National Children's Study Assembly Meeting
Implementing the National Children's Study:
Scientific Progress, Challenges, and Opportunities
November 29–30, 2005
Omni Shoreham Hotel
Washington, DC

This meeting was held in conjunction with the National Children's Study, which is led by a consortium of federal agency partners: the U.S. Department of Health and Human Services (including the National Institute of Child Health and Human Development [NICHD] and the National Institute of Environmental Health Sciences [NIEHS], two parts of the National Institutes of Health, and the Centers for Disease Control and Prevention [CDC]) and the U.S. Environmental Protection Agency (EPA).

Day 1 Plenary Session

Welcome

Duane F. Alexander, M.D., Director, NICHD, NIH, DHHS

Dr. Alexander opened the plenary session and welcomed the participants to the fifth Study Assembly Meeting of the National Children's Study (Study). As Director, NICHD, it is Dr. Alexander's responsibility to lead and implement the Study. He declared this to be an exciting time for the Study because the many ideas and concepts that have been proposed, discussed, and evaluated over the past 4 years of planning are now being implemented through the Study Plan, the sample design and selection, the Vanguard Centers, and the plans for recruitment and retention at the 105 Study sites.

This scientific study will embrace the many opportunities provided by the improved ability to measure environmental factors—biological, physical, chemical, behavioral, social, and cultural—and the improved ability to perform genetic analyses. One of the greatest potential benefits of the Study will be a better understanding of gene-environment interactions. Because environmental health is an understudied area of pediatrics and child development, research is needed to determine how the environment interacts with a child's genetic constitution to influence developmental processes and ultimately determine health across the lifespan. The Study intends to overcome the obstacles and inadequacies of past studies to answer questions about the long-term impact of multiple exposures over a child's life. The Study will assess parents' exposures as well. The eventual goal is to modify exposures to ultimately promote better children's health and development. The Study is the key to filling the void in this critical area of pediatric research.

Within NIH, both NICHD and NIEHS have played key roles in planning the Study, as have EPA, CDC, and DHHS. With more than 40 departments and agencies involved in the planning and design, this is a government-wide study. With input and participation of the scientific and advocacy communities interested in children's environmental health and factors affecting health and development, this is a community-wide study. This meeting allows the scientific, advocacy,

and parental communities to provide input into the Study's implementation. The Study appreciates the valuable input and hopes that the scientific, advocacy, and parental communities appreciate the opportunities for input provided by the Study. The Study's greatest impact will be in the many, diverse communities across the United States.

The goal of this meeting was to describe the progress so far—in developing the Study Plan and moving toward a protocol, in selecting the sample and its methodology, in identifying the Study sites, in awarding contracts for the Vanguard sites and the Coordinating Center, and in developing information technology and data processing. In addition, principal investigators (PIs) from the seven Vanguard sites introduced their teams and characterized their sites.

Dr. Alexander acknowledged the uncertainties of future funding but assured participants of the certainty of the baseline planning funding for fiscal year 2006. Although many factors affect future funding, the Study will continue to demonstrate its dedication and determination by gathering information to improve children's health and well-being. Initial scientific findings from the Vanguard Centers should generate excitement to move the Study forward to full implementation. Dr. Alexander expressed his hope that the Study would answer many important questions, test critical hypotheses, and evolve beyond a strictly federal research effort.

Environmental Health Issues and the National Children's Study

William F. Raub, Ph.D., Science Advisor to the Secretary, Deputy Assistant Secretary, Office of Public Health Emergency Preparedness, DHHS

Dr. Raub described his experiences during the early conceptualization phases of the Study. The idea for an interagency collaboration to study environmental health and safety risks to children began in the 1990s and developed from interactions between the heads of EPA and DHHS. As enthusiasm for studying environmental exposures and health outcomes in children grew, the agency heads chose a very deliberate course of preliminary studies, field tests, and pilot analyses to build the case for a national study. Although this kind of study was very exciting, it was going to be very expensive. Other departments and agencies such as NIH and CDC were recruited to join the collaboration. Together, these departments and agencies created an evidence base upon which to build the case for a large longitudinal study of children.

Historically, large-cohort, long-timeframe, longitudinal studies have been worthwhile endeavors, despite initial concerns. Dr. Raub cited several examples of successful DHHS-funded "mega" studies that laid the groundwork for the Study: the Framingham Heart Study, the Human Genome Project, and the Multiple Risk Factor Intervention Trial. These large longitudinal studies have very much proven their value within the health and scientific communities. In particular, the Framingham Heart Study broadly affected human health in ways not foreseen at the start of the study. Many of the primary interventions in the Multiple Risk Factor Intervention Trial, such as controlling cholesterol, exercising, and eating "healthy," were eventually adopted by all study subjects, including controls, which improved their health but also affected the study outcome, with the secular trend overtaking the basic thesis of the study.

Dr. Raub explained that the Study will benefit from two externalities: genomics and environmental exposures. The recently completed International HapMap Project focused on single nucleotide polymorphisms (SNPs) and examined locations and associations of the estimated 10 million SNPs in the human genome. The outcome of the HapMap Project is a mechanism for whole genome association studies. Scientists hope to learn how SNP "tags" relate to disease development. The challenge is to then relate genomic and phenotypic information. The Study will create a rich body of phenotypic data and, when combined with emerging genomic information, will generate knowledge on gene interactions and phenotypic expression. Environmental influences on gene expression, growth, and development are important areas of focus in the Study. Researchers often know the hazards of certain exposures but cannot directly measure the effects of these exposures on humans. In the absence of data, researchers rely on exposure and risk estimates. The Study will provide the necessary data to move beyond estimates, and generating these data is one of the primary rationales for the Study. The Study will also generate new and vigorous methodologies to measure environmental exposures.

In concluding, Dr. Raub said that the Study is poised to produce a rich body of high-quality phenotypic information about early child development, some new and better tools for associating genomics with that evidence, and some new and better tools for determining environmental exposures. To the extent that these three elements can come together, they can reinforce one another conceptually and operationally, and they reinforce budget justifications.

A Strategic Juncture for the National Children's Study

Peter C. Scheidt, M.D., M.P.H., Director, National Children's Study, NICHD, NIH, DHHS

Dr. Scheidt reviewed the current status of the Study and described the focus of the meeting. He provided highlights of the Children's Health Act of 2000 (PL106-310), listed the lead federal agencies, and described the aims of the Study. The Study involves a large consortium of government departments and agencies, both within and outside the lead agencies. Because of this, the Study is an unprecedented government-wide collaboration. Dr. Scheidt credited the Interagency Coordinating Committee (ICC) for the success of this collaboration. Dr. Scheidt said that the Study planners embrace sequencing of the human genome and hope to interact with the Human Genome Project. Study planning to date has involved:

- A federally chartered advisory committee
- 22 Working Groups
- 28 completed workshops
- Pilot studies (10 completed, 12 in progress)
- Scientific reviews and white papers (12 completed, 4 in progress)
- More than 2,500 individuals contributing to the scientific development thus far.

Details on the Study's planning efforts can be found at http://www.nationalchildrensstudy.gov/ and in publications such as *Environmental Health Perspectives*.

Dr. Scheidt reviewed the status of implementing the Study, including the Study sample and the selected Study sites. He noted that centers of excellence will conduct the Study because of their expertise and input, capability and facilities, and support and ownership. Center-based

implementation of a national probability sample is challenging and unique, requiring flexibility and adaptation to the scientific design, creativity, and strong, effective coordination. Dr. Scheidt compared Study sites and centers:

- Sites—geographic locations (counties) from which participants will be recruited
  - Selected by stratified probability sample of primary sampling units
  - 105 sites
- Centers—entities or institutions that will carry out the Study at the sites
  - Selected by a competitive process
  - Each will cover more than one site
  - 30–50 centers.

Dr. Scheidt characterized activities at the Study's Program Office:

- Transforming the Study Plan into the Study Protocol
- Establishing the infrastructure and machinery to carry out the Study
- Relating to interest in the Study at all levels
  - Public and potential participants
  - Communities
  - Local and regional organizations
  - Advocacy groups
  - Scientific community and organizations
  - The Administration and Congress
  - Internationally.

Interest and responses to the Study include the following media placements to date:

- 138 print placements
- 206 online placements
- 184 television placements
- 29 radio placements
- 557 total media placements with a total estimated audience of 49,624,799.

Dr. Scheidt noted that the responses and comments have been universally positive and supportive. He quoted several responses from Vanguard community members and listed some of the 49 organizations supporting the Study.

This Study Assembly Meeting was strategically placed at the intersections of planning for the Study, establishing the first centers to begin the Study, and preparing for the remaining centers to carry out the full Study. To this end, the goals of the meeting were to:

- Introduce the first Study centers (the Vanguard Centers)
- Share scientific developments and progress to date
- Address challenges in moving forward.

The challenges for the Study include developing a bold plan (the President's Task Force on Environmental Health Risks and Safety Risks to Children, January 2000, declared: "Be bold") and implementing the national probability sample.

Introduction of Vanguard Centers and Coordinating Center Principal Investigators

Peter C. Scheidt, M.D., M.P.H., Director, National Children's Study, NICHD, NIH, DHHS

Dr. Scheidt introduced the PIs for the seven Vanguard Centers and the Coordinating Center.

Vanguard Center for Duplin County, North Carolina: University of North Carolina at Chapel Hill (UNC) with Battelle Memorial Institute (Battelle) and Duke University (Duke)
PIs: Barbara Entwisle, Ph.D., and David Savitz, Ph.D., UNC

Dr. Entwisle presented an overview of Duplin County, NC. She noted that the Vanguard Center for this site is not located in that community. Duplin County is in the southeastern portion of the state, about a 2-hour drive from Chapel Hill. Duplin County is a rural, agricultural county with a population of about 52,000. Dr. Entwisle listed the county's largest employers in 2000. In that year, the largest employer was a pork and poultry production company, with 2,400 employees. Only four companies employed more than 1,000 people. Dr. Entwisle characterized Duplin County's racial diversity in 2000:

- White 58.7 percent
- African American 28.9 percent
- Some other race 10.9 percent
- Two or more races 1.1 percent
- American Indian/Alaska Native 0.2 percent
- Asian 0.2 percent
- Native Hawaiian or Other Pacific Islander 0.2 percent.

In 2000, Duplin County's ethnic diversity was characterized as 85 percent not Hispanic or Latino and 15 percent Hispanic or Latino (of any race). In 2005, the county's Hispanic population is estimated to be about 20 percent. Because of this diversity, language will be a challenge to implementing the Study in this site. Other than the county seat of Kenansville, there are 12 major towns in the county. Their distances from Kenansville range from 9 to 27 miles.

The 2003 female population by age was estimated as follows:

Age Range (Years)	Number
12–17	2,029
18–24	2,144
25–29	1,811
30–34	1,794
35–39	1,971
40–44	1,826

The number of Duplin County resident births for 1998–2003 is as follows:

Year	Number

1998	750
1999	758
2000	832
2001	787
2002	802
2003	728

Dr. Entwisle provided birthing statistics for the top five hospitals for Duplin County births, noting that residents of higher socioeconomic status often give birth outside the county. She also provided 3-year totals for 2001–2003 and the percentages of total births for each hospital. Over this 3-year period, Duplin County General Hospital, in Kenansville, had 1,548 births (66.8 percent of the total).

Dr. Entwisle presented the following indicators of infant and child health:

Indicator	Duplin County	NC Average
Infant mortality, 1998–2002	9.4	8.7
Low birth weight babies, 2002	9.6	9.0
Child deaths, 0–17 years, all causes (per 100,000)	106.4	79.9
Children in poverty, 2000	22.9	16.1

The Vanguard Center collaborators and their roles and relationships are as follows:

- UNC—primary contractor
  - Epidemiology, obstetrics and gynecology, child development
  - Liaison with Duplin County
  - Research methods
- Duke—subcontractor to UNC
  - Pediatrics
  - Child mental health
  - Environmental exposure assessment
- Battelle—subcontractor to UNC
  - Coordinate sampling with Coordinating Center
  - Recruitment and enrollment
  - Field data collection in homes and clinics.

Dr. Entwisle presented a management chart for the Duplin County site. She and David Savitz, Ph.D., are the PIs. Nancy Dole, Ph.D., is the co-PI. All three are at UNC. The management chart listed team leaders for the various contract components.

Vanguard Center for Orange County, California: University of California-Irvine with Children's Hospital of Orange County
PI: James Swanson, Ph.D., University of California-Irvine

Dr. Swanson presented a map of the Vanguard Centers and Study sites. He noted that most Study sites correspond to a single county. However, 6 of the 96 sites include more than one county due to the small number of anticipated births in those areas. Dr. Swanson explained that Orange County, CA, is the seventh largest county in the United States. The county is located in Southern California; its estimated 2005 population was 3,056,900. It has a diversity of settlements and communities, a diversity of races and ethnicities, and a range of socioeconomic statuses among its residents. To further characterize Orange County, he presented a map of the county and provided information on:

- Estimated percentage of children in a ZIP code living below 200 percent of federal poverty level
- Air pollution levels by Census tract, which included estimated benzene concentrations and traffic densities.

The primary collaborating organizations for this Vanguard Center are:

- University of California, Irvine
- Children's Hospital of Orange County
- Children and Families Commission
- Orange County Health Care Agency.

Dr. Swanson noted that:

- Children's Hospital of Orange County has an ongoing cord blood collection program
- Children and Families Commission is funded by Proposition 10 tobacco tax revenues, which channels the funds to a school readiness program for children younger than 6 years of age
- The Vanguard Center team has many existing community networks and relationships, which will provide community outreach and engagement from multiple sources.

The collaborating organizations have links with the Bridges for Newborns Program (Bridges), which aims to increase the proportion of Orange County newborns that are insured and have a health care home. Bridges seeks to ensure that newborns are linked with health care coverage, receive their first well-baby checkup, a Kit for New Parents, and up-to-date immunizations. Bridges is a network of Orange County hospitals, Family Resource Centers, and community agencies that work together with the California Children and Families Commission of Orange County to help provide a healthy start for children. These agencies are all committed to improving the lives of children born in Orange County so that they are healthy and ready for success in school by age 5.

In 2004, there were 44,758 live births in Orange County. Dr. Swanson listed 21 hospitals and the number of live births for each hospital for 2004. During that year, there were 103 live home births. Dr. Swanson said that all 29 birthing hospitals in the county agreed to participate in the Study; each hospital provided a letter of commitment. Multiple pediatric programs across the county will participate, as will many community agencies and organizations.

Dr. Swanson presented the organizational structure of the Vanguard Center and listed the names of the Executive and Steering Committee members and other important organizational entities.

The upper tier of this structure includes the Executive Committee, the Community Board, and the Academic Board. Dr. Swanson listed the programs responsible for early Study visits:

Visit	Program
Sample of women in the Study	Center for Occupational and Environmental Health (D. Baker, co-PI)
Live births in 20 Orange County hospitals	Center for Well Being of Mothers and Children (P. Wadhwa, co-PI)
Live births in 20 Orange County hospitals	Children's Hospital of Orange County Cord Blood Program (L. Sender) and University of California-Irvine Neonatology (F. Waffarn, co-PI)
Follow-up of infants in Study	Early Child Care and Youth Development (A. Clarke-Stewart)
Clinic visit at 3 years of age	University of California-Irvine Child Development Center (Dr. Swanson, PI)

Vanguard Center for Queens, New York: Mount Sinai School of Medicine with Columbia University Mailman School of Public Health, New York City Department of Health and Mental Hygiene, University of Medicine and Dentistry of New Jersey, and Columbia University Department of Obstetrics and Gynecology
PI: Philip Landrigan, M.D., M.Sc., Mount Sinai School of Medicine

Dr. Landrigan thanked Dr. Alexander and Dr. Scheidt, Program Office members, and meeting participants for their efforts in planning and implementing the Study. He commented that the Study cannot be fully realized without broad support across the United States and without adequate funding.

Dr. Landrigan presented an overview of Queens, NY, which is one of five boroughs—or counties—in New York City. Queens is a densely populated urban community that includes two major airports and a national park. Dr. Landrigan characterized this Study site's demographics:

- Total population in 2000 was 2,229,379—a 14.2 percent increase from 1990.
- 24.3 percent of Queens' residents receive some form of public assistance.
- Land use is predominantly (35.8 percent) one- or two-family residential buildings.
- Queens covers 71,779.6 acres and 112.2 square miles.
- 14.6 percent of Queens' residents live below the poverty level.

Dr. Landrigan characterized the diversity in Queens:

- Queens is the most ethnically diverse county in the United States.
- More than 150 languages are spoken in Queens.
- Newspapers sold in Queens are printed in 40 different languages.
- 46 percent of Queens' residents (1,028,339 people) were born outside the United States.
- Foreign-born residents come from more than 100 nations.
- In 2001, 19,377 (71 percent) of babies born in Queens were born to foreign-born mothers.

To further characterize Queens' diversity, Dr. Landrigan presented a chart listing ethnic diversity and economic indicators by neighborhood for 2000. The indicators included population size, percentage foreign born, percentage without high school education, top three countries of origin, and percentage living in poverty. Dr. Landrigan also presented a map depicting the locations of selected hospitals and clinical centers that will be used for Study clinic visits. The Vanguard Center is a consortium of five academic institutions:

- Mount Sinai School of Medicine
- Columbia University College of Physicians and Surgeons
- Columbia University Mailman School of Public Health
- New York City Department of Health and Mental Hygiene
- University of Medicine and Dentistry of New Jersey.

Dr. Landrigan commented that each partner institution brings a unique strength to this collaborative effort. The Queens Vanguard Center draws on rich resources, which include:

- Deep expertise in children's environmental health
- 3 of the nation's 11 Children's Environmental Health and Disease Prevention Research Centers
- The New York City Health and Nutrition Examination Survey project
- Extensive experience with ongoing birth cohort studies in the United States, South Africa, and Europe
- Collaborations that were forged after September 11, 2001 (World Trade Center/Pentagon terrorism attacks).

Dr. Landrigan concluded by presenting the Queens Vanguard Center organizational chart.

Vanguard Center for Montgomery County, Pennsylvania: Children's Hospital of Philadelphia and Drexel University School of Public Health with University of Pennsylvania School of Nursing
PIs: Jennifer Culhane, Ph.D., M.P.H., Drexel University College of Medicine, and Donald F. Schwarz, M.D., M.P.H., M.B.A., Children's Hospital of Philadelphia

Dr. Culhane presented an overview of Montgomery County, PA. This suburban county is located just west of Philadelphia. It is ranked the 27th richest county in the United States (ranked by personal per capita income). The county seat is Norristown. There are 62 municipalities, 23 school districts, 97 private elementary schools, and 27 universities within the county. There is a high diversity of religious groups. Dr. Culhane characterized the county:

- Area—482 square miles, ranging from rural farmland to urbanized centers
- Population (2002 estimate)—766,517
- Occupied housing units—286,098; of these
  - 798 had inadequate plumbing
  - 984 had inadequate kitchens
  - 1,567 had no telephone
- On five leading economic indicators, ranked third among Pennsylvania counties
- Approximately 9,400 live births per year

- Voters—492,293
  - 54 percent Republican
  - 33 percent Democrat.

The county's population was described as:
- Race/ethnicity:
  - White—87 percent
  - African American—7.3 percent
  - Asian—4.0 percent
  - Other—2.2 percent
  - Hispanic—2.0 percent
- Uninsured—28,452 (5.1 percent)
- Median family income (2003, inflation adjusted)—$75,418 (In contrast, bordering Philadelphia County had an estimated family income of $41,577 in 2003.)
- Unemployment rate (2003)—3.3–4 percent.

Dr. Culhane listed the per capita income for three municipalities:
- Lower Merion $55,898
- Pottstown $19,078
- Norristown $17,977.

Dr. Culhane characterized the county's two urbanized areas:
- Norristown
  - Population—31, 282
  - 54.3 percent White; 34.8 percent African American
  - Median household income (2000)—$35,714
- Pottstown Borough
  - Population—21, 859
  - 77.5 percent White; 15.1 percent African American
  - Median household income (2000)—$35,785.

Dr. Culhane presented a map that depicted the distribution of poverty rates in the county in 2002. She also presented a chart that listed race/ethnic composition and key birth outcomes for the county as a whole and for its two urbanized areas (Norristown and Pottstown).

Montgomery County contains many brownfields (abandoned, contaminated industrial sites). It is listed in the top 20th percentile for the number of Superfund sites, and it is listed in top 10 dirtiest counties in the United States. The county's total acreage is 310,000, much of it rural; but development has increased steadily over the past 66 years:

Year	Number of Acres Developed
1940	35,000
1970	99,000
2000	167,00

Dr. Culhane presented an organizational chart of the Montgomery County Vanguard Center. The primary collaborating entities are the Children's Hospital of Philadelphia, Drexel University School of Medicine, the Community Advisory Board, the Montgomery County Board of Health, the University of Pennsylvania School of Nursing, and affiliated faculty members. Dr. Culhane also presented an organizational structure depicting the relationships among the Vanguard Center's key personnel.

Vanguard Center for Waukesha County, Wisconsin: University of Wisconsin-Madison with Medical College of Wisconsin, National Opinion Research Center, Marquette University, University of Wisconsin Marine and Freshwater Biomedical Sciences Center/Institute for Environmental Health, and Children's Service Society of Wisconsin
PIs: Maureen Durkin, Ph.D., Dr.P.H., University of Wisconsin-Madison, and Christine Cronk, Sc.D., Medical College of Wisconsin/Children's Research Institute

Dr. Durkin presented an overview of Waukesha County, Wisconsin. This county is located in the Milwaukee-Waukesha-West Allis, WI, Metropolitan Statistical Area. It is a metropolitan, noncertainty Study Vanguard site. The Study site is about 65 miles from the University of Wisconsin-Madison and about 15 miles from the Medical College of Wisconsin in Milwaukee. Dr. Durkin presented a map of Wisconsin and the Waukesha County region, as well as a county map depicting townships and municipalities. Waukesha County has become increasingly suburban over the past two decades. From 1987 to 1997:

- The number of farms declined from about 820 to about 630.
- The acreage of farmland decreased from about 127,000 to about 105,000.

The racial/ethnic distribution in Waukesha County is:

- White 93.1 percent
- Latino 2.6 percent
- Other 1.2 percent
- Asian 1.7 percent
- African American 1.0 percent
- American Indian 0.5 percent.

Other facts about Waukesha County births include:

- Increasingly diverse infant population—largest increase is in Hispanic and Asian births, which increased from 6 percent of county births in 1996 to 12 percent of births in 2004
- 23 percent of births are to women 35 years of age and older.

Dr. Durkin commented that a looming concern for the county and for the Vanguard Center is the increasing number of undocumented immigrants. She noted that Waukesha County is generally a very healthy county, with a low poverty rate. About 3.7 percent of the county's children live below the poverty level. Dr. Durkin presented a chart comparing demographics across the 10 counties that comprise the 7 Vanguard sites. The chart provided the following information:

- Population in 2000
- Percentage population change from 1990 to 2000

- Numbers of persons per square mile
- Median income
- Percentage of population that is White, non-Hispanic
- Number of live births
- Number of births per 1,000 population
- Infant mortality rate
- Percentage of newborns with low birth weight
- Percentage of mothers receiving early prenatal care.

Dr. Durkin characterized Waukesha County environmental exposures:

- Maternal smoking—10 percent according to maternal reporting between 1996 and 2000
- High levels of and intracounty variability in radium, arsenic, trihalomethanes, and nitrates in the water supply
- Radon—a high percentage of the homes in Waukesha County have radon levels above the U.S. EPA guideline
- Lead—nearly 20 percent of existing households in Waukesha County were built before 1950
- Expansion of housing—25 percent of the housing structures in the county in 2000 were constructed after 1990
- Widespread agricultural pesticide exposures
- Outdoor air pollution—air quality cancer risk, hazard index, and fine particulate matter highest in Wisconsin.

Dr. Durkin presented two charts showing:

- Crude birth rate for larger civil divisions in Waukesha County 2000–2003
- Hospitals with more than 5 percent of deliveries to Waukesha County residents by county and city.

There were differences in and variability among the crude birth rates for the five depicted civil divisions. The four birthing hospitals in Waukesha County accounted for almost 50 percent of the births among county residents. Most other births occurred in Milwaukee-area hospitals.

Dr. Durkin explained that the key personnel among the Vanguard Center team have academic affiliations. The team has a strong representation of nurses and nursing organizations, a strong consortium of community agencies, and the appropriate technological infrastructure for home-based surveys. The key partners in the Waukesha County Vanguard Center collaboration, as well as their roles and areas of expertise, are as follows:

- University of Wisconsin-Madison
  - Neurodevelopment, asthma, injury
  - Environmental health, epidemiology
  - Demography/population sciences
  - Longitudinal studies
- Medical College of Wisconsin/Children's Research Institute
  - Community-based participatory research
  - Medical community engagement

  - Environmental health
  - Gene-environment interaction
- Marquette University Colleges of Nursing and Communication
  - Biometry/data collection, perinatal data
  - Hospital-based data collection
  - Risk perception
  - Outreach
- National Opinion Research Center (University of Chicago)
  - Field operations
  - Recruitment and retention
  - Sampling/segment selection
- Children's Service Society of Wisconsin
  - Recruitment and retention
  - Interviewing
  - Community connection
- University of Wisconsin-Milwaukee
  - Environmental health, built environment
  - Community outreach and education
  - Psychosocial development
- Wisconsin Department of Health and Family Services
  - Environmental health
  - Vital records
  - Maternal and child health.

Other partners in the Waukesha County Vanguard Center collaboration are:

- Hospitals and health systems
  - ProHealth Care
  - Covenant Health Care
  - Froedtert and Community Memorial
  - Aurora Health Care
  - Waukesha Family Practice Center
- Waukesha County (Executive offices, County Board of Supervisors, and Department of Health and Social Services)
- State legislators
- City governments (Waukesha, New Berlin, Merton, and Pewaukee)
- Other community agencies and institutions
  - Casa de Esperanza
  - Wisconsin Association for Perinatal Care
  - University of Wisconsin Extension
  - St. Joseph's Clinic
  - March of Dimes
  - Waukesha Women's Center
  - Catholic Charities
  - Waukesha County Technical College

- University of Wisconsin-Waukesha
- Addiction Resource Council.

Dr. Durkin presented the organizational structure for the Waukesha County Vanguard Center as well as the core management structure of the field operations. She concluded by listing the study teams for the first two phases of implementation:

Phase 1	Phase 2
Community outreach and collaboration	Community outreach and collaboration
Protocol development	Recruitment and enrollment
Sampling and characterization	Data collection and handling
Testing and research	Quality assurance and control
	Analysis, reports, and deliverables

Vanguard Center for Salt Lake County, Utah: University of Utah
PI: Edward B. Clark, M.D., University of Utah

Dr. Clark presented an overview of Salt Lake County. He presented maps showing the location of Salt Lake County within Utah and of the topography surrounding the county. About 75 percent of the county extends along the Wasatch Front. Dr. Clark provided the county's population characteristics, which were from the 2004 American Community Survey:

- Total population 920,666
  - Male 465,579 (50.6 percent)
  - Female 455,087 (49.4 percent)
- Median age (years) 29.6 (U.S. median = 36.2)
  - 0–5 86,841 (9.4 percent)
  - 18+ 644,153 (70.0 percent)
  - 65+ 71,548 (7.8 percent).

Dr. Clark listed some of the county's economic characteristics

- Number in labor force (16+ years) 494,058 73.4 percent
- Median household income $48,578 (U.S. median = $44,684)
- Median family income $55,751 (U.S. median = $53,692)
- Families below poverty level 7.9 percent (U.S. median = 10.1 percent)
- Individuals below poverty level 10.9 percent (U.S. median = 13.1 percent)

Dr. Clark listed some of the county's social characteristics:

- Population 25 years old+ 536,530
  - High school graduate+ 86. 5 percent
  - Bachelor degree+ 28.8 percent
- Foreign born 98,879 10.7 percent
- Language other than English at home 132,994 15.9 percent.

Dr. Clark presented two charts:

- Ethnicity by birth year (percentages from 2000 to 2003) for Whites, African Americans, Native Americans, Asians, Pacific Islanders, other entries, and not reported.
- Hispanic by birth year (percentages from 2000 to 2003).

From 2000 to 2003, the number of births in Salt Lake County ranged from 18,104 to 18,559. For this same period, the percentage of Hispanic births ranged from 10 percent to 11 percent; the percentage of Hispanics born in the county is rapidly increasing. Dr. Clark characterized Salt Lake County:

- Urban region surrounded by mountains and wilderness
- All births link to the Utah Population Data Base
  - 10 million records and genealogy of more than 4 million individuals
- High birth rate; large family size
  - Young population—10 percent younger than 5 years, 23 percent younger than 18 years
- Ethnic and cultural considerations
  - Large undocumented community
  - 81 languages spoken; health literature in 24 languages
- Environmental issues
  - 11 National Priorities List (Superfund) sites
  - Air quality compromised by "stagnant bowl" effect
  - Critical water supply (underground aquifers, surface water capture).

Dr. Clark described the process of organizing the Salt Lake County Vanguard Center and listed the steps for developing the proposal:

- Evaluate request for proposal (RFP)
  - Do not underestimate the scope of the project
  - Define the Study as related to your community (strengths, weaknesses, opportunities, and threats)
  - Decide if you can commit the time and resources to the project
- Inventory the university
  - Define resources available within the university
  - Inventory past and current research for activities in the RFP
  - Identify the gaps in skills, tools, and people
  - Seek and engage extramural partners to fill gaps and create coherent teams
- Obtain university support and inform and engage higher administration
  - Administrative support for the project
    - Engage key personnel from sponsored projects and research accounting
    - Define assets needed for the implementation
  - Financial support to offset development costs
    - Time, effort, costs—both direct and indirect—over 4 years = $500,000
  - Get approval for access to political support from community component
- Form Study working group
  - Identify and enroll key faculty and staff in a working group
  - Provide support for efforts
  - Recognize that not all components of a proposal may be funded

- Develop organizational plan
  - Assign key functions with accountabilities, deliverables, and dates
  - Develop organization structure including large and small group meetings
  - Communication tools and motivation—key components to developing the plan
    - eRoom for document sharing (maintains version control; SharePoint also good tool)
    - Fixed meeting site and date.

Dr. Clark advised that concurrent to the proposal development process, the team should:

- Assess community for Study support
  - Test the waters for a large-scale community study
  - Identify key opinion leaders
    - Political spectrum from left to right
    - Underrepresented ethnic groups
    - Faith-based groups
    - Medical community
    - Business and labor
    - Local and state health departments
    - All others who will have a stake in the project, including special interest groups
- Form a community advisory committee
  - From the prior groups, draw individuals who will speak for and about the Study
  - Serve as trust builders with the more skeptical segments of the community
  - Identify individuals who are credible with regional and national groups
- Identify neighborhood champions
  - Assess regions of the community likely to be sampled
  - Use community assessment strategies to define key issues
  - Use focus groups and individual discussions to find bubble-up champions.

Vanguard Center for Brookings County, South Dakota, and Lincoln, Pipestone, and Yellow Medicine Counties, Minnesota: South Dakota State University

PI: Bonny Specker, Ph.D., South Dakota State University

Dr. Specker began her presentation by noting that, compared with Brookings, Yellow Medicine, Pipestone, and Lincoln (BYPL) counties, Duplin County, NC, is not very rural. The BYPL counties were combined as a single Study site to provide a sufficient birth rate. Dr. Specker provided an overview of these four counties to justify her opening statement. She acknowledged the BYPL Vanguard Center team by listing names and areas of expertise for the following:

- South Dakota State University investigators
- Local advisors and consultants
- Cincinnati Children's Hospital Medical Center investigators
- Cincinnati Children's Hospital Medical Center tier II investigators
- University of Cincinnati investigators.

Dr. Specker displayed the BYPL Vanguard Center organizational structure and said, "We are this population," indicating that the individuals comprising the team actually live in the Study communities. The structure has a strong community nursing component.

Dr. Specker presented a map of the four counties and several photographs of typical environments in the counties. The counties are characterized by vast amounts of open space. Agriculture is the main economy. Dr. Specker provided three tables with population characteristics (data from 2000 U.S. Census) for the four counties:

Characteristic	B	Y	P	L	Total
• Population	28,392	10,677	9,681	6,159	54,909
• Square miles	794	758	466	537	2,555
• Population density (#/mi^2)	36	14	21	12	21
• Urban					
– % inside urbanized areas[a]	0	0	0	0	0
– % inside urban clusters[b]	69	18	42	0	44
• Rural					
– Farm[c] (percent)	6	18	17	23	12
– Nonfarm[d] (percent)	28	64	42	77	44

B = Brookings; Y = Yellow Medicine; P = Pipestone; L = Lincoln.
[a]Urbanized area: >50,000 people.
[b]Urban cluster: 2,500–49,999 people (Brookings largest city: est. 2004 population = 18,700).
[c]Rural farm: operating, open-country farms and ranches; all farms are family owned.
[d]Rural nonfarm = places <2,500 population and people living in open country (not engaged in farming or ranching).

Characteristic	B	Y	P	L	Total
• Women 18–39 years of age	6,029	1,291	1,214	707	9,241
• Median age (years)	27	40	40	43	
• Number of households	11,576	4,873	4,434	3,043	23,926
• Total resident births (2003)	309	131	106	75	621
– Inside of county	177	61	52	10	300
– Outside of county[a]	132	70	54	65	321
• Non-Hispanic White (%)	96	95	96	98	96
– Median household income	$35,438	$34,393[b]	$31,909[b]	$31,607[b]	
– Persons below poverty (%)	14[c]	10[c]	10[c]	10[c]	12

B = Brookings; Y = Yellow Medicine; P = Pipestone; L = Lincoln.
[a]Majority in Sioux Falls, South Dakota.
[b]Lower than state average.
[c]Higher than state average.

Characteristic	B	Y	P	L	Total
• High school graduates (%)	90[a]	82[b]	78[b]	80[b]	85
• Bachelor's degree (%)	32[a]	14[b]	14[b]	14[b]	23

• Number of elementary schools	7	4	6	2	19
• Number of secondary and high schools	8	3	3	3	17
• Number of religious institutions	49	32	31	25	137
• Affiliated with a church (%)	61	91	99	93	77

B = Brookings; Y = Yellow Medicine; P = Pipestone; L = Lincoln.
[a]Higher than state average.
[b]Lower than state average.

Dr. Specker noted that the four counties have relatively stable populations, a strong sense of community, and diverse communities that include Hutterites, Lakota Nation, and ethnic groups. She concluded by listing the challenges for the BYPL Vanguard Center:

- Population dispersion (The counties have many tiny towns and villages, most with populations less than 30. Towns and villages are often based on heritage, for example, Danish, Swedish, and Norwegian.)
- Widely dispersed birthing centers with low birth rates
- Agrarian communities (more cows than people)
- Extreme weather (for example, tornadoes, blizzards)
- Traveling in and out of BYPL counties during hunting season (hunting is the second largest economy in the four counties).

Coordinating Center: Westat with University of Pennsylvania; Harvard Medical School (Harvard Pilgrim Health Care); Daston Communications; The Helix Group; The Media Network; Syntaxis, Southwest Research Institute; Claritas, Inc.; and Peters Consulting, Inc.
PI: Carla E. Maffeo, Ph.D., Westat

Dr. Maffeo described Westat as an employee-owned research corporation that provides consulting in statistical design, data collection and management, and research analysis work. It was founded in 1961 by a group of statisticians from the University of Wyoming; its headquarters are in Rockville, MD; and it employs more than 1,800 people, including social scientists, epidemiologists, biostatisticians, survey statisticians and analysts, physicians and other medically trained staff, and information technology staff. Westat has conducted or supported health research for government and private clients in the areas of health services research, health outcomes, epidemiological research, health education and interventions studies, and clinical trials over the past 45 years.

Dr. Maffeo noted that the RFP's statement of work was more than 30 pages and listed some of the Coordinating Center's key responsibilities:

- Setting up the Coordinating Center
- Providing scientific and meeting support
- Supporting development, implementation, and maintenance of the information management system
- Providing input into the development of all study documents and materials, including manuals of operation, data collection instruments, and data collection procedures

- Training Vanguard Center, Study site, laboratory, and repository personnel
- Developing Study plans, including outreach, recruitment and retention, human subjects, publications, and scientific outreach
- Developing and implementing portions of the sampling plan, including selection of the secondary sampling units
- Developing a plan for sampling households
- Developing statistical analysis plans
- Performing field testing and pilot testing
- Developing quality assurance/quality control (QA/QC) plans
- Managing data.

Dr. Maffeo presented the organizational structure of the entities comprising the Coordinating Center. Westat's primary partners are the University of Pennsylvania and Harvard University. In addition to Dr. Maffeo, the senior management team consists of:

- Matthew Gillman, M.D., Co-Investigator, medical expertise (Harvard Medical School)
- Jonas Ellenberg, Ph.D., Co-Investigator, biostatistics and analysis (University of Pennsylvania)
- Ruth Thomson, Assistant Project Director for Coordinating Center Operations (Westat)
- Alexa Fraser, Ph.D., Assistant Project Director for Research Coordination (Westat)
- Thomas McKenna, Corporate Officer (Westat).

The Coordinating Center team will include a Technical Expert Resource Panel (consultants who are child health experts) and the following external entities:

- Information technology contractor
- QA/QC contractor
- Logistics support contractor
- Laboratories and repositories
- Vanguard Centers and Study sites
- Clinical testing facilities.

Dr. Maffeo concluded by noting that Daston Communications, The Helix Group, The Media Network, and Syntaxis will serve as recruitment and retention subcontractors. Southwest Research Institute and Peters Consulting, Inc., will serve as contractors for measurements and laboratory QA/QC.

Planning Phase Initiatives

Moderator: Carole A. Kimmel, Ph.D., Consultant, National Children's Study Program Office, NICHD, NIH, DHHS

Dr. Kimmel explained that the purpose of the next four presentations was to describe the scientific progress during the planning phase of the Study. Many of the planning activities over the past 5 years have focused on developing methods and piloting various methodologies to help implement the Study.

Overview and Highlights of Pilot Studies

Amy Branum, M.S.P.H., Chair, ICC; Health Statistician, National Center for Health Statistics (NCHS), CDC, DHHS

Ms. Branum explained that the Study has been conducting pilot studies for the last 5 years. Many of the early studies were conducted through existing EPA mechanisms. Since then, funding has come from the four lead agencies. There are three general categories of pilot studies:

- Reviews and white papers
- Workshops
- Pilot studies.

Ideas for pilot studies have come from a variety of sources. Many pilot ideas were "born" through former Study working groups. Additional ideas came from agency scientists, Program Office staff, and ICC members. Proposals for pilot studies are sent to a review subcommittee and the Study's Federal Advisory Committee. All pilot studies are reviewed for content, scope, and relevance. All pilot studies are tracked in a database.

Ms. Branum characterized the reviews and white papers:

- Formal literature review or white paper that summarizes existing information and identifies gaps in knowledge
- Written for both peer-reviewed journals and internal use
- Cover wide range of topics including exposures, recruitment/retention, methods, ethics, information technology, and outcomes
- Many published in *Environmental Health Perspectives*
- Approximately 50 proposed, in progress, or completed.

Topics of reviews and white papers include:

- Technology needs assessment
- Measuring housing quality and characteristics
- Recall and collection of retrospective data
- Lessons learned from Children's Environmental Health Centers
- Assessment of existing linkages with local communities
- Identifying and selecting developmental measures
- Evaluation of exposure measurement methods and approaches for the Study.

Ms. Branum characterized the workshops:

- Small (3–4 people) or large (15–30 people) gatherings of experts to discuss issues and make recommendations
- Held in many different geographic locations (MD, DC, VA, GA, TX, MA, FL)
- Most workshops issued a report of findings for internal use
- Approximately 50 workshops proposed, in progress, or completed.

Workshops with the following titles were conducted:

- Psychosocial Stress and Pregnancy and Infancy

- Use of Herbal Products
- Media Effects
- Gene-Environment Interaction and Regulation of Behavior
- Racial/Ethnic Discrimination and Racism
- Collection and Use of Genetic Information
- Ethical Issues
- Sampling Design
- Capturing Day-Specific Probabilities of Conception.

Ms. Branum characterized the pilot studies:
- Many projects that cover wide range of scientific query from very small budget to large
- Most designed to test methods and measures
- Use of various contract mechanisms that allow efficiency and easier feasibility
- Approximately 62 pilot studies proposed, in progress, or completed.

Pilot studies have included:
- Focus groups: Eliciting community involvement, recruitment, and retention of subjects
- Demonstration of low-cost, low-burden exposure monitoring strategies
- Feasibility of primary care sites for subject observation and data collection
- Reliability and validity of injury reporting
- Tampa Asthmatic Children's Study (TACS)
- Methods Advancement for Milk Analysis (MAMA)
- North Carolina Cohort Study.

Update on Protocol Development

Ruth A. Brenner, M.D., M.P.H., Director, Protocol Development, National Children's Study Program Office, NICHD, NIH, DHHS

Dr. Brenner provided an update on development of the Study protocol. The initial guidance for the Study came from the Children's Health Act in 2000: "…to conduct a national longitudinal study of environmental influences (including physical, chemical, biological, and psychosocial) on children's health and development."

Dr. Brenner reviewed protocol development activities since 2000:
- Longitudinal cohort study proposed by the ICC in 2000
- Focused hypotheses and suggested measurements developed from the Study's Federal Advisory Committee and 22 Working Groups in 2001
- Since 2001, other scientific activities include pilot studies, white papers, and workshops
- Measurements database developed by the ICC in 2003
- Decision on the sampling strategy in 2004.

Dr. Brenner described events leading up the sample design decision. In fall 2002, an analysis titled "Sampling Strategies for the Proposed National Children's Study" was commissioned. This

analysis was presented to the Study's Federal Advisory Committee in spring 2003. White papers in support of the Study sampling strategies were released in fall 2003. An expert panel was convened in 2004 that recommended a national probability sample. This sample design was endorsed by The Study's Federal Advisory Committee and the Director, NICHD, in June 2004.

The Study Plan was published as part of the RFPs in November 2004. The Study Plan outlines the general study design of the Study. Its purpose was to guide offerors so that they were better able to develop their proposals. The Study Plan is less detailed than a full study protocol or operational manual, yet includes more detail than many RFPs. The Study Plan will evolve in greater detail with input from investigators from the Vanguard Centers, Coordinating Center, and initial experience.

Dr. Brenner described the scope of the Study Plan and the process of developing the protocol from the Study Plan. The current process involves:

- Filling in the details of the Study protocol and finalizing key aspects of the Study Plan
- Forming working teams with members from the Program Office, Vanguard Centers, and Coordinating Center
- Deliberation by Study teams, which are informed by previous work and by information in the submitted proposals.

Team recommendations will be brought to the full Steering Committee. The teams include:

- Sampling
- Recruitment and retention
- Topic-specific assessments (questionnaire and observational)
  - Neurocognitive and social-emotional outcomes
  - Nutrition
- Environmental specimens
- Biological specimens
- Physical examinations
- Human subjects
- Study operations
- Information management systems development.

Dr. Brenner presented the projected timeline for protocol development and review:

- November 2004—Initial posting of RFPs and the Study Plan
- September 2005—Award initial contracts (Coordinating Center and Vanguard Centers)
- November 2005—First Steering Committee meeting
- December 2005—Working teams established
- January 2006—Recommendations for measurements and key nonmeasurement aspects of the protocol
- February 2006—Integration into a unified Study protocol
- March 2006—Submission for internal governmental reviews
- April 2006—Submission for peer review
- May 2006—Period of public comment.

NC Herald Study

Pauline Mendola, Ph.D., Member, ICC; Chief, Epidemiology and Biomarkers Branch, National Health and Environmental Effects Research Laboratory, Office of Research and Development, EPA

Dr. Mendola described the background and history of the NC Herald Study. As federal plans for the Study gained momentum in 2000, there was a recognized need for pilot testing capacity. EPA worked with NIH, CDC, and the Office of the Secretary, DHHS, to develop a comprehensive scope of work in 2001 and to find a contractor with the ability to execute a longitudinal study. A competitive EPA contract was awarded to RTI, International in 2002. An Expert Panel Sampling Workshop in 2004 recommended pilot testing of recruitment.

The pilot study concepts included:

- Longitudinal cohort design
- Testing protocols and procedures for use in the Study
  - Sample selection and community engagement (Census tracts versus school catchment areas)
  - Household enumeration (commercially available mailing lists versus counting and listing)
  - Differing strategies needed for rural areas and urban areas
  - Achieving the cooperation of local medical facilities
  - Understanding reasons for participating in or withdrawing from study.

The priority outcomes are:

- Response rates (urban versus rural; Census versus school catchment; preconception, pregnancy, and birth)
- Knowing which parts of the study have the highest acceptance and disapproval
- Health (birth outcomes; variations in normal developmental).

Dr. Mendola reviewed the sample design and implementation approach of the NC Herald Study. The study locations are counties not already selected for the Study, ideally close to study investigators. The sample is to include one rural county and one urban county. There will be two study segments per county: one Census tract and one school catchment area.

Dr. Mendola explained how the two NC Herald Study counties were selected, and she presented a map that depicted the counties for the NC Herald Study, the Study, and the Vanguard Center (Duplin County). She also explained the process for selecting the study segments. Dr. Mendola characterized the counties and study segments:

- Forsyth County
  - Both segments chosen in urban Winston-Salem
  - Demographics are similar to facilitate comparisons between the two types of segments
- Davidson County
  - Rural county

  - Census tract in Lexington (characteristic of a small town)
  - School catchment area in rural northwest portion of the county.

Dr. Mendola compared details on birthing hospitals for Forsyth and Davidson residents and demographics of the two counties, including total number of households and percentage of:

- Whites
- African Americans
- Hispanics
- Rural housing
- Below poverty.

The resulting estimated sample size for the NC Herald Study is 10,000 households screened, with 950 eligible women enrolled. Among these women, it is estimated that 170 will have a high likelihood of pregnancy and that about 400 infants will be born.

The NC Herald Study will focus on:

- Timeframe from preconception to the 18-month infant visit
- Elements related to participant burden, time, and cost, including
  - Schedule of visits
  - Types and frequency of measures
- Domains that might yield data of interest to a smaller study.

Unlike the Study, the NC Herald Study has:

- Accelerated enrollment of pregnant women including some women at delivery
- No women under 18 years of age
- Its focus on logistics and participant burden, not hypotheses.

Eligible NC Herald Study participants include:

- Women likely to become pregnant
  - High likelihood—those who are planning pregnancy
  - Moderate likelihood—those not using contraception or using a contraception technique with a greater than 10 percent failure rate
  - Low likelihood—those using a contraception technique with a less than 10 percent failure rate or not sexually active (not enrolled/consented but may be recontacted)
- Women who are pregnant
- Women who have recently given birth and are still at the hospital for the delivery.

Data will be collected through questionnaires and interviews, including:

- In-person administered questionnaires
  - Using audio self computer-aided interview for sensitive topics
- Mail-back questionnaires for diet and mental health
- Event form
- Total of 30 data collection instruments.

The questionnaire domains are:

- Acceptability—maternal and partner
- Activity—maternal
- Alcohol—maternal and partner
- Chemical exposures—maternal and partner
- Child development
- Demographics
- Dental health
- Diet—child
- Diet—maternal self-administered questionnaire (SAQ)
- Diet—maternal
- Feelings about pregnancy—maternal and partner
- Health care
- Household composition
- Infant safety
- Home environment conditions
- Medical history (personal and family)—maternal and partner, child
- Medications (prescription and over the counter)—maternal
- Mental health (SAQ)—maternal and partner
- Neighborhood
- Occupation—maternal and partner
- Partner updates
- Pets and pests
- Postpartum depression
- Reproductive health
- Supplements and vitamins—maternal
- Tobacco (self and environmental tobacco smoke)—maternal and partner

Other measures include biological and environmental samples, physical exams, and community measures.

Dr. Mendola presented the following timeline for this pilot study:

- March 2004—Expert sampling panel
- July 2004—ICC explores options for a pilot cohort
- September 2004—First proposal reviewed by ICC and Program Office
- February 2005—ICC approves pilot
- March 2005—Study's Federal Advisory Committee subcommittee concept clearance
- April 2005—First *Federal Register* notice (60 day public comment)
- August 2005—Finalize questionnaires (30) and submit for EPA review
- September 2005—Second *Federal Register* notice (30 day public comment) and OMB
- October 2005—Privacy impact assessment completed
- November 2005—Institutional review board review (IRB) and approval
- January 2006—Counting and listing
- March–June 2006—Household screening and recruitment period
- September 2007—Estimated last baby born to enrolled women.

International Childhood Cancer Cohort Consortium Initiative

Terry Dwyer, M.D., M.P.H., Director, Murdoch Children's Research Institute, Royal Children's Hospital

Dr. Dwyer presented an overview of the International Childhood Cancer Cohort Consortium Initiative (ICCCC). This project has been driven by an initiative from the Study Program Office and will serve as an adjunct to the Study. Dr. Dwyer explained that because not much progress

has been made in treating childhood cancer, it would be better to focus on cancer prevention. Cancer prevention is the rationale for ICCCC. However, to prevent childhood cancer, researchers must understand the causes.

Retrospective case control studies have been the principal strategy used to examine the association of environmental exposures with childhood cancer. Because case control studies rely on human recall of environmental exposures, the information obtained may be unreliable or biased. The effectiveness of exposure assessment questions is uncertain in retrospective case-control studies of childhood cancer. However, in prospective cohort studies, environmental exposures are measured in healthy subjects who are then followed over time. Cohort studies have the potential to overcome the problem of recall bias, but they need to be very large.

Dr. Dwyer described the process for determining how large a cohort would be needed to detect effects of exposures on childhood cancer. Estimation of this cohort size first requires knowledge of the rate at which cancer cases occur in children. According to Dr. Dwyer, the number of cases of all cancers occurring in a cohort of 100,000 children followed from birth to 14 years of age is about 242. However, the number of children needed to study leukemia (acute lymphoblastic leukemia and acute myeloid leukemia) is greater than 100,000. Dr. Dwyer presented the following:

Percentage of Subjects Exposed	Minimum Risk Detectable	Power Percentage	Number Required
5	1.5	80	1,180,059
15	1.5	80	446,633
30	1.5	80	277,781

Thus, neither the Study nor any other single cohort study of children in the world involves the necessary number of subjects (about 500,000) to conduct a prospective study of environmental exposures and leukemia in children. On September 28 and 29, 2005, NICHD, the National Cancer Institute (NCI), and EPA brought together representatives of 12 child cohort studies to determine whether a collaboration of international cohorts could be brought together for such a study. Like the Study, each cohort has the capacity on its own to address hypotheses concerning causes of a number of infant and child conditions; but together, they have the large number of subjects required for a study of childhood leukemia. The 12 ICCCC members will provide a total number of subjects of approximately 700,000, which should potentially yield 450 cases of childhood leukemia.

Dr. Dwyer reviewed several studies to provide examples of the environmental causes that might be detected in the ICCCC study. There is sufficient “ecological” variation in incidence of childhood leukemia associated with socioeconomic factors to suggest that environmental and/or genetic factors must be important. In addition, there is good evidence that chromosomal translocations present at birth—probably occurring during fetal life—are important etiologically to childhood leukemia. The cohorts identified as contributors to the global collaboration have the capacity to contribute data on the environmental and genetic hypotheses of interest. Dr. Dwyer listed five hypotheses relating to prenatal, infancy, and childhood exposures that could be tested

in the large combined ICCCC cohort. He concluded that there is a high probability that the cohort data can provide insights into the etiological pathway of childhood leukemia.

Dr. Dwyer described the next steps for the ICCCC. A working group has been formed to develop collaboration involving NCI, the Study, and key cohort investigators to more carefully examine comparability of exposure data and to encourage necessary collaborative input and recruit new studies to the collaboration.

Instructions for the Breakout Sessions

Carole A. Kimmel, Ph.D., Consultant, National Children's Study Program Office, NICHD, NIH, DHHS

The purpose of the breakout sessions was to communicate the methods development and pilot study activities to date and have participants address challenges and possible solutions in implementing the Study. The breakout session topics were as follows:

- Exposures—biological and psychosocial
- Exposures—chemical and physical
- Outcomes—neurodevelopmental outcomes
- Outcomes—pregnancy outcomes, growth, and physical development
- Community engagement—recruitment and retention
- Information technology issues and data collection
- International collaboration.

Day 2 Plenary Session

Welcome

Marion J. Balsam, M.D., Research Partnerships Program Director, National Children's Study Program Office, NICHD, NIH, DHHS

Dr. Balsam introduced herself and welcomed participants to the second day of the Study Assembly Meeting. She explained that a study as complex and unique as the National Children's Study provides unique and complex challenges and opportunities. The opportunities include (1) linking innumerable exposure measures with innumerable outcome measures, (2) providing evidence-based information to influence health care policy and provision, and (3) following the actual health of children and the adults they become. The challenges span scientific, methodological, ethical, and societal issues. The following presentations addressed some of the pivotal issues for the Study.

Science, Ethics, and Society and the Lives of Children and Families

Thomas H. Murray, Ph.D., President, The Hastings Center

Dr. Murray discussed scientific, ethical, and societal issues about the lives of children and families as they pertain to the Study. He described his presentation as a serious inquiry into how the Study can think about children and their relationship with parents and society—without

either corrosive cynicism or empty sentimentalism. The purpose of this inquiry is to think deeply but clearly about the moral significance of children.

After briefly describing the Ayala case, in which the father's vasectomy was reversed so that a second child could be born to provide a bone marrow match for a first child who had chronic myelogenous leukemia, Dr. Murray listed three reasons for having children: good, bad, and none at all.

Dr. Murray noted that philosophers have tried to understand the relationships between parents and children. The usual categories of moral motivations for having children are (1) egoism/selfishness or (2) altruism. However, the paradigm of parenthood is for the parent to do well for the child to gain benefit for oneself. While helping a child flourish, a parent becomes a better person, as does the child. Dr. Murray explained that the true moral motivation is mutualism between parent and child.

Dr. Murray then asked: What is the worth of a child? An economic understanding is least important in the context of this discussion because there is little economic benefit to parents. Worth is better appreciated in the vital role that children play in the lives of caring adults and in the vital role that caring adults play in the growth and flourishing of children. What is important is: children in the context of the families in which they live. For the Study, Dr. Murray suggested that *family* be defined as broadly as possible as the circle of people with whom the child lives and whose lives are intertwined with the child's. In this context, the parent-child relationship can be presented in three models:

- Ownership
- Stewardship
- Mutualism.

Dr. Murray discussed the history and current, surviving threads of ownership and stewardship, but discounted them as viable models. Mutualism is viable, as an intense, vital lifelong relationship between parent and child.

With this framework of the worth of a child in the context of a mutualistic parent-child relationship, Dr. Murray briefly reviewed the evolution of thought on the bioethics of child research. He mentioned the Nuremberg code, the clashing philosophies of Paul Ramsey and Richard McCormick, and the first presidential commission on bioethics in research. Dr. Murray cited several examples in which a good, responsible parent might expose a child to potential, but minimal risk for the benefit of others. These examples were provided as possible analogies of the Study, in which observational research presents minimal risk but no direct benefit to the participants.

Dr. Murray observed that the Study has an astonishing potential to positively affect children and families. He concluded his presentation by noting three challenges to the Study and asking how the Study will address them:

- Children who are not flourishing (for example, due to environmental exposures or abuse)

- Children whose provider/caretaker is not a biological parent (for example, adoption or misattributed paternity)
- Role of racial and ethnic differences in health outcomes or other socially significant nonhealth outcomes.

Pivotal Issues for the National Children's Study

Challenges Facing the National Children's Study: Integrating Social, Biomedical, and Environmental Factors in One Comprehensive Study

Virginia A. Rauh, Sc.D., M.S.W., Professor of Population and Family Health, Deputy Director, Columbia Center for Children's Environmental Health, Heilbrunn Center for Population and Family Health, Columbia University Mailman School of Public Health

Dr. Rauh commented that the Study provides a remarkable opportunity of integrating social, biomedical, and environmental factors into a single comprehensive study. To succeed at this integration, the Study must know how to appropriately frame questions to fulfill its mission. Many fully integrated studies have been conducted, and many individuals have proposed social-contextual approaches to understanding environmental health, resulting in numerous reports. Dr. Rauh reported that the contextual integration of many complex domains has been achieved. The real challenge for the Study is to formulate and test research questions so as to arrive at the right answers to the right questions.

Type III errors—the right answer to the wrong question—may arise when methods designed to test hypotheses about interindividual variation are used to address questions about increases in rates over time or disparities between groups. Most epidemiologic methods were developed to study causes that distinguish individuals within a population, and research questions are best addressed with data that include substantial variation in the variables of interest. Variation is usually maximal at the individual level.

Dr. Rauh listed five reasons for conducting the Study:
- Changing patterns of disease
- Changing environments
- Unique vulnerability of children
- Environmental factors are now known to contribute to disease in childhood and adulthood
- Diseases of environmental origin are costly.

Dr. Rauh cited asthma and obesity as examples of changing patterns of disease, described what is known about each as public health problems, noted possible sources of error (that is, getting the right answer to the wrong question), and provided some possible consequences of the resulting Type III errors. She cited organophosphate pesticides as an example of changing environments.

Dr. Rauh explained that the Vanguard Centers, the Steering Committee, and all future Study sites will be working for a long time to determine the right questions by:
- Setting priorities

- Selecting the general classes of research questions that are relevant to the health of America's children
- Embracing an interdisciplinary focus
- Soliciting input from community advisors
- Allocating scant resources appropriately
- Designing an overall sampling strategy that permits the formulation of research questions concerning rates of disease, as well as individual risk of disease
- Designing a second stage sampling strategy that ensures sufficient variability in risk factors so as to permit the testing of interactions.

Community Engagement in the National Children's Study: Challenges and Opportunities

Edith A. Parker, Dr.P.H., Associate Professor, Health Behavior and Health Education, and Associate Dean for Academic Affairs, School of Public Health, University of Michigan

This presentation was based on a literature review of 20 longitudinal observational studies, community-based participatory research (CBPR), and literature on ethics in research. Based on this review, Dr. Parker noted the following reasons for community engagement:

- May enhance research by
  - Contributing to more complete and equitable assessment of environmental exposures
  - Offering greater participation of residents in study activities (recruitment and retention)
- Provides additional safeguards in ethical concerns
- Helps to ensure understanding of study by participants and broader community
- Provides foundation for "what next" (public health and local interventions that build on the research).

CBPR is a partnership approach to research that fully involves community members, organizational representatives, and researchers in all aspects of the research process. As identified in an Institute of Medicine report on housing research (*Ethical Considerations for Research on Housing-Related Health Hazards Involving Children*, The National Academies Press, 2005), there are limits to what is known about outcomes of community involvement. Published literature about community involvement in environmental health research is most commonly about CBPR strategies.

The Study's opportunities for community engagement include:

- Initial assessment
- Protocol refinement
  - Aid in defining "segments" for environmental sampling (based on functional neighborhoods)
  - How study is introduced locally and to participants
  - How people are recruited
  - How and where data are collected
  - Appropriateness of incentives
  - Missing variables/exposures/research questions

- Study implementation
  - Recruitment of participants
  - Data collection
  - Retention strategies
- Data interpretation and feedback
  - Assist with interpretation
  - Advise on local and participant feedback of results.

Challenges to community engagement in implementation of the Study include:
- Defining community
- Identification of community representatives
- Goals of community involvement
- Practical challenges.

Issues for consideration include:
- Clarity about extent of involvement and influence
- Structure of community involvement
- Resources for efforts
- Support for sites around community involvement
- Importance of initial assessment/planning phase.

Broader opportunities for the Study are:
- Demonstrate models of community engagement in more traditional observational research
- Contribute to capacity building of the communities in which the Study takes place.

Dr. Parker listed possible entities to involve in a community advisory board and gave examples of community advisory board members from the Centers for Children's Environmental Health and Disease Prevention Research. She concluded by suggesting ways in which communities may be engaged by the Study during protocol development, institutional review board considerations, and recruitment.

Combining a Probability-Based Sampling Strategy with a Center-Based Approach

David A. Savitz, Ph.D., Professor and Chair, Department of Epidemiology, School of Public Health, UNC

Dr. Savitz explained that the rationale for a national probability sample in the Study was to:
- Seek understanding of social, economic, and environmental factors, as well as biomedical influences
- Guide national public policy
- Engage broad public support
- Examine influences within and between geographic locations
- Estimate attributable fractions for influences on children's health
- Avoid dependence on medical care for inclusion or timing of enrollment in pregnancy
- Include subset with preconception enrollment

- Collect most of desired data and specimens in the home
- Improve understanding of nonresponse.

The key challenges in implementing a national probability sample are:
- Feasibility of identifying pregnancies through household surveys and recruiting those who become pregnant
- Feasibility of obtaining access to hospitals serving recruited women
  - Need to collect delivery specimens
  - Need for systematic newborn examination.

Dr. Savitz described his experience with a center-based approach:
- Prospective cohort study of preterm birth at UNC
- Identification and recruitment in early pregnancy through prenatal clinics
- Extensive data collection—blood, vaginal, and urine specimens; interviews; self-administered questionnaires; ultrasound; placenta collection.

The center-based approach was successful because of:
- Committed team of investigators, including obstetricians in clinics
- Appreciation of research by hospital and patients
- Access to medical records for recruiting patients through partial waiver of requirements under the Health Insurance Portability and Accountability Act of 1996
- Research nurse familiar with clinic activities
- Assistance of clinic staff—attending physicians, residents, nurses, clerical staff
- General clinical research center access for ultrasound and blood processing
- Offered to take over placenta management
- Centralized location enabled research staff to meet all study needs.

The key contrasts between center-based and population-based designs are:
- Random selection not based on location of research centers or health care facilities
- Pregnancies identified in community, not in prenatal clinic
- Multiple prenatal care providers and delivery hospitals serving community
- Dispersed across prenatal care providers and delivery hospitals with low volume of participants in each.

Dr. Savitz noted that the consequences of a population-based sampling strategy include:
- Variable support for research activities across prenatal care providers and delivery hospitals
  - Goodwill to accommodate study needs from clinic and hospital administrators
  - Attitude of clinicians toward patient participation
  - Staff training and quality
  - Available technology
- Multiple delivery hospitals preclude having research staff at all facilities
- Inability to institute consistent protocol at all delivery hospitals
  - Collect placenta within existing specimen handling system
  - Cord blood collection at delivery by staff person

  - Neonatal examination requires trained staff.

The logistical advantages of the population-based approach are:
- Initial engagement of women makes them an advocate for cooperation of clinician, health care facility
- Visibility and support for study in defined *communities*, not just within health care setting
- In-home data collection avoids challenges of integrating research into clinic protocol, more convenient for participant.

Strategies for in-hospital data and specimen collection include:
- Targeting facilities where deliveries will be concentrated
  - Developing formal collaboration
  - Defining procedures for flagging participant deliveries
  - Providing research staff to collect specimens and conduct examinations
- For low-volume facilities, tailoring the approach
  - Making staff aware of study
  - Developing system for staff member to respond when hospitalization for delivery occurs.

Dr. Savitz concluded by offering the following comments about combining a probability-based sampling strategy with a center-based approach:
- The design requires tradeoffs.
- Engagement of health care facilities is a key logistical challenge of probability-based sampling.
- The approach may encourage biomedically sophisticated research in community settings (if successful).
- The approach may enhance support of community health care providers for clinical and epidemiologic research (if successful).

Panel Discussion

Moderator: Peter C. Scheidt, M.D., M.P.H., Director, National Children's Study, NICHD, NIH, DHHS

Panel discussion topics and issues included the following:
- The timeframe for awarding and implementing the other 98 Study sites has not been established. To date, there is funding only for the Vanguard Centers and Coordinating Center. Future budgets will ultimately determine full Study implementation.
- Illegal immigrants/undocumented aliens will be included in the Study if they reside in secondary sampling units within a specified timeframe and otherwise qualify for Study participation. Study centers will be responsible for tracking subsequent moves of Study families out of secondary segments. Once participants are recruited, there will be designated plans for follow-up. National mobility will be a challenge to the Study.
- County and local health and human service agencies and departments often have restricted budgets and limited resources. Remuneration or direct stipends to these agencies and

departments are creative approaches to maintain community-level involvement in research projects. Individual volunteers may prove invaluable.

- The Study is not a direct provider of medical care. There are neither funds nor plans to provide medical or follow-up care. However, Study centers must have plans for appropriate referral.
- Women who volunteer for the Study will be accepted, provided they live within secondary sampling units and are otherwise qualified. Other volunteers could be "earmarked" and studied in some other fashion.
- Secondary sampling units have not yet been determined and will not be specified in any future RFPs.
- Issues involving IRB approval and informed consent for collecting and storing genetic materials have not yet been resolved. There are many unframed future questions. Some individuals question whether DNA and other genetic materials are any different than any other non-neutral medical or health information. Ethical and legal issues of human specimen materials will be addressed by appropriate Study entities.
- There are many aspects and considerations for providing incentives to Study participants. Ideally, incentives should not unduly encourage Study participation and should not be considered as fee-for-service, bribes, or market transactions. Compensations for transportation, time, and effort may be appropriate. Incentives are expressions of seriousness and commitment of a research project. IRB issues and issues of children's assent need to be considered.
- Study centers and their community partners will need to address liability issues on interpretations of data meaning by outside, activist, or "concerned" groups (that is, groups that may have philosophical or religious objections to the Study).

Moving Forward with Implementation

CDC Perspective

Marshalyn Yeargin-Allsopp, M.D., Member, ICC; Medical Epidemiologist, National Center on Birth Defects and Developmental Disabilities, CDC, DHHS

Dr. Yeargin-Allsopp presented the CDC's perspective on moving forward with implementation of the Study. She listed a few historical highlights of the CDC's participation in the Study:

- Leadership and participant in working groups for the President's Task Force on Health Risks and Safety Risks to Children, 1998–2000
- Named as one of the lead agencies in the Children's Health Act, 2000
- Ongoing collaboration with EPA and NIH, 2000–present.

The CDC's collaborative involvement in the Study includes:

- Planning efforts, including activities to promote intra- and interagency collaborations, Study Assembly meetings, workshops, and white papers
- Development of methods for assessing environmental and parental occupational exposures
- A focus on the fetal origins of health and disease, including birth defects, developmental disabilities, obesity and diabetes

- Financial support
- Leadership in oversight of the collection, storage, laboratory processing and analysis of biomarkers of exposure
- Leadership in the incorporation of genetics and gene-environment considerations in the Study Plan
- Developed a probability sampling framework that will allow for enrollment of a representative sample of women and children from the U.S. population and their evaluation and follow-up by centers of excellence during the course of the Study.

Knowledge gaps the Study can address include:
- Defining the nature and extent of the problems facing infants, children, and adolescents throughout life stages
- The impact of environmental and genetic factors on child health and development
- Exposure-outcome relationships for conditions that are of concern to the pediatric and public health communities and families, such as pregnancy outcomes, neurodevelopment, asthma, injuries, obesity, and physical development.

The CDC's health impact goals include:
- Healthy people in every stage of life—aims to ensure that all people, and especially those at greater risk of health disparities, achieve their optimal lifespan with the best possible quality of life at every life stage
- Healthy people in healthy places—aims to ensure that the places where people live, work, learn, and play will protect and promote their health and safety.

Dr. Yeargin-Allsopp explained that the Study will provide information on rates and risk factors for health outcomes included in the CDC's Health Impact Goals for infants, toddlers, children, and adolescents and will help CDC assess progress in Health Impact Goal areas. She added that high-quality research, such as the Study:
- Is critical to help the scientific community, parents, and policy makers gain sufficient knowledge and understanding of environmental influences on child health and development
- Helps to develop evidence-based interventions.

Dr. Yeargin-Allsopp concluded by noting that the future involves:
- Continued collaborations with EPA, NIH, and other Study partners
- Mutual benefits for lead agencies and Study partners
- A springboard for broader efforts to improve the overall health of children in the United States.

Children's Environmental Health: Research Complementary to the National Children's Study

Gwen W. Collman, Ph.D., Chief, Susceptibility and Population Health Branch, Division of Extramural Research and Training, NIEHS, NIH, DHHS

Dr. Collman reviewed NIEHS's role in laying the groundwork for the Study. She listed research areas of NIEHS longitudinal studies that are complementary to the Study. The focus of Dr. Collman's presentation was the Centers for Children's Environmental Health and Disease Prevention Program, a joint NIEHS/EPA effort. The purpose of this program—which included laboratory, population health effects, and exposure assessment research—was to:

- Develop and test risk management strategies in order to protect the health of children
- Promote multidisciplinary interactions among basic, clinical, and behavioral scientists and develop a future workforce
- Accelerate translation of basic research findings into clinical or intervention strategies to reduce exposures and health outcomes in young children
- Establish a national network of children's environmental health researchers.

The Centers for Children's Environmental Health and Disease Prevention Program is addressing questions about respiratory disease, growth and development, and autism. The lessons learned from the program were published in *Environmental Health Perspectives* in October 2005; they included:

- Time—to assess the full range of developmental consequences to environmental chemicals and other exposures
- Outcome assessment—both broad and narrow in scope
- Exposure assessment—environmental and personal measures working in concert with observational and ecologic approaches
- QA/QC
- Community participation is paramount to success
- Ethics.

Dr. Collman described the program's focus on exposure assessment, its biomarker research, and possible strategies for improvements in exposure assessment. She noted that more precise markers of exposure link personal exposures to body burden to biological response.

Dr. Collman concluded by describing NIEHS's new Exposure Biology Initiative. The goal of this initiative is to develop biomarkers of cellular responses in humans and animals to environmental exposures (toxicogenomics, proteomics, metabolomics), determine whether there are exposure-specific signatures, and focus on well-characterized populations with stored biospecimens to develop and validate exposure-response markers.

EPA's Role in the National Children's Study

William Sanders, III, Dr.P.H., Director, Office of Children's Health Protection, EPA

Dr. Sanders reviewed EPA's historical role in the conception and planning of the Study, declaring that EPA is proud to be a key partner is this important endeavor. EPA has been involved with the Study since the beginning, was the first agency to fund a pilot study, and provides a leadership role in the NC Herald Study. EPA is helping to develop the quality management plan for the Study and is working with DHHS on Study data management efforts.

The Study is important to EPA because it supports the agency's mission to protect human health and the environment. The Study will address multiple hypotheses as well as evolving questions and help scientists, researchers, and clinicians understand the links between environmental exposures and health outcomes. EPA also has a mandate to protect the health of infants and children. The mission of the Office of Children's Health Protection is to provide basic information to citizens and communities—as well as organizations, industry, and government entities at all levels—to enable them to take steps toward protecting their children from environmental health threats. EPA needs research data to carry out this mission, and the Study will generate valuable data to help protect children.

EPA has a continuing commitment to strongly support the cross-agency collaboration of the Study. EPA shares the perseverance, deep commitment, and sheer dedication of all individuals, agencies, and organizations that are involved with the Study. Together with its key partners and supporters, EPA is committed to reducing children's morbidity and mortality. EPA will continue its strong support of the Study with funding, staff resources, and a deep commitment to ensure that America's children are provided a safe and healthy environment in which to grow and to thrive.

NICHD Perspective

Yvonne T. Maddox, Ph.D., Deputy Director, NICHD, NIH, DHHS

Dr. Maddox explained that the Director of NICHD, Dr. Alexander, and NICHD are both fully committed to supporting the Study, both directly and through other NICHD-supported research that is vitally connected to the Study. She noted that this research focuses on the fetal antecedents of adult disease and that many common chronic disorders have modifiable factors that occur or arrive sometime during childhood. Dr. Maddox briefly discussed the Life Course Model, which provides a scientific basis for understanding the continuity between child and adult health. This model seeks to promote the well-being of the young, both because of the intrinsic value to the young and its ability to improve the health of the population at all ages. Dr. Maddox noted that the Life Course Model seems to be particularly relevant to the Study.

One of the key challenges for the Study is keeping the community engaged and informed at all stages of this research project. Other challenges include the communicating what the Study is—and what the Study is not—to each community. Results must be communicated and explained to each community as they become available. Communities must be engaged with regard to incentives for recruitment and retention, and issues of confidentiality and informed consent must be addressed. Enrollment at the Vanguard Centers must move forward. The Study sample must represent the full complement of America's diversity to produce an ethnically and socioeconomically representative cohort.

The Study provides opportunities to improve the nation's health by reducing or eliminating health disparities. The Study's results will help researchers understand the reasons for health disparities and will provide answers to why there are regional differences in health disparities. Once the answers are known, they must be communicated to communities in culturally competent ways. Communities must be engaged to help resolve health disparities, and the

message of the Study must be conveyed to America's communities. Dr. Maddox suggested that those who want to be involved with the Study should align their sites with academic health centers and center philosophies in an effort to be culturally competent and have communities fully engaged.

Dr. Maddox concluded by emphasizing how critical the established relationships and continuing collaboration among key partners are to the success of the Study. Important elements of the Study's success include funding from the lead agencies; staffing contributions to the Program Office and ICC by the lead agencies; and the intellectual support from academic, research, and advocacy communities. NIH and NICHD are committed to continued funding for the Study.

Summary and Next Steps

Peter C. Scheidt, M.D., M.P.H., Director, National Children's Study, NICHD, NIH, DHHS

Dr. Scheidt thanked Dr. Kimmel and Dr. Balsam for their dedicated efforts on planning this Study Assembly meeting. He announced that the Study's Federal Advisory Committee will hold an open, public meeting on January 24–25, 2006. Dr. Scheidt briefly reviewed the presentations of this 2-day meeting and thanked the presenters for their dedication and commitment to the Study. With the awarding of the contracts for the Vanguard Centers and the Coordinating Center, the Study is moving forward with implementation. The building of the infrastructure has begun, and real Study participants will soon generate real data. The lead agencies will hold fast to the Study's mission and goals and will continue to provide justification for funding. Once the importance of the Study is fully recognized, its full implementation will become a reality.