National Children's Study
Federal Advisory Committee 18th Meeting
April 22–23, 2008
Marriott Bethesda North Hotel and Conference Center
Bethesda, 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 (HHS), National Institutes of Health (including the Eunice Kennedy Shriver National Institute of Child Health and Human Development [NICHD] and the National Institute of Environmental Health Sciences [NIEHS]), the Centers for Disease Control and Prevention [CDC]), and the U.S. Environmental Protection Agency (EPA).

Day 1

Welcome and Introductions

Alan R. Fleischman, M.D., National Children's Study Advisory Committee (NCSAC) Chair; Medical Director and Senior Vice President, March of Dimes

Dr. Fleischman welcomed the NCSAC members, ex officio members, and other participants to the 18th meeting of the NCSAC. He acknowledged the hard work of the NCSAC, welcomed the new members, and thanked those members whose terms were ending. Dr. Fleischman reported that Jessica N. Sapienza, M.H.S., is now Executive Secretary and Designated Federal Official of the NCSAC. Former Executive Secretary, Kate Winseck, M.S.W., is the Outreach and Community Engagement Coordinator for the National Children's Study (the Study).

Dr. Fleischman reviewed the functions of federal advisory committees as defined in the Federal Advisory Committee Act. The NCSAC's roles and responsibilities include providing specific advice and recommendations to the director of NICHD, the Study Director, and the Interagency Coordinating Committee (ICC). Dr. Fleischman reviewed the Study's governance and management structure and the minutes from the November 7–8, 2007, NCSAC meeting. He also reviewed the current meeting's agenda and briefly described the roles of the Scientific Review, Ethics, and Community Outreach and Engagement Subcommittees.

Program Office Report

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

Dr. Scheidt welcomed the NCSAC members and other participants. He briefly reviewed the Study's funding history and status in the President's 2009 budget, as well as events and milestones. In 2007, contracts were awarded for 22 Study Centers, in addition to the 7 Vanguard Centers. The new Study Centers will manage 40 Study locations, 26 of which are part of Wave 1. The request for proposals (RFP) for 2008 Study locations and Study Centers was posted in March; proposals are due May 2. The Research Plans for both the pilot phase and full Study have been submitted for review by the Office of Management and Budget (OMB). The report from the

National Academy of Sciences' peer review of the Research Plan will be completed by the end of April.

On November 8, 2007, the NCSAC and full Steering Committee held a joint meeting. Since then, the Study's Executive Steering Committee has been constituted. The Executive Steering Committee has monthly conference calls and will meet in person three or four times a year. The full Steering Committee will meet in person once or twice a year. Both committees address ongoing protocol, operational issues, and major issues influencing the direction of the study. There is community representation on both the Executive Steering Committee and full Steering Committee.

Many new organizations and programs have been inquiring about partnerships with the Study to address their concerns and missions. These organizations include the National Vaccine Safety Committee, Head Start of America, and Autism Speaks. In addition, the Program Office has been engaged with the Epigenetics NIH Roadmap Initiative and the Developmental Disabilities Network of NICHD.

The solicitations for Wave 2 Study Centers and locations will be posted later in 2008. The Program Office expects to award contracts for the sample repository and the environmental laboratory in 2009. The Program Office and the CDC's National Center for Environmental Health (NCEH) are negotiating a memorandum of understanding for operation of the biological specimen laboratory.

Dr. Scheidt reported that both Program Office operations and staff continue to grow; several new staff members have been hired. He described the reviews of the Research Plan and listed Study activities at numerous conferences and meetings since November 2007. He also described the media response to the Study and listed upcoming events.

NCSAC Questions and Comments

- Myron Genel, M.D., asked whether OMB approval of the Research Plans could be politically influenced. Dr. Scheidt replied that he did not know to what extent approval could be politically influenced.

- Antoinette P. Eaton, M.D., commented that the Study could play an important role in answering questions about vaccine safety and autism. If the Study explores this type of relationship, we will increase support from the public and professional community. Dr. Scheidt said the main issue of studying vaccine safety is the difficulty in comparing subgroups within the Study. The number of children who are not vaccinated or receive delayed immunization may not be sufficient to provide adequate statistical power. The Study will collect data on vaccinations through maternal reporting in the participant care diary. Maternal-reported data may not be as accurate as provider-reported data. A Study working group is considering the feasibility of collecting fine-grained vaccine administration data. The Study will collect data on outcomes related to vaccination.

- Carol Henry, Ph.D., asked whether there are plans for congressional briefings. Dr. Scheidt noted that Study staff and NICHD employees cannot initiate such briefings. Briefings are given only when requested; however, congressional staffs are greatly interested in the Study. Congressional appropriations committees are well informed about the Study. James N. Jarvis, M.D., noted that NCSAC members can advocate for the Study on days when they are not serving as special federal employees.

Laboratory Initiatives

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

Dr. Balsam provided an overview of the Study's laboratory initiatives, which are divided into three efforts:

- Repository, which will be of unprecedented size and scope
- Biospecimen laboratories and biospecimen laboratory science
- Environmental sample laboratories and environmental laboratory science.

The costs of implementing the Study will peak during its early phase. Because both the laboratory and repository undertakings will be expensive, many of the analyses will be deferred until after the early peak. As many stable biospecimens and environmental samples as possible will be stored for future analysis. This approach allows a more efficient use of samples, as well as deferring cost. Implementation of repository and laboratory activities will need to coincide with implementation of the Study's pilot phase at Vanguard Centers in order to test procedures before the full Study and to obtain early results. The laboratory teams are developing the scientific and operational requirements for the repository and laboratories and are preparing the RFPs for these contracts.

Laboratories and Repositories

Jack Moye, Jr., M.D., Laboratory Medical Officer, Project Officer for Repository and Laboratories, National Children's Study

Dr. Moye provided information on the Study's plans and progress for the laboratories and repository. The Study presents unique challenges in its efforts to compile data on growth, health, and environment in one very large study. The Study will collect, analyze, and preserve a broad variety of biological and environmental samples over a period that exceeds that of the typical 5-year funding cycle. These activities will be conducted in the best possible manner using currently available technologies in an era of shrinking resources and rising costs.

Biological Sample Collection. The protocol defines 11 sampling points from preconception through 36 months postbirth. Samples will be collected from mothers, fathers, and participating children. Four biological sources (blood, excreta, secreta, and tissues) comprise 12 primary sample types: blood, urine, hair, nails, buccal cells, saliva, breast milk, vaginal fluid, meconium, cord blood, umbilical cord, and placental tissue. Some of these primary sample types will be subdivided into additional derivative specimen types (for example, blood will be fractionated into cells and plasma or serum). There will be 42 different sampling events in this timeframe.

Environmental Sample Collection. Environmental samples will be collected from different settings and sources. The three main environmental sample source settings are household, group care, and community. Six primary environmental sample types are soil samples, air sampling filters, water, bulk household dust, mattress dust, and special samples (for example, floor mats and food).

Participants, Visits, and Sample Materials. Dr. Moye presented graphs showing annual and cumulative counts depicting the magnitude of participants, visits, and sample materials. New household enrollment will peak at about 30,000 at year 6. The annual number of visits will surpass 100,000 in year 3 and peak at nearly 250,000 at year 6 (which translates to 1,000 per day). The cumulative count for households will reach 100,000—full accrual—at year 7, at which time more than 800,000 visits will have been conducted.

Biological and Environmental Samples. Dr. Moye presented graphs depicting the collection of samples associated with the 100,000 households and 800,000 visits over the first 7 years of the Study. Biological specimens for storage only will be acquired at 1 million per year (4,000 per day) starting in year 2 and peaking at 7 million per year (almost 30,000 per day) in year 6. The number of additional biological specimens requiring processing that will be acquired and received by the repository will increase to 1 million per year beginning in year 3 and peak at more than 3 million (12,000 per day) in year 6. The number of environmental specimens that will be collected (about half of which ultimately will be stored by the repository) will increase gradually to almost 1 million per year by year 6. The accumulated numbers of stored biological and environmental samples will reach the tens of millions by year 4. By year 7, about 27 million biological samples will have been received just for storage and 11 million more will have been processed and stored; 2–3 million environmental samples will have been collected.

Repository. The Study's biological and environmental sample repository will:

- Receive, secure, catalog, and store all samples and records submitted by Study Centers or laboratories
- Maintain samples and records in appropriate secure storage facilities that will retain their identity, integrity, and quality—even in event of natural or man-made disaster
- Prepare, aliquot, and package biological and environmental samples for subsequent analysis
- Provide shipping materials, services, and technical assistance to ship samples to laboratories for analysis
- Assure the quality of all repository operations including personnel management, sample receipt, shipment, and storage according to all federal, state, and local regulations
- Develop and maintain an automated electronic tracking system to receive, inventory, process, and track samples (compatible with the Study's information management system [IMS]).

Other Aspects. Dr. Moye listed several sample repository considerations and outlined the laboratory analysis plan. He reviewed the Study's Sample Oversight Group (SOG), which oversees use of biological and environmental samples for core and adjunct study analyses. The SOG advocates for optimal use of samples, advocates on behalf of participants to ensure that specimen use accords with intent and consent, and provides expertise in proposed methods, sample handling, and analysis requirements.

Exposure Measurement Update

Michael J. Dellarco, Dr.P.H., Senior Scientist, Project Officer for Environmental Laboratories, National Children's Study

Dr. Dellarco provided an overview of exposure monitoring as it applies to the Study. He described the approach and selection of exposure measurements to meet the Study's goals and briefly described current activities to achieve them.

In terms of environmental health, pollutant exposure can be estimated with some knowledge about sources and pollutant transport and fate characteristics. Source data can be provided by specific source emission data or by pollutant concentrations in the ambient environment. In both cases, pollutant transport to an individual or community can be calculated to determine whether sufficient toxicological concentrations exist that may lead to altered structure and function and perhaps an adverse outcome. Scientists have recently focused on so-called biomarkers of exposure that provide an opportunity to estimate pollutant concentrations in the body. An individual's recent personal history in terms of locations and activities can be used to estimate the likely sources and routes of exposure. These estimations are dependent on understanding the specificity and stability of the biomarkers to confidently relate them to environmental sources.

The Study will use these approaches wherever most appropriate to obtain information about pollutant exposures. In instances where neither environmental nor biological measurement is available, the Study will rely on indirect measurements based on questionnaires or diaries. The Study will rely on biological monitoring and biomarkers to the extent possible, given the large number of samples and length of time of the Study. Environmental measures will focus on characterizing the participant's environments.

Dr. Dellarco listed the proposed core environmental measurements and the proposed biomonitoring for chemical agents. He provided updates on activities to collect samples from indoor air, house dust, drinking water, and visual assessments of neighborhoods and built environments. Upcoming activities include (1) completing the methods evaluation for priority environmental measurements, (2) developing protocols and standard operating procedures for core hypotheses analytes, (3) identifying and evaluating environmental monitoring networks to augment community environmental measurements, and (4) coordinating neighborhood characterization with psychosocial and built environment needs.

NCSAC Discussion/General Discussion

- Kevin Y. Teichman, Ph.D., described EPA's interest in the Study's laboratory and repository initiatives and exposure measurements. EPA has a regulatory role in protecting human health and the environment. EPA is concerned with providing information on indoor air quality but has no regulatory role. EPA is interested in providing information on all environmental threats, both indoor and outdoor. One useful tool is the source–outcome paradigm, which can help describe exposure and outcome relationships. EPA gathers as much environmental information as possible to help inform regulatory and policy decision-making. Because of this approach, EPA embraces the Study's Research Plan regarding environmental measurements and health and developmental outcomes.

- Allen Dearry, Ph.D., noted that the Study will be very complex and expensive. There will be an enormous array of parameters to evaluate and a vast quantity of biospecimens and environmental samples to store and analyze. There will be many people and groups to coordinate for the repository and laboratory initiatives. All activities, assessments, and analyses will need to be conducted in a cost-effective manner. Dr. Dearry commended the Program Office staff for their hard work and dedication to developing the Study's environmental measures and identifying laboratory analyses. NIEHS remains interested in working with the Study to better integrate the Exposure Biology Program. New technologies and methodologies, such as microfluidics, will be applied over the next several years AND will allow flexibility, cost efficiency, and analytic efficiency (that is, the need for less sample quantity for analyses).

- Edwin Trevathan, M.D., M.P.H., acknowledged the importance of interagency collaboration to the Study. The coordination and collaboration across CDC's offices and centers will also be important to the Study. The logistical complexities and incredible number of the Study's laboratory analyses are impressive. NCEH staff and laboratories will contribute to the Study's laboratory analyses but require collaboration.

- Dr. Fleischman asked about challenges of sample collection at the Study Centers. Dr. Moye explained that specimen collection is one of the biggest logistical challenges for participants and Study Center staff. Sample collection, processing, and shipping will be closely evaluated during the pilot phase at the Vanguard Centers. The preanalytic variables will be closely monitored to identify any problem before the samples arrive at the repository. Dr. Dellarco said the approach has been simple in terms deployment to avoid avenues of contamination at the Study Centers. The focus for collecting environmental samples has been on devices that are preassembled, preloaded, easily deployed in the field, and able to be quickly retrieved, packaged, and returned in appropriate shipping containers to the Study Centers. Standard methods have been selected to ensure the use of methods that are used routinely and that are familiar to Study Center staff. Dr. Balsam commented that the Study has been working with NCEH on testing the predeployed contamination of collection materials, particularly heavy metals.

- In response to a question from Dr. Genel, Dr. Moye said the Study will operate 250 days per year (that is, 5-day work weeks). In response to Dr. Genel's second question regarding the readiness to collect, process, and store samples collected at the first two Vanguard Centers, Dr. Moye said these activities will be handled on an interim basis under an existing NICHD repository contract.

- Dr. Henry remarked that the approaches and technologies to measure chemical exposures are commendable. She asked how the Study will incorporate measures of biological exposures such as infectious disease and microbes that are found on particulate matter. Dr. Moye replied that one of the advantages of a repository is the ability to evaluate specimens when new technologies are developed in the future and determine exposures that are currently unknown. Dr. Dellarco said the Study is determining the best approaches to preserve the integrity of samples at the time of collection for both conventional and innovative future

analyses. The amount of samples collected must be balanced in terms of what is required for analyses versus the costs and needs of the repository. Dr. Balsam reiterated that because most of the biospecimens are stable, they will be stored soon after collection for later analysis.

- Bruce Levin, Ph.D., inquired about the reliability and validity of the samples collected in participants' homes. He asked how long the air-quality sampling devices would be placed in the homes. If there is long-term placement, will the devices be maintained (for example, recalibrated)? Dr. Dellarco explained that the Study will use simple, straightforward devices and instruments that have been successful in other similar studies and that will provide adequate measurements. They will be precalibrated, and their performance will be monitored. The devices and instruments will be placed in unobtrusive locations. Placement will follow specific requirements on where in the house, as well as where in a room, they are to be deployed. The selected devices will be reliable and will provide valid data.

- Janet Currie, Ph.D., asked whether outdoor environmental measures will include carbon monoxide (CO). Dr. Dellarco answered that an expert panel advised against monitoring CO, and therefore, the Study does not have a hypothesis regarding CO exposure and health outcomes. Dr. Currie asked whether the Study will link existing community-level environmental data with data it collects. Dr. Dellarco said the Study will enter EPA's routine environmental monitoring data into the Study's IMS. Challenges to using this data are comparable methodologies and applicable modeling. Dr. Currie recommended that the Study reconsider the monitoring of CO, given its known effects on fetal health.

- Michael Lebowitz, Ph.D., said the Study will require a number of monitoring and modeling efforts. Questionnaire data from Study participants, as well as data from outdoor monitoring, should allow some modeling of likely CO exposure. Dr. Lebowitz noted that EPA grantees have experience with these efforts and could serve as a Study resource. The lead agencies will have to collaborate to model environmental exposures. Because there are uncertainties about the long-term stability of many of the samples, the Study will need to explore the use of existing data sources. The Study should tap into the experience and work of the lead agencies, for example, linking air quality monitors with Study data. Through separate grants or contracts, the lead agencies may need to address such issues such as the relationships between biomarkers of exposure and actual environmental measures.

- Wilma Brakefield-Caldwell, R.N., asked for clarification on biospecimens. Dr. Dellarco said these are materials such as blood and urine collected from Study participants, not environmental biologics. Ms. Brakefield-Caldwell asked whether the household monitoring devices would be battery-operated. Dr. Dellarco said they will be run by batteries only. Ms. Brakefield-Caldwell asked whether the Study has developed a script to convince participants to give samples for genetic analysis. Dr. Fleischman said such a script has been developed.

- Jeffery C. Long, Ph.D., commented that the current status of information technology (IT) should be able handle the large amount of Study data. He would like to see a plan for how data storage will facilitate future IT platforms and developments. The Study's IMS will need to look creatively toward the future as it enters, processes, and stores data.

- Maria Cancian, Ph.D., remarked that census data may be stored indefinitely, whereas certain administrative data (for example, from schools, criminal justice, and child welfare programs) may expire. These data will need to be identified, collected, and archived if they are to be used; the Study will need to determine how to collect and keep the data.

- With regard to maintaining quality of samples and ensuring consistency of sampling, John L. Butenhoff, Ph.D., asked (1) how placement of environmental collection devices in a home is determined and (2) whether the amount of sample collected and precautions against loss or damage have been considered. Dr. Dellarco said collection devices will, in general, be placed in the room of greatest occupancy, although there are some problems with placing devices in the kitchen. There will be some comparative testing of monitors, and there will be input from EPA monitoring efforts. Dr. Butenhoff would like the Study to consider the variability in the placement of environmental monitors and how the placement of monitors might influence the Study results. In terms of storage and shipment precautions, the Study will rely on the experience and knowledge of previous investigators. Contamination of environmental samples during handling and shipment is a critical concern. Steps will be taken in the selection of materials and procedures to avoid contamination as much as possible.

- Robert E. Chapin, Ph.D., noted that several large corporations have existing technologies for tracking large inventories and high-volume shipping (for example, United Parcel Service, Wal-Mart Stores). The Study may benefit from lessons learned by such commercial enterprises. Dr. Moye said there are excellent existing products for tracking samples and laboratory data. The Study will not invest in developing new products. Dr. Dellarco said the Study will use existing barcode technologies and standard, existing EPA methodologies. Dr. Chapin commented that the Study should provide incentives for the development of new analytic technologies. Dr. Dellarco acknowledged that technologies will undoubtedly continue to evolve.

- José F. Cordero, M.D., M.P.H., inquired about the number of repositories the Study will have. Dr. Moye replied that there will be a single repository entity, although samples will probably be stored in at least two geographical locations. Dr. Cordero raised the concern that there is an inherent risk associated with the samples being stored in a single location or in locations with close proximity.

- Liliana J. Lengua, Ph.D., asked whether participants are given a list of the array of biomarkers at the time of consent and whether they are given the opportunity to opt out of particular analyses. If they can opt out, how will this be tracked and recorded? Dr. Fleischman explained that at each visit, participants will be told what samples will be collected and assessed. Participants can opt out of any collection or assessment. However, because future analytes will not be known at the time of collection, it is unlikely that participants will be able to opt out of a particular analysis.

- J. Ricardo Guzman, M.S.W., M.P.H., commented on the importance of the linkage between the community and the data collection entity. In previous studies, the gathering of environmental information has often depended on this linkage. If the community recognizes the importance of a study, it will "guard" the data collection apparatus.

- David J. Schonfeld, M.D., commented on the collection of potential exposures for which there are neither biomarkers nor the means to measure the amount of direct exposure. To determine the relevance of those potential exposures, the Study will need to rely on surveys and other indirect measures of exposure. Therefore, the Study needs to evaluate the methodologies and validity of those assessments as it would evaluate the samples themselves. Because levels of biomarkers (for example, lead levels in blood) do not always correlate well with environmental measures (for example, lead levels in soil), it can be difficult to determine the extent to which any one source contributes to biomarker levels. Dr. Schonfeld said the Study might benefit from collecting fewer samples with known relevance to children's health rather than more samples with unknown relevance.

- Ana V. Diez-Roux, M.D., Ph.D., M.P.H., observed that traditional environmental assessments focusing on biomarkers and personal exposure are important from an etiologic perspective. However, for public health actions and interventions, it is important to know the sources of environmental contaminants within communities. She recommended that the Study focus on both personal and community assessments. She noted that some EPA monitors have coverage problems, for example, in rural areas. A broader issue involves community and neighborhood assessments. Neighborhood-level data can be gathered from existing sources, which must be identified and archived as necessary. Through the home visits, the Study has an opportunity to conduct a systematic assessment of neighborhoods using validated instruments. She encouraged the Study to investigate these opportunities.

- Sarah S. Knox, Ph.D., clarified that the Study does have plans to collect and store biospecimens for infectious agents, microbes, and endotoxins. In addition, there is a plan for testing the long-term (more than 2 years) stability of the biospecimens.

- Peter C. Scheidt, M.D., M.P.H., explained that the Study is under enormous pressure to contain costs. There is much that the Study would like to do but cannot. The Study cannot afford to measure exposures that are already known to have adverse health outcomes (for example, CO). Dr. Scheidt also explained that a large pilot study collected and evaluated available administrative data, and a list of administrative databases is posted on the Study's Web site. Because much of the Study's IMS involves tracking samples, it will use available tracking products and will continuously evolve as new products are developed and adapted to the Study's IMS.

Report of the Expert Panel on Public Use Data Access and Disclosure Control

Jennifer Madans, Ph.D., Panel Chair, Associate Director for Science, National Center for Health Statistics, CDC, HHS

Dr. Madans explained that an expert panel was convened to (1) share the panel members' experiences and expertise and (2) offer recommendations on how to provide as much data access as possible to investigators while ensuring the confidentiality of Study participants. Prior to the meeting, panel members reviewed materials provided on the Study's design and plans for data access. There was a high degree of consensus regarding the panel's recommendations. The panel

provided clarification on disclosure control, data access versus data release, public use files versus use by the public, and confidential data versus sensitive data.

The panel offered the following general guidance:

- The data access plan must be an integral part of the Study's design and must be developed early in the process.
- The more complex the Study, the more complex the data access plan will be.
- Data access issues will be more complex than expected and more expensive and staff-intensive than expected.
- The data access plan should incorporate established best practices.

The panel emphasized the importance of establishing a link between the data access plan and the informed consent process. The informed consent should specify who has access to what data and under what conditions. The wording of the informed consent is crucial. Data access and release practices must be developed to meet the requirements of the informed consent. The Study needs to maximize data access while protecting confidentiality.

The panel's major recommendations are as follows:

- Establish a data access committee to advise the data steward.
  - The data access committee will need to be a standing committee because issues related to data access will be both ongoing and dynamic.
  - The data access committee will be needed to make evolving decisions both about who the data users are and what they will have access to.
  - The data access committee should develop a data access plan that addresses policies and practices (as noted above) as its first task.
- Establish a disclosure review board.
  - The disclosure review board should be independent of the publications subcommittee.
  - The disclosure review board will oversee the actual work of disclosure control, that is, develop strategies to carry out disclosure control and implement those strategies.
  - The disclosure review board should not set policy—the setting of policy should be separated from implementation.
  - The disclosure review board may need to review every publication for disclosure depending on access mechanism used/informed consent.

NCSAC Questions and Comments

- Elena Gates, M.D., asked whether the participants' data will be "anonymized." Dr. Scheidt replied that the data will be anonymized at some stages and deidentified at other stages in order to link environmental exposures with health and developmental outcomes. Dr. Knox commented that longitudinal analyses cannot be performed if all data are truly anonymized. Dr. Madans acknowledged that some, but not all, Study participants may be deidentified using certain demographic and geographic data. The data in public use files will be limited to guard against deidentification.

- Dr. Currie noted that "noise" has been added to available extracts of Medicare claims data to make it impossible to identify individuals. Dr. Madans said this data access mechanism was

considered by the panel. Other mechanisms under development add noise, swap data, or include synthetic data. Some users believe that noise interferes with findings. Synthetic data files may not be applicable to the Study.

- Dr. Henry asked about the policies for handling and protecting data on laptops. Dr. Scheidt explained that participant interview data will be immediately encrypted as they are entered into laptops. Data will be downloaded daily and removed from the laptops. Dr. Madans said that best practices to protect data will be used in the Study.

NCSAC Ethics Subcommittee Report on Data Access and Disclosure Control

Myron Genel, M.D., Chair, NCSAC Ethics Subcommittee, Professor Emeritus of Pediatrics, Yale University School of Medicine

Dr. Genel reported that the Ethics Subcommittee met by conference call on March 26, 2008. The purpose of the conference call was to discuss relevant Study issues related to the Report of the Expert Panel on Public Use Data Access and Disclosure Control.

Subcommittee Recommendations:

- Data use agreements lack accountability. The Study should follow the Framingham Heart Study model for data use, which requires expedited local institutional review board (IRB) review and approval for all data analyses. IRB review provides institutional oversight of the investigator to ensure fidelity to the provisions of the data use agreement.
- The limitations of certificates of confidentiality should be further investigated. The Study should seek legal opinion about specific issues related to government agency and court challenges of certificates of confidentiality.
- A highly protected data storage system is imperative. Study data should be stored in a centrally housed server with password access. Approved investigators would have access rights to analyze data but would not be able to actually possess or keep data.
- The data access and publications committees should be combined to improve efficiency. This data access and publications committee should include an appropriate community member.
- The Study should limit data analysis to test only approved hypotheses (that is, no data mining). There should be a time limit for testing hypotheses. Federal scientists from the lead agencies who are outside the Study's community of investigators should have data access privileges equivalent to those of the general scientific community.
- Data use agreements should be clear about investigators' obligations to not share data with other investigators and to not attempt to reidentify individuals.
- The obligation to ensure confidentiality outweighs the self-interests of the researchers.

The NCSAC endorsed the recommendations of the subcommittee.

NCSAC Discussion/General Discussion

- Benjamin S. Wilfond, M.D., observed that part of the informed consent process is to describe what the Study will and will not do. The informed consent can be framed a method of communication, or it can be considered a promise or contract. There is debate about these

two modes. According to Dr. Wilfond, there are several problems with the promise/contract mode and certain advantages to the communication mode. However, there are methods of communication other than the consent form.

- Dr. Schonfeld commented that because the Study is viewed as a study of our nation's children, there may be resistance if data access is too restrictive to the general public. IRB review and approval for all data analyses may constrain public access. Data sets with limited data elements could periodically be made available to public. Dr. Genel reiterated the Ethics Subcommittee's recommendation for IRB review. Some geographic and demographic data could allow deidentification of participants or could stigmatize certain groups or areas. As the data become narrower, then confidentiality becomes more critical.

- With regard to separate data access and publications committees, Dr. Madans explained that the expert panel concluded that data access issues are different from publications issues, and consideration of these issues requires individuals with different expertise and experience. There are different levels of data access and release, and a variety of data files could be created for different users. Therefore, a committee to specifically deal with these issues is needed. With regard to informed consent, participants should be informed of the data access plan and have a right to know to whom data will be released, under what circumstances it will be released, the type of data that will be released, and how the confidentiality will be protected.

- Dr. Gates said that during its conference call, the Ethics Subcommittee discussed issues about misinterpretation of Study data or misuse of findings derived from flawed analyses. The subcommittee remains concerned on how to best control these outcomes.

- Helen M. DuPlessis, M.D., M.P.H., said she was concerned about being complete and transparent in the informed consent process while striving for successful recruitment. She asked how the Study will reconcile differences among the Ethics Subcommittee's recommendations, the expert panel's recommendations, and the content of the informed consent.

- Dr. Currie said she was concerned about outsiders' access to data. An investigator outside the Study who wants to analyze data will first have to write a proposal for IRB review and approval. The investigator will need some data access to write the proposal. Therefore, the availability of data will be necessary. Dr. Currie said geographic identifiers will be needed to link exposures and outcomes to local policies. Dr. Madans clarified that the expert panel did not specify which data access mechanism the Study should use, only that there be a written, complete access plan. She suggested that the Study write an access plan that is consistent with the informed consent. With regard to data for outside researchers, data access systems can provide summary data without individual identifiers. Outside researchers can be required to sign data use agreements in which they promise not to share the data.

- Barbara Anne Nabrit-Stephens, M.D., M.B.A., remarked that there will be some data "leakage" over the 20+ years of the Study. Confidentiality risk is cumulative. What you disclose one year influences the next. It is very important to preserve the privacy and

confidentiality of participants and communities. Because of this, some researcher may not be given access to all the data they want.

- Dr. Genel commented that data are not always needed for a study rationale or concept proposal to an IRB.

- Dr. Fleischman said the NCSAC should assume that there will be public use data sets that will be appropriately deidentified and appropriately available at appropriate intervals. The focus of the expert panel, however, was on data not part of public use data sets that would be available to scientists inside and outside the Study. Inside scientists have certain obligations to maintain confidentiality. An approach to maintain confidentiality for outside scientist is data access agreements, which have certain inherent weaknesses. One weakness is the lack of accountability. Following the Framingham Heart Study model for data use, which requires IRB review and approval for all data analyses, provides institutional oversight from the scientists' home institution and allows some accountability for scientists who do not adhere to the data use agreement. Data access agreements will include criteria for publication committee review and approval.

- Dr. Scheidt noted that the expert panel recommended data access agreements for not only the investigator but also the investigator's institution.

- Dr. Madans said there are ways to reinforce the importance of the transfer of data to investigators, including site visits, reporting, and publication review.

- Dr. DuPlessis asked to what extent the language in Study Center contracts will reflect the language in data use agreements. She said other study centers have often believed that they own the data. Dr. Scheidt explained that because the Study is federally funded, the Study Centers, by contract, do not own the data. The Study Centers must provide all data to the Study's Data Coordinating Center. Local Centers will maintain identified data in order to track participants' data, but all data provided by the Data Coordinating Center will be deidentified.

- Dr. Knox clarified that the Study Center contracts specify that the Centers must abide by the policies of confidentiality that protect the participants, regardless of data ownership.

- Dr. Wilfond supported the recommendation of IRB review and approval for data analyses and said that a data access committee is sensible. Responses to requests for data should be based on confidentiality policies rather than the language of the informed consents.

- Dr. Fleischman mentioned some of the issues concerning the power and authority of certificates of confidentiality. The question for the Study is whether it should inform individuals about what NIH is communicating to investigators and the public about certificates of confidentiality. Paul Hurwitz reported that protective authority of the certificates was tested to a limited degree in court. In addition, HHS and NIH claim that the Patriot Act does not affect the protections afforded under certificates of confidentiality.

- Dr. Wilfond cautioned not to mislead Study participants about the power of the certificates of confidentiality.

- Dr. Madans said that the certificates supposedly protect investigators from being forced to provide confidential data but do not prohibit them from providing the data. However, if the informed consent language specifies that investigators will not provide data, then they are bound to honor the informed consent. The informed consent will govern the data access plan. The wording of the informed consent is very important.

- Dr. Fleischman reiterated the need for legal clarification of confidentiality obligations for federally owned and held data versus data owned and held by an institution. There is still a need for a formal written opinion from NIH or HHS lawyers.

- Dr. Henry remarked that the Study can reassure participants that it will protect the confidentiality of data but cannot completely guarantee it. To gain participants trust, the Study must be honest about its ability to guarantee the protection of confidentiality. Participants should understand the extent to which the Study has explored the issues of confidentiality and the efforts it has undertaken to protect confidentiality. Dr. Fleischman commented that there must be a balance between information that will encourage participation and information that will discourage participation.

- Dr. Fleischman explained that the informed consent promises that a multidisciplinary committee composed of professionals and community members will meet to review future data analyses. This committee will determine whether proposals are in the spirit with which consent was given and ensure adherence to the policies, mission, and vision of the Study.

- Dr. Eaton agreed on the value of informing participants that in the future there may be additional studies that cannot be defined at the time of enrollment. It is important to say upfront that the Study will do everything possible to protect confidentiality of information but there may be glitches. A balance between honesty and discouraging enrollment must be maintained.

- With regard to data access versus protecting confidentiality, Dr. Cancian commented that there should be a balance between the needs of researchers and those of participants, as well as a balance between the needs of Study investigators and data collectors and the needs of outside researchers. It is important to not focus on narrow scientific self-interests versus a broader sense of what can be done with the data. Dr. Scheidt acknowledged this inherent conflict and agreed that the Study must maximize the use of data without undermining the protection of confidentiality.

- Dr. Scheidt reported that the Publications Committee has been constituted, and a Data Access Committee is in the process of being constituted. These committees will have separate responsibilities and require different expertise. The Data Access Committee and Program Office will develop the guidelines for access and use of data for all Study elements. The data access agreement should have the approval of the Publications Committee.

- Dr. Diez-Roux noted there are many successful models from multisite studies that have developed procedures to encourage the fair use of data by outside investigators. The Study has an obligation to protect participants' confidentiality, but it also has an obligation participants and the public to ensure that the data are used and that research is not hampered.

- Dr. Henry asked whether the Steering Committee could play a role in discussing public use data access and disclosure control. Dr. Scheidt replied that because the Steering Committee is composed of principal investigators (PIs), it may not have the expertise for such a role. In addition, it may have a bias in data access and use. The Steering Committee will have some input to the process.

- Dr. Dearry cited the NIEHS-funded organization, West Harlem Environmental Action, Inc., as a possible resource on the ethics of collecting, analyzing, and disseminating environmental and genetic data.

- Dr. Fleischman said that ICC members are interested in publishing Study findings. The ICC has proposed limits on the amount of time to publish findings, once data access and use have been granted. The Data Access Committee may track data use to ensure the timeliness of publication.

NCSAC Ethics Subcommittee Report: Continued Discussion of Revealing Findings

Dr. Genel

The current protocol for revealing findings states: "The Study will reveal findings to participants that are scientifically valid, clinically relevant, and actionable." There has been some debate about this protocol. Some well-respected scientists and ethicists believe revealing too much information could induce undue burden on the participant. Others believe it is the participants' right to know this information.

Subcommittee Recommendations:

With regard to revealing findings to participants, the Ethics Subcommittee recommended the following:

- The Study should reveal scientifically valid and clinically relevant findings.
- The Study should remove the term "actionable" because "actionable" could reasonably be interpreted to mean "amenable to medical intervention."
- Study findings that are currently not considered "actionable" may become actionable in the future.
- Findings should be peer-reviewed to determine their scientific validity and clinical relevance by the Steering Committee and/or Data and Safety Monitoring Board.
- The term "clinically relevant" should be more clearly defined.

With regard to revealing findings to communities, the Ethics Subcommittee recommended that "The advice of the community should be considered; in circumstances in which there is

disagreement with members of the community about revealing findings, careful thought should be given to the means and process by which the findings are ultimately communicated."

With regard to incidental findings, the Ethics Subcommittee recommended the following:
- The obligations to share incidental findings should be examined.
- Study participants should be informed that findings from research may not be comparable to findings during clinical care.
- The Study should address participants' potential misperceptions and assumptions about data collected for research and data's inability to replace clinical tests.
- Because the Study is conducting research and not providing clinical care, the consent form should clearly state not only what the Study is going to do, but what it is not going to do.

The Ethics Subcommittee concluded the following:
- The Study should reveal peer-reviewed, scientifically valid, and clinically relevant findings. The revealing of findings need not be "actionable."
- The criteria for disclosure of information to participants should be carefully considered and include community input.
- The consent form should clearly state the difference between performing research and providing clinical care so that participant expectations are realistic.

The NCSAC endorsed the recommendations of the subcommittee.

NCSAC Discussion/General Discussion

- Dr. Fleischman described the history of the Ethics Subcommittee's review of the revealing findings protocol. During the lead agency review of the Research Plan, Warren E. Lux, Jr., M.D. (EPA's Human Subjects Research Review Official), raised the issue of the term "actionable." Dr. Lux felt that including the term decreased the amount of information that participants would receive, which would not be the appropriate approach for the Study.

- Dr. Cordero asked whether the term "findings" refer to the specifics of an individual's personal information or the broader findings of a community or group of people. Dr. Genel replied that revealing findings refers to the disclosure of personal findings to the individual.

- Dr. Cordero commented that the matter of action can be a personal decision. Given the same information, one person may decide to act, whereas another might not. Dr. Cordero cited an example of choosing to take folic acid supplements. Dr. Fleischman said better example might be newborn screening and the decision to refer for testing when there is not an efficacious treatment for the finding. Dr. Cordero responded that an actionable item at the individual level might be different than an actionable item at the public health level.

- Dr. Schonfeld remarked that "actionable" doe not mean "treatable." For example, a person with an untreatable terminal condition may take a great number of actions or steps that are relevant and important to him/her. "Actionable" should not be seen as restricted to "treatable."

- Dr. Chapin said that if he were a Study participant, he would want to know any findings about his health status, whether it was actionable or not, or whether anything could be done about it now. The Study should notify participants of findings that a reasonable person may want to know and respond to accordingly.

- Dr. Scheidt explained that there is a need on behalf of the Study to provide useful information to participants. Some investigators, however, believe that sharing any information with participants will create anxiety that will constitute a risk that should be avoided. The Study must find a balance between providing all findings and providing none. The term "actionable" provides a criterion for the type of findings that should be shared.

- Dr. Gates noted that the Study will most likely provide parents with findings about their children. Parents may seek additional information the findings to decide any course of action on the child's behalf, but children should be allowed to make their own decisions about the findings as they get older.

- Dr. Lebowitz agreed that the term "actionable" should be deleted. He recommended providing findings to children, even if the value or clinical relevance of the findings is not known. Findings can be provided to children's primary care providers. He explained that previous studies provided environmental exposure findings to participants as soon as available.

- Ms. Brakefield-Caldwell said the results of any tests or analyses conducted on a participant should be provided to the participant, whether or not actionable or relevant.

- Amelie G. Ramirez, Dr.P.H., asked how the findings will be communicated to participants, particularly if the findings will have significant impact on health. If the participants do not have resources for health care, will they be provided? Dr. Fleischman answered that Study Centers are contractually obligated to communicate findings in a sensitive manner and have appropriate referral mechanisms.

- Dr. DuPlessis proposed that in the spirit of maintaining the communities' trust and respect, the Study should clearly define "actionable." Any data or results that have the potential for influencing growth, health, or well-being of children or parents now or in the future need to be shared. Participants should be advised to make appropriate links with providers who can interpret data and results. Dr. Genel noted that the Ethics Subcommittee recommended more clearly defining "actionable."

- Dr. Nabrit-Stephens said that the term "actionable" is too loaded and has too many meanings for different people. She proposed using wording that concerns health, safety, and well-being. Any findings that can be interpreted as negative should be conveyed to participants. However, the term "health" needs to be broadly defined.

- Dr. Long said the quality of data that lead to findings must be considered. Do the data meet a high standard of data collection? Do the data meet rigorous scientific criteria? False positives should not be conveyed to participants.

- Dr. Fleischman summarized: A group should define "clinically relevant" based on specific criteria. The participants should be informed of suspicious findings from screening, and they should be told that the findings do not constitute a diagnosis but is a concern that they may or may not want to address. The informed consent tells participants that they may have pay for additional testing, which may ultimately conclude that the findings are not significant.

- Dr. Wilfond remarked that "scientifically valid" and "clinically relevant" are difficult to define. Community input may help determine local meanings of these terms.

- Ms. Shepard suggested in considering clinical relevance, the Study should use a precautionary approach and consider the environmental relevance of findings. Even if the meanings of findings are not known, the findings should be shared with participants. The terms "well-being" and "healthy lifestyle" may be more appropriate than "clinically relevant."

- Dr. Schonfeld proposed that the Study focus more on the process, core principles, and guiding principles of revealing findings than on terminology. If a variable or parameter is not potentially clinically relevant, it should not be measured. He noted that protective factors can be clinically relevant. Valid information should be provided to participants at their request. The question is what the Study should do to provide information to a participant who did not request it and did not know the information was being collected.

- Dr. Fleischman described three types of information: (1) routine information such as height, weight, and blood pressure; (2) emergent or urgent clinical information such as hematocrit levels that would be immediately shared with participants; and (3) information that is not definitive/has unknown meaning.

- Dr. Diez-Roux commented that some participants may not want findings if there is no known medical treatment for the condition. Participants may want to opt out of receiving this type of information.

- Dr. DuPlessis said that in any multicenter study, some practices and processes will need to be rigid, whereas other practices and processes will need to be flexible. With regard to revealing findings, there may need to be some minimum standard that will need to be rigid. Study Centers may need to have ongoing reviews of revealing findings and be allowed some flexibility in decisions to provide information to participants.

- Dr. Henry agreed with Dr. DuPlessis on the utility of "straddling" between rigid and flexible processes. Communications among Study Centers would inform on the type and number of incidental findings, and the Study Centers would share their approaches for revealing such findings.

- Dr. Jarvis said that because the Study is hypothesis-driven, many of the exposure–outcome relationships will not be determined until 20 years from now. In addition, because many of

the biospecimens will not be immediately analyzed—and may not be analyzed until several years after collection—the clinical relevance of findings may not be an issue.

- Dr. Lengua explained that some psychosocial findings, such as depression and suicide ideation, may be clinically relevant, and the Study may be obligated by IRBs to report, act, or intervene. She recommended that the Study focus on higher risk issues, conditions, and problems when considering revealing findings to parents.

- According to Dr. DuPlessis, findings can be categorized on a spectrum from high confidence about clinical and environmental relevance and need to reveal, to those for which relevance is unknown and therefore the need to reveal is uncertain. A mechanism is needed so that the Study Centers have not only the principles and absolute minimum criteria for when to reveal findings but have evolving principles and practices for consistent handling of findings with somewhat known to unknown relevance.

- Dr. Trevathan noted the importance of maintaining the observational nature of the Study. Providing needed health care to Study participants may alter their behavior to the extent that the population is no longer representative of the United States and the Study is no longer observational. Dr. Trevathan cited a pharmacogenomic study in which investigators decided to not share findings. Because the meanings of the findings were unknown, the investigators thought participants' behaviors could be adversely affected if the findings were revealed.

- Dr. Schonfeld reminded the NCSAC that the Study is an observational study, not a health screening or health monitoring study. Families need to understand that important incidental findings will be reported, and they should understand that the Study will benefit other children but not necessarily their own. The purpose of the Study and the circumstances under which findings will be revealed must be clearly conveyed in the informed consent.

Report from the Director's Office, NICHD

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

Dr. Alexander thanked the NCSAC members for their participation and valuable advice. He also thanked the three members whose terms were ending. He reported that NICHD has been renamed. It is now the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development. Ms. Shriver—sister of President John F. Kennedy—played a major role in the creation of the Institute in 1962. A dedication ceremony for the renaming was held March 3.

The Study remains a collaborative effort involving not only the lead agencies (CDC, EPA, NICHD, and NIEHS) but numerous other federal departments and agencies. Dr. Alexander described the Study as "gathering steam." The Program Office is recruiting outstanding new staff, and new office space has been acquired. NICHD staff have presented at many meetings and conferences and will continue these activities. The Study is waiting for the reviews of the Research Plan by the National Academy of Sciences and OMB. The Program Office is working with the Vanguard Centers and other funded Study Centers to prepare for recruitment of the first phase of the Study. The Program Office has been answering questions from potential applicants

for the next wave of funded Study Centers and waiting for the applications. Applications will be peer review and negotiated, and contracts will be awarded by September 30.

With regard to funding, the Study received $69 million for fiscal year 2007 and $111 million for fiscal 2008. It was uniquely spared the budget rescissions in 2008, indicating the Congress' high regard for the Study and advocates' success in emphasizing the Study's importance. As in fiscal years 2007 and 2008, the President's fiscal year 2009 budget does not include funding for the Study, which requires $192 for continued implementation. Fiscal year 2009 will be an unusual budget year for NIH. In past appropriations hearings, the NIH director has testified alone. This year in the House, the NIH director testified together with the directors of CDC, the Health Resources and Services Administration, and the Agency for Healthcare Quality and Research. To date, the NIH director has not testified in Senate appropriations hearings. Congress may pass a continuing resolution for the federal budget, operating at the fiscal year 2008 level until the next administration and Congress convene in spring 2009. Under this scenario, the Study would continue implementation at the fiscal year 2008 funding level of $111 million. Future implementation efforts will be impaired without increased funding. The Study will, however, continue to move forward with its current funding and assume that Congress will provide the necessary funding to ensure continuing operations.

NCSAC Questions and Comments

- Dr. Schonfeld said he was glad to see a growing Program Office staff that brings a wealth of expertise to the Study and will be able to handle an increasing work load. He asked Dr. Alexander if the NCSAC can provide advice on other expertise that may be needed in the Program Office. Dr. Scheidt explained that Program Office needs expertise in genetics, growth and nutrition, maternal–fetal medicine, and bioethics. Through its network, the NCSAC can help identify and recruit appropriate subject-matter experts for the Study.

- Dr. Jarvis asked whether there is any precedent in the United States for a 25-year project operating on a year-to-year federal appropriation. Dr. Alexander observed that all federal appropriations are a year-to-year process. The federal budget is an annual process.

- Dr. Alexander noted that during the period when Study funding was most uncertain, not a single Program Office staff member left.

- Dr. Eaton said the NCSAC Community Outreach and Engagement Subcommittee recommended that a community engagement expert be added to the Program Office staff.

- Dr. Fleischman commented that the NCSAC was very impressed with new Program Office staff Drs. Moye and Dellarco and their presentations.

- Dr. Levin related the sentiments of the scientific community during the early planning phase of the Study that it would take existing funding from other worthy projects. Dr. Alexander agreed that, at one time, this was the worst fear of some scientists. Because of the Study's size, it can only operate with new funding. The appropriations in fiscal year 2007 and 2008

provide the new funding, which resides in the Office of the Director, NIH. Funding for Program Office staff salaries and travel expenses are paid out of the NICHD budget.

Day 2

Welcome and Recap of Day 1

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.

Status of Study Center Activities

Ruth A. Brenner, M.D., M.P.H., Director, Study Centers, National Children's Study

Dr. Brenner provided an overview of the Study's sampling and implementation strategy. In 2004, the decision was made to use a representative sample, and 105 Study locations were selected, with each location a single county. In a few cases, sparsely populated, adjacent counties joined to form a single Study location. In 2005, seven contracts were awarded to seven "Vanguard" Study Centers to conduct the pilot phase of the Study at seven Study locations. Pilot study data collection will begin in 2008–2009, beginning with the Duplin County, NC, and Queens, NY, Study locations. The full Study will be implemented in three "waves," beginning in 2010. About one-third of the Study locations will be included in each wave. The organizations or entities responsible for recruitment, enrollment, and data collection at Study locations are called Study Centers. A single Study Center may be responsible for more than one Study location.

In 2007, 22 contracts were awarded for Wave 1 Study locations; 5 contracts were awarded to existing Study Centers and 17 were awarded to new Study Centers. The total number of Study Centers is now 24. Including Vanguard locations, there are 33 Wave 1 Study locations. There is a contractual mechanism to award contracts to Centers for locations in later waves. Each wave will be, to the extent possible, representative of the full sample in terms of demographics, region of the country, and population density (rural versus metropolitan). There will be 68 locations in Waves 2 and 3. Contracts have been awarded for 13 of these locations. The remaining 55 locations are included in the current procurement. The RFP for this procurement was posted March 19; proposals are due May 2.

The Vanguard Centers have begun activities related to the pilot study. They have selected the neighborhoods within each location, held numerous meetings with relevant community entities and community advisory boards (CABs), finalized the pilot protocol through 2 years of age, and submitted OMB clearance documents for the pilot study and for formative research. In preparing for fieldwork, the Vanguard Centers are obtaining requisite IRB approvals, meeting with involved hospitals and appropriate entities within the communities, securing study space, and hiring staff. Current field activities not involving participant burden or human subjects include prelisting and listing activities and engaging relevant communities. Following OMB approval, targeted preliminary work (for example, focus groups, surveys, and formative research) and enumeration and screening of households will begin. Household enumeration and screening at two Study locations should begin in September; five locations should follow in December.

Targeted start date for household enumeration and screening at Wave 1 locations is January 2010. This delay relative to initial projections allows 1 year between the pilot study and full study to accommodate adjustments and allows additional time for preliminary work such as approvals, formative research, and community engagement. Wave 1 locations are currently conducting birth counts, defining sampling strata, and developing community engagement plans. Future Study milestones and timeline are as follows:

- 2008* Reviews and approvals (OMB, peer review, IRBs)
- 2008–2009† Additional Center and location awards (Waves 2 and 3)
- 2008–2009*† Begin pilot cohort at Vanguard Centers
- 2009† Repository and laboratory procurements
- 2010*† Begin full Study for Wave 1 locations
- 2011† Begin full Study for Wave 2 locations
- Begin full Study for Wave 3 locations
- Full data set for outcomes of pregnancy.

**Pending OMB*
†Pending funding

NCSAC Discussion/General Discussion

- Dr. Fleischman observed that at the end of Wave 2 activities, there may be Study locations for which Study Center contracts have not been awarded. He described these as "orphan sites." He asked whether the NCSAC has a role in helping local entities pursue contracts for these locations. Because federal employees are limited in recruiting these entities, nonfederal employees might be able to help. Dr. Brenner was unsure of what role the NCSAC could play. If there is not a successful award, there is a mechanism for the Coordinating Center to collect data at the location. The Study recognizes the importance of local involvement in data collection, and the RFP requires Study Centers' proximity to Study locations. Dr. Scheidt predicted that there will be few, if any, "orphan sites." Procurements can be modified to target these sites, if necessary.

- Dr. Genel asked whether there is limit on the number of Study locations that each Study Center can manage. Dr. Brenner said there is not a limit, but there are requirements that the Study Center must be in the same state or an adjoining state. Dr. Genel asked whether this requirement is modifiable. Dr. Scheidt replied that the requirement can be modified.

- Dr. Levin proposed an analysis to compare the characteristics (in terms of demographics, population density, region, etc.) of a strictly random national sample with those of the Study's representative sample to determine the extent to which each sample reflects overall U.S. population characteristics. Dr. Brenner said the proposal is worthwhile to pursue. Dr. Genel asked whether the Wave 1 data would be weighted to adjust for the small imbalances in representativeness. Lester R. Curtin, Ph.D., explained that enrollment of Waves 1–3 will occur over a 6-year period, and interim analyses will be conducted to study different birth cohorts. These analyses and other intermediate assessments will require statistical weighting. Dr. Curtin acknowledged that the Study's clustered sampling reduces costs, but there are statistical tradeoffs (for example, inflated variance). Dr. Curtin elaborated on the statistical

issues of the Study's sampling approach. Dr. Scheidt noted that urban Study locations have a more clusters than do rural locations. Dr. Brenner commented that the Queens, NY, location has about 20 clusters. She reminded that 1,000 births over a 4-year period will be enrolled at each location.

- Dr. Diez-Roux asked for clarification on clusters versus segments. Dr. Brenner explained that each Study Center submits the counts of births at its location (county). The births are categorized by where they occur within the county, and geographical boundaries are drawn to create segments with roughly the same number of births. The segments are then stratified based on different variables that are defined by the Study Centers, and segments are randomly selected by the Coordinating Center.

- Dr. Chapin asked whether there are plans for listers to use Google Earth. Dr. Brenner replied that Google Earth will be used for both prelisting and listing activities.

- Dr. Curtin explained that Census tracts are divided into block groups, which are subdivided into blocks. The household segments are compiled from aggregate Census blocks or occasionally block groups. The goal is to have equal number of household in each segment. Local input will be used to correct any discrepancies in numbers and adjust segment boundaries as necessary.

- Dr. Schonfeld noted that there are Study locations for which contracts have not been awarded. He asked whether this was due to not receiving applications or lack of successful applications. Strategies for getting successful applications will be different if entities need to be encouraged to apply or mentored to achieve successful applications. Without providing detail, Dr. Brenner said it is a combination. The Program Office will take measures to ensure awards for all Study locations. Dr. Schonfeld proposed that successful applicants mentor the unsuccessful applicants for those unawarded locations. This could improve a local entity's chance for successful award.

- Dr. Jarvis asked whether there is enough flexibility in the Study's budget process to allow a Study Center to manage five or more locations. Dr. Brenner explained that under the current procurement, proposals are submitted separately for each location. An independent panel reviews proposals for a single location only. With regard to the budget, Dr. Scheidt said a certain amount of resources is required to conduct the Study at each location. The amount varies by location and is predetermined. Some level of efficiency will be achieved if a Study Center manages more than one location, but the amount of resources for a location will not be reduced for Centers managing more than one location. The Program Office is encouraging Study Centers to apply for more than one location.

- Dr. Diez-Roux observed that the Study sample in each location may not be representative of that location. She asked whether sampling people in the same building would affect Study outcomes. Dr. Curtin explained that the Study will use a probability-based sampling approach (that is, every birth in a location will have roughly equal probability of being selected). The sample size (1,000 births per location) may not be efficient to represent different population characteristics. Dr. Curtin described the sampling approach in Orange

County, CA, which is being implemented in two stages. More so than tight sample clustering, the longitudinal nature of the Study may affect outcomes because of the possibility of conditioning participants; that is, if they know the Study is looking at certain risk factors, participants may change their behaviors and, as a result, change the distribution of risk factors. Although there may be scientific tradeoffs, tight clustering may help to improve rates of Study participation.

- Dr. Wilfond asked whether the Study encourages or facilitates communication among applicants and established Study Centers. Dr. Scheidt replied that during an open procurement, the Program Office cannot be involved with or comment on such activities but does encourage them. Communication among potential Study Centers and established Study Centers happens spontaneously.

- Dr. Henry recommended that the Program Office, to the extent possible, encourage established Study Centers to mentor applicants, particularly those entities with fewer resources or less experience in large studies. Dr. Henry asked what the Program Office is doing to bring together the different Study Centers so they can learn from each others' experiences. The Study may want to provide incentives to Study Centers to collaborate and learn from one another's' experiences. Dr. Brenner said there is one Study with one protocol, which fosters some natural collaboration among Centers. There is a Steering Committee and Executive Steering Committee to help Centers collaborate and implement the Study cohesively. Both committees convene regularly through teleconferences and in-person meetings. There is a Study-wide portal for posting materials and sharing information. Working teams composed of members from various Study Centers are helping to develop various aspects of the protocol. Dr. Scheidt reminded Dr. Henry that the Study operates under a contract mechanism, not through grants. Dr. Fleischman noted the cohesion among Vanguard Center PIs and their efforts to integrate new PIs into the Study.

- Dr. Lebowitz commented that the NIH model works best for multicenter studies. He noted how successful the Study has been in fostering cooperation among the Study Centers. He remarked that response rates are directly related to the amount of community engagement. He asked for an explanation of "formative research."

- Dr. Butenhoff asked (1) what the anticipated attrition rate is, (2) whether attrition would be higher in urban areas, and (3) how attrition affects planning and outcomes. Dr. Curtin acknowledged that there will be attrition. Based on attrition rates from similar longitudinal, there are expectations. But projecting attrition rates may be based on overly optimistic assumptions. Attrition will be monitored as the Study progresses.

- Dr. Schonfeld commented that samples that are initially clustered may become dispersed over time, which could lead to rising costs to continue following participants who move. Samples that are to closely clustered may create confidentiality issues. Dr. Brenner said that these issues have been considered for both urban and rural areas. Because information on the segment boundaries and definitions will not be released, there will be certain protections to maintain confidentiality. There may be thousands of households in a segment, but people living in the segments will not know which households are eligible or participating.

- There was general concern with how the Study will maintain the representativeness of the sample over time.

- Dr. Jarvis said there will be logistical issues of how the Study Centers will operate over the 25-year period. PIs may leave, and other PIs will need to be initiated into Study operations. Younger investigators will need to be trained and mentored. There will be challenges of quality leadership and maintaining Study Center integrity.

- Dr. Nabrit-Stephens noted that the Study will require a steady influx of pediatricians. Dr. Fleischman responded that special pediatric epidemiology training programs may be developed for this purpose. Dr. Scheidt said it is a vision of Study leaders that a new generation of training programs will arise. He cited the Collaborative Perinatal Project as an example.

- Dr. Nabrit-Stephens asked how the Study will maintain a representative sample, given the changing demographics of the United States. She asked whether the Study has factored in population growth, regional migration, and attrition. Dr. Curtin explained that the Study will be representative at the beginning. It is not known to what extent it will continue to be representative. This aspect is intrinsic to all longitudinal studies. He said that the representativeness can be adjusted statistically or through new recruitment.

- Dr. Fleischman said the Study will help advance knowledge of the informed consent process, pediatrics, research ethics, and community outreach and engagement.

- Dr. Cordero asked about the Study's plans for handling participants who move out of a Study location. Dr. Brenner said many participants will move within a Study location. Participants who move outside their Study location will be assigned to other Study Centers or will be followed by the Coordinating Center.

- Yvonne T. Maddox, Ph.D., described some of the long-term beneficial outcomes of the Women's Health Initiative. She said the Study will continue to examine and address issues of recruitment, retention, and community engagement.

- Dr. Ramirez asked whether the Program Office has considered a historical or anthropological study of the Study's population. Dr. Curtin replied that the Study's statistician will be able to track the Study's population characteristics so they can be compared to overall U.S. population characteristics. Sarah A. Keim, M.A., M.S., said that, for the past 4–5 years, a communications contractor has interviewed and will continue to interview key Study figures to gather historical information. Dr. Scheidt mentioned preliminary discussions to produce a documentary film of the Study.

NCSAC Community Outreach and Engagement Subcommittee Report

Helen DuPlessis, M.D., M.P.H., Chair, NCSAC Community Outreach and Engagement Subcommittee; Pediatrician, Harbor/UCLA Medical Center

Dr. DuPlessis reported that the Community Outreach and Engagement Subcommittee met by conference call on March 25, 2008. The purpose of the conference call was to discuss several questions. In framing its discussion, the subcommittee defined the following terms:

Community outreach: the provision to a specific population of education, information—and where appropriate, counseling and referrals—related to a specific service or activity.

Community engagement: the process of working collaboratively with groups of people who are affiliated with or united by at least one common characteristic (for example, geography, culture, special interest, profession, similar situation, race/ethnicity).

Subcommittee Recommendations:

- The Program Office should adopt definitions of "community outreach" and "community engagement" in all Study documents for clarity and consistency.
- The subcommittee acknowledged the work of the existing community outreach and engagement work team and encouraged rapid inclusion of new Study Centers into that work team.
- Each Study Center should constitute a CAB with an established charge.
- Participant satisfaction surveys should be part of the Study.
- The CABs should not be a peripheral activity. They should be involved before decisions are made. Incentives should be given to participants.
- Each Study Center should be required to establish a paid, full-time, senior-level position to serve as a community representative.
- The Study should develop training and provide educational materials for the Centers to clarify expectations and orient CAB members, revisiting that training as necessary over time.
- Keep the subcommittee apprised of the work in this area. The subcommittee is willing to review the curriculum and training efforts.
- Every site should have community representation, and the structure of community involvement can be flexible, depending on the size and logistics of each Center or site.
- As the Study progresses, communities should receive reports on the findings or progress of the Study.
- The Program Office and the Coordinating Center should add staff with specific expertise in community engagement and evaluation to provide technical assistance to the Centers.
- The Study should encourage continuous quality improvement through a learning collaborative or related model.
- Study Centers should continue to cultivate CABs and relationships with key community leaders while awaiting OMB approval.
- Study Centers should seek advice from CABs and community leaders about how and when to engage the community.

Community Outreach and Engagement Subcommittee Comments

- Mr. Guzman emphasized the importance of understanding the necessity of community engagement for the Study to succeed. There are many issues to be addressed in order to engage at the grassroots level, which is very important in minority communities.

- Dr. Nabrit-Stephen reiterated her concern about the Study's approach to community engagement. For it to be successful, community engagement must be an integral part of the Study's design and implementation and must permeate all elements of the Study.

- Dr. Ramirez said the Program Office needs to convey to the Study Centers that they need to hire a full-time person to engage communities and build trust.

- Dr. Jarvis said the Study provides an opportunity for other entities to conduct community-based participatory research and help build partnerships at the local level.

- Dr. Eaton reminded NCSAC members that community engagement needs to include community health care providers. For example, health care providers may be able to play a role in determining whether findings are clinically relevant. "Community" should be broadly defined.

NCSAC Discussion/General Discussion

- Ms. Brakefield-Caldwell said the senior-level community representative hired by the Study Centers should be hired from the community. This person should be a clearly defined community leader. Ms. Brakefield-Caldwell encouraged the Study to hire community and neighborhood residents for the household enumeration/listing phase. She encouraged the Study to engage with elected officials at city, county, and state levels.

- Dr. Wilfond commented that the Study participants are community member who must also be engaged. They must be engaged directly. He suggested participant surveys to understand the things that are working well or not working well from their perspective.

- Dr. Henry said the CABs need to be chartered to clearly outline their roles in participation and decision making. She cautioned that the Study needs to be very careful about the types of decisions that CABs are involved with and the expectations of the advice and counsel they provide. It is essential that the CABs be heard, and the Study should acknowledge that they have been heard. CABs should be able to influence Study Center decisions to the extent possible. Dr. Fleischman noted that the NCSAC continues to provide advice on bettering community engagement activities. Honesty and transparency in dealing with communities and CABs is important. Community members can accept that they will not have authority as long as they are respected and their information is transmitted at the highest levels so there is an opportunity to influence decisions.

- Dr. Lebowitz suggested there be clarification on CAB memberships, oversight, and specific plans for community engagement. Existing models from other studies could inform these

activities. Community members may need training to enhance their participation on CABs and give them insight on the process.

- Dr. Schonfeld said the Study Center community representative position may not need to be a full-time position. This person may have his or her own occupation and may not want to work full time as the community representative. A more general aspect of community engagement is engaging the rest of the country, that is, beyond the Study locations. As participants move, they need to perceive and be assured that they are still part of the Study. Scientific communities, medical communities, and taxpayers should know they are part of the Study and be engaged.

- Ms. Shepard said the Study Center community representative should be a dedicated person who is paid. A CAB will not come together without this paid position. Training is critical and must go two ways. Investigators need to understand the communities in which they work, as well as the critical nature of local culture, and community workers need to be involved. Community advisors need to understand the key concepts of the Study. There should be continuing discussions among community workers, CABs, and investigators to share different perspectives.

- Dr. DuPlessis agreed that CABs, investigators, and community workers should all be engaged in training.

- Dr. Scheidt explained that by contract the Study Centers must conduct community needs assessments. The assessments are not specifically prescribed, but data must be collected systematically. The Study Centers will comment on how the Study can address some community needs. The community needs assessments cannot proceed without OMB approval.

- Dr. Scheidt strongly agreed that the Study's success depends greatly on the degree to which communities are successfully engaged.

- Dr. Gates said she was concerned about the Study's ability to align the clustered sampling approach with community engagement. Communities that have been engaged may not be included as participants, and there may be issues of exclusion and failure to meet expectations. Dr. Fleischman noted that the Vanguard Centers have voiced similar concerns.

- Juanita Sims Doty, Ed.D., reported that because they do not yet know the segments or participating neighborhoods, Study Centers have been having general discussions with CABs. She agreed that CABs need charters. Being honest and building trust with CABs is important to let them know they will be heard. CAB members will need incentives for consistent and continuing participation. Such incentives may need to be stipulated in the Study Center contracts.

- Dr. Cordero said many public health departments, as well as local and city health officials, are already involved with community engagement. These departments and officials can help Study Centers, but their strengths vary across the country. Public health workers are

generally very engaged in their communities. Dr. DuPlessis commented that some officials and departments may not understand the role they can play. Ms. Winseck said some public health officials are on Vanguard Center CABs.

- Mr. Guzman asked for clarification on data ownership. He noted that in some areas, because there is no longer significant public health outreach, community health care providers can play an important role in community engagement. Dr. Fleischman explained that data ownership is a very complex legal issue. The Study Center contracts clearly state that the data are owned by the federal government and that all data must be submitted and stored at a central data center. It is important for the Study to provide community progress reports on site-specific issues as well as national-specific issues. Study Centers will release community-relevant and national-relevant data. Communities will be engaged in the sharing of information. There will be a separate mechanism for sharing Study data for community-level adjunct studies.

- In response to a comment by Dr. Cancian, Dr. Scheidt described some aspects of Study Center contractual obligations: All Study Centers must develop a detailed community engagement plan; all must have, at a minimum, a CAB; and Study Centers must regularly report the status of community engagement. The Study Centers are exchanging information about their community engagement activities.

- Dr. DuPlessis observed that the Study's Community Outreach and Engagement Working Team appears to be challenged by some of its activities. It is developing a process for engaging the new Study Centers. Ms. Winseck commented that this will be a Study-wide process. She said that Vanguard Centers have created a number of lessons-learned documents for the new Centers. These detailed documents describe the challenges and offer recommendations based on the lessons learned.

- Dr. Diez-Roux said the Study must be honest and realistic in informing participants and communities about the types of local Study information can be provided, the extent to which they will benefit from this information, and the meaning of the results. Dr. Fleischman commented that the Study provides a unique opportunity for broadening Study entities' engagement with their communities that would have long-term benefits.

- Dr. Eaton said the Study can benefit from state public health departments' involvement at the community level. Involvement at the state level may offer a source of funding. She cited a study that hired a parent consultant at the state level. State and local public officials need to be aware of and involved with the Study.

NCSAC Recommendations

The NCSAC recommended that the Study:

- Develop Study-specific definitions for the terms "community outreach" and "community engagement."
- Encourage the hiring of a permanent senior-level position to serve as a community representative at the Study Centers, which would have discretion for a full-time or part-time

position. This should be at least a half-time position. The community representative should be from the community, have expertise in the community, and should understand community engagement. Study Centers should identify key communities within the Study locations and determine what community representation would be most appropriate, preferably from the participant community. A position description should be written.

- Encourage the Program Office and the Coordinating Center to add staff with specific expertise in community engagement and evaluation. Staff members would support and assist the Study Centers and would help engage communities on a national level.
- Each Study Center should be required to institute a chartered CAB with an established charge.
- Develop training materials and providing training to Study Centers, CABs, and other staff (for example, at the Program Office and Coordinating Center). The training process is essential to clarify roles, responsibilities, and expectations.
- Provide technical assistance to the Study Centers.
- Implement participant satisfaction surveys to assess the effectiveness of community engagement. Surveys could include broader assessments of the effectiveness of community-level engagement. Due to potential participant burden, methods other than surveys should be considered for assessing effectiveness.
- Report Study progress and findings back to the community on a regular basis.
- Accelerate the process of engaging the new Study Centers to share Vanguard Centers' lessons learned on community outreach and engagement.

Office of Management and Budget Clearance and the National Children's Study

Kenneth C. Schoendorf, M.D., M.P.H., Director, Protocol Development, National Children's Study

Dr. Schoendorf provided a brief overview of OMB processes and described current Study-related OMB activities. The purpose of OMB review is to ensure that the public is not overburdened with federally sponsored data collections. Plans for federally sponsored data collection must be reviewed and approved by OMB before studies can begin. Prior to OMB submission, *Federal Register* notices are posted to allow public comment on data collection plans.

Study submissions included supporting statements (description, rationale, burden, cost, and public comments) and appendices (data collection instruments, other communications with participants, and IRB approvals). OMB approval is necessary before the Study can interact with participants. Households cannot be enumerated and women cannot be screened before OMB approval. Households can be listed. There will be a lag between OMB approval and the beginning of field work.

Two research plans were submitted for OMB approval. The research plan for formative studies to be conducted by Vanguard Centers was submitted to OMB on February 21, 2008. The submission requests "generic" clearance of a bank of hours to conduct studies to improve federal data collection. Activities include focus groups and small methods studies. Specific studies will receive expedited approval. The submission for the Pilot Study research plan included a complete study protocol, with enumeration through the telephone interviews. All data collection

instruments and forms were provided. The research plan for the main Study (Waves 1–3) will require a separate submission for OMB clearance.

NCSAC Discussion/General Discussion

- Dr. Jarvis asked to what extent the OMB review and approval process for the Study might be politicized. Dr. Schoendorf declined to speculate on political influences. The Program Office assumes there will be none. The Program Office is willing to work with OMB to facilitate approval of the research plans.

- Dr. DuPlessis asked whether the research plan submitted for the full Study was through 1 month of age. Dr. Schoendorf replied that it was through 2 years. Because all OMB approvals are for a maximum of 3 years, the Study will have to resubmit research plans every 3 years. However, because of the Study's staging, research plans may have to be submitted more frequently than every 3 years.

- Dr. Lebowitz asked about the Program Office's plans for the formative studies. Dr. Schoendorf replied that some ideas have been discussed but nothing is final at this time. Ideas have originated not only with the Program Office but the Coordinating Center, Vanguard Centers, and new Study Centers.

- Dr. Henry asked whether it was possible for OMB to change the Study Protocol or data collection requests. Dr. Schoendorf said Program Office is less concerned with possible changes than the length of time to approve the Research Plan. Based on his experience, Dr. Schoendorf said there are some communication, questions and answers, and negotiation between OMB and the submitting entity. The interaction is generally reasonable. Dr. Fleischman commented that the NCSAC is supportive of and sympathetic to the Program Office's efforts in the process but cannot exert any influence on the process.

Introduction of Study Illustrator

Ms. Winseck introduced Lisa Brown, the Study's new illustrator. Ms. Brown will help update the Study's public materials in preparation for beginning recruitment. The photographic themes in the public materials will be phased out in order to make the materials more universal and appealing to a broader audience. The new materials will use an illustration theme featuring Ms. Brown's line drawings. A sample of Ms. Brown's work was presented to the NCSAC.

Childcare and Developmental Outcomes: Results from the NICHD Study of Early Child Care and Youth Development

Cathryn Booth-LaForce, Ph.D., FAPS, RYT, School of Nursing, University of Washington

NICHD started the Study of Early Child Care and Youth Development in 1991 to examine how variations in child-rearing contexts (for example, childcare, home, and school) are related to children's social, emotional, cognitive, and language development and health. The Study enrolled 1,364 children who were born between 1991 and 1994. Sampling was designed to ensure adequate representation of major sociodemographic niches. The children were born at 24

hospitals, and data were collected from 10 study sites. The Observational Ratings of Caregiver Environment (ORCE) tool was developed to assess childcare environments. Children were assessed at ages 1, 6, 15, 24, 36, and 54 months; at grades K, 1, 2, 3, 4, 5, and 6; and at age 15 years.

The results at 54-month assessment were as follows:

- For preschoolers, higher quality care over the first 4.5 years is associated with better preacademic skills and better language skills.
- More experience in childcare centers is associated with better language skills and more problem behaviors.
- More hours of childcare over the first 4.5 years is associated with more problem behaviors such as aggression and disobedience.

The results at grades 5 and 6 assessment were as follows:

- Higher quality care over the first 4.5 years is associated with higher vocabulary scores in grade 5.
- More experience in childcare centers is associated with more behavior problems in Grade 6.

Assessment of Childcare During Infancy

Kenneth C. Schoendorf, M.D., M.P.H., Director, Protocol Development, National Children's Study

Dr. Schoendorf reviewed the Study's proposed plan for assessing childcare during infancy. At 3 months of age, the mother or childcare provider will give information on current childcare via telephone interview. At 6 months, childcare information will be gathered via questionnaire during a home visit. A second telephone interview will occur at 9 months of age, and a second home visit questionnaire will be given at 1 year of age. Interviews and questionnaires will focus on "structural" aspects of childcare: days and hours per week, number of centers or locations, and type and size of location (for example, home or center, relative or nonrelative, and number of children and staff).

A childcare substudy will be conducted in which a subset of reported childcare sites will be assessed. The substudy will follow up from the 6- and 12-month home visits. Childcare sites will be included if the child spends 30 hours or more per week in childcare. For children who spend 10–29 hours per week in childcare, only about 10 percent of the childcare sites will be included. It is assumed that (1) about 50 percent of the children will be in childcare at the time of each home visit and (2) that data from about 20 percent of the total Study population will be included in the substudy. Telephone interviews and site visits will be used to assess sociodevelopmental environment, physical environment, and chemical environment.

For the social-developmental environment, the Berkeley-Yale Telephone Interview survey or similar instrument will be used to assess space and size, available materials, activities, interactions, and staff training. An onsite visual inspection will assess indoor and outdoor physical environments. Chemical environment assessment will include indoor dust, water, and soil.

NCSAC Questions and Comments

- Dr. Booth-LaForce commented on the Study's plans for assessing childcare during infancy. She was concerned with the measures of quality. She said the Berkeley-Yale interview tool has not been used extensively. It is a tool for interviewing childcare providers. There are separate data collection forms for family daycare homes and for childcare centers. There is not a form for informal childcare arrangements. Because the childcare provider is asked to provide information about the quality of the childcare environment, there is a respondent bias. Dr. Booth-LaForce suggested that the Study use observed quality measures (for example, children–staff ratios) as much as possible.

- Dr. Currie asked whether the Study would collect data on only childcare for infants. Dr. Schoendorf said the Study will assess childcare through preschool. Dr. Currie noted the increase in center-based childcare and suggested the Study collect data on the types of childcare centers. She asked why mothers will be asked to provide the addresses of daycare centers. Dr. Schoendorf replied that the centers' locations will be linked to existing databases (for example, ambient or environmental databases).

- Dr. Cordero asked Dr. Booth-LaForce about the proportion of children in the NICHD study with developmental disabilities such as autism. Dr. Booth-LaForce said some of the children had autism and other disabilities, but she did not know how many. These children were assessed in the same manner as other children in the study.

- Dr. Butenhoff asked to what extent the Study Protocol will consider early childhood education (for example, in the 3- to 5-year-old age group) in terms of early childcare. Dr. Schoendorf agreed that these are important issues, but the protocol has not been developed sufficiently to address them.

- Dr. Wilfond asked Dr. Booth-LaForce about (1) the willingness of childcare providers to participate in the NICHD study, (2) circumstances that required reporting, and (3) parental objection to investigators observing their children at childcare centers. Dr. Booth LaForce said that typically, about 10 percent of childcare providers do not want to participate in these types of observational studies. With regard to reporting, the study did not report findings to either parents or centers. There was mandatory reporting of child abuse. There were no objections from parents whose children were not study participants.

- Dr. Schonfeld commented on the level of sensitivity and specificity of variables being observed and the relative contribution of environmental factors to developmental outcomes. He said the observations must be related to the Study hypotheses. The Study will need to bring together childcare experts to determine the most appropriate childcare measures.

- Dr. Currie said there is no reason to believe that childcare will have the same effect on all children. She noted that the participants in the NICHD study were selected not to be particularly disadvantaged and not to have risk factors. Early childhood education can be beneficial for some children who have several risk factors. Because of its representativeness,

the Study will provide a better platform for assessing the effects of childcare. What need to be determined are the outcomes that childcare quality will affect.

- Dr. Fleischman said Dr. Schonfeld raised an important analytic question about analyses of different levels of data quality in different domains and comparing the relative impact of different exposures and the quality of the measures. The NCSAC Scientific Review Subcommittee may be able to work with the Program Office to address some of these issues. Dr. Fleischman remarked that Dr. Wilfond identified an important issue about collateral observations of individuals who are not Study participants.

- Dr. Wilfond said the Study should consider mechanisms for notifying parents of collateral observations. Dr. Booth-LaForce responded that one issue is determining how much information should be given to a class or group at a childcare center. Another issue is concern about privacy of children not participating in the Study.

- Dr. Lengua asked whether the NICHD study rated caregivers' behavior in terms of child behavior management or discipline. Dr. Booth-LaForce said these measures were included in the composite scores. She mentioned the Modernity Scale as a tool for evaluating caregiver attitudes on childrearing.

- Dr. Lengua noted that the structure of the Study's childcare study will not allow assessment of the continuum of time in childcare as a predictor of outcomes. Dr. Schoendorf explained that the Study will collect data at a number of locations of varying types of locations and caregivers from all participants at 3, 6, 9, and 12 months. The childcare site visits will be conducted for a subset of the participants.

- Dr. Scheidt asked whether the ORCE is a validated measure. Dr. Booth-LaForce replied that it has been validated.

- Dr. Scheidt asked how the Study can best capture environmental exposures related to childcare on 100,000 children. Dr. Booth-LaForce said there is a simple five-item assessment derived from the ORCE that might serve as an ideal data collection tool for the Study. This assessment can be used across a range of childcare settings.

- Dr. Levin confirmed that in the NICHD study the effect sizes were small, statistically significant, and important. When effect sizes are small in an observational study, there are questions about design, that is, whether the study is sufficiently measuring covariables and confounders to allow confidence in the findings. Dr. Booth-LaForce explained that childcare has been mostly compared with the family environment and how much variance this environment carries in terms of both proximal and distal measures.

- Dr. Lebowitz asked Dr. Schoendorf whether the Study will be collecting environmental samples (for example, dust, allergens, microbes, molds, endotoxins, and antimicrobial products) from childcare centers. Dr. Schoendorf said there are plans to collect such samples. Dr. Scheidt clarified that microbes will not be cultured. Serological analyses will be performed, and biomarkers will be assayed. Dr. Henry said that because there are "windows

of susceptibility," it might be useful to collect samples of infectious agents as a reflection of living environments. Sampling does not need to focus on a single microbe, but using new rapid screening systems, investigators will be able to sample broad microbial exposures. Dr. Schoendorf noted that many environmental samples will be stored for future analyses for such exposures. Dr. Henry emphasized that microbial exposures may be as important as chemical exposure but are more difficult to measure.

- Dr. Schonfeld said the NCSAC Scientific Review Subcommittee could work with Program Office staff to establish a mechanism to determine whether the data being collected are most likely to answer the questions of the hypotheses. The subcommittee could assist in bringing together the necessary expertise for this project. Dr. Fleischman suggested that the NCSAC might want to address some of the Study complex analytic issues (for example, using fine versus gross measures) in a future meeting.

- Dr. Schonfeld said a more substantial issue is using state-of-the-art measures to gather data that can accurately identify determinants of outcomes. For example, in order to understand learning disabilities, the learning environment must be assessed. In this example, social interactions may be more important variable than dust or chemical exposures in the childcare center. If the variables have no documented effects on outcomes, then they should not be measured. The Study may need to pay closer attention to the more relevant variables.

- Dr. Currie commented that there are validated and widely used scales to rate childcare center sanitation without directly collecting data on microbes.

- Dr. Lengua asked about the goal of measuring the childcare setting. Most of the measures discussed so far involve the physical and chemical exposures. These measures are not as important as the psychosocial exposures. It is important for the Study to adequately measure these exposures. Dr. Schoendorf replied that the purpose of measuring physical and chemical exposures in childcare centers is to provide data on the child's broader environmental exposures.

- Dr. Cordero asked how administrative data and other existing data sets will be integrated with the Study data. Dr. Schoendorf explained that the Study's IMS will be able to link extant data with Study data.

- Dr. Diez-Roux noted that many of the outcomes will be affected by multiple factors. Investigators will attempt to draw conclusions about the relative importance of different factors. The Study needs to determine whether there is a balance in the precision of measures across domains.

- Dr. Wilfond commented that cost and effort affect the precision of measures.

- Dr. Lebowitz agreed that there needs to be a balance in the precision of measures. Measures need to be as valid, sensitive, specific, robust, and precise as possible. However, there is a tradeoff between cost and the degree of precision.

- Dr. Lengua asked whether the children who are included in the childcare substudy at 12 months will be same as those included at 6 months. Dr. Schoendorf said they may not be the same.

- Dr. Diez-Roux reminded the NCSAC that adjunct studies will be able to assess many exposure-outcome relationships that the Study will not be able to do on its 100,000 children.

- Dr. Booth-LaForce offered the following concluding comments: (1) information on a child's entire history of childcare should be collected through questionnaires; (2) the Study should collect as much data as possible on informal childcare arrangement; and (3) direct observation is important and highly warranted to assess the quality of childcare settings.

Recommendations:

- Caretakers' behavior management tactics should be included in the substudy.
- Microbial agents are important exposures in childcare settings and should be included in the assessment.
- The appropriate childcare measures should be those that relate to the Study hypotheses.
- The Study must develop a policy for responding to collateral observations.
- The Study should follow the same children enrolled in the childcare substudy in order to link early exposures to subsequent development.

Future Directions: Appointing New Subcommittee Members

Dr. Fleischman

Dr. Fleischman explained that as the membership of the NCSAC changes, new subcommittee members will need to be appointed. Currently, there are three subcommittees. If there is a need for additional subcommittees, the NCSAC has the right to create them. Subcommittees are not transient work groups and must adhere to the rules and regulations of the Federal Advisory Committee Act. Because of this, subcommittees are not created unless absolutely needed and sustainable. Outside experts may serve on subcommittees for a limited time. Subcommittees meet to discuss relevant Study issues and make recommendations that are presented to the full NCSAC. Subcommittee recommendations cannot be made to the federal government without approval by the full NCSAC.

The charges of the subcommittees are as follows:

- The Scientific Review Subcommittee provides advice and recommendations concerning pilot studies, scientific questions, and aspects of the protocol.
- The Ethics Subcommittee provides advice and recommendations concerning various ethical concerns.
- The Community Outreach and Engagement Subcommittee provides advice and recommendations concerning community outreach, involvement, and engagement.

Dr. Fleischman asked those NCSAC members who are interested in serving on a subcommittee to contact him or Ms. Sapienza. He also asked for suggestions of additional topics or issues that should be pursued by NCSAC subcommittees.

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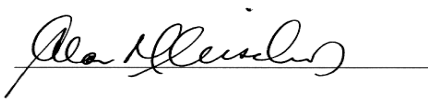
I hereby certify that, to the best of my knowledge, the foregoing minutes are accurate and complete.

06/12/08



Date

Alan R. Fleischman, M.D.
Chair
National Children's Study Federal Advisory Committee