The National Children's Study Advisory Committee (NCSAC)
Synopsis of Meeting Minutes

April 7-8, 2002
First meeting of the NCSAC

I. Introduction

- The National Children's Study (NCS) is a hypothesis driven, longitudinal study of children and their families that will evaluate environmental influences on children's health and development.
- The study will be national in scope and representative of the population of children born in America. It will involve approximately 100,000 eligible children, from before birth through the age of 21 years.
- "Environment" will be broadly defined to include physical surroundings, biological and chemical factors, geography, and social, educational, behavioral, family, and cultural influences.
- The NCS will apply knowledge gained from the human genome project to examine the impact of gene-environmental interactions on children's health and development.
- The NCS is led by a consortium of federal agency partners: the U.S. Department of Health and Human Services (including the National Institute of Child Health and Human Development [NICHD] and the National Institute of Environmental Health Sciences [NIEHS], and the Centers for Disease Control and Prevention [CDC], and the U.S. Environmental Protection Agency (EPA).

II. Influential Milestones leading to the NCS

- Acknowledgement that children are especially vulnerable to environmental exposures and at a greater risk for negative impact in comparison to adults.
- President's Task Force on Environmental Health Risks and Safety Risks to Children (1998)
    - Aim: to reduce environmental exposures to children
    - Co-chairs: Secretary HHS and the Administrator of the EPA
    - Multi-agency effort to determine the risk of environmental exposures in youth
- Children's Health Act of 2000
    - authorized NICHD to plan, implement and conduct a national longitudinal study to examine environmental influences on child health and development

III. Structure

- The NCS is the primary responsibility of the National Institute Child Health and Development (NICHD) and the Director, NICHD leads the study. The NCS

Program Office within NICHD is responsible for the planning, design and implementation of the NCS.

- **Federal Advisory Committees and Federal Advisory Committee Act (FACA)**

    - The National Children's Study has a chartered Federal Advisory Committee (NCSAC) to provide advice on all aspects of the study.
    - A federal advisory committee is constituted to provide advice and recommendations to an official federal agency or officer. All Federal Advisory Committees are governed under Public Law 92-463, the Federal Advisory Committee Act (FACA).
    - FACA requirements: clear purpose, in the public interest, have a charter, membership must be balanced by points of view and roles, financial records must be kept, two annual reports must be submitted to Congress, notices of FACA must be posted in the Federal Register, chartered advisory committees must adhere to conditions required under the Act in respect to open and closed sessions, detailed, certified minutes, all documentation including reports, transcripts, minutes, and working papers must be made available to the public, and a federal official must be in attendance of all meetings and approve the agenda
    - Additional requirements associated with serving on federal advisory committees are available at www1.od.nih.gov/cmo

- **Federal Consortium**
    - Federal Consortium consists of representatives from all federal agencies with a specific interest in the study.
    - It meets periodically to receive information of the progress of the study.

- **Interagency Coordinating Committee (ICC)**
    - ICC is comprised of representatives from the EPA, CDC, NIEHS, and NICHD.
    - The ICC responsibilities include assisting in the review of hypotheses, white papers and pilot findings, and assisting with the implementation of the NCS.

- **NCS Working Groups**
    - Working groups are convened to provide expertise for the development of hypotheses, and exposure and outcome measures**.**
    - Working Groups gather data, perform studies, draft preliminary reports, propose alternatives, and encourage the discussion of ideas (they do not render advice).
    - The incorporation of the knowledge and views of multi-disciplinary experts from within and outside the federal structure strengthens the foundation of the study.

IV. Working Group Breakout Sessions

- Each NSCAC member attended two of the Working Group sessions. One of which was assigned (name in parenthesis), and the other of the member's choice:

    - Study Design (Samet)
    - Ethics (Fleischman)
    - Community Outreach and Communications (Doswell)
    - Asthma (LeMasters)
    - Birth Defects (Goldman)
    - Chemical Agents and Exposures (Graham)
    - Development and Behavior (Bellinger)
    - Fertility and Early Pregnancy (Dudley)
    - Gene-Environment Interactions (Spence)
    - Health Services (Swartz)
    - Infection, Immunity, and Vaccines (Michael)
    - Medicine and Pharmaceuticals (Spielberg)
    - Pregnancy and the Infant (Mattison)
    - Early Origins of Adult Health (Landrigan)

V. Issues for Consideration

- Working groups are at various stages of development
- Hypotheses are at various stages of development
- NCS is primarily an observational study but will it provide interventions?
- What should be the Sampling Strategy?
- Where can the study to access resources for pilot studies?
- How can the NCS maximize study participant retention rates?
- Method of recruiting subjects and incentives
- Informed consent
- Data Collection and Management
- Competing scientific demands
- Determining sampling intervals
- Frequency of researcher visits to the participants' homes

VI. Important Decisions

- The information from each Working Group should be posted on the portal to be shared with other Working Groups
- Members of the NCSAC cannot serve on a Working Group concurrently

June 13-14, 2002
Second Meeting of the NCSAC

Note: Representatives from the ICC and the NCS Working Group Chairs were in attendance at this meeting.

I. NCSAC as Special government Employees (SGE's)

- NCSAC members are Special Government Employees (SGE's) and are required to adhere to specific laws and policies as described below.
- Distribution of the *Public Policy Activity Guidelines* for NCSAC members which includes: official duty periods, restriction of contact with members of Congress and their staff when on official duty, approved lobbying or contact with members of Congress and staff, method of approved contact with congressional staff as private citizens, coordinating interaction with officials of the DHHS and other federal agencies, ensuring the NCSAC chair is informed of all contact with non-government organizations and/or individuals.

II. NCS Timeline

- Enrollment of participants: 2005
- Core hypotheses developed: fall 2002
- Followed by secondary hypotheses
- Write the study protocol: 2003
- Office of Management and Budget approval: 2004

III. Information Management Systems Development (IMS)

- The use of cutting edge technology will be the goal for the NCS
- The IMS will be developed in phases:
    - Phase 0: planning activities, almost complete
    - Phase 1: detailed architectural development
    - Phase 2: infrastructure design and system building
    - Phase 3: making operational the information management system

IV. Pilot Studies

- Purpose is to inform the overall study design
- Three pilot studies are proposed to test:
    - the feasibility of the potential sampling strategies,
    - the benefit of using primary care sites as a uniform and available source of contact and data collection,
    - criteria needed to define injuries.
- ICC Pilot Studies focus on the assessment of fetal growth and development, standardized neonatal exams, ethics guidelines, community outreach and education, sampling strategies, deployment of technology to collect, store, archive, and analyze data, measures for evaluating cognitive development, methods for testing exposures to therapeutic agents, and repository possibilities

V. Working Group Themes and Considerations

- **Community Outreach and Communications**
  - Extensive literature reviews have determined communication methods that have been effective in previous studies similar in nature to the NCS
  - Importance of early marketing to communities
- **Health Disparities and Environmental Justice**
  - The need to consider vulnerable communities or subpopulations in the NCS sample was emphasized
  - The integration of environmental justice and disparity concerns into the study design is a necessity and reflected in the current hypotheses
- **Social Environment**
  - The term "social environment" includes but is not limited to public policy, programs, and the area in which people live and work.
  - Consider the role of the social environment in both the child and the parent over time
- **Exposure to Chemical Agents**
  - Focus is on lifecycle stages, preconceptional exposure, questionnaire data, neonatal exposure, and critical postnatal exposure periods.
  - Challenge will be to examine chemical exposures and to collect data at critical windows of exposure
- **Ethics**
  - Ethics Resource Guide posted on the portal
  - Major issues of concern: ethical implications associated with conducting a non-therapeutic study, the definition of minimal risk
  - Suggestion: expanding the Working Group by creating an Ethical Oversight Committee due to the paramount importance of ethical issues in every aspect of the study
- **Health Services**
  - NCS has the potential of influencing the allocation of health resources in the future
  - Focus on the impact health care services have on child health and development
- **Immunity, Infections, and Vaccines**
  - Focus is on infectious and chronic disease, infections in pregnancy and early childhood, autism, early onset of depression and schizophrenia, asthma and viral infections, the impact of environmental exposures on autoimmunity, and immunity and genetic disease
  - Two current hypothesis centered around vaccines and HIV infection
- **Asthma**
  - Decision made to consider respiratory ailments in addition to asthma
  - Early signs of asthma development in infancy
- **Early Origins of Adult Health**
  - Much thought was given to the life-course approach to chronic disease. This includes: environmental, social, behavioral, and biological exposures from preconception through adolescence

    - Hypotheses focus on the relationship between obesity, type 2 diabetes, and schizophrenia
- **Study Design**
    - Core hypotheses must inform the study design
    - Criteria formulated to assess potential hypotheses
    - Difficulties justifying a study design adequate for the size and scope of the NCS
- **Gene-Environment Interactions**
    - Key issues of concern: gathering data on the family triad (mother, father, infant); specimen collection, processing, and long-term storage; perceptions of genetics among study participants; and informed consent and ethical issues
- **Pregnancy and the Infant**
    - Include parental exposures at critical windows of human reproduction and development
    - A broad definition for the term "exposure" will be used to incorporate a greater range of measures
    - Issue of concern: the plausibility of enrolling participants preconceptually
- **Development and Behavior**
    - Initial focus on the early years of development (i.e. well-baby checks)
    - Areas of study: behavioral disorders (i.e. attention deficit/hyperactivity disorder (ADHD) and autism) and schizophrenia
    - Discussion of the need for adequate assessment measures in very young children
    - Study environment: home or clinical setting
- **Birth Defects**
    - Intention of recruiting preconception
    - Focus areas: impaired glucose metabolism, alcohol consumption during pregnancy, relationship between environmental exposures, endocrine disrupters, and abnormal sexual development (especially in males)
    - Raised issue of the need for a standardized instrument to assess newborns
- **Repository**
    - Need for standard operating procedures for the repository and data systems management, long-term storage of specimens, and the physical requirements of the repository
    - Estimate of 1-10 billion samples to be stored in the repository
- **Nutrition, Growth, and Pubertal Development**
    - Progress to be reported in the future
- **Medicine and Pharmaceuticals**
    - Role is to examine pharmaceuticals influencing growth and development, identify and predict future hypotheses
    - Other issues of consideration: maternal medical history, interview approach, in utero exposure to drugs in foods (i.e. caffeine)
- **Injury**
    - Injuries are the leading cause of death in the first year of life
    - Injuries may cause lifelong physical and neurological impairments

    - Pilot studies will initially focus on the first 5 years of life
- **Physical Environment**
    - The following topics will be discussed at a later date: sun exposure, electromagnetic radiation, ultrasound in utero, heat, and the built environment

September 12-13, 2002
Third Meeting of the NCSAC

I. Hypotheses

- Develop Core Hypotheses
    - Evaluate potential hypotheses from the various working groups

    (HYPOTHESES CAN BE FOUND ON THE PORTAL)

II. Community Outreach and Communications Working Group

- Varying cultural contacts within communities
- Possibility of having community members serve on the advisory committee or as an alternate option forming a community advisory panel
- Early community involvement is key

III. Working Groups

- Emphasis placed on clearly defining “core hypotheses”

December 17-18, 2002
Fourth Meeting of the NCSAC

I. Priority Outcome Themes

- Core hypotheses will be grouped into 5 themes:
  - Pregnancy outcome—preterm birth, birth defects, etc.
  - Neurodevelopment and behavior
  - Injury
  - Asthma
  - Obesity and physical development

II. Conceptual Framework

- Emphasis on a framework to guide diverse disciplines with a common vision
- Framework must allow for the blending of themes across various areas of interest
- End product will be the collaborative effort of the Working Groups in order to ensure universality of the framework
- Framework will allow for a common language across a wide span of issues
- Definition of health: *A multidimensional and developmental process that influences physical, psychological, and social functioning. Health incorporates both positive and negative aspects, including disease, disability, and the ability for the organism to function effectively*.
- Three major themes:
  - Nested environments of health-accounts for the multiple layers of influence within environments
  - Health development over time: cumulative influence of environmental and health development trajectories (physiological, psychological, and behavioral)
  - Processes and mechanisms of health development: resources which may inhibit one's development

III. Sampling Strategy

- Westat Report: presented an overview of possible sampling strategies for the NCS
- Hypotheses must drive the NCS
- Models discussed:
  - two household models
  - medical-office model
  - center model
- Possibility of a hybrid approach was discussed
- Center model versus household model was debated

IV. Preconception Recruitment Issues

- Key Points: human development occurs early in pregnancy, before women are aware they are pregnant; it is difficult to construct a pregnancy history retrospectively; enrollment of women is just as difficult prior to pregnancy compared to enrollment during pregnancy

- A pre-pregnancy population is important to include in order to better understand a variety of negative health outcomes such as mother's nutritional status and child's growth size.

V. Ethical Issues

- Concerns
  - Only one ethicist on the NCSAC
  - Institutional Review Board's (IRB's) acceptance of a study of this magnitude
  - Recruitment issues
  - Consent
  - Third parties
  - Level of risks
  - Return to the communities and individuals
  - Responsibility for remediation if environmental hazards are found
  - Health Insurance Portability and Accountability Act of 1996(HIPAA)
  - Liability issues
- Recommendations
  - The involvement of ethicists in the NCS efforts
  - The coordination of the consent process should be through a central office of communication
  - The transition of the Ethics Working Group into an additional advisory committee or a subcommittee of the NCSAC
  -

VI. Proposed Pilot Studies and Workshops

- Gardosi Growth Potential Model Pilot Study
  - Model used to identify intrauterine growth restriction
- 3D Ultrasound
  - 3D Ultrasound measures volumes, and data can be stored
  - Precise measurements of organs
  - Lacks standardized procedures
- The efficacy of frozen breast milk in accurate assessment of environmental toxicants
- Physical activity across different age groups
- Biomarkers and childhood asthma
- Methodology to assess early asthma-related health outcomes
- Cohort retention in a longitudinal follow-up
- Biological samples as surrogates for analyzing molecular and cellular events in inaccessible tissues
- Telomere length as a chromosomal biomarker of growth variation and chronic disease risk in children
- Housing quality
- Life course approach and chronic disease
- Gross and histologic placental measurement instruments
- Maternal stress on pregnancy, labor, and childhood health
- Family effects on child health

- Rurality and child health
- Environmental exposures
- Sampling environmental exposure specimens during the follow-up of the cohort
- Dietary intakes and patterns in women and young children
- Measures for evaluating cognitive development
- Methods for assessing timing of pubertal maturation
- Prioritizing child health outcomes
- Methods for fetal and newborn assessment
- The impact of the healthcare system on child health outcomes

March 6-7, 2003
Fifth Meeting of the NCSAC

I. Preliminary Discussion/Issues of Concern

- The relationship between Working Groups, NCSAC, and the ICC
- Better defined roles for each group and committee
- Substantial concern of the need to increase the number of full-time employees working on the NCS
- Assuring adequate feedback from the Working Groups, NCSAC, and the ICC
- Collaboration of diverse Working Groups may improve efficiency
- Goal of the NCS is not to determine prevalence but to establish etiology
- Multi-factorial interaction of themes must be considered
- Is the NCS trying to address too many disparate issues?
- Community Outreach Working Group
    - Community education programs needed
    - Community profiles
- Pilot Studies Update
    - Need for tracking instruments for proposals

II. Chemical Exposures Working Group Report

- Chemical compound: "present in air, water, food, soil, dust, or other environmental media"
- Described the Toxicological Paradigm
- Discussion of neurotoxicants of greatest concern: lead, mercury, PCBs, pesticides, phthalates, and others
- Sampling methods: placenta, milk, hair, fingernails, and toenails
- NHANES data can aid NCS efforts

III. Pregnancy and the Infant-Testing Feasibility of 3-D Ultrasound

- Need to evaluate ways to ensure placental growth and integrity (fetal development is dependent on placental integrity)
- Benefits of 3-D ultrasound include but are not limited to: volume measurements which may lead to outcomes, ability to obtain morphological information on the fetus, minimizes patient burden, reduces observer-induced variability, and allows the viewer to manipulate the stored images and view the organ of the fetus from different perspectives
- Pilot study will compare and contrast 2D and 3D ultrasound

IV. Program Office

- Roles
    - Pilot study management and oversight
    - Protocol development
    - Reports
    - Presentations
    - Communication

    - Infrastructure
    - Planning and finance
- Contractors
    - Circle Solutions
        - Arrange meetings and schedule conference calls
        - Set up workshops and symposia
        - Handle information management
        - Provide information technology support
        - Compose reports and directories
    - IQ Solutions and Ogilvy Public Relations
        - Creating a five-year communication plan to address various stakeholders such as policy makers, scientists, and community leaders
        - An e-update will be regularly posted on the NCS website for public view

V. Pilot Studies Update

- Injury Pilot Study
    - Focus on the cumulative effects of repeated injuries
    - Mild traumatic brain injury (MTBI)
    - Workshop to include discussion on neuroimaging, neuropsychiatric outcomes, and biomarkers
- Developmental Measures Pilot Study
    - Literature review of available measures
    - Measures of interest: physical development, health status, emotional/social function, and language and cognition

June 5-6, 2003
Sixth Meeting of the NCSAC

I. Ethical Considerations and Longitudinal Pediatric Studies

- Hiring staff from within the community is vital
- Electronic informed consent may be a possibility
- Right to know versus sharing only the information the subject can properly frame
- Minimal risk versus more than minimal risk

II. Study Design Working Group

- Key Issues: core hypothesis selection, identification of thematic areas, devising an overarching framework
- Major concern: how etiologies will drive data collection
- Question of organizational authority
- New paradigm and increased risks versus a classical paradigm

III. Health Disparities and Environmental Justice

- It is critical to examine the impact of racism
- Racism contributes to disparities in health outcomes between racial groups
- Ethnicity versus race
    - Ethnicity: must incorporate culture and biology into definition
    - Race: "a system that structures opportunity based on phenotype, unfairly disadvantaged individuals and communities, and undermines the potential of society due to unfulfilled individual potential"
    - Three levels of racism
        - Institutionalized racism: comprised of policies, structures, practices and norms (i.e. education, housing, income, employment, access to resources, environmental status)
        - Personally mediated: phenotype drives assumptions about abilities, motives, and intent of others
        - Internalized: self-depreciation
- Five strategies for dealing with the issue of racism
    - Socio-economic status (SES), race, and health outcomes
    - Racial climate
    - Measures of racisms and health outcomes
    - Differences in the onset of time-sensitive morbidity
    - Structural factors that produce differential exposures
- May prove informative to incorporate racism hypotheses throughout all aspects of the study

IV. Advocacy Group Presentation: March of Dimes

- Priority areas: birth defects and preterm birth
    - Establish the basic mechanisms of preterm labor and premature membrane disruption
    - Improve clinical approaches (risk identification/reduction)

- Improve neonatal treatment
- Foster interdisciplinary approaches

V. Protocol Development

- 2 parts: data collection and non-measurement components (i.e. recruitment/retention, informed consent)
- On-line database: tracks hypotheses as they change over time
  - Will include detailed information on sampling in the future
  - Allows for retrospective and prospective examination

VI. Clarification of Working Group lines of Reporting

- Working Groups cannot work directly with ICC members. Rather, Working Groups may only interact with NCSAC members. This procedure is necessary in order to protect the individuals within Working Groups and their institutions from potential conflicts of interest.

VII. Parental Actions

- Parental responsibility for exposures and reducing risk
- Potential core hypothesis
- Further development needed
- Possible need to incorporate issues of racism

VIII. Prenatal Substance Exposure and Developmental Outcomes, Youth Drug Use and Its Consequences

- Non-core hypotheses or areas of interest in which the study is likely to capture: prenatal substance abuse and drug use during adolescence
- HIPAA may be a barrier in obtaining this information

IX. Family Structure and Child Well-Being

- Under development

X. Sleep Problems/Disorders

- Non-core hypothesis
- Under Development

XI. Interaction Between Environmental Exposures and Genes

- The large sample size of the NCS will allow for the development of solid data
- Reorganization of the Working Group needed

XII. Sampling Issues

- Probability-based sampling has succeeded in the past (i.e. The British cohort study of the 1959's and the National Collaborative Perinatal Project)
- Mathematical extrapolation builds credibility
- Probability sampling enhances inferential power
- Four Main Arguments against a probability sample:

    - Clinics will provide better care to subjects who are also those clinicians' patients
    - Potential infeasibility due to recruitment problems
    - Intrinsic difficulty in identifying the population
    - Funding issues associated with bringing the subjects to the clinics
- All hypotheses must be developed assuming a probability sample design

XIII. Sampling Design

- Issues of Concern
    - Representativeness
    - Prepregnancy versus early pregnancy
    - Oversampling of sub-populations
    - Measures of community/neighborhood environment and characteristics
    - Stability of exposure
    - Complexity of observation
    - Sampling units, segments, design effects
- ICC is assembling a committee to address the aforementioned issues
    - Objectives: thorough consideration of sampling options, assurance that the issues are all considered, the issuance of a proposal for sampling options,
    - Committee comprised of 2 individuals from each the ICC and Study Design Working Group and 1 individual from the NICHD Program Office

XIV. ICC Pilot Study Subcommittee

- Reviews proposals and makes recommendations for funding
- Proposals may be modified and/or combined with another proposal
- Program Office reviews proposal(s)
- Program Office is equipped with a tracking system for all proposals
- High priority pilots: lead sampling strategies, feasibility of 3D ultrasound to assess fetal development, methods for assessing newborn health, development and validation of growth and histological measurement instruments, comparative value of fresh and frozen breast milk, and possibly maternal stress and pregnancy
- Medium priority pilots: subject retention methods, statistical methods for life course studies, measurements of housing quality, and social influence of child health and development
- Low priority pilots: measuring physical activity over time, rurality and child health, and a workshop on environmental exposure

XV. Genetics

- Genetic elements must be integrated into the hypotheses set
- More discussion of gene/environment interaction in the future
- Is the study too small to address genetic issues?

XVI. Hypothesis Discussion

(Potential hypotheses have been posted on the portal)

- Autoimmunity Hypothesis

- Social Environment Working Group Hypothesis Series on Family Influences on Child Health and Development
- Injury Working Group Hypotheses
- Predictors of Child Maltreatment
- Outcomes of Child Maltreatment
- Physical Aggression
- Physical Environment and Injury Risk
- Functional Outcomes of Injury: Influence of Antecedent Factors
- Cumulative Effects of Repeated Mild Traumatic Brain Injury
- Psychosocial Environment and Injury Risk
- Longitudinal Assessment of Dental, Oral, and Craniofacial Disease and Conditions During Childhood and Adolescence
- Eye and Vision Research

XVII. Program Office Timeline

- Considerations
    - Community interests
    - Engagement of field investigators
    - Provision of startup time for sites
    - Assurance that methods development and pilot study outcomes will be integrated
    - Integrating inputs from all partners
- Current and future Endeavors
    - Protocol writing, reviewing, and refinement (2003-2005)
    - Federal and local review and clearance (November 2003-August 2005)
    - Development of a coordinating function for clinical work (June 2004)
    - Establish a tissue repository (June 2004)
    - Vanguard sites will be contracted (early 2005)
    - Enrollment (2005)
    - Fine-tuning the protocol, establishing remaining sites, bringing in further enrollees**,** and tabulating incoming data (2008)
    - Funding issues
    - Developing and sustaining partnerships
    - Innovative communication tools to ensure evolving goals are relayed to partners
    - Long term pilot studies
    - Protocol adjustments dependent on technological advancements
    - Sampling strategy
    - Increase staffing

XVIII. Noted Accomplishments

- Momentum of the study is building as awareness increases within the scientific community
- NIH and NICHD support the National Children's Study
- Dr. Alexander is playing an integral role in the development of the study

- Excellent technical support and contract support
- The ICC has become the driving force within the study
- Wealth of interested parties providing multiple avenues to increase awareness

September 14-16, 2003
Seventh Meeting of the NCSAC

I. General Discussion

- Subject burden
- Economic burden
- Communities must play an active role in the Study's development (the most effective research involves the input of the individuals targeted for recruitment)
- Community-based studies consistently win the approval of Institutional Review Boards (IRB's)
- It is important to avoid influencing hypothesis development with cost information
- The size of the cohort of the NCS will provide substantial data on subgroups
- The addition of federal quality assurance (QA) experts may be needed

II. Progress

- New employees in the program office
- Contract:
    - Batelle (Support Contract): Assist with literature reviews, technical analysis, white papers, developing scientific reports from workshops and surveys of researchers, and similar efforts
    - RTI (EPA contract)
    - Circle Solutions (Logistical Support)
    - IQ and Ogilvy (Communications support)

- Study Assembly Meeting Goals
    - Communicate the status and progress of the Study to the broad membership of the Assembly
    - Improve community engagement and support for the NCS
    - Obtain feedback from Assembly members regarding hypotheses and community needs

III. Pilots and Workshops

- Lewin Report
- Westat Report
- Biomarkers database project
- A review of new and emerging technology (pertinent to the Study)
- Methods for improving community involvement, subject recruitment and retention
- Ongoing pilot studies
    - Exposure and methods development (i.e. low-cost, low-burden exposure monitoring strategies and time-integrated exposure measures

- White papers and reviews are in the developmental stages
- Workshops addressing:
    - Community interest
    - Fetal and neonatal growth and development assessment methods
    - Medications
    - Ground-breaking technologies
- Future workshops
    - Placental measures
    - Psychosocial stress and pregnancy and the infant
    - Physical activity during pregnancy and in children and various ages
    - Sampling design
    - Media and children's health

IV. Sampling Strategies

- White papers under development
- Strengths and weaknesses of probability-based sampling and center-based sampling must be assessed
- NIH consensus model
    - Science and literature aid in the effort to make informed decisions
    - Panel of unbiased experts reviews options and reaches a consensus

V. Injury Working Group

- Statistical information on childhood injuries presented
    - Deaths and disabilities
    - Unintentional versus intentional
    - Child maltreatment
    - Youth violence
    - Suicide
- Injuries are predictable and preventable
- Burden to healthcare system
- Disabilities as a result of injuries places a burden on the educational and social service system
- Risk behavior: learned or genetic
- Family structure/environment and injury
- Community differences (i.e. affordability of bike helmets, how violence is reported)
- The Study will assess the impact of violence in the home

VI. Advocacy Group Presentation: American Psychological Association (APA)

- The APA supports the NCS
- Must obtain sufficient behavioral information in order to distinguish precursors to a variety of negative health outcomes
- Must obtain mental health histories and status of parents
- Determine how families and parent/child interactions influence development
- Address disparity issues (possibly over sample in low SES and high SES groups)

- Look at positive developmental outcomes (i.e. resilience) not just disease outcomes
- Seek input from behavioral experts
- Consider seeking advice from the APA on the impact of a potential major traumatic event that would likely affect a child's mental and emotional health

VII. Exposure to Chemical Agents

- Exposure measurement and sampling (2 potential pilot studies)
- Questionnaires, time/activity diaries, and biological samples
- White paper
    - Evaluation of different types of exposure assessment related to each of the core hypotheses
    - Environmental exposure
    - Information and biomonitoring
    - Sampling
    - Analysis of information for various life stages throughout childhood

VIII. Injury Thematic Subgroup

- Four main categories for hypotheses
    - Child maltreatment
    - Aggression and the trajectory of aggression from childhood to adolescence or young adulthood
    - Traumatic brain injury
    - Unintentional injuries

IX. Altered Neurobehavioral Development, Developmental Disabilities, and Psychiatric Outcomes Thematic Sub-Group

- Issues of discussion
    - The role of siblings
        - Benefit or detract from hypotheses throughout the study?
    - Genetic studies

X. Undesirable Outcomes of Pregnancy: Birth Defects and Preterm Birth Thematic Sub-group

- Medicine and Pharmaceuticals Working Group
    - Tiered approach to be applied across the Study
- Compilation of a list of potential etiological agents or contributors to good or bad outcomes should be considered throughout the Study

XI. American Foundation for Maternal and Child Health (AFMCH)

- Concerned by the lack of documentation of intrapartum exposure to drugs and the procedures administered to the mother during labor and birth
- Pediatric neurologist needed to take part in the planning stages of the Study
- Potential hypotheses suggested

XII. Working Group Progress/Concerns

- Hypotheses must be reviewed
- Collaboration with other Working Groups may improve efficiency
- Assign responsibility of hypotheses to a specific Working Group (avoid redundancy)
- Maintain enthusiasm within the Working Groups
- Shaping the language used within the study in order to gain the acceptance of specific audiences

December 15-16, 2003
Eighth Meeting of the NCSAC

I. General Issues

- Definition of health needed
- Alignment of timelines of the NCSAC and the ICC
- Program office adds staff
- Contractors hired
- First draft protocol delayed due to personnel freeze at NIH
- National Human Genome Research Institute (NHGRI) poses possibility of merging a large adult cohort with the National Children's Study
- Funding issues delays recruitment to 2006
- Linking NCS data to established databases
- Tracking system for samples needed
- ICC and director of the NICHD make final decisions concerning the Study protocol
- First draft protocol should be available in March 2004
- Community outreach will commence at this time

II. Status of Themes and Hypotheses, ICC Document

- NCS is a hypothesis-driven study not a general survey
- Reasons for core hypotheses:
    - Establish a framework for study design
    - Draft the protocol
    - Prioritize pilot studies
    - Provide public identity for the Study
    - Help stakeholders understand the Study
- Hypotheses not meant to be representative of the Study in its entirety

III. Outcomes and Exposures

- Outcome measures:
    - Pregnancy Outcomes
    - Neurodevelopment and Behavior
    - Injury
    - Asthma
    - Obesity and Physical Development
- Exposures
    - Physical environment
    - Chemical exposures
    - Biologic environment
    - Genetics
    - Psychological milieu

IV. Report from ICC/NCSAC Executive Committee

- Working Group's, ICC, and NCSAC's role as the study evolves requires clarification
- Incorporating the continuum of health into the Study
- Subcommittees will be appointed to deliberate emerging issues

V. Pilot Studies Issues

- Burden of data collection on Study participants
- Methods for newborn assessment
- Utility of frozen breast milk in accurate assessment of environmental toxicants or their metabolites, metabolic, nutritional, and genomic endpoints (compares frozen breast milk to fresh breast milk and blood)
- Feasibility of using 3D ultrasound for fetal assessment
- Comparison and independent assessment of the abilities and functionality of two nomenclature systems for prescription drugs, over-the-counter drugs, herbals, and supplements
- Follow-up of initial focus groups for the Study
- A review exploring the measures available for evaluating health status, emotional and social functioning, mental development, and cognition
- Methods for successful cohort retention in a longitudinal follow-up of children and families
- Measuring housing quality and characteristics
- Assessing dietary intakes and patterns in women and young children
- Statistical methods for the life course approach to the development of disease: causal inference, collinearity, interactions, and sample size

VI. Completed Workshops

- Community Engagement
- Fetal and Neonatal Growth and Development Assessment Methods
- Medicines Exposure: Collection, Coding, and Classification
- International Consultation in Longitudinal Cohort Studies
- Innovative Technologies for Remote Collection of Data for the National Children's Study
- Ethical Issues in Longitudinal Pediatric Studies: "Looking Back, Thinking Forward"
- Assessing the Incidence and Outcomes of Mild Traumatic Brain Injury
- Placental Measurements
- Psychosocial Stress and Pregnancy and the Infant
- Physical Activity

VII. Upcoming Workshops

- Use of Herbal Products in Pregnancy, Breastfeeding, and Childhood Workshop
- Sampling Design
- Effects of Media
- Measures of Social environment
- Impact of Rurality

- Day-Specific Probabilities of Pregnancy
- Questionnaire and Dairy-Based Methods for the Early Assessment of Asthma-Related Health Outcomes

VIII. Sampling Design Workshop Planning Committee Update

- Panel members and chair identified
- Role of committee:
    - Distinguish documents needed to inform sampling decision
    - Develop papers
    - Coordinate workshop
- White Papers
    - Recruitment and retention rates and their impact on choice of design
    - Probability-based sampling
    - Data collection requirements for the Study
    - Initial sampling design options and criteria for evaluation
- Recommendation of using a family of study designs to adequately meet the needs of the diverse hypotheses

IX. Positive Health Framework

- Need for hypotheses on healthy development in children
- Recommendations:
    - Devise a framework to consider the influence on positive health and development
    - Assess current measurement approaches and specific measures of positive health and development
    - Formulate hypotheses testing what influences positive health and development
    - Determine ways to integrate findings into the Study
    - Request each Working Group determine how healthy development ties into their respective areas or expertise.

X. National Human Genome Research Institute (NHGRI)

- Adult longitudinal cohort under consideration
- Questions:
    - Will a collaborative effort between the NCS and the NHGRI fortify the NCS's efforts?
    - Should the NCS expand its focus to incorporate families into their analyses?
- Benefits of Collaboration
    - An improved understanding of cultural and environmental influences
    - Detailed information on parents and grandparents
    - Enrollment of several generations may improve retention rates
    - Improved funding
    - Potential to increase the number of scientific resources
    - Inclusion of parents and grandparents will be of greater benefit to the NCS in comparison to siblings

- Concerns
    - May lose focus on the children
    - Logistics issues may cause a delay for the NCS
    - Biological parents versus non-biological parents
    - The epidemiology of the studies would differ (prospective versus retrospective)
    - Expanding may overwhelm the study due to the broad nature of including children and adults. Expanding may also introduce a level of chaos with the mass addition of interested institutions

XI. President's Council on Bioethics

- Assisted Reproductive Technology (ART)
    - The President's Council on Bioethics is proposing a study be planned to consider:
        - Well-being of children, egg donors, and gestational mothers
        - Access to services
        - Movement of techniques and practices from experimental to clinical use
        - Ethical significance of new technologies

XII. Injury Breakout Session

- Injury cannot be considered purely an outcome, but must be considered an exposure that has the capacity to affect function and influence future disability
- Is parental report an acceptable method for analyzing injuries both quantitatively and qualitatively?
- Obligations for intervention upon observing child maltreatment or potentially dangerous environment
    - A study operations manual may serve to guide researchers if these dangerous situations are noted

XIII. Pregnancy Outcomes

- Maternal stress must be evaluated with the following topic areas in mind: pregnancy, asthma, development and behavior, birth defects, injury, and social environment
- The Study should include preconception and postpartum measures
- Effect modifiers
- Timing of measurements
- Gestational age and susceptibility to chemicals (toxic windows)
- Chemicals with a short half-life (critical exposures may be missed)

XIV. Asthma Breakout Session

- Expand focus to include airway reactive disease, allergies, and asthma
- Infant stress and childhood stress should be included
- Intended areas of attention: indoor/outdoor air pollution, respiratory/viral infections, and bacterial/microbial products (hygiene hypothesis considered)

XV. Neurodevelopment and Behavior Breakout Session Summary

- Core hypotheses can be applied throughout the Study
    - Synergistic/cumulative effects of exposures
    - Interactions among social, familial, and genetic environments
    - Address a broader range of adaptive and problematic outcomes, including co-morbidities
    - Anticipate adult outcomes of concern and determine the relationship between early exposures and later health and disease
- Development and Behavior variables
    - Executive functions (impulsivity, attention, planning)
    - Emotional and behavioral control (self regulation capacity)
    - Stress reactivity
    - Temperament
    - Cognitive and language development
    - Academic success
    - Productive engagement outside of school
    - Social competence
    - Risk-taking behaviors

XVI. Obesity

- Identify measures and the timing of data collection
    - Variables
        - Gene-environment interaction
        - Access to food
        - Location of grocery stores
        - Amount of television watching
        - Linkage between puberty and obesity

March 4-5, 2004
Ninth Meeting of the NCSAC

I. Contracts

- Batelle (technical support)
  - Provide background information for the Study sampling strategy
  - Identify developmental measures
  - Construct a sample protocol for the Practice Based Research Network (PBRN) feasibility study
  - Perform power analyses for social environment hypothesis
  - Review databases
  - Review literature
  - Write a white paper on measurement of housing quality
- Booz Allen Hamilton: RTI, Batelle, and Levine, Fricke, and Sanz (IT Support)
  - Determine the IT requirements for recruitment and enrollment
  - Develop mechanisms for questionnaire data collection
  - Identify means to electronically capture data

II. Pilot Update

- Approximately 30 Pilot studies Workshops, and White Papers currently ongoing

III. Protocol Development

- Critical Content
  - Environmental influences on child health and development
  - Environment broadly defined
  - Enrollment of approximately 100,000 children
  - Enrollment during or before pregnancy
  - Follow-up for 21 years
  - National in scope
- Implications
  - Communication about the evolving protocol must be in the public domain
  - Working Groups and NCSAC will have limited interaction with the Interagency Coordinating Committee (ICC) and the Program Office
  - Working Groups and NCSAC activities will take on a more passive role as a protective measure
- Tasks
  - Drafting the text of the Study protocol
  - Development of operational manuals
  - Collaborative effort with contractors to create procurement documents
  - Devise a method for the handling and processing of data
- Study Design and Methods
  - Sampling
  - Participant contacts (when and where)
  - What will occur upon contact
  - Preliminary data collection methodology
- Human Subjects in Research

- Benefits/Risks
- Confidentiality
- Consent and assent policies

IV. Repository Working Group

- Logistical Design issues (communication, data sharing, and the handling and processing of samples and specimens)
- Study database design
- Information tracking
- Specimen identification and label design
- Type, quantity, and storage of specimens needed to answer the hypotheses
- Specimen sharing between hypotheses
- Regional/satellite repositories
- Location of specimen processing (repositories or regional labs)
- Quality assurance (centralized or regional)
- Secure contractors

V. Assisted Reproductive Technologies (ART)

- Possibility of examining ART within the Study as a parallel adjunct to the Study
- Recent meta-analyses analyzing outcomes of assisted conception
- Currently, there are no ART studies ongoing in the United States
- Multiple types of ART
- 1% of pregnancies are by ART (2% in the future)
- Indications for ART are varied
- Difficult to obtain information on cause of infertility
- Necessity for Oversampling?
- Incorporating ART into the Study would require dramatic changes to the study design

VI. Positive Health

- World Health Organization (WHO) definition of health: "a state of physical, mental, and social well-being, not merely the absence of disease or infirmity"
- Development of an analytic approach in order to identify the critical determinants of optimal health in children who do not have known health problems

VII. Asthma Working Group (workshop to be held in May 2004)

- Questionnaire versus diary-based methods for assessing asthma
- Outcome measurements and biomarkers

VIII. Community Outreach and Communication Working Group

- Request-for-proposal criteria
  - Community listening sessions
  - Outreach strategies
  - Community profiles to recruit
  - Community leaders

- Community outreach advisory board

IX. Development and Behavior Working Group (workshop to be held in June 2004)

- Focus on environment and windows of vulnerability

X. Gene-Environment Interactions Working Group

- Critical influences in disease development with biological importance
- Will develop a list of candidate genes for the Study
- Will analyze the pros and cons of including siblings in the NCS

XI. Department of Health and Human Services Initiative on Electronic Medical Records

- Description of the Council on Applications of Health Information Technology (CAHIT)
- Possibility of the Agency for Healthcare Research and Quality (AHRQ) to collaborate with the Study
- CAHIT
  - Create synergy with DHHS
  - Coordinate inter agency activities across DHHS
  - Improve quality and safety in research
  - Provide an efficient and accurate method for gathering information
  - Promote timely exchange of information about DHHS activities and opportunities
  - Identify and evaluate activities and investments that complement private sector initiatives
  - Make recommendations to the Secretary to create strategic opportunities to enhance applications of health information technology in U.S. health care
- Electronic healthcare and medical system
  - Support clinical care and research activities
  - Improve health care quality and patient safety measurement
  - Improve data accuracy and reliability
  - Need for unified standards

XII. Sampling Design Workshop

- Pros and cons of alternative sampling methods
- Recruitment and retention
- Measures for the Study's core hypotheses
- Criteria to evaluate Study sampling design options
  - Ability to satisfy "givens"
  - Engage communities
  - Specialized measures
  - Prenatal recruitment (with some preconception)
  - Scientific merit
  - External validity

- Population diversity; range of exposures
- Internal Validity
- Power
- Resources for future

June 28-29, 2004
Tenth Meeting of the NCSAC

I. Program Office Update

- Media Coverage
- Battelle contract (technical support)
    - Completed tasks
        - Background for sampling strategies
        - Sample protocol for the Practice-Based Research Network (PBRN) feasibility study
        - Power analyses for social environment hypotheses
        - Estimated economic benefit of Study
    - Pending tasks
        - Review and white paper on measurement of housing quality: underway
        - Technical analysis for sampling questions: reported today
        - Review of health services measures: hold for funds transfer
        - Revise and update cost projections: proposed
        - Developmental measures for the Study: 75 percent complete
        - Review of extant databases for the Study: near completion
- Booz Allen Hamilton Inc. (RTI, Battelle, Levine Fricke, and Sanz
    - IT System tasks
        - IT requirements for recruitment and enrollment
        - Mechanisms for questionnaire data collection
        - Electronic capture of clinical data

II. Sampling Discussion

- Timeline
    - April 2002: Proposal and concept for analysis of sampling strategies to NCSAC; CDC, ASPE, Westat study commissioned
    - October 2002: Westat report compares three models: household, office-based, center-based
    - December 2002: NCSAC advises probability-based sample as feasible
    - Spring 2003: Interagency Coordinating Committee (ICC) questions feasibility and cost of probability-based representative sample
    - June 2003: Proposal to NCSAC for expert sampling design panel informed by commissioned papers and reviews
    - Summer–Fall 2003: Planning committee (composed of individuals from the NCSAC, ICC, and Program Office) commissions Battelle papers and establishes expert sampling design panel (with David A. Savitz, Ph.D., as chair)
    - March 2004: Sampling Design Workshop Panel deliberates sampling strategy and proposes probability option and alternative center-based option

    - Spring 2004: Program Office explores mechanisms, feasibility, and costs and commissions analyses to answer additional cost and feasibility questions
    - June 28–29: NCSAC and ICC deliberate sampling options with feasibility and cost considerations
- Consensus
    - A proposal acceptable enough that all members can support
    - A commitment to the decision reached
    - Each individual feels he/she has been heard, listened to, and understood by others
    - Each person can explain and justify the decision rationale
    - Each person must be willing to commit to his or her role in executing or supporting the decision
    - In the case in which a strong dissenting opinion exists, explaining the rationale and supporting the decision includes expressing and acknowledging the dissenting perspective

III. Role of the Sampling Strategy

- Collect high quality data and minimize measurement biases
- Maximize validity of inferences in exposure/outcome relationships (response rates, retention rates, selection biases)
- Capture the diversity of the U.S. population (incorporate a range and diversity of exposures and outcomes)

IV. Sampling Design Issues

- Selection of geographic location
- Recruitment of individuals within the chosen geographic location
- Timing of enrollment

V. NCS Sampling Design Options

- Nationally representative probability sample
    - Primary sampling units (PSUs) probability-based
    - Sampling of clusters probability-based
- Modified probability sample
    - PSU's and clusters probability-based
    - PSU's and clusters identified with input from the local centers
- Modified probability sample
    - PSU's not probability-based
    - Clusters identified with input from centers
- Medical center/patient-based sampling approach

VI. NCS Sampling Design: Nationally representative probability sample

- Details
    - Coordinating center/statistical team would select PSUs/clusters (counties/tracts/block groups/blocks) with known probabilities; boundaries are based on Census data.

    - Enrollment of study participants could be done by either coordinating center or local center
    - Work with local clinical sites to obtain clinical measurements.
- Advantages
    - Would likely provide national estimates
    - Has the capability of fulfilling the need to reflect the diversity of the United States, however defined.
- Concerns
    - Response rates may be unacceptably low in some clusters
    - Not clear whether it is feasible to assign clusters to a center with no input from the center or from the cluster
    - Boundaries for the designated clusters may not conform to recognized communities or neighborhoods
    - Participants' commitment to the Study in the absence of a community commitment.

VII. Options for Selecting Individual Participants Within Clusters

- Recruitment Approaches
    - Household-based
    - Clinic/physician office-based
    - Community
- Four pregnancy/contraception status categories of women
    - Currently pregnant (CP)
    - Currently seeking pregnancy (CSP)
    - Current contraception users (CCUs)
    - Other (non-CCU, non-CSP)
- Two target enrolled populations
    - All women
    - CP/CSP only
    - Two levels of average initial recruitment rates: 80 and 60 percent
- Three recruitment periods: 3, 4 and 5 years
- Two levels of monthly attrition rates:
    - CP/CSP = .0015
    - CCU/Other = .0035
- Other rates:
    - 94 percent live birth enrollment
    - 95 percent contact
    - 10 percent vacancy

VIII. Potential Times of Enrollment

- Preconception
- Early in pregnancy (less than 4 weeks)
- Prenatal care
- At delivery
- Combination of above

IX. Challenges of Preconception Enrollment

- No one sampling option will fulfill the needs of all areas within the Study

X. Recruitment Approaches

- National probability-based sample (NPBS) of households in 250 PSUs
  - Enroll all women (1) $91 million
  - Enroll CP/CSP women only (2) $48 million
- Full community approach (25 regions, four communities each)
  - Enroll all women (3) $111 million
  - Enroll CP/CSP women only (4) $45 million
- Physician's office approach (50 and 100 PSUs)
  - Enroll all women: 80,000 CP; 10,000 CSP; 10,000 CCU/Other
  - 50 PSUs (5) $21 million
  - 100 PSUs (6)$28 million
- Enroll CP/CSP women only: 80,000 CP; 20,000 CSP
  - 50 PSUs (7)$16 million
  - 100 PSUs (8)$23 million

XI. Cost Model Assumptions

- A 4-year recruitment period with all births in the 48-month window from months 4–51
- A 12-month enrollment period except for CP women in physician's office approach
- An 80 percent average initial enrollment rate
- A 95 percent contact rate requires six visits in household and physician office approaches, four visits in full community approach
- Constant hourly labor rates: $125 for physicians, $100 for principal investigators, $40 for senior staff members, $25 for junior staff members, $20 for recruiters

XII. Cohort Mobility

- Where, when, and how much will the cohort move?
- Is mobility mitigated by selecting larger numbers of clusters?
- Might be more cost-efficient to begin with fewer counties and establish mobile collection units

XIII. Validation Samples

- Y= health outcome of interest
- X_1= the "gold standard" measure of exposure (measured on a small subset of the cohort)
- X_2= a less precise measure of exposure
- Three methods to select the subset of participants in the validation sample:
  - Outcome dependent sampling (depending on Y)
  - Covariate-dependent sampling (depending on X_2)
  - Random sampling (no information)
- Validation samples helps minimize bias and error in exposure assessment

- Cost savings
- Feasibility
- Factors to consider
    - Exposure period
    - Pathways/measurements
    - Exposure metric related to disease (average, acute)
    - Continuous or binary outcome
    - Longitudinal outcomes
    - Prevalence of outcome
    - Variability of outcome measurements
    - Strength of exposure-outcome relationship

XIV. Sampling Strategy

- Probability-based nationally representative sample
- Prioritize hypotheses
- Use NPBS as much as possible

XV. Recent Definitions of Positive Health:

- WHO definition: “Health is the extent to which an individual or group is able, on the one hand, to develop and realize aspirations and satisfy needs, and on the other hand, to develop the capacities that allow them to change and cope with the environment”
- “The extent to which individual children or groups of children are able or enabled to:
    - Develop and realize their potential
    - Satisfy their needs
    - Develop the capacities that allow them to interact successfully with their biological, physical, and social environments”