Background for Discussion at the Workshop on the Design of the National Children’s Study

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This document was intended as the basis for discussion at the National Academy of Sciences’ Committee on National Statistics/Board on Children, Youth, and Families Workshop on the Design of the National Children’s Study (NCS) that was held on January 11, 2013. It covers two main topics—the collection of environmental exposure measures and the sample design. It summarizes what is known about the plans of NCS in these areas and lists questions to be addressed by invited discussants and other participants at the workshop.

Between the summer of 2011 and fall of 2012 the NCS Program Office held a series of meetings with federal and non-federal sampling experts and others to discuss the most effective sampling approach for the Main Study. In addition the NCS Program Office had multiple discussions and consultations with additional individuals and organizations. Based on these extensive discussions and consultations, the NCS is proposing the use of a multi-layered cohort approach for the Main Study.

The role of the discussions at this workshop is to inform the NCS Program Office on specific design questions, and the ideas presented will be considered for incorporation into the Main Study Design. In addition to the feedback from the National Academy of Sciences workshop, the NCS is advised by a Federal Advisory Committee and seeks input from a Federal Consortium of colleagues with expertise in specific subject areas, as well as contemporaries involved in international cohort studies. The findings of this workshop will be used by the NCS Program Office staff to construct decision points or parameters to guide the Main Study design.

The questions to be discussed at this workshop are related in that the NCS Program Office would like to learn about prenatal exposures, and the question is how much does it invest and what does it expect for that investment. The issue is not so much whether to have a prenatal cohort—at the moment, the NCS Program Office is neutral and is suggesting a balance of a 45,000 participant birth cohort and a 45,000 participant prenatal cohort. The issues are how much does the NCS Program Office need to invest to get prenatal exposure information, what is

1 This version of Background is a slight revision to the document that was made available prior to the workshop on 01/03/2013. The revision added authors’ names and affiliations and further explained the primary source of the information in the document.

2 The first four authors are from the Office of the National Children’s Study in the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the National Institutes of Health (NIH). The last author is from the Committee on National Statistics, National Research Council, National Academies of Sciences.

3 The authors prepared this paper to serve as background for the workshop. The primary source of information was The National Children’s Study Institute of Medicine Workshop Steering Committee Briefing Document, October 16, 2012. http://www.nationalchildrensstudy.gov/research/workshops/Pages/IOM-SC-white-paper-october-2012pdf.pdf
the quality of the information, can other data be used to approximate the information not directly collected, etc.

ENVIRONMENTAL MEASURES – CURRENT PLAN OF WHAT IS TO BE COLLECTED AND WHEN

The primary objective of the National Children’s Study (NCS) is to examine the relationships among exposures and outcomes that affect children’s health and development. While the NCS is considering a broad array of exposures, including characteristics of the family and neighborhood, this discussion will focus on a few exposure and outcome examples to probe some specific design questions. Current plans include, but are not necessarily limited to, collection of the following samples:

- Household dust
- Blood
- Urine
- Questionnaires on exposures and the social environment
- Placenta and cord blood at birth

These samples could be tested for heavy metals, pesticide residues, semi-volatile organic compounds, and pharmaceuticals. Outcome measures include but are not limited to:

- Linear growth rate and body mass index as a proxy for general health
- A metabolic screen of serum total protein, blood urea nitrogen, cholesterol, iron, and calcium as a proxy for nutrition and dietary exposure
- Frequency and duration of health system encounters for respiratory illness as a proxy for pulmonary health
- Timing of standard neurodevelopmental landmarks and any deviation from adjusted trajectory as a proxy for cognitive and social development.

The NCS also plans to use general exposure data collected at the municipal or neighborhood level (water quality, air quality, known industrial pollution) by either direct specimen collection or extant data collection.

The current data collection plan is based on an approach that uses a core questionnaire administered at every childhood visit, plus supplemental modules to be administered to specific participants or subpopulations based on events and conditions such as age, developmental stage, and other triggers such as specific exposures or hospitalizations.

Modules may be administered on a “missing by design” basis. There are at least two aspects of this missing by design approach: modules triggered by age, exposure, or specific events; and a “validation sample” approach. Triggered modules based on age, for example, make most sense where either scientific evidence indicates that exposures only at certain ages are likely to cause health concerns or a knowledge gap exists.

A validation approach may be useful, for example, when there might be two ways to measure a specific item, one inexpensive, the other expensive but more comprehensive. A smaller random
sample may be assigned to have the expensive measure taken, but all respondents would provide the inexpensive measure. The data from the samples with both data might be used to establish a model to provide a correction to the inexpensive data that are available for the entire sample.

This only makes sense if there is knowledge that such a model exists or could feasibly be developed and could provide an improved estimate based on the inexpensive data. In addition to questionnaires, other modalities for data capture such as sound recordings, images, geographic movements, and mapping of social interactions and networks will be used. The NCS emphasizes data collections early in pregnancy and early in child development because the largest knowledge gaps, and perhaps the most critical events, occur during those time periods. Pregnancy data collections are scheduled, if possible prior to about 20 weeks of gestation and once later in pregnancy. Data collections for children are scheduled at birth and then every three months for the first year and every six months until five years old, for a total of 13 opportunities. Seven will be face to face, including biospecimen and environmental data collection. The other six are remote collections, typically by telephone. Subsequent data collections have not been specifically scheduled but will be on average about every other year until 21 years old, for a total of 8 additional opportunities. The visit schedule is flexible in that children will not have assessments precisely at a given age, but within a window of several weeks around a particular age.

The NCS Proposed Examples of Potential Exposures and Outcomes Table http://www.nationalchildrensstudy.gov/research/workshops/Pages/nationalacademyofsciencesworkshop.aspx indicates that biospecimens of blood and urine will be collected from the mother prenatally, at birth, and when the child is 6 months and 12 months old. From ages 2 years to 5 years, blood and urine will be collected from the child. At each of these opportunities, except birth, the mother would complete a questionnaire, and household dust, among other samples, will be collected.

ENVIRONMENTAL ISSUES --Questions for Session 1 Discussion

Given the challenge as stated in the Children’s Health Act of 2000 to "perform complete assessments of environmental influences on children’s well-being" does the proposed visit schedule and sample collection balance the complex requirements? Specifically comment on the proportion of different types of data collection—primary environmental sample collection, use of biological specimens for biomarkers of exposure, and use of secondary sources including retrospective analysis for environmental exposures. Considerations may include:

1. Are the proposed measures (biomarkers, questionnaires, physical measures) the most appropriate to assess exposures of interest? If not, what measures should be taken?

2. How should the NSC prioritize decisions regarding exposure assessments? Some examples of factors to consider are:
   a) Potential public health impact of the outcome
   b) Technical feasibility including timing of data collection with regard to potential developmental vulnerability
c) Scientific opportunity to address knowledge gaps and illuminate developmental pathways

The table titled “Potential Environmental Exposures of Interest” (http://www.nationalchildrensstudy.gov/research/workshops/Pages/nationalacademyofsciencesworkshop.aspx) lists environmental exposures of potential interest to be measured in all NCS participants (general) and in a subset of participants (selective). Selective sampling will be based on the principle of enriching for a population more likely to have a risk of a particular exposure. For each exposure, corresponding examples of target analytes are listed. The rationale for biospecimen or environmental sample collection, examples of target analytes, proposed and alternative measures, and potential health outcomes of interest are provided for each exposure type. Another column lists the preferred data sampling modality method to be used by the NCS with optional approaches for the Committee’s review and consideration in adjoining columns.

The intent of the NCS is to have the highest quality biospecimen or environmental sample available, but the NCS may not have the resources to analyze each specimen or sample for each analyte in real or near time. Consequently, processing and storage of the specimen or sample are important considerations that will be based on analyte stability. The table does not represent all the specimens and samples the NCS intends to collect but is limited to those specimens and samples targeted to assess selected environmental exposures.

SAMPLE DESIGN—CURRENT PLAN FOR MULTIPLE COHORTS

Geographic Area Sampling

The original NCS plan called for about 110 primary sampling units (PSUs) consisting of whole counties or groups of counties, with each PSU expected to generate about 2,000 births over the recruitment period based on 1999-2002 birth statistics, and with stratification by county size, percent black, Hispanic, Asian, and low-weight births. After sampling of segments (groups of census blocks), and door-to-door household screening, the PSUs were expected to generate about 1,000 births for inclusion in the NCS over a 4-year recruitment period.

The NCS has abandoned the use of house-to-house screening methods due to projections based on the unexpectedly high and unsustainable resources that were expended in the initial phase of the Vanguard Study. The NCS is still planning to base the Main Study on a probability based sample with current plans to start with a probability based geographic area sample. The NCS is considering options for generating a list frame and selecting PSUs with the goal of increasing operational efficiency while maintaining a diversity of environments. One such option is to increase the size of each PSU (e.g., groups of larger counties, even entire metropolitan areas) and reduce their overall number, perhaps to 40-45 PSUs. These larger PSUs could retain a diversity of exposures (think of Montgomery County, MD, with a population of close to 1 million residing in rural, suburban, and urban environments). Taking advantage of the heterogeneity within very large counties or among several counties could increase the catchment area and also the environmental diversity while lowering costs. The optimal balance
between number of PSUs, number of births per PSU, and environmental variety is not yet known. Different contract teams are working on scenarios, but this will not be resolved prior to the workshop and therefore will not be presented or discussed.

The important point for the remaining discussion is that the NCS is currently planning an area probability sample of PSUs that is expected to generate 100,000 live births for participation in the NCS.

**The Birth Cohort**

Sample of hospitals and birthing centers, followed by a sample of women giving birth at selected centers, tentatively planned as about 45,000 participants of the overall sample. Planned 2-year initial recruitment period.

Within the current proposal, for each selected geographic PSU a list of all hospitals and birthing centers will be prepared as a sampling frame for the birth cohort. Based on data from 2006, roughly 98 percent of all births in the United States take place at hospitals or birthing centers. A random sample of hospitals and birthing centers will be selected, with probability proportional to the number of births, and recruited to participate in the study. All women who give birth at the selected hospitals and birthing centers during specific times within the planned 2-year initial recruitment period will be eligible to be sampled while at the hospital, regardless of whether they live within the selected PSU or not. A systematic sample of women giving birth will be selected.

The NCS has documented multiple studies that recruit new mothers (and fathers) in the hospital and some that collect specimens (the Fragile Families Study is one of these). The acceptance rate is high and in some cases over 90 percent. The NCS has several strategies for collecting the relatively few specimens of interest (maternal blood and urine, cord blood, placenta, and perhaps an infant second dried blood spot following newborn screening), including collection from all sampled women during the recruitment windows and then discarding specimens from women who do not consent. The NCS is also piloting a few methods in the Provider Based Sampling Vanguard sites to give some empirical data on acceptance, logistics, and costs. It is also possible in the birth cohort to attempt to collect medical records not only from the hospital or birthing center, but also from the sample member’s prenatal care provider (if any).

The birth cohort will be a nationally representative sample of births in the United States. It can include stillbirths as well as live births.

While the recruitment of a relatively unbiased sample at acceptable cost is attractive, a knowledge gap that needs to be addressed is prenatal exposure data. An essential question for the NCS is what is the scope and integrity of data that can be captured indirectly that would inform the prenatal history for a child recruited in the birth cohort.

The birth cohort mothers can be followed over time and subsequent children added to the sample. This provides an opportunity to include a sibling cohort, and to collect both

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4 The duration of the recruitment period is still under consideration.
preconception and prenatal measures for some births. Information from the Fragile Families study indicates that about 4.5 percent of women who have a child have another within 18 months, and 25 percent have another within 3 years.

Applying a similar analysis to the NCS would project the following scenario. For a sample of 45,000 births recruited over a 2 year period, allowing for about 350 stillbirths (1 in 150 of births (live and still)) and, say, 4150 attriters after the hospital interview, would leave 40,500 in the sample (we are assuming that women at the hospital would be oversampled to allow for refusals to participate). Of these 40,500, about 10,000 would be expected to have another child within a 3 year follow up recruitment period. The subsequently born children could have prospective documentation of preconception and prenatal exposures.

The Prenatal Cohort

Sample of prenatal care providers linked to sampled hospitals or birthing centers, followed by a sample of women who visit a prenatal care provider and expect to deliver at one of the selected hospitals or birthing centers, tentatively planned as about 45,000 of the overall sample.

The primary purpose of a prenatal cohort is to obtain prospectively collected exposure data. There is some evidence that exposures within the first 8 weeks of pregnancy are the most critical. However, a prenatal sample enrolled from community care providers is unlikely to recruit very many women this early in their pregnancy. It has been estimated that at 8 weeks, only about 10 percent of pregnant women may have sought prenatal care, and these are likely to be those seeking fertility assistance, or those who are trying to get pregnant or have pre-existing medical conditions and are monitoring. The prenatal cohort could, however, provide a reasonable sample of women in their third trimester of pregnancy.

The NCS will work with hospitals and birthing centers selected into the sample to identify the prenatal care providers including clinics, family practitioners, midwives, etc. that refer women to the hospitals and birthing centers. A sample of these prenatal care providers will be selected, using probability proportional to number of births. All women who are expected to give birth in one of the selected hospitals or birthing centers are eligible to be selected into the sample.

The NCS is currently exploring several options in the field with the Provider Based Sample Vanguard sites, including working with county medical societies and other professional societies and licensing bureaus as well as using birth records (where available) to construct a list of prenatal care providers in the PSU. Birth records are available in some sites, but not all sites. The logistics and resources required to prepare sampling frames of prenatal care providers as documented in the NCS Vanguard Study experience combined with information from other studies and the desire to work with selected hospitals and birthing centers for collecting birth information led to the approach described above.

The NCS’s Vanguard pilot study data indicate that the proportion of women that providers inform about the study and that actually enroll is between 35 and 50 percent. In other words, for the most efficient providers, about 1 in 2 women enroll, and for others it is about 1 in 3.
Prenatal cohort mothers can also be followed over time and subsequent children added to the sample. This provides an opportunity to include preconception measures and additional prenatal measures for some births as described in the birth cohort example. See above for further discussion.

It is not clear what population a prenatal care cohort would represent on a probability basis. If the prenatal cohort were limited to women visiting the sample of prenatal care providers within a specified time period who were in their third trimester, then the enrolled population would likely cover close to the entire population of pregnant women who receive prenatal care. However, the NCS would not be able to obtain measures of exposures earlier in the pregnancy except to the extent that medical records contained relevant information. If the cohort were extended to include all women visiting the sample of prenatal care providers within a specified time period, then its representation of women in their first or second trimesters would be incomplete and could be biased given that women vary in the stage of pregnancy at which they seek prenatal care. In either case, the prenatal cohort is likely to have the measures most uniform for women in the third trimester. Although the proportion of women who receive prenatal care is relatively high, there are women who for multiple reasons do not receive prenatal care. Women who do not receive prenatal care could only be enrolled into the Study at a hospital or birthing center.

**Preconception and special-purpose cohorts**

Currently, about 10,000 sample cases are reserved for these, as yet unspecified, cohorts.

Neither the birth nor the prenatal care provider cohort can obtain information on preconception exposures for first order births (except for what may be available in medical records for some sample members), nor will they necessarily include geographic areas of special interest (e.g., environmental “hot spots”, such as areas where natural gas fracking is under way). The originally proposed design of household screening was intended to generate a preconception sample but proved infeasible on grounds of excessive costs and time for recruitment. Following women in one or both cohorts will generate samples of subsequent births that occur within a window (of 2-3 years) that will provide both preconception and prenatal exposures. In addition, it might be possible to consider some special cohorts that could be sampled purposively or on a probability basis. For example, it might be useful to identify a small number of known environmental “hot spots” and seek to enroll all or a large sample of women of child bearing age at these locations. This cohort will be a convenience sample in addition to the other enrolled participants and is not intended as a topic of discussion for the workshop.

**SAMPLE DESIGN—Questions for Session 2 Discussion**

1) What should be the criteria for the cohort allocation decision and what evidence is available to support an assessment of each criterion? Examples include
   a) Recruitment costs, which include the costs of constructing the frame and the relative costs and efficiency of enrolling a participant;
   b) Generalizability. What population is being represented?
c) Extent of exposures and other information that can be gathered. By definition, a birth cohort will have more limited data on prenatal exposures than a prenatal cohort, while a prenatal cohort will have less information on prenatal exposures (and much less information on preconception exposures) than the cohort of subsequent births to already enrolled mothers or a separate preconception cohort.

2) What should be the allocation of sample cases among the various cohorts? Assume that 10% of the sample is reserved for preconception and special studies; then, the allocation involves the remaining 90,000.
   a) One option is the current proposal which is about a 50-50 split or 45,000 participants in each.
   b) Another option is something like an 80-20 split allocated between birth and pregnancy, with the pregnancy sample used to form the basis for imputing prenatal exposures (after using medical records for the mothers to get as much prenatal information as possible).
   c) Yet another option is like an 80-20 split allocated between pregnancy and birth, with the birth sample used to form the basis for providing generalizability to the data analysis.
   d) One extreme could be the entire initial enrollment allocated to the birth cohort, with studies of prenatal and preconception exposures using primarily the 25 percent cohort of subsequent births to originally enrolled mothers.
   e) At the other extreme, most of the sample could be allocated to the prenatal cohort with a small birth sample consisting of women who did not receive any prenatal care and are enrolled at the hospital.

**IMPUTATION AND ESTIMATION IN PROPOSED DESIGN—Questions for Session 3 Discussion**

Given the study design proposal above, and using the example cohort proportions proposed in the Session 2 questions, what enhancements can be made to address the following estimation and imputation challenges:

1) To combine the data from the cohorts to increase the effective sample size:
   a) What should the parameters for the sampling procedure, for example, using the same PSUs, be in order to enhance data combination?
   b) What sampling protocol deviances could impact the ability to combine data?
   c) What considerations (if any) for sample weights need to be taken into account in the sample design? Specifically when certain groups may be oversampled in one cohort (such as women receiving no prenatal care who would only be present in the birth cohort), should any special considerations be made for the sampling probability in order to construct appropriate weights?

2) Data imputation will be required at different levels of the proposed design, particularly for assessing prenatal exposure.
   a) What threshold level of imputation of prenatal exposure data is acceptable?
b) What should the proposed trigger for the more expensive comprehensive sampling look like—should this be a random sampling, event based trigger, or a validation subset or some combination?

3) Recalibration of the sample in the future (to be discussed if time permitting). For a study with duration as long as the NCS, additional participants may need to be added to the cohort in order to maintain representativeness or enhance statistical power. What options for cohort replenishment are acceptable, and would these be efficient?

DEVELOPING A DECISION METHOD FOR MOVING FORWARD – Question for Session 4 Discussion

From today's discussion, can you synthesize the trade-offs among factors, issues, and values that need to be balanced and considered by NCS leadership?

Tables, white papers, and commentary that may bear on the construction of the sample for the NCS and the collection of environmental measures can be found on its website for the workshop:
http://www.nationalchildrensstudy.gov/research/workshops/Pages/nationalacademyofsciencesworkshop.aspx