



National Children's Study Update January 14, 2010

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National Children's Study Description



- The National Children's Study (NCS) is a Congressionally mandated activity coordinated among Federal agencies including the
 - Centers for Disease Control and Prevention
 - Environmental Protection Agency
 - National Institutes of Health with the National Institute of Environmental Health Sciences contributing and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development serving as the program lead.
- The NCS is a large multicomponent multiyear longitudinal study that is unprecedented in scope and complexity and therefore necessitates a planning process that is systematic, dynamic, flexible, and evidence based.

National Children's Study Goal



- The NCS will examine the multiple effects of broadly defined environmental influences on the health and development of 100,000 children across the United States, following them from before birth until age 21, by providing high quality data to analyze scientific hypotheses.
- The overall goal of the National Children's Study is to improve the health and well-being of children.

National Children's Study Structure



- The NCS is being implemented in several phases
- All components and phases together form the NCS
- Current major components are the
 - NCS Vanguard Study
 - NCS Main Study
 - NCS Substudies

NCS Vanguard Study Goals



- The Vanguard Study is designed to evaluate the
 - Feasibility (technical performance)
 - Acceptability (the impact on participants, study personnel, and infrastructure)
 - Cost (personnel, time, level of effort and money)
- of
 - Study recruitment
 - Logistics and operations
 - Study visits and study visit assessments

NCS Vanguard Study Outcomes



- The outcomes of the Vanguard Study will have a continual and major impact on how the Main Study will be executed; thus, it is imperative that the Vanguard Study be planned, implemented, and monitored to a level of precision that enables it to serve as a reliable and valid platform to evaluate recruitment, study procedures, visits, scale up potential, resource requirements and other aspects for the Main Study.

National Children's Study Main Study



- The Main Study will focus on data acquisition related to the interaction of genetics, environment, growth and development on the health of children and the analyses of those data for multiple scientific hypotheses.
- The Vanguard Study and the Main Study have different goals and the assessment types and assessment techniques used in each of the NCS components may be different so there is no intent to categorically merge data among NCS components.
- The Vanguard and Main Study will run in parallel, and together with additional NCS funded substudies, will form the composite National Children's Study.

Relationship of Vanguard Study to Main Study



Vanguard Study
N = estimated 2000

NCS Main Study
N = 100 000

National Children's Study Terminology



- Studies that integrate with the Vanguard Study, are funded by the NCS and focus on a limited question with limited duration will be known as substudies
- Studies that integrate with the Vanguard Study and have independent funding will be known as Supplemental Methodological studies
- Studies that integrate with the Main Study and have independent funding will be known as Adjunct Studies

National Children's Study Activity



- The Vanguard Study began in January 2009 with 2 locations, then an additional 5 locations began enrollment in April 2009
- The Main Study will begin when there are enough data from the Vanguard Study to responsibly construct the Main Study design
- The Main Study start date will be data based and evidence driven rather than calendar driven

NCS Vanguard Study Enrollment Target



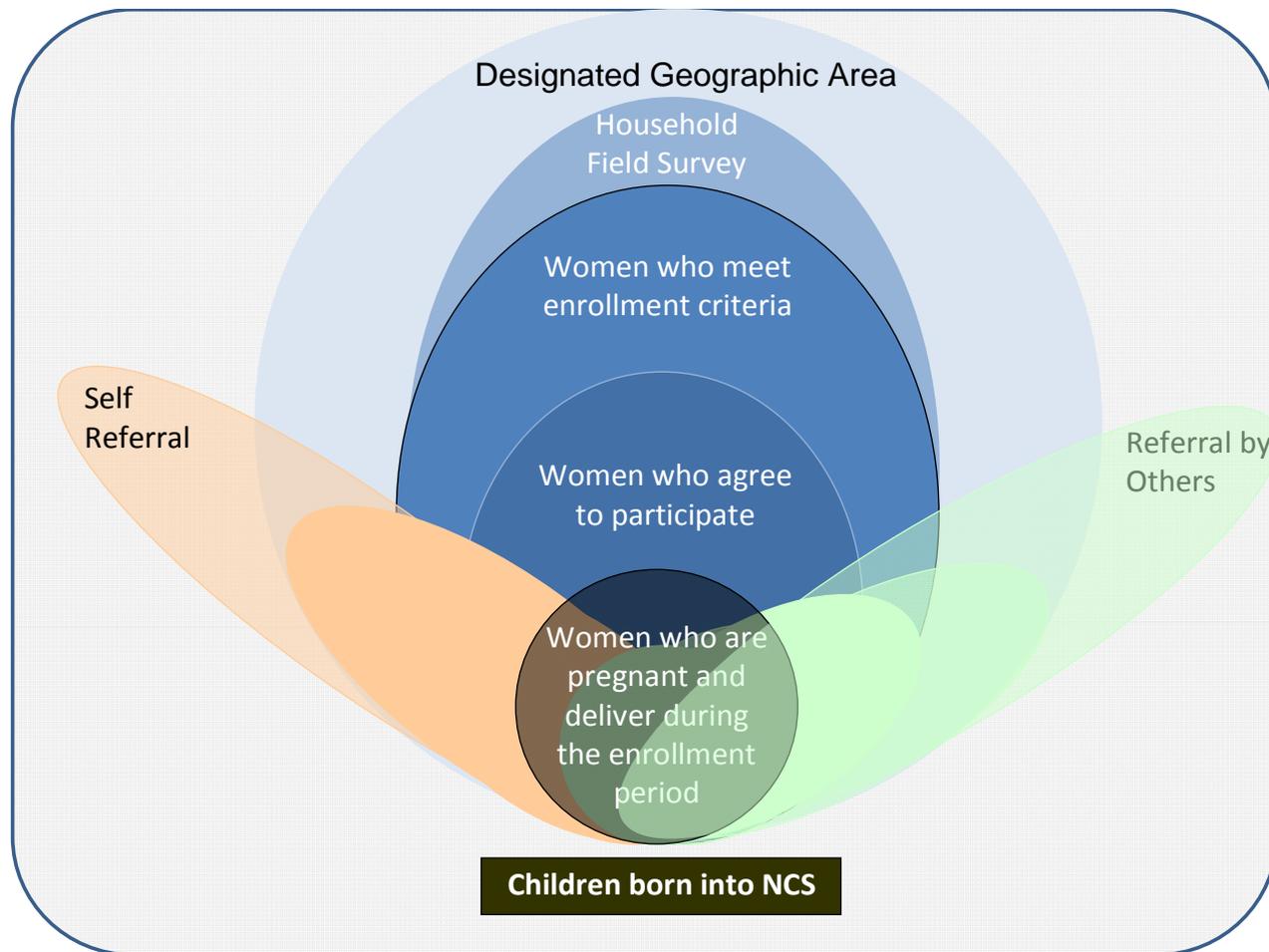
- The enrollment target for the Vanguard Study will be determined empirically by two factors
 - Recruitment data indicate a sufficient number of informative events to assess different strategies for scale up to the Main Study
 - An adequate cohort size to evaluate the study visit assessments for the duration of the study

NCS Current Recruitment Strategy



- Goal is representative sample to provide unbiased results and coverage of a broad range of environmental and population characteristics
- Representative sample achieved through demographics of predetermined geographic areas that are divided into segments
- All households within a geographic segment are eligible
- All women that meet enrollment criteria and live in the household are potentially eligible to enroll into the study
- When a woman becomes pregnant she is formally enrolled into the NCS
- The woman must live at an address in an eligible geographic segment when her child is born for the child to be enrolled into the NCS

NCS Current Recruitment Strategy



Recruitment Plans-Three comparators with current method



- Current: Continue re-enumeration in current 7 Vanguard Centers
- New Strategy 1: Provider based strategy in 10 additional locations
- New Strategy 2: Enhanced household survey enumeration in 10 additional locations
- New Strategy 3: HiLo strategy in 10 additional locations
- Total of 37 locations in Vanguard Study
- Parallel activity for improved efficiency in evaluation of recruitment numbers, community tolerance and cost to inform methods appropriate for Main Study

NCS Visit Assessments



- Visit assessments (those tests and assays administered to study participants at a visit) can be tested in all current contract sites
- Currently developing a series of analytic criteria
- About 250 different visit assessments (environmental samples, biospecimens, measurements, questionnaires, etc.) currently in NCS catalog to evaluate

Evaluating Visit Assessments for Feasibility



- Each visit has a schedule that may contain questionnaires, physical and laboratory measurements, biological samples, environmental sample collections, or other assessments
- For each outcome assessment for each visit an *a priori* analysis is underway to determine the estimated count of informative events to provide 95% confidence limits around the reproducibility of the assessment that will allow an evaluation of whether to
 - scale up with an acceptable standard deviation
 - modify the outcome assessment and retest empirically
 - eliminate the outcome assessment from consideration for the Main Study

Evaluating Study Visit Assessments for inclusion into Main Study



- Feasible, reliable, reproducible
- Informative
- Value
- Lack of redundancy
- Able to address a question that
 - has potentially important public health impact
 - requires a study of NCS size and robustness to answer
 - unlikely to be answered in another context

NCS Hypothesis Selection



- The selection of scientific hypotheses for the Main Study will be guided by
 - the empiric data of the Vanguard Study and other NCS funded substudies
 - by the efforts of the various workgroups and interested parties that proposed and vetted candidate hypotheses
 - potential scientific and public health impact
 - a perceived requirement to use the NCS and not another alternative as the data acquisition platform

NCS Target: Main Study



- All current NCS efforts are directed to inform Main Study with regard to design and elements
- Main Study design dependent upon results of recruitment evaluations
- All components for Main Study must have relative value and be scalable

Constructing the Main Study Process Considerations



- Main Study recruitment rate estimates based on Vanguard Study empiric data will determine the duration of enrollment to reach the accrual target of 100 000
- Main Study cost estimates will be based on study design factors such as;
 - **duration, effort and costs for recruitment**
 - **geographic location and resource footprint for each visit. For example, home based visits will have different requirements than clinical based visits**
 - **scale up costs of data processing, quality assurance, data archiving and data analysis**
 - **number, complexity and costs for outcome assessments**
- Additional secular factors such as health care, transportation, data security and other costs will also impact the Main Study cost estimates

Evaluating NCS Cost Drivers



- In general major cost drivers are:
 - recruitment strategy
 - number of visits
 - complexity of each visit
- The resource footprint for each visit as well as study operations is largely a function of the number of personnel involved and the level of effort required for data collection

NCS Methodology and Credibility



- Use of Established Methods
- Study Oversight
- Internal Consistency
- External Consistency

NCS Data Credibility- Use of Established Methods



- NCS Vanguard Study protocol procedures are standardized and documented in 10 volumes of the Manual of Procedures (MOP)
- Field staffs across Vanguard Study Centers are trained and certified on the MOP
- Limited and specified local variation was encouraged to determine best practices during this Vanguard Study and thereby inform the Main Study.
 - For example, some sites hired professional surveyors as a subcontractor and other sites hired field personnel directly.
 - Some sites provided specimen collection kits to the families directly and some sites provided specimen collection kits to clinic personnel.
 - Experience with each of these variations is tracked and compiled to ascertain if there is a best practice.

NCS Data Credibility- Oversight



- Management and adherence to the NCS protocol is managed centrally by the NCS Program Office.
- Field memoranda (152 memoranda to date) are distributed to support ongoing training and areas of protocol clarification.
- Weekly debriefing of field staff at the study centers maintain consistency in administration and alert needs for protocol clarification.

NCS Data Credibility- Oversight



- The NCS Program Office manages submissions to 122 IRBs overseeing the Study, OMB approvals and quarterly updates, data security and access, and incidents.
- Incidents include protocol deviations, areas of protocol clarification, data loss, adverse events and unanticipated problems.
- Incidents are required to be reported within 24 hours of occurrence, and are reviewed on a weekly basis.
- 110 incident reports have been received since inception of the Vanguard Study in January 2009. In 39 of these cases, a corrective action plan was requested and subsequently approved by the NCS Program Office.

NCS Data Credibility- Oversight



- Combined, the established infrastructure meets or exceeds human subject research protections established by OHRP and data confidentiality regulations established by the Federal Committee on Statistical Methodology.
- The production of the Revised Vanguard Study protocol document codifies these clarifications of the initial protocol based on field experience and NCS Program direction.

NCS Data Credibility- Oversight



- Additional Oversight provided by:
 - NCS Independent Study Monitoring and Oversight Committee
 - Interagency Coordinating Committee
 - Office of the Director, National Institutes of Health

Internal Consistency



- Internal consistency is an indicator of reliability of data. The data collected in the NCS Vanguard Study has been internally consistent in that Study Centers are reporting similar values on a Center basis from month to month over the past 6 months
- For example, among key parameters such as pregnancy rate of Study identified women, the data have been consistent.
- To date, the pregnancy rate is 3.2% on average. High and low values include Duplin County, North Carolina—a rural community (5.8%) and Montgomery County, Philadelphia (2.1%) and Orange County, California (2.3%)—both suburban communities.

External Consistency with other studies



- The proportion of pregnant women formally enrolling into the Vanguard Study (about 60%) is within the range of surveys with similar target populations and study designs.
- NICHD Study of Early Child Care and Youth Development (SECCYD) (1991): 25% participation rate (1,364 enrolled/5,416 eligible; 8,986 screened) using hospital-based recruitment shortly after delivery. Extensive exclusion criteria.
- Health Outcomes and Measures of the Environment Study (HOME) (2003): 32% participation rate (413 enrolled/1,263 eligible) using a provider-based list frame and direct mail recruitment. This included 55 participants who declined participation after the "run-in" period, specifically designed to allow families to decline further participation before we conducted expensive interventions.

External Consistency with other studies



- Danish National Birth Cohort: Approximately 30-35% of total pregnancies.
- Early Childhood Longitudinal Study—Birth Cohort ECLS-B (ECLS-B) (2001): 74% participation rate (10,700 completed interviews among consented/14,000 eligible; 15,500 screened) using household enumeration techniques and a birth certificate sampling frame when infants were 9 months of age. Numbers are rounded to protect respondent privacy, per ECLS-B conventions. Response rate does not multiply due to rounding of denominator and numerator.
- The Fragile Families and Child Wellbeing Study (1998-2000): 85% participation rate (interviewed/eligible in the first five cities) to enroll infants through hospitals shortly after delivery.

NCS Methodology and Credibility



- The NCS Vanguard Study employs established study methodology to recruit pregnant women into the Study.
- Its infrastructure, directed by the NCS Program Office and supported by a nationally recognized data collection and research organization, supports high quality data collection.
- The Vanguard Study has produced data that are internally consistent and consistent with other studies.

National Children's Study



- For further information, please inquire at ncs@mail.nih.gov