National Academies Releases Assessment of National Children's Study; NIH Director Puts Main Study on Hold

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On June 16, the National Academy of Sciences' (NAS) Panel on the Design of the National Children's Study and Implications for the Generalizability of Results released its assessment of the National Children's Study (NCS). While the Panel endorsed a number of elements in the proposed design, "because of a lack of information and related reasons, … it concluded that achieving a scientifically grounded and cost-effective design and implementation for the Main Study will require an expansion of the scientific expertise in the [NCS] Program Office, the establishment of an authoritative multidisciplinary oversight structure to review the Program Office's decisions, and regular independent outside review." The NAS panel was chaired by Greg Duncan, University of California, Irvine.

The National Children's Study was originally authorized by the *Children's Health Act of 2000*. It is being implemented by a program office within the *Eunice Kennedy Shriver* National Institute for Child Health and Human Development (NICHD). The Study is intended to be a "longitudinal observational birth cohort study to evaluate the effects of chronic and intermittent exposures on child health and human development in U.S. children."

Following NAS's discharge of its report, National Institutes of Health (NIH) director Francis Collins released a statement acknowledging the "significant concerns about the design, management, and oversight" of the NCS and that he takes them very seriously. Based on the report, Collins indicated that he was putting the Main Study on hold, "effective immediately, in order to determine the best path forward." According to the NIH director, a number of "critical questions" need to be answered:

1. Is this study, as currently outlined, actually feasible in the face of significant budget constraints?
2. If so, how do we move forward to implement necessary changes, including some of those outlined in the NAS report?
3. If not, are there new methods to answer key research questions that are most important to pediatric health today that capitalize on research and technology advances developed in the intervening years since the inception of the study?

To answer the questions, Collins announced that he is "assembling a team of experts in pediatrics, clinical study design, environmental science, genomics, computer bioinformatics, and other relevant areas within the next several weeks" to advise him. He emphasized that the deliberations regarding the NCS' future "will be transparent and embrace scientific and public input."

There have been several iterations of the NCS' study design. Implementation of the study as envisioned—that is, the collection of a broad range of environmental exposure measures for a national probability sample of approximately 100,000 children followed from birth or before birth to age 21—has been delayed several times in the approach to the study, including recruitment. The most recent review of the revised study design was requested by Congress in 2013 and stipulated that the NIH could not issue contacts for the NCS Main Study until 60 days after completion of the NAS review (see Update, September 9, 2013). Congress specifically called for a comprehensive review with a report outlining proposed methodologies and whether those methodologies would product "scientifically sound results that are generalizable" to the U.S. population and subpopulations.

NAS Panel's Recommendations

The Panel made 21 recommendations dealing with the overall design of the NCS; proposed supplemental samples for the NCS; the loss of opportunity to recruit more prenatal cases if the preconception group is retained; the importance of beginning data collection during the prenatal period; probability sample design, size, and composition; content and visit schedule; release of the data; field costs; and leadership of the NCS.

The recommendations as outlined in the report include:

1. The scientific framework for the NCS should be based on current understanding of the determinants of children's health and development and an informed consideration of the likely future trajectory of scientific discovery. The paradigms of developmental biology and life-course epidemiology, coupled with findings from other social and behavioral sciences research on the prenatal and early life periods, should guide development of the design for the Main Study.
2. The Main Study should use a national probability sample with the largest feasible sample size and an approximately equal probability of selection design, and it should recruit nearly the entire cohort as early in pregnancy as possible in order to facilitate scientific discovery during and after NCS data are gathered.
3. The Main Study should use valid and standardize data collection measures and methods, while maintaining flexibility to revise or develop new instruments.
4. The proposed strategy for the Main Study to collect detailed data on children's health status, conditions, symptoms, and behaviors should be followed to the extent possible, taking into account constraints of costs, operational feasibility, and the need to not overburden respondents.
5. The supplemental sample of preconception exposure information on 5,000 first-birth children being proposed should be dropped because of high costs, the lack of any evidence of the value of such a sample, the lack of detailed plans for both selection and analysis, and potential limitations in the proposed data collection schedule.
6. The other supplemental convenience samples proposed for the Main Study should be dropped from the design, including samples of children exposed to natural disasters or geographically defined environmental exposures, samples of additional members of disadvantage groups, and samples of siblings born outside four-year recruitment period. The potential added value of the supplemental sample cases is less than the value of the additional cases in the probability sample they would replace, specifically, the value of the additional prenatal cases in the probability sample.

7. The Main Study sample should be stratified by characteristics that will achieve variability in socioeconomic status within important population groups to support analysis of health disparities, as well as achieving variability in environmental exposures and geography to support analysis of relationships between exposures and health outcomes.
8. NCS should be stratified by characteristics that will achieve variability in socioeconomic status within important population groups to support analysis of health disparities, as well as achieving variability in environmental exposures and geography to support analysis of relationships between exposures and health outcomes.
9. A detailed plan for sampling recruitment, and minimizing attrition bias for the Main Study should be fully developed and evaluated by sampling and survey experts independent from the NCS and approved by the proposed independent oversight committee before the study moves forward.
10. Prior to proceeding with the Main Study, the NCS should develop scientifically well-grounded exemplar hypotheses that should be used to guide and evaluate decisions regarding the NCS design and data collection schedule and domains.
11. Because the hypotheses will change over time, the NCS should implement a strong and public process to revise and develop new exemplar hypotheses to guide future study implementation, engaging with the extramural and intramural research communities.
12. The Main Study should collect data during the prenatal period at multiple times for as many of the study participants as the budget will allow.
13. The panel does not endorse the current proposal for a substantial birth enrollment stratum. If the NCS retains such a stratum, the NCS should conduct a full pilot test of recruitment and data collection during the birth visit before the Main Study is implemented.
14. The NCS should document and provide justification development of the data collection schedule, content, and methods now and going forward. The documentation should be sufficient to guide use of the study data by future researchers.
15. The NCS should finalize the study visit data collection protocols that it intends to use for the Main Study, including questionnaires and other measurement, at least through age one, and then pilot test the protocols before implementing the Main Study. The protocols and findings of the pilot tests should be peer reviewed and approved by the proposed independent oversight committee prior to initiating the Main Study.
16. The relevance to health disparities should be an explicit criterion for selecting constructs that will be assessed as part of the Main Study, the measures that will be used to assess them, and the timing of the assessments. The NCS should obtain input from experts on health disparities in childhood as part of the documented process through which the measures for inclusion are selected and which should approved by the proposed oversight committee.
17. The NCS should consider producing an “early release” version of the data from the Main Study that includes data collected in the early years of each wave’s data collection cycle and make those data available to analysts under the terms of restricted access data centers.
18. Given the goal for the NCS to understand the links of environmental exposures to child health and development and its cost structure, if major reduction s in the cost of the study needs to be made, they should be reductions in sample size rather than exposure domains. The NCS should also reconsider whether to oversample minorities in order to maintain the ability to evaluate health disparities with a reduced sample.

19. NICHD should consider and implement one or more means to enhance the scientific expertise of the NCS program office by recruiting experts in relevant fields from within the NIH, other federal agencies, and outside government. NICHD should consider contracting with experts outside of government to work part time on the NCS as a means to bolster the scientific expertise that is focused on the NCS.
20. NIH should strengthen the oversight and leadership of the NCS by establishing an oversight scientific management structure to include a full range of relevant expertise, with review and approval authority for NCS design decisions.
21. The NCS program office should establish a mechanism to conduct periodic comprehensive outside scientific reviews of the design and operations of the Main Study. To facilitate the work of such a committee and transparency for the study more generally, the NCS program office should promptly post on its website all scientific studies conducted for the NCS.