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NATIONAL CHILDREN'S STUDY: STATUS IN 2010

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Abstract

The National Children's Study (NCS) will examine the effects of the environment and genetics on the growth, development and health of children across the United States; it will follow participants from before birth until age 21 years. The goal of the Study is to improve the health and well-being of children and contribute to understanding the role various factors have on health and disease. Findings from the Study will be made available as the research progresses, making potential benefits known to the public as soon as possible.

A robust pilot or Vanguard Study is underway to generate data for designing the subsequent Main Study. The goals of the Vanguard Study are feasibility, acceptability and cost and the goals of the Main Study will be exposure-response relationships and biological, environmental and genetic interactions.

The initial Vanguard Study experience among 7 Study Centers was successful in many ways including delineating the topics to explore for the next phase of the Vanguard Study. Three different recruitment strategies are under evaluation to determine what approach to use for the Main Study. The organization of NCS operations is currentlybased on a new decentralized business model.

The Children's Health Act of 2000 (Public Law 106–310) mandated the National Children's Study (NCS). The National Institutes of Health (NIH), in partnership with the Centers for Disease Control and Prevention (CDC) and the Environmental Protection Agency (EPA), is responsible for implementing the NCS. Section 1004 of the Children's Health Act with the title "Long-term Child Development Study" states that "It is the purpose of this section to authorize the National Institute of Child Health and Human Development to conduct a national longitudinal study of environmental influences (including physical, chemical, biological, and psychosocial) on children's health and development."

The National Children's Study is a prospective longitudinal observational study that will examine the effects of the environment and genetics on the growth, development and health of children across the United States, following them from before birth until age 21 years. Environment is broadly defined to include factors such as air, water, diet, sound, family dynamics, community and cultural influences.

[Callout] The National Children's Study (NCS) is a prospective longitudinal observational study that will examine the effects of the environment and genetics on the growth, development and health of children across the United States,

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A dedicated Congressional appropriation funds the NCS and the NIH Director's Office administers the funds. Study implementation is through a contract mechanism with multiple contractors for field operations at various locations throughout the United States and additional contractors for infrastructure support. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) awards the contracts and provides oversight.. The NICHD Director is responsible for the overall design and conduct of the study. Within the NICHD, The NCS Study Director functions as the principal investigator and the NCS Program Office Staff provide day to day management and scientific oversight as well as long term planning and analysis.

VANGUARD STUDY AND MAIN STUDY

The NCS has several components, including

- A pilot or Vanguard Study to examine the feasibility, acceptability and cost of recruitment, study operations and logistics, and study visit assessments
- A Main Study, which is designed using the data and evidence from the Vanguard Study, will focus on exposure response relationships
- Substudies embedded in the Vanguard Study or, when applicable, the Main Study, intended to address specific operational or scientific questions
- Formative research, that includes some Substudies, that addresses technical or methodological questions required to responsibly and effectively design components of the Vanguard Study or Main Study.

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In addition the NCS provides a platform for other externally funded studies to integrate with. Supplemental Methodological Studies are studies with external funding that study methods or feasibility and are integrated with the NCS Vanguard Study. Adjunct Studies are studies with external funding intended to study exposure response relationships and are integrated with the Main Study when it is launched.

The NCS Governance Structure has several components with strategic advice provided by the Director of the NIH, an Interagency Coordinating Committee and a chartered Federal Advisory Committee. All meetings of the NCS Advisory Committee are open to the public and meeting summaries are posted on the NCS website. Tactical input is provided by a Steering Committee and Executive Steering Committee of the NCS Contract Investigators. Human subject protection and data integrity and data access oversight is provided by an Independent Study Monitoring and Oversight Committee. Fiscal oversight is conducted by the NICHD Contracts Management Branch, the NICHD Director's Office, the NIH Director's Office and the federal Office of Management and Budget. Regulatory oversight is

provided by the NIH Director's Office, the Office for Human Research Protection and the Office of Information and Regulatory Affairs of the federal Office of Management and Budget.

STUDY SAMPLE

The NCS uses a national sample frame based on randomly selected geographic areas to provide an unbiased sample that can be generalized to the United States population. (reference Montaquila, Brick and Curtin, Statistics in Medicine, 29:1368 (2010)). The total current sample has about 100 study locations, but the number, size and selection process for study locations may evolve.

The NCS plan is to follow a proportion of women, currently targeted at about 20%, from preconception through pregnancy and then follow their children. The larger goal is to enroll as many women as feasible as early in pregnancy as possible to acquire data that can be used to elucidate associations between prenatal exposures and events and subsequent outcomes.

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The NCS statisticians developed a probability instrument utilized in the field that categorized women into high, moderate and low probability of pregnancy. High probability women could enroll at the time of initial contact with NCS recruiters. An NCS phone call center followed women classified as low or moderate probability of becoming pregnant with enrollment offered when a woman became pregnant.

The initial recruitment model incorporated several assumptions including the incidence of pregnant women, the proportion of all potentially eligible women that would be in the high probability group and the proportion of eligible women that would enroll in the study. The projected birth rate following attainment of steady state was about 250 children born the NCS per study location per year.

To be eligible for the NCS, participants had to reside in a predesignated geographic area. Recruitment implementation was through local field staff who would contact dwelling units identified through a listing process by first sending a postcard and subsequently going door to door to inform potential participants about the study. The NCS field staff would offer all women in these areas that were pregnant or were aged 18 to 49 years and could potentially become pregnant an opportunity to enroll.

VANGUARD STUDY

Initial Phase

A review panel of the National Research Council and Institute of Medicine recommended in 2008 (http://www.ncbi.nlm.nih.gov/bookshelf/picrender.fcgi?book=nap12211&blobtype=pdf) that the NCS institute a pilot study prior to beginning the Main Study.

Subsequently, the NCS Program Office developed a pilot or Vanguard Study protocol with the intent to enroll about 1500 to 2000 children over about an 18 month period and then merge the Vanguard Study into the Main Study. The Main Study was to begin enrollment in

waves, with study locations following the initial Vanguard Study sites designated as Wave 1 to be followed by a Wave 2 and then a Wave 3 and potentially even more sites.

The NCS began field operations in January 2009 with two study locations: Duplin County in North Carolina and Queens County in New York. In April 2009 additional locations in Orange County, California; Waukesha County in Wisconsin; Salt Lake City in Utah; Montgomery County in Pennsylvania; and a composite location of four adjacent counties in South Dakota and Minnesota were activated for a total of 7 study locations.

Recruitment rates were lower than the initial assumptions had predicted. The empiric data suggested that the projected overall birth rate of children enrolling into the NCS would be no more than about 40% of predicted. Late in the summer of 2009, the NCS began the process of identifying alternate recruitment strategies.

By August 2010, about 1300 women had enrolled and about 520 children were born into the NCS among all seven initial Vanguard locations. The observed eligibility rate was about 0.7% of women contacted with an estimated pregnancy rate of about 0.5% of all women contacted. About 64% of potentially eligible women consented to participate, of whom about 70% were pregnant at the time of enrollment. Compliance with the initial scheduled visit was about 78% for pregnant women and 87% for non-pregnant women. The seven initial Study Centers are currently following collectively about 20 000 women through telephone call centers. Further details on recruitment in the initial Vanguard experience are listed in Table 1.The initial Vanguard Study Centers also collected about 122 000 environmental samples and biological specimens including house dust, soil, air, water, blood, hair and nails, which are currently undergoing systematic analysis for stability and characterization.

The initial Vanguard Study experience was by any measure successful in implementing a complex protocol, achieving an enrollment rate near the top of the published range for similar populations and rapidly identifying the challenges of conducting a large scale cohort observational study in the United States. Through the comprehensive efforts of the NCS Coordinating Center and the initial seven Study Centers, a process to transition to the next phase of the Vanguard Study with a firm scientific and empirical basis was facilitated.

Current Phase

The NCS Vanguard Study was recast at the end of the summer of 2009 as exclusively a pilot study that would not merge with the Main Study, but would always anticipate each phase of the Main Study and continue independently for 21 years after completion of enrollment. The Vanguard Study and the Main Study will function in parallel, with the Vanguard Study preceding the Main Study by a fixed time interval.

A new protocol for the Vanguard Study was produced in October 2009 and vetted through the NCS Governance Structure. Consequently, the Main Study launch was delayed until sufficient data are generated by the Vanguard Study to inform design of the initial phases of the Main Study and provide a reasonable estimate of needed resources and costs.

The current Vanguard Study goals are to determine the feasibility (technical parameters), acceptability (impact on participants, study infrastructure, and personnel), and costs (level of effort, resources, time and money) of recruitment, study operations, and all the assessments and measures, including environmental samples and biospecimen collections, performed during scheduled visits for the Main Study.

The Main Study will focus on exposure-response relationships and biological, environmental and genetic interactions. While data from the Vanguard Study could potentially be included in some analyses that use data from the Main Study, the Vanguard Study is not intended to provide definitive analytic datasets for exposure outcome relationships.

ALTERNATIVE RECRUITMENT STRATEGIES

Recruitment is a resource intensive phase of any study. In the NCS, with goals of a large and unbiased national sample that can be generalizable and robust data acquisition plans, the approach to recruitment can be a major limitation to accurate assessment of the feasibility, acceptability, and costs. Since early data from the seven original Vanguard Study sites indicated that the recruitment strategy which they were employing was insufficient alone to meet the needs of the Main Study, the NCS Program Office initiated a systematic process of literature review, consultation, and conferences to determine other recruitment and enrollment strategies. Data from the initial Vanguard Study experience showed that most participants learned about the NCS through contact at their home or dwelling unit. The new recruitment strategies were designed using how participants learned about the Study as the organizing principle. Thus, three general strategies were selected: (1) enhancements to the previously used household based contact approach, (2) initial contact through health care providers (using a broad definition that includes physicians, public health nurses, midwives and others) to refer potential participants to the Study, and (3) a direct to potential participant approach emphasizing media campaigns, direct mail, social media, community events, and word of mouth with Study registration through telephone, internet, and surface mail.

The Vanguard Study protocol was amended to include three groups, one for each recruitment strategy, of 10 new study locations each, thus activating a total of 30 new locations around the United States to begin enrollment.

Each recruitment strategy will continue to enroll until a fairly constant rate of recruitment and enrollment is reached. At that time, the Vanguard Study enrollment will be completed and analysis of the different strategies can lead to development of one or more recruitment strategies for the Main Study. Current estimates are that the Vanguard Study cohort will total about 3000 children, but the actual number will be determined empirically.

The initial seven Vanguard Study locations will continue to enroll participants but no longer perform new household contacts. Instead, the pool of participants may be expanded through pregnant women referred into the Study by themselves or by others such as health care providers, friends and neighbors, or follow up through the call centers.

INITIAL VANGUARD INFORMATICS MANAGEMENT SYSTEM

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

This new approach is termed the “facilitated decentralization” model. In this model, the NCS Program Office develops evaluation questions and plans; data fields, tables and relationships; operational data elements; study data acquisition instruments; data formatting and transmission standards; a central data archive; and specifications and guidelines for data

security, participant confidentiality, and regulatory compliance. This facilitated decentralization model offers distinct advantages over a completely centralized structure: it allows study centers under contract with the NCS to select or develop their own case management systems, data acquisition platforms, and as appropriate, data collection modalities to acquire the data. The model builds on local study center expertise with existing informatics systems and supports adaptation or development of new systems, with an emphasis on open-source, non-proprietary platforms. All NCS data systems are certified and accredited per the requirements of the Federal Information Security Management Act of 2002 (FISMA) and related regulations. All NCS data specifications are consistent with international medical research standards such as those developed by the Clinical Data Interchange Standards Consortium (CDISC).

The new approach to informatics for the NCS is informed by several trends in informatics, including

- modular architecture (building systems in discrete modules that can be independently changed or substituted)
- use of standardized terminology with curation (using well defined terms whose meanings are maintained in a readily accessible glossary)
- semantic awareness (use of terms in defined contexts rather than in isolation)
- scalability (capacity to function independent of sample size)
- defined transmission standards (the use of standards to transmit data from one site to another)
- non-proprietary open architecture platforms with development communities (the software code is freely available without intellectual property protections and the software is developed and maintained by teams that welcome external input)
- vertical and horizontal integration of process (the operations and data flow are consistently designed to work together)
- interoperability (components of a system can easily interact with each other within the system and in any other system that conforms to the same standards)

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

TERMINOLOGY

In addition to addressing technical challenges, the NCS must confront the general absence of consistent child health oriented terminology. The NICHD, in collaboration with the National Cancer Institute, began a terminology initiative in 2008 using the innovation of linking concepts and the related terminology through developmental stages. The initial work of harmonizing the nomenclature and definitions for developmental stages, establishing content domains and development of a logical model is complete and can be referenced at http://www.nichd.nih.gov/health/clinicalresearch/terminology Part of the formative research program at the NCS is to develop further the terminology needed for the Main Study.

DATA OWNERSHIP AND DATA SHARING

Because the NCS is conducted through a contract mechanism, the federal government owns all the data. The NCS Study Centers and investigators are all contractors and must sign a data use agreement. The incorporation of robust security procedures into the data systems allows local retention of collected data. However, the NCS data use agreement does not allow local sites to share or pool data except to transmit it to the NCS central data archive.

Study data without personally identifiable information are transmitted centrally and stored. Data from the NCS central data archive are intended to be shared broadly with the research community. NCS investigators do not have priority access to any of the data other than those that are stored locally.

Access to the data is through a Data Access Committee that reviews applications for data use. The focus on transmitting and storing data consistent with international data standards is to maximize options to link NCS data with other data resources including, disease, condition, or intervention specific registries, data archives, warehouses from other studies, and U.S. census data. The robust local security and data access policies are parts of a broader program to ensure the highest quality data and address privacy and protection concerns. The NCS model with a data access committee and data access policies facilitates responsible data sharing with the scientific community and provides secure archives for future generations. The NCS data access policy and further details are available on the NCS website at http://www.nationalchildrensstudy.gov

OPPORTUNITY FOR A LEARNING COMMUNITY

Except for the focus of the Study remaining on the health of children, all other aspects of the NCS are potentially subject to re-evaluation and change. The concurrent deployment of three different recruitment strategies plus a formative research program provides an exceptional opportunity for launching a learning community with structured and systematic training, feedback, process maps, process improvement, modeling, and simulations.

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The NCS has adapted these approaches both centrally and in the field, particularly in the alternate recruitment substudy, to build an effective learning community.

Other operations that are specifically decentralized include training in study procedures, with a cohort of initial Vanguard Centers forming an NCS Consortium Training Center, community outreach and media campaigns, Community Advisory Boards, and local NCS related events.

The principal focus on the health of children will place emphasis on reference standards and operational definitions of health and health outcomes that are particularly relevant to pediatric populations. However, the Vanguard Study focus on feasibility, acceptability, and cost will yield not only logistical information to inform the design of the Main Study, but will also inform clinical research methodology in general.

The National Children's Study is an open system and encourages collaboration through Supplemental Methodological Studies to the Vanguard Study to explore new methods and technologies. Further details and an application are available at

http://www.nationalchildrensstudy.gov/research/SMS/Pages/default.aspx. When the Main Study is launched a similar program to explore exposure-response relationships will be available. The current portfolio of NCS contractors has important connections to the NIH Clinical and Translational Science Awards (CTSA) Consortium, with 22 of 36 NCS Study Centers holding CTSA awards. The NCS and CTSA communities share some scientific goals and personnel and are formally coordinating efforts to leverage opportunities. The NCS is also in dialogue with multiple international partners, including the World Health Organization, the International Childhood Cancer Cohort Consortium, and several national studies in Europe and Japan to leverage resources, practices, and findings.

CONCLUSION

The NCS has adopted a data driven, evidence based approach to designing and implementing the Main Study. Multiple initiatives are underway to generate the data for informed decision making. The NCS is positioned as a platform for innovation and collaboration that is an investment in providing resources, data, and opportunities that have the potential to benefit generations to come.

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Table 1

NCS Vanguard Study Recruitment, September 2010

Recruitment Activities		**Percent**
Potential households to contact ~**80000**	Households contacted 67177	*86%*
Women identified in households ~**32740**	Completed pregnancy screener 30063	*92%*
Women meeting eligibility criteria **2425** (~0.8% of 30063 women screened)	Eligible women identified through telephone call center 560 (of 2425)	*23%*
Women who could enroll **2229** (196 of 2425 potentially eligible women changed status after screening)	Women who did enroll 1397 (of 2229)	*63%*
Pregnant when enrolled **968** (of 1397 women enrolled)	Not pregnant when enrolled 429 (of 1397 of women enrolled)	*70%/30%*
Pregnant women who completed first pregnancy data collection **810** (of 968 pregnant women enrolled)	Non-pregnant women who completed pre-conception visit 305 (of 429 non-pregnant women enrolled)	*84%/71%*
Children born into the study **594**		