

The National Children's Study: An Introduction and Historical Overview

Mark L. Hudak, MD,^a Christina H. Park, PhD,^b Robert D. Annett, PhD,^c Daniel E. Hale, MD,^d Patricia M. McGovern, PhD, MPH,^e Thomas J. McLaughlin, ScD,^f Nancy Dole, PhD,^g Jill L. Kaar, PhD,^h Marion J. Balsam, MD^b

abstract

The National Children's Study (NCS) was an ambitious attempt to map children's health and development in a large representative group of children in the United States. In this introduction, we briefly review the background of the NCS and the history of the multiple strategies that were tested to recruit women and children. Subsequent articles then detail the protocols and outcomes of 4 of the recruitment strategies. It is hoped that lessons learned from these attempts to define a study protocol that could achieve the initial aims of the NCS will inform future efforts to conceptualize and execute strategies to provide generalizable insights on the longitudinal health of our nation's children.



^aDepartment of Pediatrics, University of Florida College of Medicine-Jacksonville, Jacksonville, Florida; ^bNational Institute of Child Health and Human Development, Bethesda, Maryland; ^cDivision of Child Development, University of Mississippi Medical Center, Jackson, Mississippi; ^dDivision of Endocrinology and Diabetes, University of Texas Health Sciences Center, San Antonio, Texas; ^eDivision of Environmental Health Services, University of Minnesota School of Public Health, Minneapolis, Minnesota; ^fDepartment of Pediatrics, University of Massachusetts, Worcester, Massachusetts; ^gCarolina Population Center, University of North Carolina, Chapel Hill, North Carolina; and ^hDepartment of Pediatrics, School of Medicine, University of Colorado Denver, Denver, Colorado

Dr Hudak conceptualized the manuscript; acquired, analyzed, and interpreted the data; drafted the initial manuscript; critically reviewed and revised the draft and subsequent manuscripts; and coordinated incorporation of the critical review and suggested revisions of all authors; Dr Park acquired, analyzed, and interpreted the data, and critically reviewed and revised the draft and subsequent manuscripts; Drs Annett, Hale, and McGovern conceptualized the manuscript, interpreted the data, and critically reviewed and revised the draft and subsequent manuscripts; Drs McLaughlin and Dole interpreted the data, and critically reviewed and revised the draft and subsequent manuscripts; Dr Kaar critically reviewed and revised subsequent manuscripts; Dr Balsam interpreted the data and critically reviewed and revised the draft and subsequent manuscripts; and all authors approved the final manuscript as submitted.

DOI: 10.1542/peds.2015-4410B

Accepted for publication Mar 1, 2016

Address correspondence to Mark L. Hudak, MD, Department of Pediatrics, University of Florida College of Medicine—Jacksonville, 653-1 W 8th St, Jacksonville, FL 32209. E-mail: mark.hudak@jax.ufl.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2016 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Supported in part by NICHD contracts. Funded by the National Institutes of Health (NIH).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

To cite: Hudak ML, Park CH, Annett RD, et al. The National Children's Study: An Introduction and Historical Overview. *Pediatrics*. 2016;137(s4):e20154410B

EARLY HISTORY OF THE NCS

In the 1990s, a diverse group of scientific disciplines highlighted the imperative for the United States to fund a large, national, longitudinal study of children's health, growth, and development. The rising prevalence of some chronic childhood diseases (eg, asthma and autism) and a surge in the prevalence of some adult diseases presenting in children (eg, type II diabetes) pointed toward environmental exposures as potent etiologic factors. These advocacy efforts culminated with congressional passage of the Children's Health Act of 2000. Section 1004 of this legislation authorized the National Institute of Child Health and Human Development (NICHD) "to conduct a national longitudinal study of environmental influences (including physical, chemical, biological, and psychosocial) on children's health and development."¹ Furthermore, Congress explicitly instructed the NICHD to follow a prospective cohort composed of diverse populations of children from birth to adulthood to investigate how environmental factors might influence children's well-being for the better or for the worse, and enabled the study of prenatal exposures and health disparities. Congress anticipated that the main study design would allow extrapolation of findings so that refinements in public policy could optimize the health and safety of all children in the United States. In the early 2000s, the National Institutes of Health (NIH) sponsored serial scientific workshops and funded a variety of expert reports on issues related to study design. In 2002, an independent NCS Federal Advisory Committee was empaneled and in 2003 the NIH established a dedicated NCS program office (PO) to oversee study design and implementation.

In June 2004, the NCS PO, the Federal Advisory Committee, and an NCS Sampling Design Workshop Panel agreed upon the desirability of

enrolling a national representative probability sample of children. In conjunction with the National Center for Health Statistics, the NCS undertook development of this sample from the 3141 US counties or county equivalents by using a multistage area probability sampling design in consideration of metropolitan status, geography, annual number of births, and other demographic characteristics.² In all, this methodology identified 110 primary sampling units (PSUs) in 43 states to yield 105 study locations. Most, but not all, PSUs were single counties. Smaller geographic areas within each county, known as the secondary sampling units or segments, served as the geographic basis for recruitment of participants. Over 4 years, the study's designers envisioned enrolling 100 000 infants.

Per the congressional mandate, initial designs for the NCS placed strong emphasis on elucidating interactions between environment exposures and child health from the prenatal period through at least 21 years of age. To accomplish this goal, the NCS planned to collect and bank serial environmental samples and biological specimens for each mother-child dyad to allow later measurement of exposures and genetic and epigenetic analyses.

INITIAL VANGUARD STUDY

After vigorous discussion about the relative scientific, operational, and economic merits of different methodologies, the NCS PO selected household-based door-to-door recruitment, rather than an alternative proposal for provider-based recruitment (PBR), as the methodology for the pilot study. It was reasoned that the former method was the accepted gold standard for obtaining a representative national probability sample and it allowed a more robust opportunity to gather environmental samples

and biological specimens in the preconception and early prenatal periods, thus improving the ability to discriminate the effects of environmental exposure at the vulnerable periods near the time of fertilization and during fetal development. The NIH issued contracts in 2005 to 7 academic study centers (SCs) and a coordinating center to start the study's data collection effort. Two subsequent waves of contracts (to 23 additional SCs in 2007 and another 26 in 2008) anticipated broader implementation of the NCS pending results of the Initial Vanguard Study. Between January and May 2009, the NIH NCS PO initiated data collection for the Initial Vanguard pilot study in 7 PSUs that included 10 counties (the Initial Vanguard Centers, or IVCs) with broad geographic distribution and urban/rural variation to evaluate the performance and feasibility of household-based recruitment.

The 7 IVCs had regular meetings with the NCS PO and shared strategies and materials that proved most effective in their communities. Over time, the IVCs incorporated community outreach and engagement activities within the secondary sampling units in which recruitment occurred. Outreach to and collaboration with the medical community where eligible women sought prenatal care or delivered their infants was essential for multiple reasons: some providers assisted with the collection of NCS ultrasounds and facilitated prenatal recruitment and visits; collection of NCS birth outcome data and specimens at the hospitals required cooperation from clinicians, hospital administrators, and research gatekeepers; and it became apparent that many women asked their clinicians if they should participate in the study. The IVCs tested and applied different approaches in their settings to increase recruitment rates as the field operations evolved.

The final outcomes of the IVCs were initially summarized by Baker et al.³ Across the 7 IVCs, over 75 000 dwelling units were eligible for enumeration in the sampled segments; 89% were enumerated; and 44% of the dwelling units housed age-eligible or pregnant women. Among age-eligible women, 88% completed the screener that provided a “probability of pregnancy,” and 61% of study-eligible women consented to participate in the study. These investigators also highlighted the value of integrating community and provider outreach and engagement activities into study procedures. Trasande et al⁴ further detailed the preliminary experience of community-based recruitment at the Queens County IVC.

THE ALTERNATE RECRUITMENT STRATEGY SUBSTUDY AND PROVIDER-BASED SAMPLING RECRUITMENT

Late in 2009, the NIH NCS PO conducted an interim efficacy analysis of the pilot study. A document released by the NCS PO entitled “Schema for the Alternate Recruitment Strategy Substudy” (May 25, 2010) noted that while the target enrollment for the initial 12 months of data collection for all IVCs was 1750 pregnant women, only 800 had been enrolled. Shortly thereafter, the PO decided to explore different recruitment methodologies for the Main Study. Active recruitment of women at the IVCs was halted in September 2010, although passive recruitment continued through February 2012. In September 2012, participant retention and follow-up activities for the 7 IVCs were transferred to a contracted survey research organization.

On December 23, 2009, the NCS PO requested that funded SCs submit letters of intent to participate in the evaluation of 3 alternate recruitment strategies (ARSs) for the main study. These methodologies

were enhanced household-based recruitment (EHBR); recruitment by direct outreach (DO); and PBR. This announcement stated that the ARS substudy would “evaluate (1) alternative strategies for recruitment, (2) study visit assessments (those events and assessments that are scheduled during study visits), and (3) study logistics and operations,” with the primary goal to compare the feasibility, acceptability, and cost of the 3 methodologies. Funded centers submitted competitive letters of intent that outlined special factors that investigators believed might enhance the success of 1 or more of the 3 recruitment strategies in their counties. The NIH PO selected 10 SCs to participate in each recruitment strategy.

In the interval between the suspension of active recruitment at the IVCs and the resumption of study enrollment in November 2010 at the ARS SCs, the NCS PO made 3 other significant changes in study procedures. First, the NIH PO chose to discontinue the contracted coordinating center and its proprietary system for data collection and management in favor of a strategy of “facilitated decentralization,” on the basis of open-source systems. Each operational SC assumed responsibility for either developing database and data entry programs or allying with an outside vendor or other SCs to acquire these capabilities. Second, because there was no longer a centralized coordinating center, it became the responsibility of the SCs to fully implement the rigorous standards set by the Federal Information Security Management Act (FISMA) of 2002 pertaining to local data collection, storage, and transmission activities. At the start of the study’s data collection, the IVCs had been subject to FISMA requirements, although their meeting these requirements was significantly less complicated

because the contracted coordinating center managed the entry interface and storage of the study data and another subcontractor performed the FISMA readiness assessments at the IVCs. Decentralized data entry, storage, and submission at the time the ARS SCs were engaged to collect data triggered higher levels of FISMA security measures for the ARS and IVC SCs. The NIH made additional resources available to each SC to assist with meeting these requirements. In retrospect, the mandate for FISMA adherence prepared many SCs to be more competitive in later grant applications that required demonstration of FISMA capabilities. However, the combination of the 2 directives exceeded the scope of work in the initial award, delayed initiation of ARS field activities, and impeded timely and accurate data submission to the central data repository. A third change was the implementation of a tiered Federated Institutional Review Board (IRB) model. At the discretion of an investigator’s institution, the NIH allowed its own internal IRB to function as that SC’s “Federated” IRB of record.

The first 30 ARS SCs initiated field operations between November 2010 and February 2011. The PO tracked recruitment outcomes by combining individual SC statistics tailored for each of the 3 ARS on a biweekly basis. Early results were judged to favor the PBR methodology and the PO began to work with a sample design contractor to develop a fourth recruitment strategy designated as provider-based sampling (PBS). By October 6, 2011, the PO had compiled preliminary data for the 30 ARS SCs that allowed a direct comparison of recruitment efficacy and an indirect comparison of cost across the 3 ARSs. For comparison, analogous data for the IVCs showing good concordancy between preliminary⁵ and final³ analyses are also shown in Table

TABLE 1 Assessment of Efficacy of Recruitment

	IVCs: Preliminary Data as of September 2010 ⁵	IVCs: Final Data as of September 2010 ³	ARS: Data as of October 6, 2011		
	Household-Based Recruitment	Household-Based Recruitment	Provider-Based	DO	Enhanced Household-Based
Identified women eligible by age and geography	32 740	34 172	2340	12 535	22 687
Pregnancy screens	30 063	30 062	1598	10 768	15 050
Study eligible women	2229	2285	1435	1831	2113
Enrolled (consented) women	1397	1399	1152	1497	1311
Birth visits	594	594	347	113	293
Cumulative weeks in field	515	515	313	355	379
Number of women enrolled per week	2.7	2.7	3.7	4.2	3.5
Enrollees per 100 women identified to be eligible by age and geography, %	4.3	4.1	49.2	11.9	5.8

1. These data demonstrated that enrollment efficiency was highest in the PBR substudy, in which far fewer contacts with potentially eligible women were needed per participant enrollment. Based on these findings, the PO advised these 30 ARS SCs to cease active recruitment of new participants by November 2011 and passive recruitment by February 2012 while it moved forward with plans to develop and launch the PBS methodology at an additional 3 SCs. After November 2011, the focus of the 30 SCs within the ARS substudy shifted to participant retention.

During the course of the EHBR, DO, and PBR substudies, many but not all SCs actively engaged in intense quality improvement activities within each recruitment strategy. The IVCs vitally assisted ARS SCs by providing guidance, materials, and lessons learned about study protocols and community and provider outreach and engagement enhancements. The DO investigators and staff received intense training by using rapid plan-do-study-act cycles designed to optimize participant recruitment and retention and improve operational efficiencies. Later, many centers within the EHBR and PBR groups chose to participate in a

Collaborative Improvement Network (CoIN) that fostered creativity, learning, and camaraderie across research teams with the goals of improving participant recruitment and retention. Notable outreach, engagement, and recruitment strategies developed or refined by the CoIN included obtaining permission to locally brand and distribute a highly engaging cartoon advertising the NCS that was produced by 1 of the initial IVCs; creating models for training and supporting champions in childbirth education and parenting groups to inform women about the NCS; developing partnerships with early learning centers and day care centers; cosponsoring baby showers to recruit pregnant women into the study; and creating a Partnership Action Index to facilitate community relationship building. Specific strategies developed by the CoIN to enhance data collection in the DO ARS included mailed (versus telephone) pregnancy self-screeners with small incentives (versus none) to determine study eligibility, as well as scripts for screening, enrolling, and converting women to various levels of study participation.

Field operations at the 3 PBS SCs began in November 2012. Unlike

the 4 preceding methodologies, PBS consisted of a multilevel probability design that established a prenatal provider sampling frame from which a sample of providers was identified. This list included all possible prenatal care providers (eg, physicians, regardless of specialty; midwives; nurse practitioners; and traditional healers) and was stratified by the number of annual births per provider location. Within the provider sample, pregnant women who had an initial prenatal care visit at the sampled provider were further sampled to be recruited into the study. To improve the representativeness and hence the generalizability of the PBS sample, a birth subcohort was added to the prenatal subcohort to include a random sample of women who had never accessed prenatal services or who had not visited a prenatal provider in the sampling frame.

Recruitment of women in 3 PBS SCs enrollment concluded by midsummer 2013. Participant retention and follow-up activities at all 40 SCs were transitioned to 4 Regional Operation Centers from June 2012 to September 2013. Recruitment and retention efforts continued until December 12, 2014. On that date, after intensive review by the Institute of Medicine⁶

and a Working Group of the Advisory Committee to the NIH Director,⁷ the Director of the NIH suspended further NCS field operations.⁸ The director stated that the goals of the NCS could be accomplished through existing funded grants and focused investment in new research plans.

The ensuing series of manuscripts describe the 3 ARS substudies and the PBS methodology: their unique approaches, their study populations, the major recruitment outcomes, and the lessons learned for each of the 4 strategies. A fifth manuscript details the impact of community outreach on recruitment at DO SCs. Within each manuscript, the authors have provided a record of the success of each recruitment strategy and pertinent details that offer a rich characterization of the implementation and relative effectiveness of these strategies in field operations.

RELEVANCE OF THE NCS EXPERIENCE

The NCS had promised to provide rigorous new insights into environmental determinants of children's health and common disease conditions. Its termination greatly disappointed the many scientists, public health officers, legislators, and study staff who had devoted substantial energy to plan and implement this ambitious study. Nonetheless, the results of the 5 different recruitment strategies still offer important lessons for future pediatric studies that may seek to efficiently assemble a nationally representative probability sample of mother-infant dyads.

The NCS pilot studies have shown that recruitment strategies that partner with obstetric providers can approximate a nationally representative probability sample with greater efficiency than the gold standard household-based recruitment method. Provider-based methodologies were the

most effective in securing a high percentage of enrollments in the first trimester, but as implemented did not recruit the preconceptional cohort (<5%) that many scientists have argued to be critical for measuring environmental determinants before the onset of pregnancy. In contrast, samples recruited by the household-based and DO approaches had over 25% representation from a preconceptional cohort.

Testing of the different strategies across diverse communities led to evaluation of methods for provider and community engagement and identification of palettes of best practices from which a subset can be chosen to interact best with the demographics of a particular community.

Many investigators believe that the goals of the NCS are even more relevant today than at its conception. Pediatricians and their families would gain much with a more robust understanding of the environmental determinants of children's health and disease. Pediatricians were key supporters of the NCS. Through familiarization with the accomplishments as well as the failures of the NCS, pediatricians can be better advocates for future proposals of longitudinal studies that are cost-effective and scientifically valid.

ACKNOWLEDGMENTS

The Writing Team sincerely thanks the thousands of mothers, fathers, siblings, and other family members who altruistically supported the concept of a National Children's Study that would inform us about children's health and development and so improve the outcomes of children yet to be born. We also thank thousands more community members who contributed to many local NCS activities. We are also grateful to hundreds of fellow investigators across the SCs with

many of whom we have established not only continuing professional relationships but also friendships.

ABBREVIATIONS

ARS:	alternative recruitment strategy
CoIN:	Collaborative Improvement Network
DO:	direct outreach
EHBR:	enhanced household-based recruitment
FISMA:	Federal Information Security Management Act
IRB:	institutional review board
IVC:	Initial Vanguard Center
NCS:	National Children's Study
NICHHD:	National Institute of Child Health and Human Development
NIH:	National Institutes of Health
PBR:	provider-based recruitment
PBS:	provider-based sampling
PO:	program office
PSU:	primary sampling unit
SC:	study center

REFERENCES

1. The Children's Health Act of 2000, Pub. L. 106-310, 114 Stat. 1101 (Oct. 17, 2000)
2. Michael RT, O'Muircheartaigh CA. Design priorities and disciplinary perspectives: the case of the US National Children's Study. *JR Stat Soc.* 2008;A171(part 2):465-480
3. Baker D, Park C, Sweeney C, et al. Recruitment of women in the National Children's Study Initial Vanguard Study. *Am J Epidemiol.* 2014;179(11):1366-1374
4. Trasande L, Andrews HF, Goranson C, et al. Early experiences and predictors of recruitment success for the National Children's Study. *Pediatrics.* 2011;127(2):261-268
5. Hirschfeld S, Songco D, Kramer BS, Guttmacher AE. National Children's Study: update in 2010. *Mt Sinai J Med.* 2011;78(1):119-125

6. Duncan GJ, Kirkendall NJ, Citro CF, eds. *Panel on the Design of the National Children's Study and Implications for the Generalizability of Results. Committee on National Statistics, Division of Behavioral and Social Sciences and Education, and Board on Children, Youth, and Families, Institute of Medicine. National Research Council and Institute of Medicine. The National Children's Study 2014: An Assessment.* Washington, DC: The National Academies Press; 2014
7. National Children's Study (NCS) Working Group. Final Report – December 12, 2014. National Institutes of Health Advisory Committee to the Director. Available at: http://acd.od.nih.gov/reports/NCS_WG_FINAL_REPORT.pdf. Published December 12, 2014. Accessed September 28, 2015
8. Collins F. Statement on the National Children's Study. The NIH Director. Available at: www.nih.gov/about/director/12122014_statement_ACD.htm. Published December 12, 2014. Accessed September 28, 2015

The National Children's Study: An Introduction and Historical Overview
Mark L. Hudak, Christina H. Park, Robert D. Annett, Daniel E. Hale, Patricia M.
McGovern, Thomas J. McLaughlin, Nancy Dole, Jill L. Kaar and Marion J. Balsam
Pediatrics 2016;137;S213
DOI: 10.1542/peds.2015-4410B

Updated Information & Services

including high resolution figures, can be found at:
http://pediatrics.aappublications.org/content/137/Supplement_4/S213

References

This article cites 4 articles, 1 of which you can access for free at:
http://pediatrics.aappublications.org/content/137/Supplement_4/S213#BIBL

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
<http://www.aappublications.org/site/misc/Permissions.xhtml>

Reprints

Information about ordering reprints can be found online:
<http://www.aappublications.org/site/misc/reprints.xhtml>

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

The National Children's Study: An Introduction and Historical Overview

Mark L. Hudak, Christina H. Park, Robert D. Annett, Daniel E. Hale, Patricia M. McGovern, Thomas J. McLaughlin, Nancy Dole, Jill L. Kaar and Marion J. Balsam

Pediatrics 2016;137;S213

DOI: 10.1542/peds.2015-4410B

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://pediatrics.aappublications.org/content/137/Supplement_4/S213

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2016 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 1073-0397.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

