. The degree of additional involvement of prenatal care providers may vary by Study Center. At some Centers, prenatal care providers may actively participate in enrolling women in the Study whereas in other Centers providers may inform their patients about the Study and obtain permission to share patients' contact information with Study Staff, enabling Study Staff to approach women, at a later date, for enrollment in the Study. Combining Study data collections, that occur during pregnancy, with routine prenatal care visits is potentially a means to increase participation and decrease participant burden. Thus, this approach is encouraged when feasible.

D.4 Retention

Maintaining participation in the study through retention of the cohort must be one of the highest priorities for the Vanguard Center staff as well as the NCS-CC and the Federal Government. The full range of standard methods used for tracking, encouraging and supporting participation and retention will be employed. These include but are not limited to:

- Providing financial incentives – adequate and appropriate financial incentives will be provided for Study participants (see section VII.B.2).
- Providing or reimbursing for transportation and child care during study activities – guidance and support will be coordinated through the NCS-CC, however, locally meaningful means to enable participation should be proposed.
- Maintaining contact with participants will be a joint responsibility of the NCS-CC and Vanguard Centers. Remote contacts e.g. telephone contact and mailings, are the primary responsibility of the NCS-CC as is tracking of those lost through the routine contact process. The Vanguard Centers will be involved in locally important tracking measures and tracking efforts that involve visits and travel within, or within a reasonable distance of the, Vanguard Location.
- Additional methods to encourage retention under consideration include providing devices that are both useful for data collection and for tracking, such as cell phones.

The Study must anticipate significant mobility of the cohort participants. The Census Bureau estimates that roughly 46 percent of all persons aged five years or older have moved at least once between 1995 and 2000; however the majority of moves (54%) are within the original county of residence. By year 5 of the NCS, it is estimated that approximately 15,000 of the 100,000 children enrolled in the study will have moved to a county other than one of the initial Study Locations. However, with the current sampling design, only about 2500 children would live more than 100 miles from a participating county. Therefore, for participants moving within the U.S., the NCS-CC will track participants and coordinate a pass off of follow-up from one center to the center closest to the participant's new location. Through these steps, loss of retention in the study can be further minimized.

E. Data Collection Schedule – Home and Clinic Visits

Both women at risk of pregnancy and women who are in the first trimester of pregnancy will be eligible for enrollment, as outlined above. The schedule of face-to-face data collections prior to pregnancy is determined by the woman's risk of pregnancy. Once pregnant, the schedule of in-person data collections is the same for all groups.

It is anticipated that over the four-year enrollment period (five-year for Vanguard Sites), a woman's risk of pregnancy will not be stagnant. Thus, a woman initially at low risk of pregnancy could move into the group that is planning pregnancy. For this reason, participants will be contacted at least yearly during the enrollment period to assess their risk of pregnancy. Data collection schedules will be modified based on the most current information on risk of pregnancy. Further, women could experience more than one pregnancy during the study period, and subsequent pregnancies will be eligible for inclusion. It is estimated that in the full sample of 100,000 livebirths approximately 8000-10,000 births will be the result of subsequent pregnancies.

E.1 Data collection schedule prior to pregnancy

Subgroup: High risk of pregnancy

In this study, women at high risk of pregnancy are defined as women planning to become pregnant, with no current history of infertility. It is estimated that, 70-90% of women in this group will become pregnant within 6 menstrual cycles.

Women at high risk of pregnancy will be approached for enrollment in the study. Partners of women planning to become pregnant will also be invited to participate in the study but inclusion of the female is not contingent on participation of her partner. Among those who choose to enroll in the study, the first home visit will occur within 2 weeks of enrollment.

Because this is the group that is most likely to provide data about exposures that occur around the time of conception, including interview data as well as biologic and environmental samples, follow-up is most intense in this group. Home visits will occur every other month up to a maximum of four home visits prior to conception. In addition to the face-face contacts, the NCS-CC will contact women in this group, by telephone, to assess pregnancy status during the intervening months in which there is no home visit. Women will also be asked to notify the study if they become pregnant. If, after six months of this relatively intense follow-up, a pregnancy has not occurred, the scheduled contacts will be reduced to phone contact every three months, comparable to women with moderate risk of pregnancy.

Subgroup: Moderate risk of pregnancy

Women at moderate risk of pregnancy are defined as women between the ages of 18 and 40 years, who are sexually active, not planning pregnancy, but using either no contraception or a method with a known failure rate $\geq$ 10% (for example rhythm or barrier methods). Women from this group, who choose to enroll in the study, will be visited one time in the home within 2 weeks of enrollment. In addition to this face-face contact, the NCS-CC will contact women in this group by telephone every three months throughout the four-year enrollment period to assess risk of pregnancy status and women will be asked to notify the study if they become pregnant.

Subgroup: Low risk of pregnancy

Women at low risk of pregnancy are defined as women between the ages of 18 and 40 years, who are not sexually active at the time of the screening interview, or women who are sexually active and utilizing a method of contraception with a known failure rate of <10%. If there is no change in their "risk of pregnancy" status, the only face-to-face contact with women in this group will be at the time of screening and enrollment. The NCS-CC will contact women in this group annually to update contact information and risk of pregnancy status and women will be asked to notify the study should they become pregnant.

All study participants will receive passive contacts such as mailings of newsletters and birthday cards.

E.2 Schedule of data collections following pregnancy

Following pregnancy fifteen face-to-face Study visits are planned over the course of the entire Study. Although the complete proposed schedule of visits is outlined in the table below, the number of visits is clearly dependent on the level of funding. Thus, this should be viewed as a framework, particularly for periods beyond 3 years of age. Depending on availability of funds, the number of visits could increase or decrease in future years.

AGE OF CHILD	LOCATION OF VISIT
Preconception	As outlined above
1st trimester	Home
2nd trimester	Clinic
3rd trimester	Clinic
Birth	Place of delivery
1 month	Home
6 months	Home
12 months	Home
18 months	Home
3 years	Clinic
5 years	Clinic
7 years	Home
9 years	Clinic
12 years	Clinic
16 years	Home
20 years	Clinic

F. Measurements

The primary purpose of the NCS is to support epidemiological analyses of relationships between exposures and outcomes. Exposures of interest can be broadly categorized into the following domains: biological, chemical, physical, and psychosocial. Outcomes of interest can be categorized into pregnancy and birth outcomes, child development, and medical events. Examples within each of the domains are provided below. **Please note that this list is not intended to be inclusive of all measurements to be obtained in the NCS, but rather to provide examples of general areas of interest.**

F.1 Exposure and Outcome Domains

EXPOSURE DOMAINS

Biological

- Bioallergens
  dust mites, pet dander, pollen, and arthropod and rodent antigens
- Biologics
  viruses, bacteria, biomarkers for vaccinations (antibody levels)
- Genetics
  chromosomal abnormalities, allelic variation, gene expression

Chemical

- Persistent Organic Compounds
  PCBs, organochlorine pesticides, brominated flame retardants.
- Non-persistent Nonvolatile Organic Compounds
  pyrethroids, phytoestrogens.
- Non-persistent Semi-volatile Organic Compounds
  organophosphate pesticides, polycyclic aromatic hydrocarbons (PAHs), phthalates, environmental tobacco smoke (ETS).
- Non-persistent Volatile Organic Compounds
  formaldehyde, benzene, vinyl chloride.
- Bioaccumulative Inorganic Chemicals
  lead, mercury, cadmium.
- Nonbioaccumulative Inorganic Chemicals
  arsenic, iron, perchlorate.
- Criteria Air Pollutants
  ozone, particulate matter, carbon monoxide, nitrogen dioxide, sulfur dioxide

Physical

- Housing Characteristics
  age of housing, heating/ventilating/air-conditioning system, safety devices
- Neighborhood Characteristics
  parks and open space, traffic, housing density
- Radiation
  radon, ultraviolet, electromagnetic
- Noise
  indoor, outdoor

Psychosocial and Behavioral

- Demographics

maternal/paternal age, education, income, parity

- Culture
  subjective norms, religious practices
- Neighborhood Environment
  social cohesion, crime
- Family Influences
  family composition, parenting, conflict
- Daycare/School
  student/teacher ratio, bullying
- Health Behaviors
  diet, smoking, physical activity
- Psychological Stress and Social Support

OUTCOME DOMAINS

Pregnancy and Birth Outcome

- Fetal growth
- Pregnancy duration (preterm birth)
- Congenital Malformations
- Stillbirth, fetal death
- Maternal outcomes related to pregnancy (post-partum depression, medical conditions)

Child Development

- Functional
  Activities of daily living, quality of life
- Physical Growth, Motor Development, Sensory development
  Weight, height/length, puberty, bone density, fine and gross motor skills, vision, hearing
- Physiologic
  Lung function, cardiovascular reactivity, insulin resistance
- Cognitive
  General intelligence, learning and memory, executive function, attention, language, achievement
- Social/Emotional/Psychiatric
  Social competence, attachment, emotional competence, temperament, specific psychiatric and behavioral screens (e.g. screens for autism, depression, or ADHD)

Medical Events

- Deaths, hospitalizations
- Events resulting in limitations of activity
- Health care utilization
- Medical conditions or diagnoses

Each of the above domains carries with it special requirements with regards to measurement. Overarching issues considered in developing the schedule of data collections for the NCS include the need to a) evaluate the effects of both chronic and intermittent exposures b) capture the trajectory of growth and development to maximize benefits of the longitudinal study design c) minimize respondent burden to the extent possible d) maintain a study that is no more than minimal risk e) maintain costs within a reasonable budget.

Feasibility considerations (e.g., participant burden, logistics, costs) are likely to limit the use of intensive, costly measurements for the entire cohort. It is probable that these more intense, targeted, data collections will be limited to subsets of participants. In contrast, this document focuses only on those measurements that will be included in the core protocol. The core protocol is the protocol that will be followed at all of the Study sites.

Details are provided about data collections scheduled at each of the face-to-face contacts that occur prior to pregnancy **through 3 years of age.** These include face to face interviews, examinations, and collection of environmental and biological samples. The NCS-CC will have primary responsibility for remote data collections, e.g. telephone interviews, mailed questionnaires and diaries, specified remote computerized data collections, etc.

All materials needed for the collection of environmental samples and biospecimens will be provided to the Vanguard Centers from the NCS-CC. Specimens are to be sent to the central repository or to designated study laboratories for processing. Vanguard Centers will be responsible for appropriate collection, handling, and storage of specimens prior to mailing. They will also be responsible for shipping specimens according to specifications to be outlined in the procedural manual.

F.2 Data collections

In the tables that follow, the domains and classes of measures are listed by the age at collection and the type or characteristic of the measurement. At this time the specific measurements or instruments are not provided or specified in the Study Plan. A great deal of work has been done and is still under way to determine the specific measurements best suited to test the Study hypotheses with this large cohort study design. Those interested are referred to related hypotheses statements, workshop reports, and working group summaries on the study website, www.nationalchildrensstudy.gov. Final decisions about specific measurements and instruments will be made as the full protocol is developed with input from the NCS-CC and Vanguard Centers. Through the steering committee and other processes, the Vanguard Center investigators will participate in these decisions. The general type of specimen and data to be collected, the schedule of visits, and the setting and anticipated duration of face-to-face data collections, are outlined in the tables below so that prospective centers can determine scope and resources necessary to prepare proposals to carry out the Study. Ultimately, decisions regarding the timing and domains for measurement will be finalized with input from the Steering Committee and approval by the NCS-PO.

F.2.a Preconception

All women identified prior to pregnancy will receive the screening and enrollment interview. Women at high or moderate risk of pregnancy will be visited in the home within two weeks of the screening interview. At this visit women and their partners will be asked to complete a face-to-face interview. Biologic and environmental specimens will be collected and both women and their partners will be given a brief physical examination, primarily to obtain anthropometric data. Additionally, women will be given and instructed in the use of pregnancy test kits. Initially, two kits will be provided to each participant with additional kits provided as needed. Women planning pregnancy will also be given and instructed in the use of fertility monitors. Women in the high risk of pregnancy group could have up to three additional home visits, scheduled at two month intervals, as outlined in the table below. It is important to note that in instances where the woman chooses to participate in the study, but her partner either refuses or does not respond to the screening interview, the targeted woman will still be enrolled in the study. Thus, although partners will be encouraged to participate, enrollment of females is not dependent on participation of their partners.

[A table follows on the next page]

Face to face data collections - Preconception Cohort
[Duration of visit, type of specimen and information to be collected]

	Time 0	Time 2 weeks	Time 10, 18, and 26 weeks
	Initial Screening and Enrollment All Groups	**Home visit #1** (Women at moderate or high risk of pregnancy)	**Home visit #2-4** (Women at high risk of pregnancy)
Estimated length of visit *	10-30 minutes	1-2 hours	1 hour
Interviews Respondent	Adult household member Eligible women	Enrolled women and their partners	Enrolled women
Domains	Basic eligibility and contact information	Demographics, medical and family history, exposure history	Update exposure data, verify risk of pregnancy group
Biologic Samples	----------	Maternal and paternal: Blood, urine, hair, saliva, nail clippings Maternal: self collected vaginal swab Paternal: Semen **	Maternal and paternal: Urine and blood***
Physical Examination	----------	Maternal and paternal anthropometrics, blood pressure	Maternal anthropometrics and blood pressure
Environmental Samples	----------	Air, paint, dust, water, soil	Air, dust

* Assuming 2 staff persons for each home visit
** A kit for collection of semen will be left with male partners of women in the high risk of pregnancy group, with instructions to mail semen specimens to a designated laboratory.
*** Maternal and paternal blood will be collected at the initial visit at 2 weeks post enrollment, at 10 weeks post enrollment and at 26 weeks post enrollment.

F.2.b Pregnancy

Women will be seen three times during pregnancy, once in the home and twice in a clinical setting. In addition, an oral glucose tolerance test will be scheduled at approximately 8-10 weeks gestation. [Note this is in addition to any screening for glucose intolerance that may be conducted later in pregnancy as part of routine clinical care. The earlier timing of this GTT is related to hypotheses examining the relation between subclinical aberrations in maternal glucose metabolism and birth defects and other developmental outcomes in the children.] The home visit will occur during the first trimester. During this visit both environmental samples and biological specimens will be obtained, and women and their partners will be interviewed. Note that interviews and specimen collections are more in-depth for participants for whom this is the first full study visit than for woman who have already had study visits as part of the preconception cohort. For example, this would include women who were in the first trimester of pregnancy at the initial screening interview or women recruited through prenatal care providers. If it is the first study visit, both women and their male partners will have a brief physical examination. If there has been a previous study visit the physical exam will apply only to the pregnant female. As with the preconception cohort, inclusion of the pregnant woman in the study is not contingent on participation of her partner.

Study visits during the second and third trimesters will occur in a clinical setting. The primary justification for this choice is the need to obtain fetal ultrasounds. At this point, it is anticipated that two-dimensional ultrasounds will be obtained in both the second and third trimesters. Both data and images, in a standard universal digital format, will be submitted to the NCS-CC. All Vanguard Centers will follow a common Study protocol that will be developed with input from the successful offerors. Depending upon the development of standard examination and analytic protocols, 3-D fetal sonography may be performed on all or a subset of the study population. Data and images collected from these scans will also be submitted to the NCS-CC in a standard digital format. Other details of data collections during pregnancy are outlined in the tables that follow.

Face to face data collections during pregnancy
[Duration of visit, type of specimen and information to be collected]

	Early 1st trimester **1st study visit** Home Visit	**Early 1st trimester** **Prior home visits** Home Visit	**Mid 2nd trimester and Mid 3rd trimester** Clinic Visits
Estimated length of visit *	2-3 hours	1-2 hours	2-3 hours
Interviews Respondent	Enrolled Women and their partners	Enrolled women and their partners	Enrolled women
Domains	Maternal and paternal: demographics; medical, family, and exposure history; psychosocial; occupational exposures; health behaviors Maternal: diet, medications, product use, treatments, and medical events, (maternal only)	Maternal and paternal: psychosocial, occupational exposures, health behaviors Maternal: medications, treatments, and medical events, product use, diet	psychosocial, health behaviors, update exposure history, medications, treatments, and medical events, product use, diet
Biologic Samples	Maternal and paternal: blood, urine, hair, nail clippings Maternal: self collected vaginal swab	Maternal and paternal: blood, urine, nail clippings Maternal: self collected vaginal swab	Maternal blood and saliva, cervical swab, vaginal swab
Physical Examination	Maternal and paternal: anthropometrics, blood pressure, Maternal: periodontal screen	Maternal anthropometrics, blood pressure, periodontal screen,	Maternal anthropometrics, blood pressure, 2-D Ultrasound Fetal Heart Rate
Environmental Samples	Air, paint, dust, water, soil	Air, paint, dust, water, soil	
Other	Oral glucose tolerance test at approximately 8-10 weeks gestation		

* Assuming 2 staff persons for each home visit

F.2.c Birth through age three years

Because this procurement covers only the first 5 years of implementation, with at least two of these years devoted to start-up and pregnancy, anticipated measurements are described through 3 years of age. A total of six face-to-face contacts are scheduled during this time period, the first is at the place of delivery, and the 6th visit (at 3 years) is in a clinical setting, the remaining visits are in the home.

In contrast to measurements prior to pregnancy and during pregnancy, which follow the mother as the index study subject, measurements following birth center primarily around the child. Thus, data collection centers on the child and the child's environment.

Birth

All women will be visited at the place of delivery. This is seen as a critical aspect of the Study for a number of reasons, including the need to collect cord blood and placental tissue, the need for a standardized neonatal exam, and the need to capture information about labor and delivery from medical records. It is clear that reliable collection of biological samples at birth (e.g. cord blood and placental tissue) is one of the most challenging aspects of this study. Collection of these specimens will require either standardized, hospital-wide procedures for collection of specimens of interest for all deliveries or on-site/on-call Study staff that would be able to attend a very high percentage of the deliveries.

During the first year of life, face-to-face data collections will occur in the home when the child is one month, six months, 12 months and 18 months of age. All of these data collections will include developmental and physical assessments of the child, collection of interview data from caregivers, collection of biological samples, primarily from the child, and collection of environmental samples from the home. At three years the child will be seen in a clinical setting. The justification for a clinical visit at this time is the need to obtain a variety of more complex measurements that require specialized equipment with data collectors that are familiar with the use of the instruments and have expertise in the administration of more complex examinations and assessments. In-person data collections during the first three years of life are summarized in the tables below.

[A table follows on the next page]

Face to face data collections: Birth through 6 months
[Duration of visit, type of specimen and information to be collected]

	Birth Place of birth	**1 month** Home	**6 months** Home
Estimated length of visit	N/A	30-60 minutes	2-3 hours
Interviews Respondent	Mother	Mother or other primary caregiver	Mother and father or other primary caregiver
Domains	Recent medical, social and environmental history, planned health behaviors	Psychosocial, occupational exposures, product use, maternal health behaviors, child development	Psychosocial, Assessment of maternal/paternal cognition, occupational exposures, product use, child development
Biologic Samples	Cord Blood Infant blood spot Placental Weight, photo and tissue Meconium Maternal Blood Vaginal swab	Breast Milk	Breast milk Infant blood (finger stick) Infant Urine Maternal Saliva
Examinations	Standardized neonatal examination, Bioelectric impedance analysis (BIA), Hearing screen, Quantitative Ultrasound (bone)	Limited physical examination of infant, anthropometrics, and heart rate response	Standardized physical and developmental examination of infant, BIA Observation of parent-child interaction
Environmental samples and observations	None	Dust (special emphasis on sleep environment), air, food	Air, dust, water, food, soil
Other	Medical record review		

* Assuming at least 2 staff persons for each home visit

[A table follows on the next page]

Face to face data collections: 12 months through 3 years
[Duration of visit, type of specimen and information to be collected]

	12 months Home	18 months Home	3 years Clinic
Estimated length of visit*	1-2 hours	1-2 hours	Up to 4 hours
Interviews Respondent	Mother or other primary caregiver	Mother and father or other primary caregiver	Mother or other primary caregiver
Domains	Child development Child and parent health behaviors Psychosocial	Occupational update Child development Child and parent health behaviors Psychosocial	Occupational update Child development Child and parent health behaviors Psychosocial
Biologic Samples	Child blood, urine	Child hair, urine, saliva	Child blood, hair, urine, saliva
Examinations	Standardized physical and developmental examination of infant Quantitative Ultrasound (bone)	Standardized physical and developmental examination of infant, BIA	Standardized physical and developmental examination of infant, Child observations and parent- child observations in controlled clinical setting, Lung function Dual-energy X-ray, Absorptiometry (DXA), Auditory – play, audiometry
Environmental Samples	Air, dust water, soil	Air, dust water, soil	None

* Assuming 2 staff persons for each home visit

F.3 Additional Environmental Samples

In addition to the environmental samples listed above, a basic battery of household environmental samples will be obtained with each **change in residence**, including dust, air, water, paint and soil. Environmental samples will also be obtained from the **mother's place of employment** during her pregnancy.

Samples to be collected from **neighborhoods** will include air, soil, dust, water, and samples of food from local grocery stores. Observational data documenting such items as available open space, grocery stores, neighborhood structural conditions will also be collected. It is anticipated that most of these measurements will be collected at baseline and one additional time in the first three years of life.

Recognizing that many children spend time in a variety of settings, including multiple primary households and multiple sites of **childcare**, there will be a need to obtain samples from multiple sites of care. It is anticipated that both indoor and neighborhood specimens and observations will be collected in those environments in which the child spends at least 30 hours per week. It is further anticipated that there will be a baseline data collection shortly after entry into the new environment, and yearly thereafter, through age 3 years.

All of the above data collections will be the responsibility of the Vanguard Center.

Finally, data will be collected from regional monitoring systems e.g. local air monitoring and water sampling. The collection of information from these routine systems will be the responsibility of the NCS-CC.

F.4 Other data collections

A number of additional data collections are envisioned; however, because the NCS-CC will have primary responsibility for these efforts, these data collections are not included in the above tables. Data collections covered under this category include telephone interviews, self-administered questionnaires and diaries, self collected biospecimens, and environmental samples. During the routine face-to-face contacts, staff from Vanguard Centers will distribute and provide appropriate instruction and training in the use of materials needed for self-administered data collections.

Following delivery, mothers will be asked to complete brief questionnaires or telephone interviews every three months. The primary purpose of these data collections is to ascertain discrete events and transient exposures that are subject to recall bias. Examples include the child's respiratory illnesses, use of medications, and injury events. Participant documented diaries are another data collection instrument that may be used during the course of the Study. One example of such a tool is a 24 hour food record, in which a child or parent is asked to record all food consumed over a 24-hour period. Another example may be asking the parent to record, on a daily basis, sleep patterns or viral respiratory symptoms over a defined 1-2 week period during infancy or childhood. In general, these questionnaires and diaries may be introduced to the participants during a home visit. Instructions concerning proper completion of the diary will be given, along with instructions for sending the completed instrument to the NCS-CC.

G. Handling, storage, and shipping of specimens

The NCS will be collecting a wide variety of samples, both biological and environmental, using a number of collection devices. For instance, biological samples will include blood, urine, hair, placental tissue, cord blood, etc. Similarly, environmental samples will include filters from air samplers, dust wipes, soil samples, water samples, etc. The Vanguard Center will receive the collected samples from the field sample collectors and do all necessary preliminary processing and then store the samples temporarily prior to shipping them to their destination. Some sample types may be stored at room temperature while others may require freezers or low-temperature freezers. The specific storage requirements for all sample types will be specified in the Study Protocol.

Generally, it is the intent of the NCS to have all aliquoting of the primary samples done at the repository but for some sample types (to be specified in the Study Protocol) aliquoting may need to be accomplished at Vanguard Centers. Also, for some sample types some preliminary processing must be done at the Vanguard Centers to preserve the integrity of the sample for future analyses (e.g., acid quenching, centrifuging).

The Vanguard Centers will be responsible for using the NCS Information Management System (IMS) sample tracking features to ensure a proper chain of custody of each sample from the original collection to its submission to either the study repository or directly to a laboratory. The Vanguard Centers will then ship the samples to the appropriate destinations in the manner specified in the Study Protocol. When specimens are classified as potentially hazardous samples, the Centers shall adhere to processing and shipping requirements for potentially hazardous samples.

H. Quality Assurance and Quality Control

To achieve the goals of the NCS, it is essential that a strong program of Quality Assurance and Quality Control (QA/QC) be implemented so that data collected from the many cooperating data collection organizations and laboratories can be combined into a comparable national data set.

In a study of the breadth, complexity and duration of the NCS strong adherence to the study protocol and procedures is essential. Therefore at all participating entities (e.g. the NCS-CC, the Vanguard Centers, Study Centers, Laboratories, Repository, etc.) the QA/QC program begins with effective initial and follow-up training of all Study personnel in the appropriate areas of the protocol and procedures. Each entity will be responsible for ensuring that all study personnel

attend and successfully complete all required training. All participating entities will keep the NCS-CC informed as new personnel are hired and will arrange for the appropriate training to be done.

Another key component of QA/QC in the NCS will be the use of field audits by the NCS-CC of all recruitment/enrollment and data collection activities. On a schedule to be established in the Quality Management Plan (QMP) for the Study, staff from the NCS-CC will accompany Study Center (Vanguard Center) personnel as they do recruitment/enrollment and data collection visits (at participants' homes and clinic sites). They will observe adherence to Study Protocol and procedures and will initiate corrective actions as specified in the QMP or the Quality Assurance Project Plan for the specific entity. Similar visits will be undertaken to the participating laboratories and the repository. Illustrations of items to be observed include: building rapport with subjects of interviews, the consent process, appropriate collection of environmental samples e.g. proper technique for dust wipe, and appropriate processing in the repository. Scheduling of visits (especially to the homes) will be the responsibility of the Vanguard Centers, using the Study IMS.

Because of the importance of biological and environmental samples to the NCS, specific actions will also be taken to ensure they are appropriately analyzed. All laboratories will need to demonstrate acceptable performance on blind quality control samples as specified in the Study Protocol prior to beginning analysis of study samples. During the course of the Study laboratory performance will be monitored through the use of blind quality control samples being inserted by the Vanguard Centers into the main stream of Study specimens sent to the laboratories.

Specific QA/QC activities will be implemented to ensure that data entry and data processing are accurately completed. Vanguard Centers will be required to cooperate with the NCS-CC when field audits of their office procedures are conducted.

I. Adjunct Studies

In addition to the core protocol, Study Centers (Vanguard and subsequent centers) are expected and encouraged to undertake adjunct studies that build on the core protocol. These studies can be performed on all or a portion of the cohort. Two types of Center-initiated adjunct studies are anticipated: 1) community focused and 2) Center focused. Adjunct studies may be initiated and funded from outside the contract through alternative mechanisms including public-private partnerships. Award of a contract for an organization to serve as a Vanguard Center does not constitute approval for proposed adjunct studies. Following establishment of the Steering Committee a process for evaluating and approving adjunct study proposals will be developed

I.1 Community focused adjunct studies

As described previously, to ensure community engagement, each Vanguard Center is expected to conduct community needs assessments that focus on community concerns regarding the core NCS protocol and additional concerns (e.g., health issues) that may be considered for special studies. The Center is encouraged to consider and propose one or more adjunct studies that address concerns specific to their community that are identified through the community needs assessment. These studies should utilize and build on the core protocol and the established cohort at that Center. Such studies will be based on the identified concerns and needs of the community with input through the community engagement process.

I.2 Center focused adjunct studies

Many, if not all of the Centers, will have unique research capabilities and opportunities that may not be incorporated into the core NCS protocol. The combination of the Center specific research capabilities and the cohort established at that Center as part of the NCS, may provide unique research opportunities to advance a scientific area beyond that planned for the whole cohort. In such circumstances, Centers are encouraged to undertake adjunct studies that utilize and build upon the core NCS data collection and use the same cohort and data collectors. Such studies would take advantage of the capacities, expertise and/or unique population or geography related to the Centers. Centers are encouraged to seek funding support for adjunct studies from alternative sources such as government or foundation grants or public-private

partnerships. Where alternative support is not applicable or feasible, proposals for support of qualifying adjunct research is encouraged as a component of the proposal to become a Center and will be evaluated as part of the original proposal.

V. MONITORING SUBJECTS AND CRITERIA FOR WITHDRAWAL FROM THE STUDY

The NCS is relatively non-invasive and the research protocol has no interventions. Additionally, the Study and all procedures are of no more than minimal risk. Thus, there are no conditions envisioned, either due to Study procedures or unrelated to Study procedures, which would preclude continuation in the Study. The only situation in which we would discontinue follow-up with the family is if there is a pregnancy loss or an enrolled child dies, and the occurrence is beyond the enrollment period such that it is beyond the point when subsequent pregnancies would be eligible for enrollment in the study. If study subjects develop a condition that renders them incapable of providing the continuing informed consent required of the study, continuing consent will be sought from the legally appropriate party.

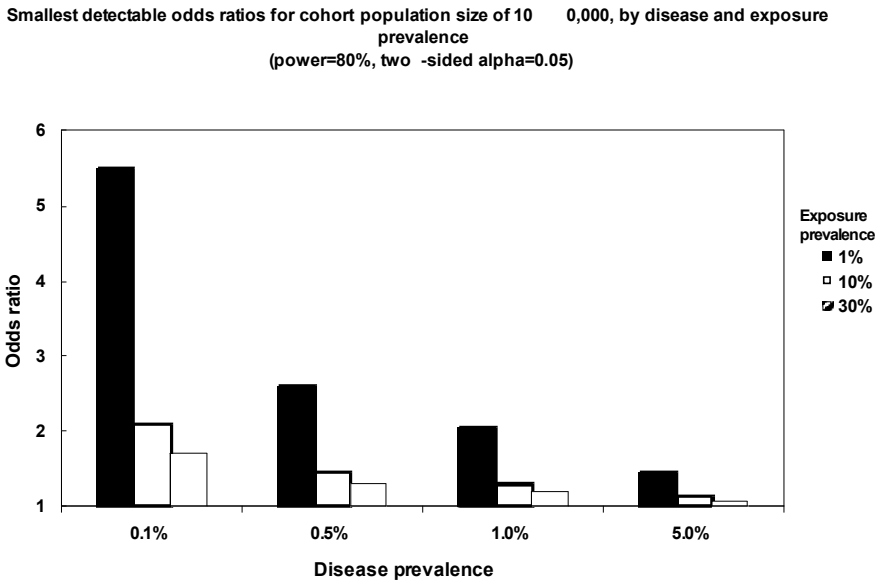
All participants may withdraw from participation in the NCS at any time and declining participation or withdrawal from the study will in no may affect their relationship with the local research sites or associated medical institutions. In the event of withdrawal from the study or inability of the study to locate participants (lost to follow up) data and samples obtained up to that point will be maintained for use in future analyses unless the participant explicitly requests that biologic samples be discarded and not used in any future analyses. Since there will be anonymized data and sample data sets developed periodically, it will be impossible to eliminate individual data from those data sets if a participant withdraws from the study after the time that the data is anonymized. If a participant becomes deceased all data will be maintained in the data sets for all subsequent analyses. Participants will be informed of these policies.

VI. ANALYSES

The selection of the NCS study population via a national probability sample will enable the estimation of national rates of certain exposures and conditions among US infants, children, and pregnant women. However, the main purpose of the NCS is to examine the often complex associations between specific exposures and health-related outcomes. Even with the large sample size planned for the NCS, it is important to understand the relationships that can be explored within this Study design. The text below explores some basic examples of the types of exposure-outcome relationships that can be examined within the NCS.

Any study's ability to find a relationship between exposure and disease is influenced by the prevalence of the exposure, the prevalence of the disease in the population, and the differential risk of disease in the exposed versus the unexposed population. It is important to recognize that, by necessity, the simple calculations included here do not consider the many factors that will influence the NCS's ability to answer specific research questions. The clustered sample design, longitudinal data collection with repeated measures, missing data, different forms of outcome and exposure data (e.g., dichotomous, categorical, continuous) are some of the issues that will influence analytic power. In addition, the desire to examine relationships in specific subgroups of the population, including those defined by genetic variation, will have large effects on the Study's power.

The chart below shows a series of the smallest detectable odds ratios expected from simple dichotomous exposure-outcome analyses, given varying disease and exposure prevalences. Two specific examples, using sample hypotheses, follow the general descriptions. These calculations are based on 0.8 power, two-sided alpha of 0.05, and the planned total cohort size of 100,000. In general, the NCS is well-powered to uncover a two-fold increase in risk for simple associations between diseases with a prevalence as low as 1/1000 and fairly common exposures (prevalence of approximately 10% or greater). However, even with its large sample size, the NCS has adequate power to find only relatively large associations between less common exposures and relatively rare outcomes.



A simple example of the potential ability of the NCS to examine a relatively rare disease is the hypothesis addressing the relationship between autism and intrauterine exposure to infection and inflammation. The prevalence of autism in the US is approximately 0.3% (3 per 1,000); evidence of chorioamnionitis is found in approximately 2% of full-term pregnancies (though much higher in preterm births). The full cohort of 100,000 births provides power to find a relative risk of autism of 2.4 among children exposed to antenatal infection. Thus, the examination of even less common outcomes will require either a higher prevalence of exposure or a more substantial relationship between exposure and disease.

In the NCS, common conditions can be examined in more detail. One example is the potential interaction between sub-optimal fetal growth, subsequent "catch-up" growth, and impaired glucose metabolism in adolescence. The estimated prevalences and relationships used in this example are taken from the literature, but should be considered as examples, only. Approximately 10% of births can be considered to have had sub-optimal fetal growth, a common statistical definition. A similar definition can be used for rapid postnatal growth during infancy and early childhood, though the literature varies regarding that percentage. Approximately 2% of children aged 12-19 may have impaired glucose tolerance. Given independent relative risks for impaired glucose tolerance of 1.5 for sub-optimal fetal growth, 1.2 for rapid postnatal growth, and a two-fold multiplicative interaction between the two, a sample size of approximately 50,000 is sufficient to explore those relationships. Thus, the NCS should allow for relatively in-depth analyses of relationships between somatic growth and aspects of diabetes and metabolic syndrome.

As noted above, a number of issues will require consideration in addition to the issues related to analytic power to identify exposure-outcome relationships. Some of these considerations are listed below.

- The ability to measure chemical exposures is influenced by the stability of the agent in the environment and in the body. Intermittent exposures to non-persistent compounds are especially problematic in this regard because they may be missed if environmental and biological samples are not taken at the time of exposure. There is no perfect solution to this problem but one approach is the use of in-depth validation studies in a subsample of the cohort to assess the accuracy of broader measures used in the entire group.

- The longitudinal nature of the data collection raises several issues. The influence of non-independent individual-level data on power was mentioned above; appropriate statistical methods to address those data must be employed. In addition, measurement of the same domain over time will require different assessment tools. For instance, parenting techniques change as the child develops and the definition of appropriate discipline will

change markedly as a child matures. This complicates repeated measures analyses because different measures are used to compare the same domain.

- The ability to assess the influence of multiple environmental exposures on a single outcome is an important facet of the NCS, but will be difficult to model. Threshold toxicity levels are usually based on tests of dose/response relationships related to single chemicals. Little is known about the synergistic effects of simultaneous exposure to multiple chemicals; the extent to which mixing reduces the toxicity level of individual chemicals is also uncertain. Similarly, potential interactions between physical, chemical and psychosocial risk factors are an important area of study for the NCS, but will require sophisticated analytic approaches.

- Outside databases containing contextual and administrative data will enhance the information available at the community level, but integrating these databases with the study data may present methodologic challenges. For instance, community-level data from some sources (e.g., zip codes), may not match the as yet undetermined boundaries of communities defined in the NCS. In addition, confidentiality concerns may limit the reporting of specific locations, making the linking of external data more complicated.

VII. HUMAN SUBJECTS PROTECTIONS

The NCS is primarily observational in nature and will have a low level of subject risk and reasonable subject burden. The number and diversity of the participants, as well as the plan to collect biologic, environmental, social and behavioral measures, and the creation of enduring data and biologic and environmental sample repositories with the potential for future studies not yet defined, make the human subjects review complex and challenging. This section provides an overview of human subjects considerations for the core study.

A. Study Population

A.1 Rationale for Subject Selection:

The NCS will employ a national probability sample (see Sampling Strategy). There are no exclusions based on gender, race or ethnicity. Women, children, and minorities, as well as men, and members of all of the racial and ethnic groups and economic strata represented in the United States will be subjects in this study. The rationale for this approach is to accrue and follow a population of children that captures the range and diversity of exposures and outcomes experienced by children in the United States.

A.2 Strategies/Procedures For Recruitment

Strategies for recruitment are outlined in detail in prior sections. Briefly, the primary approach involves screening and recruitment from households located in neighborhoods targeted for inclusion in the study, and through providers of prenatal care. A variety of materials and strategies will be utilized to increase public awareness of the study and to aid with recruitment of study subjects. This includes but is not limited to messages transmitted through local media (newspapers, radio, and television), and distribution of a variety of study materials e.g. study brochures, question and answer sheets, newsletters.

A. 3. Special Classes of Research participants

Pregnant women and fetuses

The NCS will recruit and follow women prior to and during pregnancy. The NCS fulfills the requirements for research involving pregnant women and fetuses as described in section §45 CFR 46.204 of the Code of Federal Regulations, subpart B. The purpose of the NCS is to develop important biomedical and psychosocial knowledge about the impact of natural biologic, environmental, social and behavioral exposures prior to and around the time of conception, during pregnancy, and as the child ages, on the future health and development of children. This information cannot be obtained

by any other means. Risks to the women and fetuses are not greater than minimal and the research will in no way affect medical decisions about pregnancy management and outcome. Provisions in this section of the regulations also state that consent from the father of the fetus is not necessary when the research imposes only minimal risks to the fetus.

Pregnant adolescents

The NCS will enroll pregnant adolescents who are identified during the household screening or through sites of prenatal care and are otherwise eligible for participation in the study (e.g. 1st trimester of pregnancy). Women under 18 years of age will not be eligible for inclusion in the preconception cohort.

Laws regarding the legal status of pregnant adolescents vary by state. In some jurisdictions, pregnant adolescents are considered "emancipated" from their families and can be treated as adults for the purposes of obtaining informed consent for this research project. Additionally, in many jurisdictions adolescents who are pregnant may legally seek medical care for pregnancy without involving their parents. In these jurisdictions, IRBs may permit pregnant teens to consent for participation in research in studies such as the NCS without parental involvement if they may consent for their medical care for pregnancy in that jurisdiction. Finally, even in jurisdictions where pregnant adolescents are not considered emancipated or able to consent for their medical treatment, IRBs may waive involvement of parents in the informed consent process under certain conditions [Section §45 CFR 46.408(c)]

Children and adolescents

Investigating the effects of environmental exposures and gene-environment interactions on the outcome of pregnancy and the growth and development of children is the primary aim of the NCS. Thus, children from newborn to adulthood will be the subjects of this longitudinal study. The permission of each child's parent or guardian will be obtained for participation in the study. It is the expectation that children, as young as toddlers and continuing through adolescence, will be informed about the study and its goals in developmentally appropriate language, using creative methods such as newsletters, comic books, websites and DVDs. IRBs will receive all informational materials for review and approval prior to implementation. Issues related to consent and assent are described below.

Adults who are cognitively impaired or mentally ill

It is anticipated that some of the pregnant women who are eligible for the study will be cognitively impaired or mentally ill. Consistent with applicable laws of the local jurisdiction, if a subject is unable to provide full and informed consent, the legally authorized representative will be approached to give informed consent for the subject's participation and in addition, the subject will be asked to assent or at least not object to participation. This approach is consistent with Section §45 CFR 46.116-117 of the federal regulations. Adults who are cognitively impaired or mentally ill will not be eligible for inclusion in the preconception cohort.

Economically or educationally disadvantaged individuals

It is anticipated that some of the participant families in the NCS will be economically or educationally disadvantaged. Section §45 CFR 46.111(b) of the federal regulations requires the IRB to assure that additional safeguards are provided in a study when some or all of the subjects are likely to be vulnerable to coercion or undue influence because of being economically or educationally disadvantaged. The NCS will have such additional safeguards designed into the recruitment and retention activities for all participants so as to encourage informed participation of all eligible subjects.

Each study center is to develop meaningful and enduring partnerships with the communities from which participants will be recruited. It is anticipated that these activities along with the informed consent process described below will result in no coercion or undue influence on potential participants.

Foster children and wards of the state

Because of the subject matter of interest to the NCS and the probability-based sample design, it is important that every eligible child be enrolled and retained in the study. Some children eligible for enrollment in the study, or at some later point after enrollment in the study, may be in foster care, or become wards of the state. Permission for continued participation of the child in the study will be sought from whatever administrative agency or institution that is responsible for the care of the child and, in addition, from the foster parent. Foster children who are wards of the state are permitted to participate in research without any additional procedural safeguards, when risks are minimal or when there is the prospect of direct benefit to the child (§45 CFR 46.409). Only when the research involves greater than minimal risk and no prospect of direct benefit is there a requirement for the IRB to provide additional procedural safeguards through the appointment of an advocate. Since the NCS is primarily an observational study with a minimal level of risk, no such procedural safeguards are required. Because knowledge about the child's living environment is essential to the study, a foster parent will be approached to give permission for the child's continued participation in the study. The foster parent will be fully informed about the purposes and procedures involved in the study and written informed consent will be obtained for participation of themselves (as caregiver) and for continued participation of the child.

A.4 Justifications For Exclusions

The reference population for this study comprises births that occur in targeted study areas during the period in which the cohort is assembled (approximately the first 4-5 years following initiation of enrollment). Thus, women who know at the time of recruitment that they will not live in the study area at the time of delivery are excluded. For the preconception cohort, women who are cognitively impaired or mentally ill are excluded, as women must have the capacity to understand the consent and follow-up procedures. Finally, women who are surgically sterile are excluded because they have an exceedingly low probability of pregnancy.

B. Evaluation of Benefits and Risks/Discomforts

B.1 Potential Risks

Each of the procedures, measurements, and assessments associated with the NCS is designed to fulfill the definition of "minimal risk" in the federal regulations [§45 CFR 46.102(i)]. In addition, the NCS is committed to minimizing risks even when the risks are minimal. Thus, well-trained and competent individuals who have experience with children of that age will perform each procedure that might include discomfort or pain, such as a blood stick.

Another potential risk relates to confidentiality and unintended use of the data. All efforts will be made to protect the privacy of individuals in this study. Names and other personal identifiers of living persons will be kept only on logs where the name will be linked to a study ID. Paper forms (logs and data forms) will be stored in locked files and computer files will be password protected. All computer datasets generated from this study will be void of personal identifiers (last name, address, social security number, etc.) Publications from the NCS will describe aggregate data and identify no individual participants. Participants will also be informed that no identifiable individual data will ever be made available to anyone or published in any form without their permission.

Collection of genetic information presents a special potential risk to confidentiality. Participants will be informed that the NCS will not provide genetic information to participants or family members. Genetic information will not be released in public datasets in a way that allows identification of the individual. The informed consent process will include reference to the reasons and importance of obtaining genetic information on each participant and will explicitly discuss obtaining permission from participants on behalf of themselves and their child to obtain samples for genetic analysis. Reference will be made in the informed consent document to the planned present uses of the genetic information and the expectation that stored samples will be used for future research not yet conceptualized and with technologies not yet available or even conceived.

B.2. Benefits and Compensation

Although it is possible that individual participants may benefit from the findings of the NCS, the study is observational and thus there is no direct benefit to participants, as there might be in an interventional study. There may be some indirect benefits of participation in the study including health education, increased awareness of medical and social services available in the communities studied, and serendipitous findings of clinical relevance or of predictive value to participants and their families.

Recruitment and retention for the NCS will be a significant challenge in light of the observational nature of the study and the long-term commitment required of participants. Reasonable incentives will be part of the strategy for recruitment and retention of participants. Compensation for participation will include reimbursement for expenses incurred by participation in the study, such as travel to and from the research site, parking, etc. In addition reasonable payment will be provided for time spent in participation in the research. Small "gifts of appreciation" for continued participation may include such token items as T-shirts, tote bags, toiletries, books, and CDs. Gifts will not have sufficient monetary value as to unduly affect the voluntary basis of informed consent or continued participation in the study.

Although the precise amount of monetary compensation has not yet been determined, it is expected that it will be in the range of $10 per hour plus set "inconvenience units" assigned to procedures. Based on the samples and procedures currently planned, it is expected that the average incentive for a face-to-face visit will be $50.

C. Revealing findings/informing participants, families and others

The NCS is committed to revealing relevant and important information to participants and their families in order to inform participants of individually relevant findings and to protect the health and well being of the children who are participants in the study. Periodically, the NCS will provide individual level data to participant families concerning information on environmental exposures, physical and psychological examination findings, and routine laboratory test results. Some data obtained through the NCS will be of uncertain relevance to the health or well being of individual participants. Such data will not be routinely reported to participants. Further guidelines regarding this topic will be developed as part of the Study Protocol.

VIII. ADVERSE EVENT REPORTING AND DATA MONITORING

Any urgent, clinically relevant findings will be reported to participants in a timely manner. Information systems will be created to alert research staff at regional sites and at the NCS-CC of any data obtained that fall outside pre-determined normal ranges for that measure. A process will be in place to assure that the principal investigator at the local site is informed about each urgent, clinically relevant finding and that appropriate systems for informing the participant are in place. Systems will also be in place to document that participants have been informed about all urgent, clinically relevant findings.

A Data and Safety Monitoring Board (DSMB) consisting of five to ten individuals who are not associated with the NCS with expertise in biostatistics, epidemiology, environmental toxicology, pediatrics, genetics, psychology, social determinants of health, ethics, and other appropriate disciplines will be created to periodically review data. The DSMB will report to the Steering Committee. It will review standard process data such as accrual rates and adverse events and possibly other appropriate aspects of study data as determined by the Steering Committee. The DSMB will alert the Steering Committee if data become available that might require participants to be informed about the finding. An Ethics Advisory Committee will be established to review relevant situations at the request of the NCS Study Director or the NCS Steering Committee.

During the course of the NCS, environmental findings may reveal information that could be relevant not only to participants but also to members of the community from which participants have been recruited. The Ethics

Advisory Committee of the NCS will be established to assist in considering which information is of this type and will be available to assist the regional sites, in partnership with their local community advisors, to develop a strategy for dissemination of this information in an appropriate manner.

IX CONSENT AND ASSENT PROCESSES

A. Adult participants

The NCS will initially recruit women (pregnant and non-pregnant) and, in some groups, partners of participating women. Information about the study will presented in person at the time of the initial screening interview. Interviewers will read an informed consent statement, stressing the voluntary and confidential nature of the study. To further inform potential participants about the study, a variety of materials will be provided in both computer-based and in hard copy paper formats. Cultural sensitivity, regional variation, and low literacy will be taken into account in preparing the materials. Potential participants will be encouraged to share these materials and discuss participation with family and friends and can either enroll in the study at the time of the screening or at a later date. Informed consent will be documented by signature (written or electronic) and witnessed by research staff. A copy of the informed consent document will be made available to the participants electronically or as a paper copy (or both) as desired.

The informed consent document will include information to inform the parent that one of the risks of participating in this study is that if we observe the child to be in imminent danger of harm or to be the subject of child abuse we will report this information to the legal authorities in order to intervene to protect the interests of any child participant. A Certificate Of Confidentiality will be sought for this study. The parent/guardian will be informed that responses provided will remain confidential according to the provisions of the Certificate of Confidentiality.

B. Pregnant Women <18 years of age

Issues relating to participation of teen mothers are detailed above. In jurisdictions where teen mothers are able to consent for themselves to be participants in a research study, the procedures will be the same as those noted above. Once enrolled in the study, teen mothers are considered the parent of their child and have the authority to provide permission for their child to participate in research studies. Thus, teen mothers are the appropriate persons from whom permission should be sought for enrollment of their children in research.

C. Children and Adolescents

Appropriate assent and informed consent processes and documents will be developed for children participating in the study, beginning at age seven years. These processes and documents will be presented to the IRBs prior to implementation. Briefly, assent for participation in the Study will be sought from children when the child is developmentally and cognitively ready to become an active participant in the consent/assent process. It is anticipated that this will be at about the age of 7 years. The process for obtaining and documenting "child assent" will be presented to the IRBs prior to implementation and will include a description of methods used to determine if an individual child is developmentally and cognitively appropriate to be approached for assent. The assent process will continue until the child is legally able to provide consent. Developmentally appropriate materials will be developed for each age group. When adolescent participants in the NCS reach the legal age of majority in each jurisdiction (generally 18 years), a fully informed consent will be obtained for continued participation in the study.

D. Third parties

The NCS will routinely obtain standard information concerning close relatives, family members, and household members as part of questionnaires given to subjects who have provided consent to participate in the study. This type of information is similar to information obtained in routine clinical practice. If additional personal information or a biologic sample is desired from such a "third party," the NCS participant will be asked to inform the "third party" and obtain verbal permission to be contacted by an NCS research staff member. A full informed consent process and document will be

developed for the specific purpose of obtaining additional personal information and/or a biologic sample from a family member or household member of the Study participants.

X. OWNERSHIP AND USE OF DATA

The NCS is committed to protecting the quality and integrity of all data. All data from NCS participants collected at any site or by any individual or group will be the sole property of the NCS. Individual sites or other contractors may maintain duplicate sets of data collected at that site. NCS will encourage timely and maximal use of NCS data to produce high quality publications of findings in various formats that can be shared among scientists, policy makers, and the public. For all planned or proposed analyses and reporting of findings derived from data sets other than the public-use file described below, the analysis plan and final manuscript must be submitted to a publication process that will include review and input from members of the federal government as well as PIs from study sites.

Fully de-identified (anonymized) data set will be available at intervals as user-friendly public data sets for use by anyone. A registry of users, findings and publications will be maintained. All requests by NCS investigators or other scientists for use of NCS data prior to the public release of the data will require review and approval according to procedures to be established by the Steering Committee.

XI. PRIVACY/CONFIDENTIALITY, INCLUDING HIPAA

The NCS is committed to protection of the privacy and confidentiality of all participants to the fullest extent possible under the law. The information systems of the NCS at the Study Centers and the NCS-CC will be created with confidentiality as a very high priority. Consistent with state and federal laws, the NCS will not reveal any information about individual participants to anyone and a Certificate of Confidentiality will be obtained from the NIH to protect all data from subpoena.

The NCS will obtain specific medical information about participants from health professionals' offices, emergency rooms, and hospitals as part of the database for each participant. HIPAA compliant consent forms will be obtained from each participant in order to obtain such information. The general NCS informed consent form will inform participants that they will be asked to provide such medical information to the NCS and that they will need to provide additional consent because of the HIPAA regulations.

In order to maintain close follow up of participants and track any participants who become lost to follow up, the NCS will use standard publicly available databases to track participants. These include the use of social security, IRS, and census data. The informed consent document will inform the subjects of this procedure for finding individuals who have not formally withdrawn from the study and have been lost to follow up.

[References follow on the next page]

REFERENCES

Websites From The National Children's Study

Main Website:

http://nationalchildrensstudy.gov

Evaluation of Sampling Design Options for the National Children's Study – Appendices:

http://www.nationalchildrensstudy.gov/events/advisory_committee/other_work_062004.cfm

National Children's Study Workshops:

http://www.nationalchildrensstudy.gov/events/workshops/index.cfm

National Children's Study Hypotheses:

http://nationalchildrensstudy.gov/research/hypotheses

Growing UP Healthy Document:

http://nationalchildrensstudy.gov/get_involved/learn_more

Bibliography available upon request