

**National Children's Study Federal Advisory Committee Meeting
Discussion Questions
April 2010**

National Children's Study Update

1. Do you have any suggestions for additional data items to further characterize Study recruitment, logistics, or operations?
2. Do you have any suggestions on field management and data collection practices and methodologies?
3. Are there particular operational analyses you would like performed?
4. Are there types of data collection instruments or methods evaluations that you would like to recommend for our evaluation of Study visit measurements?
5. Are there open source informatics platforms that you have experience with that may be applicable to the National Children's Study Vanguard Study?
6. Do you have comments on the facilitated decentralization approach to data security or Federal Information Security Management Act of 2002 compliance?
7. Do you have specific comments related to the phase in approach to building complexity in the Study visit assessments?

National Children's Study

1. Do you have additional suggestions for the National Children's Study Communications Plan?

National Children's Study: Study Visits Assessments Evaluation

1. Do you have additional suggestions on the methodologies for qualifying Study visit assessments?
2. Do you have additional comments on the priority of analysis for Study visit assessments?

National Children’s Study Federal Advisory Committee Meeting
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July 2010

NCS Policy and Practice on the Return of Research Results:

Revealing clinically relevant and actionable findings to individual participants is seen as an ethical obligation. The NCS has operationalized the definition of “clinically relevant and actionable” as requiring the existence of a national or other widely recognized threshold or regulatory standard. This topic is much debated in the literature. At this time, there are not clear best practices for longitudinal cohort studies and biobanks.

The ability to link to individual records does exist within the NCS and is integrated into the current process; however, there is an unknown temporal lag between collection and analysis and an inability to define which potential analytic results may be relevant to participants. Due to this lack of certainty, the Independent Study Monitoring and Oversight Committee (iSMOC) was developed to independently review analytic plans and make recommendations regarding the advisability of reporting of specific results to participants.

Current NCS Policy and Practice on the Return of Research Results includes anthropometric measurements such as height, weight and blood pressure, would be shared immediately with participants. Other data such as analytes from environmental samples and biological specimens would be stored indefinitely. The iSMOC is charged with determining which analyses may yield analytically valid, medically relevant, and actionable research results. The planned mechanism for reporting of research results is direct communication of results to the Study Center principal investigator with a recommendation to repeat the evaluation with appropriate referral as needed.

NCS staff members are also committed to informing participants and communities of aggregate data, which will be done on a periodic basis as findings become available. Participants will be continuously informed of Study progress and aggregate findings via newsletters and other communications. It is anticipated that individual Study Centers also will integrate a local process to this national process to report some of the aggregate findings of interest to the local community.

1. Is the current NCS Policy and Practice on the Return of Research Results sufficient if real time analysis is instituted? What additional policies or clarifications, if any, should be incorporated into this NCS policy? Specifically, the NCS real time analysis would be performed in research laboratories with equipment dedicated to research, and would not be clinical grade or CLIA certified.
2. What are the possible downsides/risks of sharing research laboratory data in an observational study enrolling a broad population and how can we minimize those risks?
3. If the NCS policy for incidental findings follows other longitudinal study policies for incidental findings, health care providers would be informed. What recommendations would you make about the nature and extent of information provided to health care providers? In your opinion, how prepared are

health care providers to use research findings, particularly from environmental measurements or genetic analyses, in interactions with potential study participants? What recommendations would you make if a health care provider cannot be identified or contacted?

5. Under what circumstances, if any, would you recommend that community organizations or authorities be informed of environmental findings; for example if known toxins or carcinogens are found that appear to exceed allowable limits?

6. If genetic analyses are performed, under what circumstances, if any, should results be shared with participants? Should results be shared only for health related information, that is, no information about ancestry, physical traits, etc.? Should results be shared if requested by the participant? Should health related information be restricted to those conditions included for newborn screening?

7. For each scheduled visit, current NCS policy is to provide participants prior to the visit a Visit Information Sheet as a guide to the contents of the visit. As assays and analyses are identified as potentially yielding results that could be conveyed to participants and critical values are determined; should the NCS prospectively incorporate language within the Visit Information Sheets, in addition to the general language in the protocol and consent forms, to better communicate the possibility of sharing findings with either participants or health care providers?

Environmental Assessments:

1. Recent discussions suggest that questionnaires intended to assess environmental exposure have inconsistent or little predictive value.

a. Can you cite questionnaires that have been validated in pregnant women and children that have predictive value and should be considered for evaluation in the NCS?

b. Should the NCS initiate activities to develop and validate environmental exposure questionnaire instruments that would be consistent with the design, principles, rigor and precision used in domains that have validated questionnaire instruments?

2. Environmental contaminants of potential interest have multiple assay standards. Recent discussions suggest that consistent terminology and centrally accessible databases that exist in some research domains are absent for the environmental topics of interest.

a. Can you cite terminology and databases that have been vetted and validated for pregnant women and children that may be utilized for NCS environmental assessments?

b. Should the NCS initiate activities to develop consensus standards and a framework in conjunction with other partners to assure consistency, scalability, adaptability and interoperability for environmental assessments with other databases and data sources for future integrated analyses?

National Children's Study Federal Advisory Committee (NCSAC)
Discussion Questions (DRAFT)
October 14, 2010

Environmental Assessments:

Prior discussions of this committee endorsed an approach to perform "Real Time Analyses" of environmental samples and biological specimens collected during the National Children's Study. An alternative business model of collecting environmental samples and biological specimens and storing them until researchers and resources are identified at a future date was not endorsed due to risks of potential sample instability, missing scientific opportunities and delaying deliverables.

The NCS Program Office is exploring the development of environmental profiles- small panels of analytes- that may be informative regarding child health and general environmental conditions.

1. Do you have comments regarding the feasibility of such an approach with regard to technical challenges and opportunities, potential components, profiles, and sources (for example soil, water, air, blood, urine)?
2. Do you have experience or knowledge of how environmental profiles can relate to specific child growth and development parameters?

The NCS Program Office is also exploring the option of a hierarchy of environmental substances, using a subset of a larger class as index analytes that, if found to be outside identified parameters, would trigger additional analyses. For example if a standard panel contained four heavy metals and 2 or more of the heavy metals were above a threshold, the sample would be analyzed for additional heavy metals.

3. Do you have comments regarding the feasibility of such an approach with regard to technical challenges and opportunities, the linkages and correlations among substances of a particular class, preferred classes of substances and potential sources (for example soil, water, air, blood, urine)?
4. Do you have comments regarding preferred units or terminologies if environmental analytes are grouped into panels for profiles?

Data Acquisition and Management:

The Initial Vanguard Study utilized a centralized model of data management including case management systems and data capture systems. Based on the first year of experience with the centralized model and identification of multiple technical and logistical challenges in planning scale up, the NCS Program Office has implemented an approach to provide greater flexibility and permit exploration and innovation to determine preferred methods. The new approach is termed facilitated decentralization model. In this model, the NCS Program Office will develop evaluation questions and plans; data fields, tables and relationships; formatting and transmission standards; a central data archive; and specifications and guidelines for data security, participant confidentiality, and regulatory compliance. Distinct from the centralized model, however, the facilitated decentralization model allows study centers under contract with the NCS to select case management systems, data acquisition platforms, and as appropriate, data collection tools to acquire data whose content, format and security requirements have been established by the NCS Program Office. All data systems are certified and accredited per the Federal Information Security Management Act of 2002 (FISMA) and related regulatory compliance. All data specifications are intended to be consistent with international medical research standards such as those developed by the Clinical Data Interchange Standards Consortium (CDISC).

The facilitated decentralization model encourages the use of open-source, non-proprietary data capture and case management systems. It builds on local study center expertise with existing systems and supports adaptation or development of new systems.

1. Do you have any comments regarding the use of open source non-proprietary data systems as the basis for the NCS Informatics System?
2. Do you have experience with relevant data platforms or systems that the NCS should consider during the Vanguard Study?
3. Do you have architecture or process recommendations for the informatics systems?

National Children's Study Advisory Committee

Discussion Questions

January 26, 2011

1. Compensating Providers

- a. Please provide comments on the use of capitation fees.
- b. What type of provider incentives might be considered potentially coercive?
- c. Please provide examples of non-monetary incentives and any relevant experience.
- d. Provide additional comments on the use of monetary incentives particularly if tied to hourly compensation, if indexed to reimbursement rates for health care services, and potential caps on maximum payments.

2. Sharing Educational Materials with Potential Participants and Communities

- a. Please provide comments on the risks and benefits of providing eligible Study **communities** with evidence-based health information in the National Children's Study (for example, the NICHD Back to Sleep campaign).
- b. Provide examples of potential sources for acceptable material—for example, only federal programs, only HHS, only HHS and National Children's Study partner agencies, any credible not-for-profit source, any credible source, including commercially sponsored information packages.
- c. Once an information dissemination program is initiated, what should the commitment be? Should it continue with refreshers of the core package periodically? Should only new information be subsequently distributed?
- d. Please comment on potential modes for distribution of materials.
- e. Should the distribution and comprehension of the material be formally assessed?
- f. Should the analytic plan for the Study be adjusted to account for potential confounding or bias introduced by dissemination of information?

3. Vanguard Study Recruitment Data Update and Presentation Plans for Legacy Vanguard Data

- a. Are the proposed formats and content informative?
- b. Please provide additional suggestions or analyses.
- c. Should the Alternate Recruitment Substudy Analysis Plan provide additional analyses not captured in the Legacy Vanguard Data Analysis Plan?

4. Rapporteur comments

Recruitment Strategies:

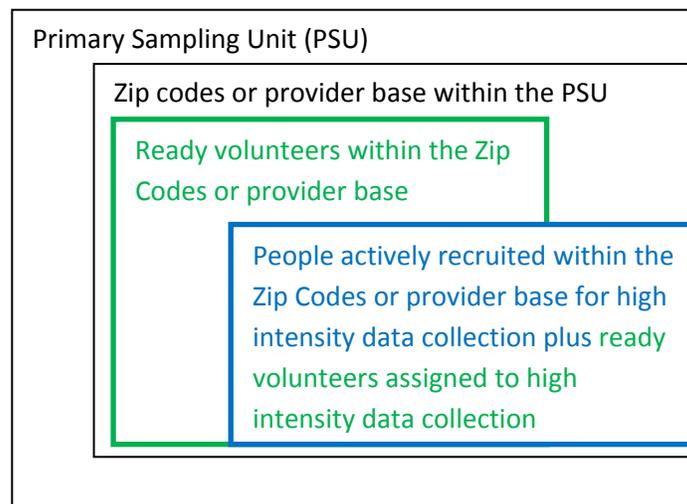
Please comment on

1. Any changes you recommend for implementation to any of the recruitment strategies.
2. Any changes you recommend to the reporting of the data for any of the recruitment strategies

Sampling Strategy

Please comment on

1. Any questions you may have about the selection of the primary sampling units
2. If the stringency of the secondary sampling units should be adjusted from the current segment structure to any alternative
3. If the basis for participant selection should be the residence of the participant or the location of the health care provider where the participant seeks or intends to seek prenatal care
4. On the acceptability, including any particular limitations, of
 - a. allowing participants that meet general eligibility criteria regarding age, pregnancy status and location based on primary sampling unit or some other geographic area such as Zip Code or provider base to enroll without restriction and
 - b. then based on demographics grounded in the 2010 census, assigned to high intensity or low intensity data collection. High intensity data collection would be the primary data analysis and low intensity would be a supplemental data analysis.
 - c. The low intensity pool could serve as a reserve population for the high intensity pool
 - d. Populations that are underrepresented in ongoing demographic analyses of enrolled participants would be targeted for enrollment with additional outreach and contact
 - e. with a potential oversampling of hard to reach populations to provide a buffer for any attrition over the course of the study.



NCS Advisory Committee Draft Questions

Draft NCS Main Study Protocol

1. Various models of retention and attrition at different stages of the proposed NCS Study schedule indicate a plausible but optimistic projection of 1 to 2% attrition per year. Additionally, models and projections of compliance (or alternatively item completion and unit completion) for responding to the array of questions, observations, biological specimen and environmental sample collections yield plausible estimates of between 55 to 70% of all potential data points may be collected. In order to examine conditions or exposures that have a 5% or lesser prevalence in the general population, the NCS has targeted a study population of 100 000 remaining after 21 years. Given attrition between women enrolling into the study and giving birth into the study and an estimated 1.5% annual attrition, the target number of women to enroll is on the order of magnitude of 250 000. Do you have suggestions or comments on the target enrollment population?
2. In order to enroll 250 000 women in a reasonable time frame such as about 2 years per study location, the NCS needs to make adjustments to the sampling frame. The NCS is also committed to a probability sample to minimize bias meaning that any eligible woman has an equal chance of being enrolled as any other eligible woman. Adjustments to the current sampling frame that are under consideration are increasing the size of secondary sampling units, consolidating locations into new primary sampling units such that the expected yield of live births per year is increased, adding additional locations and primary sampling units, and pooling less dense locations into larger primary sampling units. Do you have comments or additional suggestions on adjustments to the sampling frame?
3. The Main Study will incorporate the collection of operational data elements to inform the ongoing recruitment and data collection process. The NCS plans interim analyses on some of the operational data elements in combination with an adaptive design to allow adjustments in recruitment strategies and tactics. For example, an interim analysis at landmarks such as one to follow the first 5000 women enrolled, then 10 000, 20 000, 50 000, 100 000, 150 000 and 200 000 could allow ongoing adjustments to recruitment strategies. All adjustments would be prospectively defined and described in the protocol and activated based on objective trigger conditions. Please comment on the general concept of using an adaptive approach to monitor and adjust recruitment.
4. The Main Study will utilize recruitment approaches informed by NCS Vanguard Study data and attempt to align particular recruitment strategies based on projections about the local environment. For example, in some localities a house to house recruitment approach may be efficient and cost effective while in others a provider based recruitment approach may be the more advantageous approach. Particular populations may be more responsive to one approach over another and the NCS would like to maintain flexibility to assure as complete and unbiased a sample as feasible. Please comment on using a flexible approach to recruitment.

5. The Main Study protocol emphasizes early data collection with a target of two visits during the first 20 weeks of pregnancy with the first as early as pregnancy is detectable and the second no less than 4 weeks and no more than 8 weeks after the first visit. A third pregnancy visit is targeted during the second half of pregnancy. Do you have additional comments or suggestions on the timing of visits during pregnancy?
6. The Vanguard Study currently has about 20% of enrolled women identified prior to conception and completion of a preconception visit. The efficiency of women contacted and enrolled in a preconception pool to those from that pool who become pregnant and give birth in the study is less than expected. Do you have any comments or suggestions on approaches to enrich the pool of all eligible women for efficient identification of women likely to become pregnant?
7. Continuing the theme of early data collection, the Main Study protocol is targeting data collection at birth, 2 months, 4 months, 6 months, 9 months and 12 months and then every 6 months until 60 months. Do you have any suggestions of comments on the proposed visit schedule?
8. Some child visits are scheduled as face to face visits and others as remote follow up using telephone, e-mail or web based modalities. The strengths of face to face visits are ability to collect specimens and samples by trained personnel and direct observation. The challenges of face to face visits are the resources and need to schedule. Please comment on the proposed balance between face to face and remote visits. What factors should we consider if we substitute any face to face visits with a remote visit or the reverse?
9. The proposed visit schedule targets landmark dates in the life course of each participant. If meeting a schedule is logistically and socially challenging, an alternative is a flexible visit schedule where, for example 3 visits should be scheduled in the first 6 months with a minimum of 4 weeks between visits? Similarly, subsequent visit schedules could be twice a year with a minimum of 5 months between visits. Potential advantages of a flexible visit schedule would be logistical options to cluster visits with NCS teams in selected geographic areas several times a year and analytic options to collect data on children at various ages. Please comment or provide suggestions on a flexible approach to the timing of data collection.

Provider Based Sampling

10. If the location within a Primary Sampling Unit of a provider service facility is the primary determinant of geographic eligibility, one option is that all women who visit the provider be eligible, no matter where they live. An alternative is that both the provider service facility address and the woman's residence address are within the Primary Sampling Unit. Please comment on both options.

11. An early step in developing a provider based sample is characterization of the provider practice with regard to the demographics and distribution of the women who seek care at the provider facility. Please comment on potential approaches when a provider practice has a unique demographic profile and the provider is not responsive or declines to work with the National Children's Study.
12. Recruitment into the Main Study is currently targeted for 2 year duration at any location. Please comment on potential approaches if a provider withdraws involvement with the study after several months.
13. Although most women seek prenatal care, not all do. Please comment on potential approaches to enroll women who do not seek prenatal care.
14. Some Primary Sampling Units may have fewer than 5 provider facilities and some may have more than 100. Please comment on approaches to provider selection and potential substitution in areas with few or many providers.