

# National Children's Study Federal Advisory Committee 13th Meeting January 24-25, 2006

**Gaithersburg Marriott Washingtonian Center  
Gaithersburg, MD**

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 \(DHHS\)](#) (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 One

### Welcome and Introductions

*Alan R. Fleischman, M.D., National Children's Study Advisory Committee Chair, Senior Advisor, New York Academy of Medicine*

Dr. Fleischman welcomed the National Children's Study Federal Advisory Committee (NCSAC) members and other participants to the 13th meeting of the NCSAC. He noted the following:

- This meeting marks the fourth anniversary of the NCSAC's inception.
- Five NCSAC members have completed the 4-year maximum tenure and will rotate off the committee.
- New NCSAC members have been nominated and submitted for approval. They will be introduced at the next NCSAC meeting (May 31–June 1, 2006, in Bethesda, MD).

Dr. Fleischman welcomed NCSAC ex officio member Robert F. Spengler, Sc.D., Director, Office of Public Health Research, CDC, as the new CDC representative on the Federal Advisory Committee. He thanked Marion J. Balsam, M.D., NCSAC Executive Secretary, and Jessica Sapienza, M.H.S., NCSAC Committee Liaison Officer, for their work organizing the meeting.

**Federal Advisory Committees.** Dr. Fleischman noted the following:

- The federal government may obtain advice on long-range planning and development of programs from groups of outside experts through the formation of advisory committees.
- The Federal Advisory Committee Act (Public Law 92-463; passed on October 6, 1972) creates standard and uniform procedures governing the operation of all advisory committees.
- The function of the NCSAC, as with all federal advisory committees, is to advise—to think carefully and deeply about issues and to make recommendations and give advice.
- Advisory committee meetings are generally open to the public with specific limited exceptions.
- The advice of the NCSAC goes to the Study Director, Peter C. Scheidt, M.D., M.P.H.; to Dr. Alexander, M.D., Director, NICHD; and to the Study's Interagency Coordinating Committee (ICC).

Issues discussed at the September 21–22, 2005, NCSAC meeting included:

- Update on the Study

- National Research Council/Institute of Medicine Report: *Ethical Considerations for Research on Housing-Related Health Hazards Involving Children* (2005)
- Roles of behavioral and psychosocial factors in the Study
- Ethical considerations: Informing participants, families, and communities of information learned
- Role of genetic information in the Study
- Peer review of the Study protocol
- Process for adjunct and core Study “outside” proposals
- Clinical, economic, and regulatory implications of the Study
- Dr. Alexander’s report on the Study and his advice to proceed with planning and implementation of the Study.

## Welcome and Overview of the National Children’s Study

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

Dr. Scheidt welcomed NCSAC members. He noted that much has happened regarding the Study since the last NCSAC meeting in September 2005. Contracts were awarded for the Clinical and Data Coordinating Center and seven Vanguard Centers.

The Coordinating Center is a consortium of Westat, 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. Principal investigator is Carla E. Maffeo, Ph.D., of Westat.

- The Vanguard Centers and their principal investigators are as follows:
- Vanguard Center for Duplin County, NC
  - University of North Carolina at Chapel Hill with Battelle Memorial Institute and Duke University
  - Principal investigators: Barbara Entwisle, Ph.D., and David Savitz, Ph.D., University of North Carolina at Chapel Hill
- Vanguard Center for Orange County, CA
  - University of California-Irvine with Children’s Hospital of Orange County
  - Principal investigator: James Swanson, Ph.D., University of California-Irvine
- Vanguard Center for Queens, NY
  - 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
  - Principal investigator: Philip Landrigan, M.D., M.Sc., Mt. Sinai School of Medicine
- Vanguard Center for Montgomery County, PA
  - Children’s Hospital of Philadelphia and Drexel University School of Public Health with University of Pennsylvania
  - Principal investigators: Donald F. Schwarz, M.D., M.P.H., M.B.A., Children’s Hospital of Philadelphia, and Jennifer Culhane, Ph.D., M.P.H., Drexel University
- Vanguard Center for Waukesha County, WI
  - 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

- Principal investigator: Maureen Durkin, Ph.D., Dr.P.H., University of Wisconsin-Madison
- Co-principal investigator: Chris Cronk, Sc.D., Medical College of Wisconsin
- Vanguard Center for Salt Lake County, UT
  - University of Utah
  - Principal investigator: Edward B. Clark, M.D., University of Utah
- Vanguard Center for Brookings County, SD, and Lincoln, Pipestone, and Yellow Medicine Counties, MN
  - South Dakota State University with support from the Cincinnati Children’s Hospital Medical Center and the University of Cincinnati
  - Principal investigator: Bonny Specker, Ph.D., South Dakota State University.

Dr. Scheidt noted the following activities:

- Local events were held at each Vanguard Center to announce and celebrate awards.
- The Study has received much attention from the media.
- A Study Steering Committee was established.
- Protocol development continues.
- A Study Assembly meeting was held November 29–30, 2005.
- The budget for 2006 was released.

Dr. Scheidt gave the following details about the announcements of center awards:

- September 29, 2005, 1:00 p.m., National Press Club.
- Lead federal agencies
  - DHHS—U.S. Surgeon General, Vice Admiral Richard H. Carmona, M.D., M.P.H.
  - NICHD—Director, Dr. Alexander
  - EPA—Assistant Administrator for Science, William H. Farland, Ph.D.
  - CDC—Deputy Director, Dixie E. Snider, Jr., M.D., M.P.H.
- Other partners include the March of Dimes, the American Academy of Pediatrics, the National Medical Association, the National Hispanic Medical Association, and the Children’s Environmental Health Network.
- Attendees included principal investigators for Coordinating Center and Vanguard Centers.
- Local media events were planned and carried out at each Vanguard Center.

Dr. Scheidt characterized interest in and responses to the Study by the number of 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.

The Study’s Steering Committee composition and structure are as follows:

- Voting membership/participating individuals
  - Coordinating Center—1/5
  - Each study (Vanguard Center)—7/14
  - ICC members 3/3—representing NICHD, EPA, CDC

- Project officers 2/2—Vanguard Centers, Coordinating Center
- Chair—Study Director, appointed by the Director, NICHD
- Meetings
  - November 9–10, 2005
  - November 29, 2005
  - January 10–11, 2006
  - March 21–22, 2006
  - July 18–19, 2006
  - November 7–8, 2006.

Steering committee roles and responsibilities include:

- Identifying problems and best practices that arise in the conduct of the Study
- Giving scientific input/expertise to support decision making
- Making recommendations regarding scientific content of a Study component
- Reviewing and approving (not the only approval) adjunct/add-on studies
- Decision making about nondirection-changing (and budget neutral) issues related to the protocol and manual of operations (MOP)
- Proposing changes to the protocol
- Assessing progress for achieving goals in data management and collection
- Monitoring safety issues
- Reviewing proposals for analyses from the Study
- Acting as first line of determining action on ethical issues of the Study
- Serving as a conduit of information from the Study Program Office/ICC to field entities
- Identifying additional training needs
- Determining subject matter prioritization and authorship for results and hypotheses.

Many individuals are working to develop the Study protocol, which stems from the Study Plan:

- The Study protocol is the document that specifies the data collection procedures.
- It is essential for specific planning and resource allocation, peer review, institutional review board (IRB) review and approval, and Office of Management and Budget (OMB) review and approval.
- Teams have been formed for Study protocol domains, with teams composed of Study Program Office, Coordinating Center, and Vanguard Center investigators.
- Availability of the draft Study protocol is planned for February–May 2006
  - For review by ICC
  - To Steering Committee
  - For OMB and peer review.

Dr. Scheidt presented highlights of the Study Assembly Meeting, which was held November 29–30, 2005, in Washington, DC:

- 306 attendees
- Introduced the Coordinating Center and Vanguard Centers
- Presented the results of pilot studies in posters and breakout sessions
- Considered major challenges to the Study
- Quote of the meeting from one attendee—“the most significant epidemiological research since John Snow removed the Broad Street pump handle.”

- Dr. Scheidt reviewed the Study's funding status as of January 2006:
- Planning phase: fiscal years 2000–2003
  - \$20.7 million (from existing NICHD, EPA, CDC, and NIEHS budgets)
- Start-up: fiscal years 2004–2005
  - \$12 million per year (from existing lead agencies' budgets)
- Implementation: fiscal years 2006–2007
  - Fiscal year 2006 about \$10.5 million from existing budgets; no additional funds from congressional appropriation
- \$69 million required for fiscal year 2007 to proceed on current timeline
- To conduct full Study during fiscal years 2008–2034
  - About \$120 million per year for 25 years.

In concluding, Dr. Scheidt presented the following projected Study timeline

2000-Present	Pilot studies/methods development
2004	Developed Study design and Study Plan; posted requests for proposals (RFPs) for Coordinating Center and Vanguard Centers
2005	Awarded initial contracts (Coordinating Center and Vanguard Centers)
2005–2007	Start-up phase for Vanguard Centers
2006	Completion of the Study protocol
2006–2007	Requisite reviews and approvals (OMB, peer review, IRBs)
2006–2007*	Post RFPs for additional Study centers
2007*	Award additional Study centers (contracts)
2008–2012	Enroll participants and begin the full Study at Vanguard Centers
2007–2008*	Start-up phase for additional Study centers
2009–2012*	Enroll participants and begin full Study at additional centers
2009*	First Study results become available (methods, pilots, preliminary)

2013–2033*	Hypothesis-specific data analysis; publish data; public-use datasets
*Pending funding for fiscal year 2007	

After Dr. Scheidt’s presentation, comments and questions addressed the following topics:

- *A paper by the Michigan Alliance for the National Children’s Study titled “Making the National Children’s Study a Real Partnership with Academic Pediatrics,” which appeared in Pediatrics in November.* Dr. Scheidt noted that the paper addressed an important concern that funded investigators have about the impact of the Study on other research agendas. The paper makes the point that the Study is much more of an asset and facilitator of additional research than an obstacle to research in academic centers. The article was distributed to the NCSAC members.
- *A request that the Study timeline be provided in print form for the NCSAC.* Dr. Scheidt said he would be happy to share the timeline and noted that all the presentations are publicly available.
- *Plans for the eighth Vanguard Center.* Dr. Scheidt responded that the eighth Vanguard Center is still in the negotiation phase and could be still be awarded, despite the budget situation.
- *A suggestion that the emphasis be placed on the \$120 million annual appropriation needed for the Study rather than the total cost of the Study.*
- *Concerns by professional societies (the Pediatric Academic Societies and the Society for Gynecologic Investigation) that the Study would draw potential ROI funds away from investigator-initiated research.* Dr. Scheidt responded that funds for the Study are not drawing funds away from investigator initiated research. That is why Dr. Alexander has always believed that the funding for the Study needs to come from congressional appropriations. Dr. Scheidt clarified that existing funds refers to funds previously earmarked for the Study.
- *The roles and responsibilities of the ICC versus other Study entities.* Dr. Scheidt explained that the role of the ICC was primarily oversight. It is composed of senior staff and scientists from the agencies that have been providing the leadership and funding of Study development over the past 5 years. Its primary role is review and guidance and to ensure that the Study stays on track with regard to the mission of those agencies and original mission of the Study. Dr. Fleischman commented that the NCSAC provides advice and recommendations to the Study in a public process. Other Study entities are responsible for decision making and implementing the Study.
- *The absence of the National Institute of Nursing Research (NINR) as a lead agency for the Study and the role of NINR and other NIH Institutes with respect to the Study.* Dr. Scheidt explained that the Study’s lead agencies—DHHS, NICHD, NIEHS, CDC, and the EPA—were part of the task force that first proposed to the President that this study be planned and implemented. Those agencies were committed to carry out the Study, and the ICC was formed of members from those agencies. A number of other federal agencies including the NINR are participating in the Federal Consortium, which is a much broader group that provides input and helps with the Study. It was thought best not to greatly expand the ICC, but there is ample opportunity for agencies to provide input into the Study.
- *The role that the NCSAC will have on protocol development and the protocol.* Dr. Scheidt replied that Study planners felt that role of the NCSAC was to provide recommendations about relatively broad areas, emphasis, and direction rather than about fine details, such as the specific instruments and tests that will be included in the protocol. He noted that the NCSAC would receive information about the protocol at this meeting and in the future as the protocol goes forward, and the NCSAC’s response to that information would be useful. Dr. Fleischman noted that the NCSAC was instrumental in the

hypothesis development phase of the Study in an iterative process involving the Working Groups and workshops. That work is incorporated in the protocol.

- *What NCSAC members can do to help to secure funding for the Study.* Dr. Fleischman commented that NCSAC members are special government employees only on the days they are in session or directly working as NCSAC members. On all other days, they are citizens who can bring their concerns and interests to their legislative leaders and can help to convince the appropriation committees of the Senate and House that this is a critical study for the future of America's children. Dr. Fleischman added that the Friends of the NICHD and members of other advocate groups were aggressively working in this area. The role of NCSAC members, as scientists and clinicians and leaders in health, is to help make the case as to why this Study is so critically important for America's children and future adults. He asked that members let him know about any efforts in this area and that they ask for help or information as needed. NCSAC should not interpret the budget that came out of the OMB as an expression of disinterest or lack of enthusiasm by key legislators in Congress. Interest in the Study is still high, and if there is interest in their constituencies, legislators need to know that. An NCSAC member encouraged all NCSAC members to contact their legislators and mentioned a congressional briefing on the Study last year that was well attended.
- *Whether the Vanguard Centers were selected on a scientific basis so that they would be representative of the country and whether there was a plan to add other representative sites if full funding is not received.* Dr. Scheidt responded that the selection of the Vanguard Centers was exclusively based on the science and the capability to carry out the work, and the Vanguard Centers were randomly chosen for geographic distribution but are not necessarily representative of the country as a whole. Additional centers will be added if funding allows.
- *Community engagement, community representation on the Steering Committee, and the need for tools of engagement in communities that lack an infrastructure for participation.* An NCSAC member expressed concern about the construction of the Steering Committee and the need for a mechanism for communicating community-level concerns, recommendations, or criticisms of the Study to Study leaders and decision makers. The need to have a place now on the organization chart for the inclusion and participation of future community representatives was emphasized. Dr. Scheidt replied that community engagement and ethical issues have been on the forefront of concerns about the Study since the first meeting and are important issues. However, the Study does not yet know which neighborhoods within the sites will be selected as Study segments. The Study needs to know what communities will be included in the Study before it can begin to establish mechanisms to get input from those communities. He said that NCSAC members would hear later in the meeting about the selection process for those neighborhoods and when that information will be available. Dr. Scheidt noted that the structure and the process for community engagement is both site specific and local segment specific. Dr. Fleischman suggested that there is a need for a structural solution to the issue of "representation" of community interests at all decision making levels in the NCS including the Steering Committee.
- *A suggestion by one NCSAC member to include a community representative on the Steering Committee from each Vanguard Center.* Dr. Fleischman responded that the NCSAC could recommend that the Program Office, the Study Director, and the NICHD Director address the question of how to represent community interests at the decision making tables including the Steering Committee but need not make a specific recommendation for how such representation will be accomplished.
- *The functions of the Steering Committee.* Dr. Scheidt said the Steering Committee has a number of responsibilities as encompassed in the slides he presented and is the entity that deals with the operational experience of the Study. The Steering Committee is where problems will be identified and solutions proposed as the centers implement the Study in the field.

### *The Probability Sample: Creating the Segments*

*L. Randy Curtin, Ph.D., Senior Statistician, National Center for Health Statistics, CDC, and J. Michael Brick, Ph.D., Senior Statistician, Vice President, Westat*

Dr. Curtin provided an overview of the Study sample design. He explained the first stage of this process—how the primary sampling units were selected—and discussed the issues for the Study’s second stage of the probability sample—creating the secondary sampling units.

Dr. Curtin listed the following background issues that were discussed and addressed in choosing a national probability sampling approach for the Study:

- Probability versus nonprobability sampling
  - White papers
  - Workshops and conferences
- “National in scope”—coverage
  - Geographic/environmental
  - Health disparities (race/ethnic)
- Participation/response rates
- Observational unit(s)
  - Child from moment of birth/delivery hospital
  - Pregnant women/physician-service provider
  - “Prepregnant” women
  - Father
- Study center involvement.

Initial Study design decisions included:

- Sample size: at least 100,000 births
- Four years of enrollment
- Area probability sample (PPS)
- Multistage design
  - Primary sampling units (PSUs)
  - Segments: Secondary sampling units
  - All households in segment.

A PSU is defined as a single county (3,141 counties in the United States). Small counties will be combined to meet the minimum number of births required. A priori criteria for combining counties include geographic adjacency, births by residence, and distance measure (number of square miles). The number of suggested PSUs ranged from 30 to 800. A smaller number provide a data collection advantage, whereas a larger number provide better geographic coverage. The Study decided on 100 PSUs, based on workload/coverage considerations and an estimated 1,000 births per PSU.

With regard to geographic/metropolitan control, Dr. Curtin listed the following:

- Options
  - National only
  - Four Census regions
  - Nine Census divisions

- 10 EPA regions/divisions
- 51 states (including Washington, DC)
- Decision—Utilize the nine Census divisions
- 1990 metropolitan/nonmetropolitan (rural health)
- 18 “major” strata formed.

Stratification variables for a hierarchy with 18 major strata include:

- Stratum size = 160,066 resident births
- Self-representing (>100,000 births)
  - Locations versus PSUs (for example, Los Angeles)
  - 13 locations/18 PSUs
- Non-self-representing hierarchy
  - If metropolitan, then size of metropolitan area
  - Percentage American Indian
  - Percentage Asian
  - Percentage Hispanic
  - Percentage Black
  - Percentage low birth weight.

Dr. Curtin presented a table of initial PSU allocation by metropolitan self-representing, metropolitan non-self-representing, and nonmetropolitan areas and by geographical location.

The selection of Vanguard Centers was based on the 96 locations/101 PSUs. Details include:

- Eight locations; two in each of four Census regions
  - Two large metropolitan areas from the West and East
  - Two nonmetropolitan areas from the Midwest and South
  - Four metropolitan areas—one from each region
- Selected at random.

Dr. Curtin characterized the final PSU design:

- Some augmentation was needed and additional PSUs were added to result in 105 locations
  - Large self-representing hierarchy as “multiple” PSUs: 110 PSUs total
  - 23.6 percent rural (as opposed to 17 percent of the United States)
  - Some locations are multiple counties
  - 120 counties in 41 states are in sample.

Dr. Brick listed the objectives of Study’s second stage of the probability sample:

- Define segments
- Determine number of segments to be sampled in each PSU
- Determine stratification variables for segments for each PSU
- Select segments
- Evaluate selection
- Collect data.

Some important decisions for the second stage of the probability sample included:

- No oversampling by extra screening of households
- Equal probability sample, to the extent possible
- No single measure to determine design
  - Geographic distribution of disease/risks
  - Geographic distribution of environmental exposures.

Competing objectives and remaining decisions include:

- National versus county coverage
- Costs versus analysis
  - Number of segments to be sampled in each PSU
- Definition of segment
  - Community engagement
  - Analysis/data linkage
- “Controlled selection” (that is, stratification and allocation) of segments.

Needs and assumptions for segment selection include:

- How many households yield how many births who will participate in the Study
  - National design/PSU based on national average
  - Local birth probability model(s)—trends
  - Response/participation rates
- Screen all dwelling units in segment for eligible women
- No additional screening for characteristics.

Response rate assumptions include:

- Brief household screener
- Extended screener
- Screener-to-birth retention
- Vanguard Centers provide input on specific rates
- Product of these rates should be no less than 75 percent.

Working assumptions include:

- Segments based on Census geography
  - Combination of Census blocks
- Sample size same for each segment
- Number of segments will generally range between 10 and 20, with fewer in the smaller counties/PSUs and more in the larger ones.

Dr. Brick presented maps of hypothetical segment samples for Duplin and Orange counties and described how segments will be defined and selected by Census data and birth data (2002–2005) geocoded to block level by the Vanguard Centers. He presented the following examples of Census geocoding results for two of the Vanguard Study sites:

- Duplin, NC, average of
  - 2,283 households per tract
  - 481 households per block group
  - 8 households per block
- Orange County, CA, average of
  - 1,621 households per tract
  - 512 households per block group
  - 37 households per block.

## General Discussion

After the presentation by Dr. Curtin and Dr. Brick, comments and questions addressed the following topics:

- *Effects on community engagement of using Census tracts or blocks, which may not be natural neighborhoods or communities, to determine segments.* Dr. Brick responded that the Vanguard Centers would help determine the segments in a way that makes sense at the community level, and community involvement will be sought from the communities selected as segments. Dr. Fleischman commented that the Study's statisticians would maintain the integrity of the probability sample during the iterative process of defining the segments. Dr. Curtin added that the sampling team has struggled with the definition of a community. The experiences of the Vanguard Centers will help to identify issues related to segment selection for future sites.
- *How the location of the Vanguard Centers relates to the sampled counties.* Dr. Curtin explained that after the PSUs (single or multiple counties) for the national sample were selected, a subset of PSUs was selected as vanguard sites or locations. Vanguard Centers were then selected to do the work for these sites.
- *Plans for future centers.* Dr. Scheidt replied that an announcement for centers to carry out the work will be forthcoming and that institutions would be asked to propose to do the work in more than one site. He estimated that there would be approximately 40 centers awarded on a competitive basis. Each center will cover, on average, two to three locations, and there will be some limits on the locations that a center might cover. Dr. Scheidt stressed the importance of distinguishing between locations and centers. Locations are the counties where the population will come from that will participate in the Study. There are 105 of them, selected by a national probability process. Centers will carry out the work in those counties.
- *Whether sampling segments would vary inversely with population density.* The response to this question was yes.
- *Engaging and obtaining input from local health departments.* Dr. Curtin said the Vanguard Centers' infrastructure involves teams that often include the local health department, and in any case the Study will need data from the local health departments. Dr. Scheidt noted that partnering with the local health department is a one measure of successful community engagement. The sampling team is looking for specific data from health departments for incorporation into the definitions of the segments. It was noted that the Study has used mailings and conference calls to communicate with local health departments about the Study.
- *The meaning of a 75 percent response rate for households.* Dr. Brick explained that there is a process from the time the Study finds a woman of childbearing age in a household through enrollment to giving birth. Across all households in a PSU, from all stages up to birth, the Study expects to get about 75 percent of all the births that happen in the sample households.

- *The number of households it will take to yield one eligible woman of childbearing age.* Dr. Curtin responded that, based on national data, probably between 12 and 15 homes (over a 4-year period) would be needed, but that estimate can be fine-tuned now that the PSUs have been selected.
- *Use of a provider practice based approach to identify pregnant women to participate.* Dr. Scheidt said that because the household approach will miss some individuals, there are plans to supplement the enrollment with recruitment through prenatal care providers and to use other community-based approaches in the segments, such as campaigns to encourage eligible women to volunteer.
- *The implications of having scattered segments in metropolitan areas for the collection of community-based data (for example, from day care centers, youth-serving groups, and schools).* Dr. Curtin said that this is the generic problem the Study faces dealing with a variety of population sizes by county. In four counties in South Dakota, the Study may be sampling 80 percent of the residents. In Orange County, the sampling team would prefer more segments of a smaller size to get better coverage, but then more hospitals and school districts will be involved. The team decided against targeting the sample to a single school district for several reasons. Dr. Brick commented that many families will move frequently and children will be changing schools, which will be a challenge for data collection.
- *Involvement of state health departments.* Committee members commented on the importance of involving state health departments, including the state health directors and the state maternal and child health programs.

### ***Environmental Measures and Exposures: An Overview***

*James Quackenboss, M.S., Environmental Scientist, Human Exposure Research Branch, National Exposure Research Laboratory, EPA, and Warren Galke, Ph.D., M.S.P.H., Environmental Epidemiologist, Study Program Office*

Mr. Quackenboss and Dr. Galke presented an overview of Study environmental measures and exposures, including:

- Process for developing exposure assessment approach
  - Hypotheses to agents
  - Approach and “proposed” measures
- Integrating input from Coordinating Center and Vanguard Centers
- Quality management plan (QMP) development
- Measurement error adjustment approaches
- Alternative measurement methods.

The technology-environmental measures group—composed of Study Program Office staff and other federal personnel, with some contractor support—began its efforts in January 2005 to:

- Identify what the Study needs to support testing of Study hypotheses (that is, not a “survey”)
- Provide a starting point for environmental measurements (what, when, and how)
- Identify rationale, suggested methods, and alternatives considered. The technology-environmental measures group evaluation process was described in a detailed chart.

Key Study hypotheses for environmental measurements include:

- Nonpersistent pesticides and poor neurobehavioral and cognitive skills
- Environmental exposures and genetic variation interactions and asthma
- Indoor and outdoor air pollution and asthma risk

- Disparities in asthma and physical environment risk factors, psychosocial stress, and health-related behaviors
- Chemical environmental agents and the endocrine system and age at puberty
- Genetics, environmental exposures, and type 1 diabetes
- Early exposure to bacterial and microbial products decreases risk of asthma
- Maternal subclinical hypothyroidism.

The four exposure domains are biological, chemical, physical environment, and psychosocial. The broad classes of chemicals/agents in the chemical and biological domains include:

- Persistent organic compounds
- Nonpersistent nonvolatile organic compounds
- Nonpersistent semi-volatile organic compounds
- Nonpersistent volatile organic compounds
- Bioaccumulative inorganic chemicals
- Nonbioaccumulative inorganic chemicals
- Criteria air pollutants
- Bioallergens.

To identify priority chemical analytes, the Study hypotheses were used to support the potential inclusion of chemicals/agents. Classes of chemicals/agents were assessed for potential measurement in environmental and biological sampling media. The technology-environmental measures group identified a minimum set of target analytes and assumes that others may be available from the same analysis run. To describe how hypotheses are related to priority chemical analytes, Mr. Quackenboss presented a chart listing analyte classes, target analytes, and related health and development outcomes.

The information used to identify exposure measures includes:

- Study hypotheses
- Study Plan (aims, domains, visit schedule)
- The Exposure to Chemical Agents Working Group's white paper, other pilot studies, and *Environmental Health Perspectives* papers
- Federal scientists consulted for advice on specific methods and approaches
- Approaches used in other major field studies and "standard methods" (where available).
- Considerations/rationale for selection of measures include:
  - Hypothesis-based selection of agents
  - Analytical methods that provide additional analytes
  - Maturity of technology
  - Environmental and biological measurements
    - Rely on environmental when no suitable biomarker exists
    - Rely on biological for persistent chemicals and chronic exposures
    - Limited sample availability (parent chemical in blood)
    - Consider environmental measures for nonpersistent chemicals and intermittent exposures
    - Concern about specificity and interpretation of metabolite measurements
- National scope of the Study
- Link measurements at different geographic scales (regional, community, individual)
- Adequate method sensitivity

- Adopting approaches from similar studies or using established methods
- Consider sampling and analytical cost and participant burden
- Sample storage stability and potential for future evaluation as technology evolves.

To provide some examples of environmental measures, Mr. Quackenboss presented a simplified summary of measures by visit—from prepregnancy, through pregnancy, to postnatal periods. Mr. Quackenboss noted that exposures from food/diet were not depicted in the chart.

The Study environmental team is integrating input from the Coordinating Center and Vanguard Centers. The team includes:

- Susan Viet, Coordinating Center (Westat)
- Mr. Quackenboss (EPA)
- Dr. Galke (NICHD)
- Sarah S. Knox, Ph.D. (NICHD)
- Carole A. Kimmel, Ph.D. (NICHD)
- Stephen Bedosky (LFR Levine Fricke)
- Peter Blood (Westat)
- Chris Williams (Westat)
- Information Technology (IT)/Information Management System (IMS) coordinators (Booz Allen Hamilton; Westat).

Vanguard Center representatives include:

- Steve Colome (CA: University of California, Los Angeles)
- Bruce Lanphear (SD/MN: Cincinnati Children's Hospital Medical Center)
- Rod Larson (UT: University of Utah)
- Paul Lioy (NY: Environmental and Occupational Health Sciences Institute).

The environmental team is chaired by Susan Viet from the Coordinating Center and reports to the Study Program Office. The team's organization and approach to developing measures is as follows:

- Environmental sample collection group
  - Finalize proposed exposures/methodology/visits
  - Develop standard operating procedures
- Environmental questionnaires/observations group
  - Develop questionnaires and observation instruments
- Statistical group
  - Strategy for subsampling and target sampling
  - Validation studies (measurement error adjustment)
  - Ensure that measures will support outcome.

The environmental team coordination provides input to other teams regarding:

- Biospecimen team support (biomarkers)—interface between biomarkers and environmental sample collection
- Measures team support (diet)—ensures that diet instrument addresses environmental contaminants

- IT group—support development of IMS components for environmental sample collection
- Geographic information system (GIS) group (support)
  - Strategy for use of GIS in subsampling and community measures
  - Potential use of GIS in exposure assessments.

Discussions with Vanguard Center environmental representatives have been held to:

- Obtain feedback on proposed measures from all Vanguard Centers
- Collect information (not deciding on approaches)
- Request relevant protocols, standard operating procedures, and questionnaires.

The next steps for environmental team coordination are to:

- Prioritize when to consider/address comments by timing relative to OMB (burden)
- Assign to appropriate development group and bring proposal back to full team
- Incorporate into overall protocol for environmental measures (for review).

Dr. Galke provided an overview of the Study’s QMP development, which has been a joint effort of the Study Program Office, EPA’s Office of Research and Development (ORD), and contractor Neptune and Company, Inc. Dr. Galke listed the challenges to ensuring quality data in the Study:

- Multi-disciplinary objectives and perspectives
- Complexity and scope of proposed Study measures
- Geographic and environmental diversity with 100+ different Study locations
- Comparability of data collected by 30+ Study center teams
- Multiple laboratories and other testing facilities.

The background for developing the QMP is as follows:

- NCSAC raised the topic of quality assurance/quality control (QA/QC) needs for the Study
- Study Program Office
  - Established QA/QC requirements in RFPs
  - Initiated an interagency agreement with EPA’s ORD to develop a QMP for the entire Study
- EPA’s ORD issued a task order with Neptune and Company, Inc., to develop the QMP
- Neptune and Company, Inc., began working with the Coordinating Center, Vanguard Centers, and Study Program Office to develop the QMP
- Coordinating Center will oversee and implement the QA/QC aspects of the Study.

According to American National Standard E4, a QMP is defined as “a formal document or manual, usually prepared once for an organization, that describes the quality system in terms of the (1) organizational structure; (2) functional responsibilities of management and staff; (3) lines of authority; and (4) required interfaces for those planning, implementing, and assessing all activities conducted.”

Dr. Galke listed two “understandings” for adapting a QMP to the Study’s structure/needs:

- The Study can take advantage of existing guidelines and approaches but does not need to be hamstrung by them.
- The Study is a unique and specific enterprise, and a QMP can be designed accordingly.

The proposed approach for developing the Study QMP is as follows:

- Create an umbrella document
- Keep the total Study (big picture) in mind
- Document what is important for the Study
- Build on what is in place
- Avoid reinventing elements of Coordinating Center's quality documents and procedures such as the Study protocol, MOP, quality assurance program plan, and training guidelines.

Elements of the QMP include:

- Quality policy from Study management
- Organizational structure including roles and responsibilities critical to the Study approach to QA/QC
- Breakdown of the Study into work processes (technical work activities) to
  - Define inputs and outputs
  - Identify products/activities key to successful study performance
- Identify quality tools to address critical Study processes
  - Planning documents
  - Operating procedures
  - Training
  - Reviews and audits.

Measurement error adjustments (validation studies) are being developed by the Study Program Office, Battelle Memorial Institute, and Harvard School of Public Health. Measurement error adjustment provides a “level of detail” for environmental measurements that:

- Increase “level of detail” often associated with increased costs and/or burden
- Provide options for selection of measurements, including
  - Method (sampling, analytical) specifications for accuracy, precision, detection limits, and more
  - Frequency of measurements (relative to temporal variability) and number of sampling locations (for example, within the home)
  - Selection of media (for example, by life stage) and chemicals/agents relative to “true” exposure (and dose) and to priority outcomes
  - Scale of measurements (for example, regional, community, household, individual).

Dr. Galke presented a chart depicting the range of alternatives for exposure assessments—from a lower level of detail to a higher level of detail—for air, dust/soil, and food/diet. Results from previous work on validation samples (from Battelle Memorial Institute, Harvard School of Public Health, and EPA) were also presented. It was noted that optimal designs depend on characteristics of exposure and health outcome of interest.

Battelle Memorial Institute and Harvard School of Public Health teams are currently developing a software tool to allow Study planners to research the benefits and limitations of alternative exposure assessment designs relative to testing Study hypotheses. Output will be provided on cost, sample size, and power across a range of designs. The software interviews users on critical design input regarding:

- Health outcome (and time points)
- Exposures and relationship between exposures (effect modifiers) and outcome

- Exposure assessment approaches and methods
- Sample size and resource constraints.

The decision pathway for Study exposure assessment consists of steps to characterize true exposure, effect modifier, outcome measure, and measurement methods.

It is envisioned that the Battelle Memorial Institute/Harvard School of Public Health validation sampling tool will allow optimal design recommendations for Study exposure assessment. Potential applications for measurement error adjustment include:

- Validation sampling may allow the Study to conduct more cost-effective data collection while still retaining necessary power to test Study hypotheses.
- The validation sampling tool for considering various exposure assessment approaches allows Study planners to identify optimal sampling strategies using validation studies.
- Designs are highly sensitive to design input.
  - Need to identify appropriate surrogates and their relationship with “true” exposures.

Dr. Galke concluded by presenting examples of environmental measurement “tools,” including:

- Air—pesticides, particulate matter, volatile organic compounds
- Outdoor and ambient air
- House dust for metals, pesticides, allergens
- Drinking water and soil
- Time-activity data, using tools such as an activity timeline and accelerometer.

After the presentation by Mr. Quackenboss and Dr. Galke, comments and questions addressed the following topics:

- *Privacy issues with respect to monitoring practices.* Mr. Quackenboss said that consent will be required from participants to place monitors in their homes. Certainly there will be a privacy and consent issue with regard to obtaining access to do the sampling in the home or outside the home. Monitoring done in schools or workplaces would require obtaining permission to do so. Biological monitoring done on a participant would automatically include all the environments the person visits.
- *Data collection with regard to domains other than chemical exposures.* Mr. Quackenboss noted that Dr. Brenner’s presentation would address this question and that the enabling legislation for the Study calls for environment to be broadly defined to include chemical, physical, social environments. The teams are addressing all of these environments. Observations and measurements in the home on the child might cover some of the social environment, and there will be observations at the community level. All these pieces will be integrated and the burden implications across all the measures will be considered.
- *The temporal sequence for collecting and analyzing samples and how the Study will deal with a finding that exceeds a threshold and has potential hazardous consequences.* Mr. Quackenboss responded that many other studies have had to grapple with this issue. Some of the samples will need to be analyzed shortly after collection, as they have a very short shelf life. Results will be forthcoming as fast as the data are processed, quality assurance checks are done, and the Study is satisfied that the results are a real value. Results would likely be reported to the investigators, who would report to the individual and the individual’s physician if there were direct implications to the health of the participants and their family members.

- *How environmental sampling will be affected by Study participants' mobility over the course of the Study.* Mr. Quackenboss said that this issue has come up in many discussions around sampling design. Calculations were made about people moving from one area to another, and the likelihood is that many people would move into another area that is also a Study site. For participants who move to a non-Study area, there are various ways that some data collection could continue, for example, through self collections and completion of questionnaires that would be mailed in. This could be managed through the Coordinating Center or other entities. There could be some follow-up on individuals to obtain exposure and outcome measures, and some clinic visits would need to be arranged.
- *The implications of advances in biomonitoring technology over the course of the Study.* Mr. Quackenboss commented that a group had addressed the technology issues and had organized a technology workshop that looked at forecasting and taking advantage of new developments. This issue folds into the quality assurance issues. The Study will need to be flexible enough to incorporate new technologies along the way, and it must consider what new techniques represent relative to measures taken before. The Study will also have to repeatedly update what is monitored. Dr. Galke explained that a critical component of the Study will be its sample repository for both biological and environmental samples. Some of the samples that will be collected will go to the repository without being analyzed to be stored for future analysis. However, the planners must first determine what will be collected and when.
- *Interpretation and communication of biomonitoring data and risk levels to people when few standards exist.* Mr. Quackenboss agreed that this is a significant problem, not just for the Study, but for other studies that collect these kinds of samples. In some cases, such as blood lead, there is a clear understanding of when people must be notified, but this information is not available for many other chemicals. As the Study collects samples and makes linkages, it will help improve the ability to determine the significance of exposures and to estimate risk. It is difficult to convey uncertainty about risk at the individual level. Dr. Fleischman commented that the process within the Study to evaluate evolving science and address the meaning of data is expected to involve a Data and Safety Monitoring Board, the Ethics Subcommittee of the NCSAC, and the directors of the Study and NICHD. One NCSAC member stressed the need to do more up front to address what levels from biological samples mean in terms of exposure and estimates of risk, even if the information is imperfect. Another member emphasized the importance of a research agenda to determine the toxicity of chemicals so that the data can be used to inform people about risk. Dr. Fleischman noted that informing without understanding the meaning has potentially negative consequences.
- *The practical difficulties of recording the activity of a toddler on a daily basis.* Mr. Quackenboss noted that the challenges go well beyond time-activity diaries to all the things the Study will be asking people, some of which relate to exposure measures, including time and location. The information need not always be very detailed, however. Dr. Galke noted that the Study would need to integrate snapshot assessments of exposures into children's life stages. More resolution will be reached over the next few months about how best to approach some of these topics, and input from parents and grandparents about the practicality of some of these ideas will be solicited.
- *Whether the Study will take subsamples of subjects from each of the centers or from one center to reach standardization of observations across the country.* Mr. Quackenboss said that individual or community specific subsampling was planned rather than center-specific subsampling.

### ***Prepregnancy and Pregnancy Protocol Development***

*Ruth A. Brenner, M.D., M.P.H., Director, Study Protocol Development*

Dr. Brenner reviewed the background for Study protocol development from 2000 to 2004, as follows:

- Longitudinal cohort study proposal (2000; by ICC)
- Federal advisory committee and 22 workgroups (2001)
- Development of focused hypotheses and suggested measurements
- Other scientific activities (2001–present)—pilot studies, white papers, and workshops
- Development of a measurements database (2003; by ICC)
- Decision of the sampling strategy (2004).

Dr. Brenner characterized the Study Plan:

- Published as part of RFPs in November 2004
- Outlines the general study design
- Purpose was to guide offerors so that they were better able to develop their proposals
- Less detailed than a full Study protocol or MOP, yet more detail than many RFPs
- Study Plan is now evolving in greater detail with input from investigators from the Vanguard Centers, Coordinating Center, and initial experience.

Dr. Brenner characterized the Study protocol as the document that will detail more specifically the data collection procedures. It specifies both measurement and nonmeasurement aspects of the Study—who, when, where, what, and (more or less) how. Completion of the draft protocol is planned for spring 2006.

Development of the Study Plan into the Study protocol occurred from January through November of 2005 and involved the following:

- Study Program Office work groups
  - Exposure assessments (psychosocial and environmental)
  - Developmental outcomes
- Continued pilots and other contracts
  - Development of the information management system
  - Specific pilots (for example, NC Cohort Study, electronic capture of medical events)
- Currently receiving input from Coordinating Center and Vanguard Centers.

Dr. Brenner described the current Study protocol development process:

- Formation of working teams with members from the Study Program Office, Coordinating Center, and Vanguard Centers
- Deliberations of the working teams are informed by previous work, expert input, and information in the submitted proposals
- Recommendations of the teams are brought to the full Steering Committee.

Dr. Brenner listed the Study protocol development teams:

- 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
- IMS development.

Dr. Brenner reviewed the content of the Study protocol (preconception and pregnancy). She began by describing the scope of the Study Plan:

- Sampling strategy and Study locations (generally counties)
- Does not specify secondary sampling units (neighborhoods)
- Target sample size—250 births per location per year
- General approach to recruitment, household sampling approach
- Does not specify approach to community engagement
- Schedule and location of face-to-face visits
- Very broad specification of the general domains and types of measurements at each visit.

Dr. Brenner presented a proposed timeline for 2006–2008, with the following tasks and start/finish dates:

- Finalize content of all data items and measures (February 15, 2006)
- Study Program Office review and “whittling down” content to reach target burden levels (February 15, 2006–March 15, 2006)
- Format data collection instruments and finalize procedures required for OMB/IRB submission (March 15, 2006–May 15, 2006)
- Peer review of protocol (May 15, 2006–July 14, 2006)
- Prepare OMB/IRB submission packages (May 15, 2006–July 14, 2006)
- Finalize segment selection (June 1, 2006–June 24, 2006)
- Develop Study procedures (March 15, 2006–September 15, 2006)
- Requirements definition/refinement/database design (May 1, 2006–December 31, 2006)
- Develop/integrate IMS (January 2, 2007–September 28, 2007).

The schedule of face-to-face contacts prior to pregnancy involves the following:

- Initial screening visit for eligibility and to determine the probability of pregnancy
- Women with low probability of pregnancy—only telephone follow-up
- Women with moderate probability of pregnancy—one additional data collection visit
- Women with high probability of pregnancy—up to a maximum of four additional visits.

Over the 21-year course of the Study, there may be 16 face-to-face contacts, occurring most frequently early in the Study. Two working teams are finalizing the schedule of visits for:

- Preconception visits—high probability of pregnancy
- Obstetric visits—number and timing; fetal ultrasounds; oral glucose tolerance test; feasibility and burden, other measurements.

Dr. Brenner characterized the present schedule of face-to-face visits during pregnancy:

- No change to the number or location of visits prior to pregnancy or during pregnancy

- Content of one of the clinical visits during pregnancy modified
  - Removed the first trimester oral glucose tolerance test
  - Added a first trimester ultrasound
- Timing of visits during pregnancy
  - Home visit—as early in pregnancy as possible
  - Clinical visits at 10–12, 22–24, and 32–34 weeks.

The schedule of face-to-face visits following birth will involve:

- Birth—hospital or place of birth
- 1 month—short home visit
- 6 months—home
- 12 months—home
- 18 months—home.

Dr. Brenner presented charts depicting participants' contacts for sampling, household screening, preconception visits, and pregnancy visits. She summarized the contacts as follows:

- Broad overview from sampling through pregnancy
- Draft process flow sheets for each potential point of face-to-face contact
- Flow sheets include mothers, fathers, and children
- Next steps—filling in operational details as the scientific details are defined.

Dr. Brenner characterized the preconception data collection:

- Low probability of pregnancy
  - Extended screener and contact information only
  - Yearly contact by telephone
- High and moderate probability of pregnancy—initial data collection
  - One in-depth data collection visit within 2 weeks of the screening visit
  - Questionnaire, biological specimens, environmental samples, physical assessment
  - Targeted total length of the visit is 1–2 hours
  - Location is in the home
- Proposed questionnaire domains—preconception visit 1
  - Demographic information
  - Personal and family medical history
  - Medications, pharmaceuticals, and supplements
  - Occupational history and current information on occupation and hobbies
  - Home environment and product use
  - Mental health
  - Partner information
- Proposed physical assessment and biological specimens—preconception
  - Maternal anthropometric
  - Weight, height, skin folds, circumferences
  - Maternal blood pressure
  - Maternal blood
  - Still discussing other biospecimens
  - No planned paternal physical assessments preconception

- Biological specimens prior to conception among partners of planners still under discussion
- Additional preconception visits high probability group (visits 2–4)
  - Questionnaire
  - Update on environmental exposures, current practices, and behavioral domains (for example, household products, medicines, stress)
  - Both maternal and partner
  - Environmental samples
  - Biological specimens
  - Blood—only maternal, first and second visit
  - Other specimens—under discussion
  - Physical measurements
  - Repeat maternal weight and blood pressure at each visit
- Other contacts
  - Moderate probability
  - Telephone contact every 3 months
  - Shortened version of the extended screener
  - Update contact information
  - High probability
  - Contact every month
  - Face-to-face, telephone
  - Questions related to pregnancy status but also other questions.

Dr. Brenner provided the following overview of pregnancy visits:

- Four visits, one in the home, three in a clinical setting
- Maternal questionnaire, biologic specimens, physical assessment each trimester
- First trimester home visit—environmental samples and primary visit for partner assessment
- Ultrasounds at each clinical visit (total of three)
- Targeted duration of visit
- Home visit—2–3 hours
- First clinical visit—30 minutes
- Second and third clinical visits—2 hours.

The proposed maternal questionnaire items for pregnancy visits include:

- Demographic information
- Past medical history
- Medical update
- Medications, pharmaceuticals and supplements
- Diet, alcohol, and tobacco use
- Occupation and hobbies
- Physical activity
- Home environment and product use
- Mental health (such as depression and stress)
- Visit-specific modules such as financial security, support, culture, family process, attitudes, and beliefs.

Proposed partner assessments questionnaire items include:

- Demographic information
- Past medical history
- Medications, pharmaceuticals, and supplements
- Diet, alcohol, and tobacco use
- Occupation and hobbies
- Physical activity
- Mental health (depression and stress)
- Attitudes and beliefs.

Proposed physical and biological assessments include:

- Maternal weight, blood pressure, and arm circumference each visit
- First trimester—possibly oral health exam (decayed surfaces, missing teeth)
- Paternal weight, height, circumferences, skin folds, and blood pressure—first trimester
- Maternal blood—each visit
- Paternal blood—first trimester
- Other biological specimens under discussion.

The physical assessment working team's considerations for selecting measures are:

- Usefulness in a large, broad, multisite study
- Validity, reliability—training
- Interpretability
- Burden to individual participant
- Burden to the Study
- Temporal continuity
- Comparability with previous and current studies
- Avoid redundancy.

Dr. Brenner characterized fetal ultrasound measures:

- Early crown-rump length for dating
- Fetal growth—biparietal diameter and head circumference, femur length, abdominal circumference
- Fetal fat and body composition—mid-thigh circumferences, abdominal wall thickness.

### ***NCSAC Discussion and Recommendations/General Discussion***

The NCSAC did not make any specific recommendations but discussed the following issues:

- *The recruitment of adolescents at risk of pregnancy who are minors living at home with their parents through household visits.* Dr. Brenner responded that in the Study Plan, such women would not be eligible to participate in and would not be recruited for the Study's preconception groups. If a woman who is a minor becomes pregnant, she would be eligible to participate. This is a dilemma because from a sampling perspective, consistency in eligibility criteria across groups would be preferred. A team will be looking at all of these issues and competing needs. This issue has been discussed in the

Steering Committee, and certainly there is an interest in and a need to look at adolescent pregnancies. Dr. Scheidt noted that the Steering Committee had considered whether to exclude adolescents altogether. The NCSAC member commented further that he would be reluctant to exclude adolescents and his concern was related to the door-to-door sampling. Adolescents could be recruited from clinical sites where they go for services. It was noted that the numbers of pregnancies to adolescents younger than age 16 were small. There would be fewer ethics issues and IRB concerns by focusing on adolescents who are ages 16 and 17, which is the group being considered now.

- *Inaccurate paternity reports, which are common and could cast doubt on data about the paternal effect on the child.* Dr. Brenner responded that this is an evolving protocol, and there is not a detailed plan to address this issue right now. The Study will rely on the female contact to identify the father. Dr. Fleischman added that the Study would not do testing to specifically determine paternity.
- *How the Study will handle environmental assessments in the home if there is movement to different houses.* Dr. Brenner replied that there is a plan to visit the home again after a move and a plan for obtaining samples from a second home where a child spends a lot of time. Women who are planning to move out of a segment before the delivery will not be followed.
- *The use of incentives to ensure that women continue to cooperate over the course of the Study, as long-term follow-up is vital.* Dr. Brenner said that reasonable and appropriate incentives are planned and are outlined in the Study Plan. This is one of the issues that will be addressed through a Study team. Dr. Fleischman added that the NCSAC has developed some general principles about incentives at a previous meeting.
- *Whether there will be screening for high-risk behaviors (such as alcoholism) that would predict that a person would not be likely to follow through and the percentage of women that will not follow through.* Dr. Brenner responded that information about behaviors will be collected from all participants, and the plan is to follow all the women. The target for screening to delivery is 75 percent, and there is no other prediction at this time. Retention will likely vary by location and population.
- *The need for community involvement in protocol development, inclusion/exclusion criteria, and measures of social class.* Dr. Brenner responded that inclusion/exclusion criteria are in the Study Plan and have not changed, for the most part, although age boundaries are being revisited. The main exclusion criteria include women who are surgically sterile, women who are not able to complete the consent process (primarily due to cognitive impairments), and women moving out of the Study area before delivery. Inclusion is primarily by age and residence. All births to a target woman would be included in the Study. Social class is a domain but the measure has not been decided yet.
- *Translation of materials into different languages.* Study teams are first trying to find measurement instruments that have been validated in multiple languages, but translations will be needed into a number of common languages; the specific languages have not yet been determined. The Vanguard Centers will be able to hire people who are native speakers of the participants' languages to administer instruments in those languages.
- *Implications of eliminating the first trimester oral glucose tolerance test for the related hypothesis related to diabetes, and what alternative tests would be performed.* Dr. Brenner responded that a group of obstetricians from the Vanguard Centers and people from the Program Office participated in discussions about this issue, including whether there was another measure and the feasibility of doing the measures. After much deliberation, the group concluded and recommended to the Steering Committee that other measures would be easier to obtain on a broader population than the oral glucose tolerance test, which is a burdensome measure. Alternative tests might include a fasting glucose and insulin levels.

- *Whether the Study was turning to outside experts to help answer questions (such as related to periodontal disease).* Dr. Brenner replied that outside expertise is being obtained when needed by the teams.
- *Concern about the household based recruitment process and contacting neighbors for information.* Dr. Brenner said that sort of contact is only in the first phase, and the type of information asked of a neighbor would be very general, such as whether there is a female of childbearing age in the household. This would be similar to what is done in other studies. Neighbors would be contacted only after multiple efforts to make contact with a household.
- *Making consent explicit in terms of what will be involved, particularly with regard to consent to collect prepregnancy data.* Dr. Brenner noted that there will be different consent forms depending on the group the person falls into.
- *Whether there will be relationships and agreements with community or county clinics where women receive prenatal care.* The member also commented about the difficulties that women encounter getting care, the need to build relationships in communities of color, and the need for community events to introduce the researchers to the communities. Dr. Brenner responded to the first point and said that although there might be an advantage to combining some Study assessments with clinical visits in terms of the burden for participants, only one of the Vanguard Centers indicated that it might be feasible in its response to the RFP. Most of the offerors concluded that it would be difficult to integrate visits and have kept Study clinical assessments separate from routine care. One center will try sending research staff to the clinical visit and is starting very early to build relationships with providers as part of their community work.
- *Lack of specificity regarding sociocultural environment measures and what questions will be asked about attitudes, beliefs, social support, health and illness behaviors, and use of health services.* Dr. Brenner noted that her presentation was a summary and was not comprehensive and that there has been progress in trying to identify specific tools to measure specific domains. More details of the protocol will be available during the period of peer review between May and July 2006. Dr. Fleischman cautioned that the NCSAC would not act as peer reviewers for details of the protocol.
- *Whether the protocol would address pregnancies that do not come to term.* Dr. Brenner said that the protocol would address such pregnancies and the women would be followed for subsequent pregnancies.
- *Whether the Study would be conducted under a Certificate of Confidentiality.* The answer to this question was yes.

### ***NCSAC Ethics Subcommittee Report: Informing Communities of Information Learned***

***Myron Genel, M.D., Chair, NCSAC Ethics Subcommittee, Yale University School of Medicine***

Dr. Genel explained that the Ethics Subcommittee is still considering questions regarding the Study's commitment to revealing relevant and important information to participants and families. The specific remaining questions are:

- Should the Study inform "communities" about local findings? What? How? Whom?
- Who is the community?
- Who represents the community?
- How should the community be engaged?
- Should community permission be required before revealing findings?
- Specific discussion issues are:

- The Study will not follow a strict community-based participatory research approach but is committed to engaging the community in a meaningful way.
- Engaging the community can benefit the Study.
- A community can be involved in consultation without being given the power of consent.
- Consultation with the community can influence the process of revealing findings even if the community's opinion is not determinative of action.
- Prior to revealing information to communities, the Study's data and safety monitoring board can determine the scientific validity of Study findings.
- The Ethics Subcommittee can give advice (through the NCSAC) to the Study concerning revealing findings to communities.

Dr. Genel listed the following conclusions and recommendations from the Ethics Subcommittee:

- The Study has an obligation to share clinically relevant individual-level data with individual participants and families.
- There is also an obligation to share community-level data of importance with the broader community at each site.
- There may be potential risks to individuals (participants and nonparticipants) and to the entire community of revealing information found in the Study. Therefore, revealing information to communities must be done thoughtfully and with some level of preparation.
- Prior to revealing findings to a community, community leaders should be engaged and informed.
- Community members should serve as consultants for issues related to informing communities about findings.
- However, because there is a potential for conflict between the interests of individuals and the interests of the community related to reporting of findings, the advice of the community should be considered but need not be determinative of action.
- The Study should have a structure in place, including a data and safety monitoring board (DSMB) and the Ethics Subcommittee, to obtain advice and assist the Study Director and the Director, NICHD, to make decisions about revealing findings to communities.

After the presentation by Dr. Genel, additional thoughts from and issues discussed by the Ethics Subcommittee and NCSAC included the following:

- *The need to have ethicists who are not part of government agencies advise the Steering Committee on a range of issues.*
- *The need to create clear expectations about the boundaries of disclosure from the beginning of a relationship with a community.* It was noted that the Study should be clear concerning who makes decisions and how the Study and the community can work together to think about how the information is communicated. Having a way to understand what the community thinks is important and what the community may view as risky or nonrisky information will be important.
- *When the DSMB will have the authority to take action and to what entity it will report.* Dr. Fleischman said that the present plan is that the DSMB would report to the Director, NICHD.
- *Whether findings will be reported at the county, Census tract, or Census block level and the implications for community representation.* Dr. Fleischman replied that the data will be available in various ways, and there will be an iterative process to think about that as the data become available. The Study will aggregate data regularly for all communities to see, but the DSMB will play a role when there is a question of the meaning of some local data, for example. If the findings are real, then

community people would be involved at the appropriate level concerning how to reveal the findings. However, community members may disagree about revealing findings.

- *Women of diverse income levels and race/ethnicity will be participating in the Study.* Dr. Fleischman agreed and noted that there will be a broad spectrum of socioeconomic status and that ethical concerns may differ among different groups.
- *The need to be cautious about the release of data at the local block level that could pose a confidentiality problem.* Dr. Fleischman suggested that biostatisticians and ethicists would assist the Study to protect individual confidentiality of data.
- *The meaning of “clinically relevant” individual data and who decides what data are clinically relevant and how they are reported.* Dr. Genel noted that this question was discussed at the September meeting and that clinically relevant data would include finding something of importance that would potentially need some medical or other intervention or that the person should know about. Dr. Fleischman explained that there are several levels of information using the concept of clinical relevance, including clinically critical levels, in which the Study would have an obligation to inform participants and families in a timely manner about findings that could have immediate health implications. Most people agree that there is an ethical obligation to assure there is a system in place to inform and help families deal with clinically critical findings. A second level of findings might not need to be dealt with immediately but ought to be dealt with. Then there will be information of lesser importance that may be optional for participants to receive and that would be available upon request. Some findings may be given to families directly or through their clinicians, and the participants will likely be responsible for telling the Study how they want that information revealed.
- *The role of the DSMB in assessing the meaning of Study findings.* An Ethics Subcommittee member commented that the DSMB’s role would not be to look at individual test values but to look at patterns that suggest a community risk, for example. The researchers would use cutoffs for test values to decide what to report to a provider or family. Dr. Fleischman added that the DSMB would help determine the meaning of elevated biomarkers in a group, and if the meaning is not known, then the Study should not create unintended negative consequences. A member commented that there are many gray areas where the meaning of an individual test result is not clear.
- *Making resources available to help communities change environmental factors, even if that means changing Study outcomes.* Dr. Fleischman commented that the NCSAC had previously discussed the obligation to intervene at the community level even if it meant changing the outcomes for the children. The NCSAC has said that it wishes to help in developing strategies at the national and local level for empowering communities to make change, since that might not solely be the job of the centers.
- *The importance of working with community health care providers and the need to educate primary care providers about the Study.* Dr. Fleischman noted that embedded in this comment was the creation of a strategy of obtaining permission to inform primary care providers of study results. The centers cannot share health information with a participant’s primary care providers without the participant’s permission. Dr. Scheidt commented that the RFP for the Vanguard Centers stipulated that the centers convey plans to refer to and access primary care providers and how they would deal with serious circumstances, such as fetal death, as well as straightforward clinical referrals—and not just plans to refer but also to follow through and make sure the problem has been addressed.
- *A suggestion that the centers be required to meet some minimum Study standards on the transfer of information.* An Ethics Subcommittee member suggested that critical values need to be determined at the national level before the first participant is enrolled. When critical values are not known, results can be reassessed as the Study goes forward and more information is available. Dr. Fleischman said that this fits in with the QMP and the IMS system described earlier in the meeting.

## ***NCSAC Discussion and Recommendations/General Discussion***

The NCSAC concurred with the report of the Subcommittee, and, in addition, discussed the following issues:

- *The role of the Steering Committee in making Study decisions.* Dr. Scheidt clarified that there is a hierarchy of decision making for the Study subject to iterative input and review. Steering Committee decisions will be reviewed by the ICC, the project officers, and the directors of the Study and NICHD. There will be an opportunity to reconsider some decisions in the future, and decisions about the protocol for beyond age 18 months have not yet been made. Dr. Scheidt noted that the Steering Committee made a policy decision that it will only reconsider a previous decision by a two-thirds vote of the members.
- *Tapping the experience of researchers who were involved in other major longitudinal studies such as the Collaborative Perinatal Project.* Dr. Scheidt replied that there has been much effort to tap that experience, and the Steering Committee has asked to meet with scientists from relevant large cohort studies to benefit from those experiences as questions emerge. A member suggested asking such a person to speak at a future NCSAC meeting about the problems encountered. Dr. Scheidt said that it would be important to frame the questions to be addressed.
- *Integration of the social environmental and biological perspectives in the Study.* A member commented that assessment of the biological domain in pregnant women in the protocol presentation received more weight than the social environmental domain. She added that the construct of “culture” assumes racial or class differences, and anger or depression about racism or classism can have biological effects. She stressed that integration of the social and biological sciences needs to occur early. Another member agreed and said that more attention needs to be paid to psychosocial variables and how they will be measured and integrated into the hypotheses. Dr. Scheidt responded that the protocol presentation focused on a certain set of variables that are underway, and social and behavioral variables would be presented at future meetings. The challenge of undertaking the biologic and environmental science together with the behavioral and social science was highlighted at the Study Assembly meeting. Dr. Fleischman mentioned that since this is such a massive undertaking, teams have been looking at different ways to measure aspects such as racism; the other issue is how those will be used in the analytic frame. Dr. Scheidt noted that with regard to segment selection, there had been concerns about the degree of clustering and how cluster size affects the ability to define and describe characteristics of communities, especially social characteristics. Dr. Knox commented that the Study planners have been looking at measures related to racism, discrimination, and stress, and how these variables influence birth outcomes and neurodevelopmental trajectories.

## **Day Two**

### **Welcome and Recap of Day One**

*Dr. Fleischman*

Dr. Fleischman welcomed participants to the meeting’s second day and reviewed the highlights of the first day and the agenda for the second day.

### ***Human Subjects and IRB Issues***

*Kristina C. Borrer, Ph.D., Director, Division of Compliance Oversight, Office for Human Research Protections (OHRP), DHHS*

Dr. Borrer noted the federal regulations and policy pertaining to the Study’s human subjects and IRB issues:

- §45 CFR 46—Basic DHHS Policy for Protection of Human Research Subjects (originally adopted May, 1974; revised January 13, 1981; revised June 18, 1991)
  - Additional protections for vulnerable populations in Subparts B–D
- Federal Policy for the Protection of Human Subjects—“The Common Rule” (June 18, 1991)
  - Departments of Agriculture, Energy, Commerce, Housing and Urban Development, Justice, Defense, Education, Veterans Affairs, Transportation, and Health and Human Services; National Science Foundation; National Aeronautical and Space Administration; Environmental Protection Agency; Agency for International Development; Social Security Administration; Central Intelligence Agency; and the Consumer Product Safety Commission.

The regulations contain three basic protections for human subjects: institutional assurances, IRB review, and informed consent. Dr. Borror characterized an institutional assurance as documentation of institutional commitment to comply with the Common Rule, principal mechanism of compliance oversight, and OHRP federalwide assurance.

Assurances are required from each institution that is “engaged” in the research (see OHRP guidance <http://www.hhs.gov/ohrp/humansubjects/assurance/engage.htm>). Obtaining an assurance is a two-step process: (1) ensure that the IRB(s) to be designated under the assurance are registered with OHRP and (2) complete the assurance application, including designation of one or more registered IRB(s).

Dr. Borror defined an IRB as “a committee charged with the review of human subjects research to assure that the rights and welfare of human subjects are adequately protected.” IRB review is necessary because:

- No one can be objective about his or her own work.
- People underestimate the risks involved in things they are very familiar with.
- People overestimate the benefit of things that are important to them.

According to §45 CFR 46.114, cooperative research is defined as follows:

*“Cooperative research projects are those projects...which involve more than one institution. In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy. With the approval of the department or agency head, an institution participating in a cooperative project may enter into a joint review arrangement, rely upon the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort.”*

Dr. Borror presented a chart depicting a joint review arrangement, with a central IRB and four local IRBs. Under joint review arrangements:

- IRBs develop an agreement about their respective areas of responsibility.
- The local IRBs might assume responsibility for issues such as assuring knowledge of local research context, reviewing consent forms, and assuring compliance with local laws.
- The local sites list the central IRB on each of their assurances.
- This is also referred to as “facilitated review.”

Another approach is to rely on the review of another qualified IRB. Dr. Borror presented a chart depicting this review arrangement for a group of five institutions. In such a scenario:

- Each institution designates the central IRB on its federalwide assurance.

- The central IRB performs all review functions.
- The central IRB may be one of the IRBs from the five institutions, a commercial IRB, or an IRB created specifically for the study.

Dr. Borrer characterized IRB authorization agreements:

- If an institution relies on the IRB of another institution or organization, this arrangement must be documented in writing between the two institutions/organizations, usually by an IRB authorization agreement.
- The agreement must be kept on file at the institutions and available for review by OHRP upon request, but it should not be submitted with the federalwide assurance form.
- Any IRB relied on by an institution must be designated under that institution's assurance.
- The advantages of local review include:
- IRB must know local context; the local IRB is best situated to know the local context; IRB means "*institutional* review board."
- Each institution conducting research is responsible for safeguarding the rights and welfare of human subjects and for complying with the regulations; assurance is the mechanism of compliance oversight; an institution has more control over its own IRB.

The advantages of centralized review include:

- Avoid duplication of effort.
- Review and approval may occur more quickly.
- Some central IRBs may have members with expertise that might not be available to the average IRB.
- Can reduce total IRB burden.

Dr. Borrer explained that informed consent:

- Should be sought from each prospective subject or the subject's legally authorized representative, in accordance with and to the extent required by 46.116 [45 CFR 46.111(a)(2)]
- Must be documented by the use of a written consent form and signed by the subject or subject's legally authorized representative (LAR) [45 CFR 46.117(a)] unless documentation is waived.

Forms of informed consent documentation include:

- Written consent document that embodies the elements of informed consent required by 45 CFR 46.116. [45 CFR 46.(b)(1)]
- A short form stating that the elements of informed consent have been presented orally to the subject (or LAR); requires a witness to the oral presentation and an IRB-approved written summary of what is to be said to the subject (or LAR); short form signed by subject, witness signs short form and summary; person obtaining consent signs the summary; copy of the short form and summary given to the subject (or LAR) [45 CFR 46.117(b)(2)].

To waive documentation of informed consent, an IRB must find and document either:

- The only record linking the subject and the research would be the consent document, and the principal risk would be potential harm resulting from a breach of confidentiality; each subject will be asked

whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or

- The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

Dr. Borrer concluded by noting the OHRP Web site: <http://www.hhs.gov/ohrp/>.

### ***Informed Consent and the Participation of Children in Genetics Research***

*Benjamin Wilfond, M.D., Associate Investigator, Social and Behavioral Research Branch, Head, Bioethics and Social Policy Unit, Deputy Director, Bioethics Core, National Human Genome Research Institute, NIH, DHHS*

Dr. Wilfond prefaced the session by stating that his presentation did not represent the views of the National Human Genome Research Institute, NIH, or DHHS. He explained that important, but not unique, characteristics of genetic information include:

- Probabilistic and complex information
- Special cultural meaning
- Familial implications
- Reproductive decision-making impact
- Primarily psychosocial risks.

Potential risks are primarily related to disclosing genetic information, including intended disclosure, unintended disclosure, and no disclosure. Dr. Wilfond listed details about these types of information disclosure:

- Intended disclosure
  - Uncertain meaning
  - Confusion
  - Anxiety
  - Familial implications
  - Stigmatization
  - Discrimination
- Unintended disclosure
  - Above concerns
  - Privacy
- No disclosure
  - Community harms
  - “Harmless wrongdoing.”

Dr. Wilfond characterized efforts for minimizing risks:

- Psychosocial impact
  - Nondisclosure of data to subjects
  - Genetic counseling/education when disclosing data
- Confidentiality
  - Nonlinkage of samples/data with identifiers
  - Database encryption for linked samples/data

- Oversight
  - Community involvement in protocol
  - IRB review
- Informed consent.

Key informed consent (permission) questions for the Study are:

- Is getting parental permission a valid way to enroll children in genetic epidemiology studies?
- What happens when the children become adults?
- What information about the research is necessary for valid parental permission?
- Justifications for enrolling children in research based on parents' decisions include:
- Presumption of parental authority for decision making about children
- Pediatric consent/assent/dissent
- IRB review of benefits and risks—limitations on parental decision making
- Public/community acceptance of the social value of conducting research with children—what does the public think about children in genetic research?

Dr. Wilfond presented and discussed the results of a survey of public attitudes about genetic research with blood samples. The survey was conducted by 5 universities during 30-minute telephone interviews with 1,193 individuals. The survey involved the following Study consent vignette:

- Suppose that when you were an infant, your parents gave their permission for a blood sample of yours to be used in research on children's health.
- Your doctor collected samples from hundreds of infants this way.
- Since then, your blood sample has been stored in a freezer along with a unique identification number and some background medical information about you.
- Several decades have passed and all of the infants whose blood samples were collected are adults.
- The researcher now wishes to continue to use your sample for research.

The results indicated that:

- 66 percent were not at all or not very concerned that research had been done with their parent's permission on their childhood blood sample
- 46 percent said researchers should get their permission now to continue using their sample
- Of these 46 percent, 75 percent were willing to give their permission for a researcher to continue using their sample
- However, of those 75 percent willing to consent to further research, 55 percent said it is not acceptable to use their sample if researchers were not able to locate them and obtain consent.

Dr. Wilfond described the survey's implications for consent about genetic research in children. Most adults are not concerned about their parents' decisions about enrolling them in genetics research. He noted that there are limitations in interpretation of the survey data and that it is not clear what role public attitudes should play in relation to minority viewpoints for research ethics policy.

Balancing minority views with the value of research involves:

- Conceptual analysis about appropriateness of pediatric genetic research—value of the genetic research to society balanced with potential harms to children and potential objections by some people

- Understanding the rationale of the objections—the psychological value of participation in decisions
- Interactive community engagement to address value of continuing research beyond age of consent (if not able to contact subjects)—would preclude ongoing analysis of pediatric data sets for cancer or infectious diseases, for example.

Dr. Wilfond listed the parental permission implications for the Study:

- Parental permission for genetic research in children is reasonable.
- Child/adolescent participants should be asked for their consent for further research at a developmentally appropriate time.
- Conducting research on previously collected data/samples when the adolescent/adult is not available is acceptable.
- Community engagement about these issues is warranted.

Dr. Wilfond discussed the types of information that are necessary to disclose for informed consent to be “valid.” He reviewed studies on unspecified consent forms, explicit consent statements, possible options for explicit consent, the extent to which consent forms at NIH approach informed consent for genetic research, and the information domains. Concerns about genetic-specific risks include discrimination, misattributed paternity, familial health information, ambiguity of results, and upsetting nature of information.

Based on his review of informed consent studies and their implications for the Study, Dr. Wilfond recommended the following:

- Develop a study protocol that addresses scientific and ethical issues—rely on advisory committees, IRBs, data and safety monitoring boards, and other community groups to minimize research risks.
- Develop education/consent processes and materials that are simple, short, and easy to understand—avoid complex and confusing options and make the “fine print” available as supplemental information.
- Use focus groups to pilot test communication materials (understanding) and willingness to participate based on materials.

### *Human Subjects, Informed Consent, and Institutional Review Board Issues*

*Dr. Fleischman*

Dr. Fleischman listed some of the Study’s issues related to human subjects:

- No “prospect of direct benefit” claimed
- Collateral benefits of participation
- Participant burden “moderate”
- Level of risk “minimal”
- Other issues include:
  - Genetic sampling and biobanking
  - Observing children in imminent harm
  - Revealing findings
  - Confidentiality
- Informed consent/assent.

Federal policy for protection of human subjects (§45 CFR 46) describes the permissible research involving children:

- Minimal risk (§46.404)
- Greater than minimal risk with the prospect of direct benefit (§46.405)
- Minor increase over minimal risk and no prospect of direct benefit (§46.406)
- Significant risk and special opportunity (Secretary DHHS review) (§46.407).

An Institute of Medicine (IOM) report (*Ethical Conduct of Clinical Research Involving Children*, 2004) defines the prospect of direct benefit as a likely tangible positive outcome (for example, cure of disease, relief of pain, increased mobility, or provision of specific services). Collateral or indirect benefits are not considered “prospect of direct benefit.”

Federal policy for protection of human subjects (§45 CFR 46) defines minimal risk: “That the risks of harm anticipated in the proposed research are not greater, considering the probability and magnitude, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests [§46.102(i)].” The IOM report clarifies that minimal risk involves a focus on “equivalence of risk” in daily lives or experience of routine exams and minimizing risks even when risks are minimal.

- Suggested positions on genetic sampling and biobanking for the Study are as follows:
- Genomic data are private, intimate, sensitive, affect others, and create the potential for stigmatization and discrimination.
- Genetic sampling will be optional.
- The Study will not provide genetic data to participants/families except in the unusual circumstance of a future finding of clinical relevance—when informing will be voluntary.
- All future use of stored samples will require the approval of a multidisciplinary Study committee to assure fidelity to Study mission.

The Study’s responsibilities when observing children in imminent danger include:

- Legal obligation to report suspicion of child abuse/neglect
- Moral obligation to intervene to protect the interests of any child thought to be in imminent danger of harm
- Responsibility of principal investigator and senior research staff to assess each instance and decide appropriate course of action
- All Study staff will be trained concerning the issue of observing behaviors or environmental issues that place children in danger.

The Study’s responsibilities and obligations with regard to revealing findings include:

- Scientifically valid and clinically relevant findings will be revealed to individual participants/families.
- Clinically “critical” findings will be revealed in a timely manner.
- Participants will be educated and helped to interpret findings.
- Scientifically valid aggregate findings will be revealed to participants and the general public through presentations, newsletters, Web sites, journal publications, and other means.
- Revealing site-specific findings will require sensitivity to community concerns.

With regard to confidentiality, the Study will:

- Use unique identifiers
- Develop sophisticated information management technologies
- Use a federal certificate of confidentiality
- Train all Study staff in issues related to privacy and confidentiality.

Informed consent/assent from participants (prepregnant and pregnant) and others involved in the Study may be sought during prepregnancy, pregnancy. In addition to the women who are the primary participants, consent/assent will also be obtained as follows:

- From partners, foster/adoptive families, and third parties
- Child assent
- Adolescent assent
- Adolescent consent.

Informed consent during prepregnancy and pregnancy will use a unique methodology. This newly developed interactive video (E-consent) approach involves:

- A research person being available during the process
- All elements of informed consent
- English and Spanish versions—other translators available as necessary
- Concerns for health literacy, cultural sensitivity, and cultural/racial diversity
- Assessments of essential elements of consent
- Capture of written electronic signature.

The Study's suggested IRB review strategy is as follows:

- The Study will not create a central IRB.
- To facilitate uniform review of the protocol and acceptance of informed consent process, the Study will convene IRB "thought leaders" from Vanguard Centers prior to IRB submission.
- The Study will obtain IRB approval from NICHD, Coordinating Center, and Vanguard Center IRBs.
- The Study will encourage use of "Cooperative Agreements" (§46.114) among regional IRBs.

The Study's IRB review strategy will adhere to §45 CFR 46.114, Cooperative Research, which states:

*"Cooperative research projects are those projects covered by this policy which involve more than one institution. In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy. With the approval of the Department or Agency head, an institution participating in a cooperative project may enter into a joint review arrangement, rely on the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort."*

#### ***Informed Consent: An Interactive, Multimedia Approach***

*Mildred Z. Solomon, Ed.D., Vice President, Education Development Center, Associate Professor of Social Medicine, Medical Ethics, and Anesthesia, Harvard Medical School, and Jennifer C. Stempel, M.B.A., Ed.M., Project Director, Education Development Center*

Dr. Solomon explained that the problems with informed consent have been discussed and well-documented in the literature. She listed 10 references and cited the following IOM statements about improving informed consent:

- “IRBs cannot assume that parents understand information about the research project that has been disclosed to them. To ensure that parents understood the project, researchers would need to test their comprehension.” (*Ethical Considerations for Research on Housing-Related Health Hazards Involving Children*, 2005, p. 105)
- “An HRPPP [Human Research Participant Protection Program] that demonstrates that it can ensure informed consent because it has data showing that participants understand the protocols in which they are enrolled could begin to supplant or augment paper audits of signed informed-consent forms.” (*Preserving Public Trust: Accreditation and Human Research Participation Protection Programs*, 2001, p. 16)

The Study has an opportunity to improve the informed consent process using an electronic approach. According to Dr. Solomon, there are four benefits to such an approach to informed consent. An electronic approach can improve:

- Understanding by use of visuals, easy-to-understand colloquial speech, and monitoring respondents’ answers to key questions
- Inclusiveness by picturing people from diverse ethnic groups, socioeconomic classes, and regions of the country
- Transparency by making it clear how the Study was explained during the informed consent encounter
- Standardization by ensuring that everyone has the same things explained to them, and in the same manner.

Ms. Stempel provided an overview of the E-consent tool that is being developed for the Study. The primary goals of the E-consent tool are transparency, standardization, and making an informed decision about Study participation. The tool has three specific functions:

- Inform the subject—provide information about the purpose and scope of the Study, what participation involves, and the risks and benefits of participating
- Assess understanding—evaluate whether or not a potential subject’s understanding of the information presented is sufficient to consent to the Study
- Obtain consent—give those who have demonstrated understanding of the information an opportunity to sign their consent.

Using a flowchart, Ms. Stempel described the structure of the E-consent tool. She then presented and discussed a mock-up of the tool, noting that:

- Questions are always presented in pairs, so that only one of two choices can be made.
- There are two versions—one for preconception, one for women who are pregnant.
- The tool uses a touch screen technique.
- Informed consent for genetic testing is separate.
- The target time for completing the informed consent is about 20–25 minutes.
- The tool will use simple English (that is, “oral” or conversational English); a Spanish language version will also be developed; translators will be available for other languages.
- A Study research assistant will sit with the person who is using the E-consent tool.

- The tool allows electronic capture and storage of participants' signatures.
- The tool's developers are consulting with language and cultural competency experts.

### *NCSAC Discussion and Recommendations/General Discussion*

The NCSAC did not make any specific recommendations but discussed the following issues:

- *The difference between simple English and colloquial English and the fact that colloquial English can be complicated and imprecise.* Dr. Solomon responded that the language will be reviewed by reading experts, IRB chairs acting as a focus group, and Study staff. The goal is clarity and transparency.
- *Whether people who are not computer literate will be trained to use the computer during the consent process.* Ms. Stempel replied that there will be a person there who can control the computer and assist the participant to use it. She noted that computer literacy for women in the target age group is high and the touch screen nature of the program is quite simple.
- *The need to obtain child abuse and criminal record clearances for researchers in certain states.* Dr. Fleischman commented that obtaining such clearances or approvals is being handled by the Vanguard Centers as a local site issue.
- *Sensitivity to the views of American Indian communities about the sample repository.* Dr. Scheidt said that the Study is very much aware that these communities are sensitive subpopulations to work with and has begun processes of engagement including interacting with the Indian Health Service. Dr. Fleischman added that he believes that the Indian Health Service will approve and support the work of the Study and expects that the Indian Health Service IRB will be involved.
- *Lack of clarity about what counts as genetic versus nongenetic aspects of the Study and the strategy of asking for consent to genetic testing at the end of the consent process.* Dr. Fleischman responded that genetics is a critical part of the Study and agreed that it is difficult to determine what counts as genetic information and what does not. He noted that public perception is that genetic testing is different from other types of testing, and storing samples for genetic testing may be seen as problematic as well, but perceptions will likely evolve over time. In the consent process, the main part of the consent form will state that the Study will include genetic testing, and more information will be given toward the end of the consent process.
- *The screening process prior to obtaining informed consent.* Dr. Fleischman explained that the screening process will determine whether women are eligible based on broad screening criteria. Those found to be eligible will then be given the opportunity to consent. Dr. Borrer commented that from a regulatory standpoint, if one interacts or intervenes with people for research purposes, they are human subjects, and there is a need for consent or for consent to be waived. It may be appropriate for the IRB to waive informed consent for the screening process.
- *Whether the consent process will occur in the home.* The answer is "yes."
- *The role of the group of IRB leaders looking at the protocol and the consent process; consideration by local IRBs about whether the Study protocol is minimal risk.* Dr. Fleischman responded that the strategy includes having an independent group of IRB leaders look at the protocol and informed consent process prospectively and then bringing together the IRB leaders from the sites and allowing them to voice their concerns. Dr. Solomon clarified that the IRB reviewers looking at the consent tool are not an ad hoc IRB committee; they are helping to anticipate what issues IRBs might have with this new consent tool. With regard to the protocol's risk level, Dr. Fleischman said that the intention is to have a protocol that is minimal risk. If a local IRB concluded that the protocol is more than minimal risk, that decision would mean some additional complexity at that site.

- *Appreciation of the multiple levels of assent and consent being written into the Study, which will build a level of trust with the participants; the need to involve different ethnic communities early in the process of generating the informed consent tool.* Ms. Stempel said that there are several advisors, including an adult literacy advisor and cultural competency advisors; advisors include a Latina social scientist who is a researcher in medical interpretation and an African American. Part of the development plan is to present an alpha version to focus groups of women.
- *Flexibility of the video consent process to handle local IRB modifications.* Ms. Stempel said that the program is being designed so that there are places in the presentation known as “hooks” where information specific to a center can be inserted. There will also be a “hook” for local IRBs to insert specific language, if needed, prior to capturing the signature.
- *Separate consent for women when they become pregnant.* Dr. Fleischman noted that there will be a prepregnancy consent form and a separate consent form that will be required when a woman becomes pregnant.
- *Questions asked during screening and HIPAA privacy issues.* Dr. Fleischman noted that the Study will embed in the consent form sufficient language to cover HIPAA, but there will also be a “hook” to allow additional local IRB language if desired. In some cases a written document may be needed. Dr. Borrer suggested consulting with the DHHS Office for Civil Rights, which implements HIPAA, to try to get approval of language regarding the privacy regulations; this might help with local IRB acceptance of the language.
- *Whether there is some sort of credentialing organization for IRBs that maintains some consistent standards from one IRB to another.* Dr. Solomon replied that there is an association that accredits IRBs and research organizations using a set of criteria; accreditation is done on a voluntary basis at this time. One of the IRB-associated reviewers for developing the consent tool is the associate director of that association. Dr. Borrer elaborated that the association (the Association of Accreditation of Human Subjects Protection Programs) accredits the entire human subjects research protection program at an institution, not just the IRB. There is a cost in terms of both time and money to go through the accreditation process.
- *Responses to finding a problem with a woman’s ability to understand the consent process.* Dr. Solomon said that various approaches were being discussed, including using a computer program to analyze wrong answers and leaving it up to the other person in the room to assess why the woman is getting wrong answers. Dr. Fleischman reminded the group that one of the eligibility criteria is that women must have the cognitive ability to participate and understand the informed consent. If people cannot understand simple assessment questions, the Study will need to determine whether there is a communication or cognitive problem and work that into the training process.
- *The potential for media reports to cause public misconception about the Study and the risk that entails.* Dr. Fleischman responded that a video explaining the Study will be used in communities and the media will be involved as part of community engagement prospectively. The Study would like to work with the media and will be proactive in addressing negative or inappropriate perceptions.
- *The need for neurologic assessments of children.* Dr. Scheidt responded that extensive batteries of neurologic and developmental assessments are being developed, but there was insufficient time to allow discussion of them at this meeting. He noted that there was an extensive report to the Steering Committee 2 weeks ago about the work that has been done in this area, and the NCSAC would receive that information in the future.

**Community Engagement—University of Mississippi Report  
Strategies for Minority Recruitment in the National Children’s Study: Issues of Trust**

*Juanita Sims Doty, Ed.D., Senior Outreach Advisor, NICHD, NIH, DHHS*

Dr. Sims Doty noted that the NICHD's mission includes ensuring that every person is born healthy and wanted, that women suffer no harmful effects from the reproductive process, and that all children have the chance to fulfill their potential for a healthy and productive life, free of disease or disability.

It is hoped that the Study's results will provide prevention strategies, health and safety guidelines, educational approaches, and possibly new treatment and cures for medical conditions.

Dr. Sims Doty explained that the U.S. population will become more diverse. In 2010, it is anticipated that minorities will comprise 32 percent of the population, and in 2050, 50 percent or more of the population will be minorities. Dr. Sims Doty estimated that in 4–6 years, 32 percent of the Study's children and families will be from minority backgrounds; and by the end of the Study, about 40 percent will be minorities.

One of the critical issues to be addressed in the Study is health disparities in different groups and communities of Americans. Finding ways to close the gaps in health disparities could be one of the most important accomplishments of the Study. In an effort to close the health disparity gaps, the Study will have to actively engage a diversity of communities. According to Dr. Sims Doty, strategies for minority recruitment in the Study involve issues of trust. Community engagement has begun through a variety of local events at the Vanguard sites.

To engage communities, they must first be defined. Communities can be defined through faith-based and other community leaders, community advisory boards and steering committees, and a diversity of community partners. Questions from community representatives include:

- Confidentiality of results?
- Results shared when?
- Who is leading this study?
- Community involvement?

Dr. Sims Doty noted that Alpha Kappa Alpha Sorority, Inc., is happy to partner with the Study and the NIH to enhance the health of America's children. She explained that every community is different, and because of this, the Study researchers and Vanguard sites must know their communities and engage them in meaningful ways.

### ***Trust and Research Participation Among Minorities***

*Sharon B. Wyatt, Ph.D., R.N., C.S., Professor of Nursing, University of Mississippi Medical Center, and Karen Winters, Ph.D., R.N., Assistant Professor of Nursing, University of Mississippi Medical Center*

Drs. Wyatt and Winters provided an overview of trust issues for research participation among minorities. The Study has a remarkable opportunity to:

- Learn what it is to engage large numbers of families, particularly minorities, as research collaborators
- Integrate issues of trust and research participation into the social, biomedical, and environmental outcomes anticipated for the Study
- Demonstrate models of community engagement and research participation within this longitudinal, multisite study.

Preliminary work for the Study identified trust as “the most important potential barrier to participation.” David Satcher, M.D., Ph.D. (16th U.S. Surgeon General and former Assistant Secretary of DHHS, February 1998–January 2001) once said, “This distrust is hurting us. I think we really have to focus on it.”

Drs. Wyatt and Winters reviewed some aspects of trust, as related to research participation among minorities, including a literature review supplemented by their experiences with the Jackson Heart Study. Their white paper was organized by the participant, organization, protocol, community involvement (POPCI) model; made recommendations regarding best practices for engendering trust and engaging communities for research participation; and provided overarching recommendations for embedded longitudinal study of research participation.

Dr. Wyatt quoted:

*“All of our possibilities and potentialities in our various life situations are possible because of personal and cultural history. And so it is that all of human life, including research, takes place within an ontological circle.” (Benner, P. Interpretive Phenomenology: Embodiment, Caring and Ethics in Health and Illness. Thousand Oaks: Sage. 1994.)*

Dr. Wyatt described aspects of the ontological basis of trust:

- Expectation that something will occur based on past occurrences (experiences) at multiple levels, including interpersonal, institutional, and societal
- Expectant trust—historical and cultural context
- Experiential trust—the possibilities for creating new contexts.

With regard to expectation, examples of the contextual legacy of mistrust are:

- Tuskegee and “double consciousness”
- Racism and discrimination
- Medical and research mistreatment
- Government responses to Hurricane Katrina and terrorism (such as secret “spying” on U.S. citizens).

The POPCI model of research participation allows:

- Compatibility of participants and investigators/staff—ethnic match/cultural synchrony
- Study organization and institutional climate—power relations, communication
- Continuity—accessibility and aesthetics.

The POPCI model protocol is characterized as follows:

- Research design—conceptual models of recruitment and retention; shared protocol development
- Consent—multiple institutions, community involvement, and processes
- Accommodation to participants
- Quality assurance, tracking, and participant feedback—quick response time.

With regard to participants, the POPCI model considers:

- Demographics and social networks
- Health status and risk factors

- Health beliefs, attitudes, and experiences
- Research beliefs, attitudes, and experiences.

Community engagement involves community mobilization, community partnership, translation of research findings, and social context. Participation in research turns on trusting relationships and reciprocal partnerships. Trust is built “one pebble at a time.” Community engagement requires significant investment of time and resources to recollect the past toward creating a future of new possibilities for research comporment.

To achieve community-specific outcomes, the universal process of engagement includes:

- SWOT (strengths, weaknesses, opportunities, and threats) analysis of each individual community—full community assessment
- In-depth interviews with key constituencies and stakeholders (including faith, political, underrepresented ethnic groups, health care providers, business, civic organizations, neighborhood organizations, child care/schools/child-focused groups, environmental groups); need to be continuous across the Study
- Form community research collaboration board (not “advisory”).

Research participation involves a complex web of issues, including:

- Deep-seated and well-founded fears and apprehensions of research that lie alongside optimism, hope, and desire to contribute to the greater good
- The extent to which and methods by which the Study can penetrate this complex web to engender trusting research communities.

As the Study moves toward a science of research participation, it must:

- Compare community-specific recruitment and retention processes and outcomes
- Use specific conceptual approaches
- Incorporate multimethod approaches to chart participant and researcher:
  - Attitudes and beliefs
  - Measures of trust
  - Impact of POPCI factors
  - Experiences and meaning of research participation
- Address ethical and cultural dimensions of research participation
- Detail trust-building and damaging factors and strategies across duration of the Study.

Drs. Wyatt and Winters explained that their findings echo those of multiple white papers for the Study (for example, recruitment, community-based participatory research, racism, and focus groups) from the perspective of recruitment literature and Jackson Heart Study experiences. They emphasized that no matter how well researchers identify sampling strategies, select study sites, organize study operations, or plan protocols, there will be no meaningful findings unless and until they systematically address the issue of trust across all study components by integrating and engaging communities in study design, implementation, evaluation, and dissemination.

## *NCSAC Discussion and Recommendations/General Discussion*

The NCSAC did not make any specific recommendations but discussed the following issues:

- *Whether the Study intends to track its recruitment, retention, and community engagement efforts to identify approaches that are effective and ones that are not effective.* Dr. Scheidt said that the concept has been discussed, but instruments to address these important factors have not yet been developed.
- *The responsibility to maintain long-term relationships and involvement with communities after studies are completed and how that can be accomplished.* Dr. Wyatt responded that the Jackson Heart Study is expected to extend to multiple generations, similar to the Framingham study. The responsibility for maintaining widespread community involvement to recruit and retain the cohort and for ongoing translation of findings into practice in the community is built into the study contractually. Strategies include a partnership for community organization and health awareness and a community health advisor network, in which community members are trained to carry out cardiovascular health education.
- *The responsibility for creating infrastructure for community engagement where such infrastructure does not exist.* Dr. Wyatt noted the Jackson Heart Study's strong commitment to capacity building, including funding 40 minority scholars who are getting undergraduate educations in public health.
- *Strategies used by the Jackson Heart Study to interact with community health care providers about abnormal findings.* Dr. Wyatt responded that the study worked early to engage the entire health care community. Its strategies have included creation of a referral network, a detailed results reporting protocol, and training of staff in how to report findings at different levels of urgency. Results are reported to participants in writing and, with permission, to their health care providers. If an immediate referral is needed, participants are sent, with their permission, to their health care provider or to the emergency room if necessary.

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I hereby certify that, to the best of my knowledge, the foregoing minutes are accurate and complete.

04/22/06 Date

Alan R. Fleischman, M.D.

Chair

National Children's Study Federal Advisory Committee