National Children's Study
Federal Advisory Committee 16th Meeting
June 26–27, 2007
Gaithersburg Marriott Washingtonian Center
Gaithersburg, MD

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

Welcome and Introductions

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

Dr. Fleischman welcomed the National Children's Study Federal Advisory Committee (NCSAC) members and other participants to the 16th meeting of the NCSAC. He introduced Kate Costella, M.S.W., who is the new NCSAC Executive Secretary. Ms. Costella described her roles and responsibilities as Executive Secretary and Outreach and Communications Coordinator for the Study. Dr. Fleischman thanked Jessica Sapienza, M.H.S., NCSAC Liaison Officer, for her work organizing the meeting.

Dr. Fleischman assured NCSAC members that their work is important to the Study. NCSAC recommendations are taken seriously and are the template upon which discussion begins in deliberations of many organizational components of the Study. In addition, NCSAC members can serve as Study "ambassadors" to promote and raise awareness of the Study. The Program Office can provide materials to assist in these efforts.

Dr. Fleischman briefly reviewed the functions of federal advisory committees as defined in the Federal Advisory Committee Act and noted that the meeting was open to members of the public, who were invited to participate at appropriate times during the meeting. Dr. Fleischman reviewed highlights of the December 2006 meeting. He said the NCSAC was unable to meet until now because the Study chose to not have public meetings during the time of the solicitation for new Study Centers. Dr. Fleischman reviewed the meeting's agenda and highlighted upcoming presentations.

Welcome and Study Update

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

Dr. Scheidt discussed the Study's current funding status, the solicitation of additional Study Centers, notable Steering Committee activities, and the status of and review activities for the Research Plan. He listed other Study activities since December 2006 and noted upcoming plans.

The Study's Funding Status. About $50 million was spent between fiscal year 2000 and fiscal year 2006 from the existing budgets of NICHD, CDC, EPA, and NIEHS. For fiscal year 2007, $69 million was appropriated specifically for the Study by Congress on February 14, 2007. For fiscal year 2008, no Study funding was provided in the President's budget, but $111 million has been designated in the House and Senate mark-ups of the fiscal year 2008 budget. About $3 billion is required to conduct the Study from fiscal year 2008 to fiscal year 2034.

Additional Study Centers. In October 2006, a special notice of intent to post a request for proposals (RFP) for award in 2007 was released. The RFP was posted February 15, 2007. It specified that all Study locations are available for bidding. Locations must be in the state of the Study Center or a contiguous state. For ease of review, there will be separate east and west competitions. Multiple locations and Study Centers are encouraged as options. Start-up will be staged to achieve the most representative sample. The response to the RFP was good, and the reviews have been successful. Awards will be made by October 1, 2007.

Steering Committee Notable Activity. The Steering Committee did not meet during the open Study Center solicitation period; it did, however, meet May 22–23. Highlights include:

- As the new Study Centers come on board, the Steering Committee will become larger and require restructuring.
- Some future Steering Committee meetings may coordinate with meetings of the NCSAC and Study Assembly.
- Marion J. Balsam, M.D.; James J. Quackenboss, M.S.; and Eric Sampson, Ph.D., Division of Laboratory Sciences, National Center for Environmental Health, CDC, discussed the Study repository and laboratory.
- Guidelines on data use and publications and a publications policy manual were discussed.
- Methods development studies such as a consent methods evaluation trial and a process for local methods development studies were discussed.
- Ruth Brenner, M.D., described Protocol issues and provided an update on the Research Plan.
- Experiences and lessons learned from other studies were presented. Kathryn Porter, M.D., discussed the National Health and Nutrition Examination Survey (NHANES), and Germaine Buck-Louis, Ph.D., discussed the Longitudinal Investigation of Fertility and the Environment (LIFE) Study.

The Research Plan. Dr. Scheidt compared the Research Plan and Protocol. The Research Plan describes the background, rationales, and specific approaches for peer review (National Academy of Sciences [NAS]) and lead agency reviews; it will be posted for public comment. The Protocol describes the specific methods and instruments to be used in the Study. The Protocol will be submitted to the Office of Management and Budget (OMB) and will be used to prepare operational manuals. The contract with NAS for peer review of the Research Plan was signed April 24, 2007. The review is expected to be completed in 6–9 months. Lead agency reviews are underway. The Research Plan will be posted for public comment in the near future.

Recent Activities. Since the last NCSAC meeting, the Study has participated in the EPA Initiative on the Early Indicators of Environmentally-Induced Disease grantees meeting (January 9), the Genetic Measures Workshop (March 23), OMB meetings (May 4 and 11), the Canadian

Partnership on Children's Health and the Environment meeting (April 23), and the Public Policy Forum at the Pediatric Academic Societies meeting (May 5).

Genetics Measures Workshop. Dr. Scheidt listed some of the main outcomes of this workshop. He noted that main effect gene association studies are the primary target of interest. Genome-wide association studies are the most efficient approach for gene association studies, but the high costs make this approach unfeasible at this time. Cell lines would be the most dependable and versatile method to conduct genetic studies. RNA studies are important but samples must be stabilized immediately after collection to be effectively studied. The use of grandparent DNA is urged; specimens such as saliva could be mailed for analysis.

Future Plans. Dr. Scheidt noted programmatic needs and upcoming meetings and presentations. The Program Office staff needs to be expanded by September 30 to manage the workload resulting from the new Study Centers. If funding is appropriated for fiscal year 2008, RFPs for the repository and laboratory, as well as for a second "wave" of Study Centers, will be posted. The Federal Consortium meeting will be held July 25. A Study panel will participate in the Joint Statistical Association meeting on July 30. The International Childhood Cancer Cohort Consortium will meet in Copenhagen August 29–30.

Discussion. After Dr. Scheidt's presentation, he responded to comments and questions that addressed the following topics:

- *Response to the RFP for new Study Centers.* John L. Butenhoff, Ph.D., asked how many proposals were submitted in response to the RFP for new Study Centers. Dr. Scheidt said he could not comment on the submissions until the contracts are awarded.

- *Response to Research Plan comments.* Allen Dearry, Ph.D., asked how the Study is going to respond to comments from the Research Plan review and whether the Research Plan will be modified in response to comments. Dr. Scheidt explained that enrollment will begin in 2008. The Research Plan may not be able to be modified based on review comments prior to enrollment. However, the first year of the Study is considered a pilot phase, and the Research Plan may be restructured or refined based on the pilot experience and review input. Implementation of the full Study begins in mid 2009.

- *Relationships of Study entities.* Michael Lebowitz, Ph.D., asked about the communication and decision-making processes and lines of interaction among Study entities, particularly the NCSAC. Dr. Scheidt said the roles and responsibilities of the NCSAC, as well as those of other entities, will evolve as the Study is fully implemented. The NCSAC will provide more advice on implementation and will be less involved in planning. There may be more interactions with the Steering Committee. The NCSAC will also provide specific advice on ethical issues and community engagement. The Study's major decision makers are the Director, NICHD, Duane Alexander, M.D.; the Study Director, Dr. Scheidt; and the Interagency Coordinating Committee (ICC). The NCSAC's primary role is to offer advice and recommendations to these decision makers.

- *International collaboration.* J. Ricardo Guzman asked whether the Study will be collaborating with longitudinal studies in Mexico or countries in the Caribbean. Dr. Scheidt noted the developing U.S.-Canadian partnership, which resulted from discussions among North American Free Trade Agreement (NAFTA) representatives. There were no subsequent discussions with Mexico, and because there are no similar initiatives in Mexico or the Caribbean, collaborations have not been pursued. British investigator Jean Golding met with the Program Office and expressed an interest in conducting a study in Jamaica.

- *Level of progression of new Study Centers.* Antoinette Pabisi Eaton, M.D., asked how, with the anticipated increase in funding, the new Study Centers will be added. The fiscal year 2008 funding will be used to fill the gaps remaining after the current solicitation, Dr. Scheidt said. Future solicitations will add new Study locations but not necessarily more Study Centers. Contracts for about 20 Study Centers will be awarded this year. Full implementation of the Study may require about 35 Study Centers. There will be a greater need to expand the number of Study locations as enrollment increases. Much of future funding will be used for staff, equipment, infrastructure, data collection, and data analysis.

- *Public posting of the Research Plan.* Janet Currie, Ph.D., inquired about when the Research Plan will be available to the public. Dr. Fleischman said the plan will be posted in the near future and the NCSAC will be informed when it is. The Research Plan's posting to the Study's Web site will be announced on the Study's general listserv. Hard copies are available for the public to borrow upon request.

The Research Plan

Ruth A. Brenner, M.D., M.P.H., Director of Protocol Development, National Children's Study

Dr. Brenner compared the Study Plan, Research Plan, Protocol, and Manual of Procedures. The Study Plan was the first public documentation outlining many aspects of the general study design. It was published with the RFP for Vanguard Centers in November 2004. Its purpose was to guide offerers in preparing their proposals. Although it provides less detail than the Research Plan or the full Study Protocol, it was anticipated that the Study Plan would evolve in greater detail with input from investigators from the Vanguard Centers and Coordinating Center, the ICC, and the NCSAC. The Research Plan is a detailed 600-page document that describes the Study's background, rationale, and hypotheses and provides an overview of study design and measurements. It was prepared for peer review, agency review, and public comment. Volume 1 includes a précis and describes the background and significance, study design, Study management and support, and aims and summaries of the hypotheses. Volume 2 contains six appendices. Overall, the Research Plan has 17 chapters and a reference list.

The Study Protocol's multiple documents will focus on study design and measurements. It will include full questionnaires, protocols for collection of samples and specimens, and other operational aspects. The Protocol will be reviewed by institutional review boards (IRBs) and OMB reviewers and will provide the basis for preparation and implementation manuals. It will

be prepared in stages; the current draft will cover the period from preconception through early infancy. The Manual of Procedures will comprise multiple procedural and training manuals that detail the "how" of all data collections. It will be developed based on the Study Protocol.

NCSAC Discussion and Recommendations

Dr. Fleischman posed a series of questions to frame the discussion and generate comments and recommendations.

1-In light of finite resources provided for the Study and reasonable limitations on participant burden, does the Research Plan respond to the directive of the President's Task Force (1999), Children's Health Act of 2000, and Congress?

- Dr. Currie noted the Children's Health Act specifies that the data be used for making causal inferences about the effects on health. She also noted the methods section of the Research Plan does not mention several methods that are used by researchers to determine causal inferences, such as instrumental variables methods or use of "natural" experiments. Such approaches would allow investigators to assess causal inferences by merging data from different sources, such as merging the Study's data with data on policies or on geographical features of neighborhoods. Merged datasets could, for example, help determine effects of proximity to hazardous waste on health. Dr. Currie said the Research Plan does not describe how outside researchers would access Study data with identifiers to merge with other data. Chapter 11 states data made available to the scientific and research community will be available in de-identified datasets. Dr. Currie said de-identified datasets will not allow researchers to merge health data with data from a geographically defined area. If merging de-identified data is anticipated, prospective geocoding will help the process. Neither the geographic information system (GIS) section nor the section on data availability describes provision for GIS coding or matching of the data to other data sources.

- Nancy Neveloff Dubler, L.L.B., expressed concern about the psychosocial sections in the document's color pullout where the injuries are repeated mild traumatic brain injury or behavioral exposures or antecedents and resiliency to traumatic life events in childhood. There is a need to precisely define the injury where there seems to be the most latitude for slippage in the eyes of the investigator and a need for the causal relationships to be more specifically identified. She thought that these injuries and behaviors were not defined precisely enough to keep the values and perspectives of the viewer or investigator from becoming a factor in what was listed as data.

- Dr. Lebowitz asked whether the President's Task Force defined the environmental exposures and whether the task force indicated any prioritization concerning exposures and their effects. He asked whether the Children's Health Act defined each of those environmental exposures and provided some weight of evidence, prioritization of the exposures, or population-attributable risk. In Dr. Lebowitz's opinion, the hypotheses encompass a broad range of exposures and outcomes, and there appears to be unequal representation

among them. Understanding the weight of evidence used by working groups and subcommittees would shed light on how the hypotheses were developed and prioritized. Dr. Lebowitz said he did not see a chapter on how the Study Centers involve communities and enhance their participation. Whether the approach is population-based or community-driven, the extent of community involvement influences how a study is conducted.

- Liliana J. Lengua, Ph.D., commended the choices of psychosocial factors and children's social and emotional development measures. She said the current Research Plan may not be able to address an emerging focus on child characteristics that play an evocative or selective role in a child's environment (for example, behavioral characteristics that may put a child at risk). In this context, a child's characteristics may determine environmental exposures and may change the experience with an environment. Dr. Lengua suggested that an impulsive child may be more likely to get injured. Without appropriate measures, the Study may miss important predictors of injuries and adjustment problems such as aggression and substance use. She noted that the Research Plan includes an early assessment of infant temperament at 6 months but there do not appear to be other assessments of those characteristics that might place children at risk.

2-Are the "priority outcomes" of sufficient public health importance and scientific interest to be the major focus of the Study?

- Robert E. Chapin, Ph.D., said the priority outcomes are sufficient to be the major focus of the Study. He noted that the Study's outcomes are not the only ones that could be evaluated, but the planning efforts and hard work of the ICC, various working groups, and the Program Office had identified the most tractable hypotheses.

- Michael Lebowitz, Ph.D., observed that two important public health concerns—cardiovascular disease and cancer—were not included in the priority outcomes and asked why these outcomes had not been included. Previous studies of clusters of childhood leukemia have demonstrated the importance of studying potential environmental exposures and childhood cancer.

- Helen M. DuPlessis, M.D., M.P.H., commented that maternal oral health has a significant impact on child health. For example, oral health can affect pregnancy and lead to premature birth. Oral health has implications for child health and development and school readiness. Dr. DuPlessis explained that oral health should be considered an exposure rather than an outcome. Within school settings, oral health can be as significant as asthma and is the leading cause of absenteeism for most children in large school systems.

- R. Gary Rozier, D.D.S., agreed that oral health is a major contributor to poor health in pregnant women and children. The question is where oral health fits in the spectrum of exposures, outcomes, confounders, and effect modifiers. He proposed that the effects of a woman's periodontal health on birth outcomes should be considered very carefully in the

Research Plan. The role that access to dental care might play as an effect modifier between a woman's periodontal health and birth outcomes should also be considered.

- Gary Q. Peck, M.D., said there are two basic public health epidemics that should be considered priority outcomes: dental health and mental health. Mental health appears to be addressed in the Research Plan, but dental health is not addressed adequately and should be considered a top priority.

- James N. Jarvis, M.D., noted that the NCSAC had previously discussed oral health as an exposure, not an outcome. It was his understanding that maternal oral health status was going to be measured as an exposure and is mentioned in the Protocol. Childhood cancer as a primary outcome is problematic because its incidence is quite low. Dr. Jarvis estimated from his experience with rheumatic diseases in children that out of the Study's 100,000 children, about 20 would have juvenile rheumatoid arthritis and about 3 would have lupus. Cancer as an outcome would not be particularly robust because of an incidence even lower than rheumatic diseases and far lower than outcomes such as asthma and obesity. As many as 40 percent of the cohort could be obese. Dr. Jarvis agreed with Dr. Chapin that the Study's priority outcomes are robust and of enormous public health and scientific interest.

- Dr. Fleischman commented that the issue raised by Dr. Lebowitz is the predisposition to adult disease. Even though the incidence of cardiovascular disease and cancer is low in children, it will be important to look back at childhood exposures as the Study's children become adults. Cardiovascular disease and cancer are major public health issues that may not be relevant as childhood outcomes but as predispositions to future outcomes. Dr. Jarvis suggested linking Adverse Childhood Experiences Study data with data from the National Children's Study.

3-Are the plans for genetic and genomic analyses appropriate to study the effect of genetics and gene-environment interaction on the health, growth, and development of children?

- Jeffrey C. Long, Ph.D., said, within the scope of the Study, the plan to study genetics is good. The recommendations from the March 23, 2007, Genetic Measures Workshop were very sound. Decisions about including DNA from parents and grandparents have not been made. Dr. Long noted collecting and analyzing this material would enhance the Study but would use valuable resources. The information might not be particularly useful if parent samples are missing. There is an even greater chance of missing grandparent samples. Basic study designs that can be implemented for the Study are being used successfully for other large cohort genetic studies of children. Dr. Long mentioned recently published research on genes that contribute to disease, for example, diabetes complex diseases.

- Dr. Jarvis explained that the Study's plan for preparing and storing RNA for gene expression studies is good, but cost-effective methodology is not available and the technology is evolving rapidly. The contributors to the Research Plan have done the best that can be done at this time. Saving whole-blood samples should result in very valuable data in the

future. Given that the technology will improve, the Study will be well positioned for gene expression profiling studies. Epigenetics is changing and will be of interest to the Study. The plan for collecting and storing samples should be good for epigenetic analysis. One question is whether methods to study proteomics will be advanced enough to use the samples. For systems biology, gene expression, and proteomics, the plans for collecting and analyzing samples are as good as can be currently achieved. The Study's design will allow investigators latitude for exploratory science.

- Dr. Fleischman asked Dr. Long, who participated in the Genetic Measures Workshop and saw materials previously sent by the Program Office, whether the Research Plan reflects sufficient information so that those reading it without his knowledge of the Study could come to the same conclusion. Dr. Long answered "yes." The Research Plan is somewhat generic, as it must be. However, because it is generic, it allows for individual interpretation. Dr. Jarvis agreed with Dr. Long.

- Dr. Chapin observed that the Research Plan is not designed to defend its decision to omit certain outcomes. Individuals with knowledge of science and public health might note that the document does not include, for example, cancer. The document is not, however, designed to explain the omissions. This position is not necessarily bad.

- Dr. Long said the Research Plan is fairly inclusive and much research will be generated from it. The elements that are included should be emphasized instead of the elements that are missing.

- Dr. Genel commented that one of the values of adjunct studies is the capacity to add either to the Study as a whole or to a subpart. The capacity for adjunct studies is built into the Research Plan.

4-Does the plan for data and sample repositories create an effective platform for future study and analyses of questions not yet posed or currently recognized?

- Janet Currie, Ph.D., reiterated that the Research Plan does not describe how existing data could be merged with Study data. Investigations involving merged datasets would not necessarily be considered adjunct studies. The Study's public-use files would not be appropriate for such investigations. The Research Plan discusses public-use dataset and adjunct studies but does not discuss the type of study—which is fairly common in epidemiology—that would merge the Study's identified data with outside datasets. Dr. Fleischman acknowledged the Research Plan has not been clear on how that kind of investigation might be conducted for the Study..

- Bruce Levin, Ph.D., posed several meta-scientific questions. If the Study were, for example, a 3-year, randomized, double-blind, clinical trial, certain safeguards would be in place to safeguard prespecified hypotheses through the conduct of the study, have interim analyses, and not change the course of the methods, protocols, or scientific questions except under extraordinary circumstances when it becomes necessary. What are the

analogous safeguards in the Study? Will there be interim analyses? Will there be hunches, signals, or hints from the data that will lead to changes in the hypotheses? How will late-breaking developments, the evolution of techniques, and new ideas affect the Study? Dr. Levin expressed concern that, in observational and especially in long-term longitudinal studies, changes will create post hoc findings. Given that the hypotheses have been adequately prespecified, what is the plan to evaluate whether they are still relevant, whether they are supported after 5 years, and whether they can be modified in a scientifically provable way?

- Giselle Corbie-Smith, M.D., M.S., following up on Dr. Levin's comment, asked how participants and the public will be made aware of any new developments or changes in direction or modifications to the Study.

Robert F. Spengler, Sc.D., explained that, as investigators implement a large and complex study, there will be opportunities for adjunct studies and scientific explorations, and many complex issues will arise. There is a need to determine how adjunct studies and scientific explorations will ultimately be controlled, who is responsible for what, who has the lead for particular hypotheses, and how the fidelity of the hypotheses will be protected through the Study life cycle to ensure that the data do not change over time and prevent getting the ultimate answers. In his review of the Research Plan, Dr. Spengler did not see an explicit explanation of how the Study will maintain safeguards. The issues include logistics, management, supporting the research environment, and ways in which datasets can be merged to produce more leverage and address more types of research questions. Dr. Spengler asked when the data would be made available and how much identifiable information there would be to help with the linkage.

- Ms. Dubler asked whether there is an official data safety and monitoring board (DSMB). The Research Plan does not mention DSMBs. It is possible that some interim analyses would be so powerful as to require a public health or public policy intervention long before the end of the Study. It is a much more commonplace way of stating the safeguard issues. She asserted that DSMBs and intervention mechanisms are extremely important. Considerations of the types of interim studies to monitor participants and community safety are ethically mandatory.

- Dr. Butenhoff commented on the storage of samples and their value for future studies, which is a very important aspect of the Study. The long-term storage of biological samples needs to be carefully considered in terms of preservation techniques and integrity of the samples. The processes for long-term storage and decisions regarding future studies and the use of biological samples need to be clearly established within the Research Plan.

- Dr. Chapin echoed Dr. Jarvis' comment about the potential association of hypotheses and the importance of supporting preliminary examinations of data without excessive layers for approval of access. Preliminary data examinations could foster creative and motivated science. Balance among issues such as privacy and scientific rigor must be maintained, but at the same time, the Study should not impede the creativity, curiosity, and enthusiasm of scientific pursuit. Dr. Chapin urged the Study to create a system to support an investigator's preliminary examinations of data.

- Dr. Currie noted that the National Center for Health Statistics is now making data available in Census data centers for researchers. She asked whether the Study had considered making secure data available in these types of environments.

- Dr. Fleischman expressed his understanding that none of the comments involved ideas or issues that had not been considered or addressed by the Program Office and Research Plan developers. Noting the NCSAC's concern about a lack of clarity and specificity in the Research Plan, he described it as an evolving document. Input from current reviews will further the document's evolution. In this context, Dr. Fleischman asked for broad comments on how to enhance understanding of the document's utility.

- Dr. Peck asked some basic recruitment and retention process questions. He noted three areas of concern: finance, humanitarian and ethical aspects, and children in foster care. The Research Plan does not address reimbursement for medical personnel and other professionals who will provide the resources and opportunities to sample. Dr. Peck noted that some pediatricians and primary health care providers are unable to give immunizations due to lack of reimbursement. He asked: How is the Study going to recruit and retain medical professionals to be involved and retain participants and their families if the professionals are not reimbursed? The humanitarian and ethical aspects involve the number of needle sticks and the number of samples collected. How does this burden relate to the number of immunizations? With regard to participant inclusivity, Dr. Peck asked what methods will be used to ensure a broad spectrum or adequate sampling of children in foster care or children whose families have alternative lifestyles. How will the Study assess the environmental and social aspects of these children?

- Dr. Corbie-Smith commended the Research Plan's authors for their tremendous efforts. She observed that the section on community engagement was "thin" and was framed from the researchers' perspectives. It appeared that community engagement was limited to what the community could do for the Study, not what the Study will be doing for communities. Communities will be specifically looking for this broader framework in the Study. For example, the information management system (IMS) section, which is proposed as one of the communication platforms, states that communities and the public will have access to data. The IMS section elaborates on security measures but appears to discourage and limit the use of data by anyone outside the research enterprise. The Study needs to consider how communication platforms can serve as a mechanism for communities to bring their concerns and research questions to investigators and for meeting those concerns. There are existing paradigms for using electronic resources, and the Study needs to be creative in fully exploiting these resources. Dr. Corbie-Smith assumed that the Protocol will have greater detail than the Research Plan about how communities will be involved. Previous NCSAC discussions were prescriptive about how and where community involvement will be and the level at which community leaders and representatives will make decisions. The NCSAC needs to continue these discussions. The theme of community involvement and decision making should be integrated throughout the Research Plan. Communities should be allowed access to data to answer questions, observe progress, and receive "snapshots" to share with elected officials in support of the Study. Such innovative approaches need to be balanced with data security. The NCSAC has emphasized the importance of community engagement and involvement and it should be more clearly manifested in the Research Plan. Engaging communities will help maintain public trust.

- Dr. Spengler offered his kudos to those involved in developing the Research Plan, which answered many of his questions about the Study, and he identified three concerns: (1) tracking and mobility, (2) a master plan describing what investigators lead which hypotheses, and (3) governance. To improve the document's clarity and better define certain aspects, he made several suggestions. First, he noted that the Study's anticipated 2

percent attrition rate may be too conservative. Based on his experience with the Agency for Toxic Substances and Disease Registry and its involvement with the national exposure registries, a 35 percent attrition rate over 10 years might be more realistic. Because women of reproductive age are a highly mobile population, the Research Plan needs to provide more detail on tracking participants. The Study needs to consider ways to retain its cohort. The same level of attention needs to be given to tracking and monitoring participants as is given to collecting and preserving samples. Dr. Spengler said the Research Plan is not clear on who leads the investigations of each hypothesis and whom investigators should approach about adjunct studies involving the hypotheses. Decision-making pathways need to be more clearly delineated. Management, logistics, and governance need to be addressed. For example, how will the Steering Committee evolve and how will it be composed? Engagement and involvement of additional Study Centers, as well as the lines of authority among them, will be need to be specified.

- Dr. DuPlessis suggested creating an executive summary or highlights for each section of the Research Plan when it is posted for public review. These summaries would provide more detail than is given in the table of contents.

- Dr. Eaton expressed her concern about participant retention. The Academy of Pediatrics Council on Research expressed a similar concern. Retention is a critical issue that needs to be addressed.

- Dr. Levin noted that very few studies have recruited on time and on target. He asked what contingency plans Study has if early recruitment is lagging. He also noted that recruitment shortfalls were not mentioned in the Research Plan.

- Dr. Brenner found the NCSAC's comments and suggestions to be very helpful. She noted that some areas of concern are mentioned in the Research Plan but need to be expanded or clarified, and areas that are missing need to be added.

- Dr. Scheidt agreed with Dr. Brenner's impressions, and he thanked the NCSAC for their thoughtful input and questions. In addition, he suggested that the NCSAC can help with two issues. The first is stewardship or guardianship of the biological specimens. Because these specimens are extremely valuable, there is a special responsibility on how to best structure the guardianship over the many decades of their utility. The lead agencies will own the specimens and will oversee the guardianship. The second issue is the tension between the use of Study data, especially by communities, and the obligation for confidentiality of individual participant data.

- Glen Hanson, Ph.D., D.D.S., commented as a member of the public. He noted that, since the Study's inception, the National Institute on Drug Abuse (NIDA) has been interested in the opportunities to study substance dependence and abuse, which are critical issues to children's development, both in terms of personal exposure as well as social and familial exposure to these substances. Based on the discussion, Dr. Hanson had two impressions: (1) that specific substance abuse questions were not being addressed in the Research

Plan, and therefore, NIDA will need to partner with the Study to create adjunct studies of substance abuse; and (2) that the processes for adjunct studies are not well developed. There needs to be more specifics on interagency collaboration for adjunct studies. NIDA's current director, Nora D. Volkow, M.D., is very interested in partnering with the Study and wants to learn about processes for adjunct studies. Information on these processes needs to be available to other Institutes within NIH to maximize the Study's value. Dr. Hanson suggested the Study re-engage other Institutes and invite them to participate in adjunct studies in an effort to help achieve their missions.

5-Are the specific aims of the Study clear and able to be addressed by the Research Plan?

- Dr. Chapin answered that the Study's specific aims are clear and the Research Plan will be able to address them.

- Dr. Currie said the neighborhood and community section of the Research Plan discusses how neighborhood measures will be incorporated into the Study, but it does not address how non-Study researchers would, in the future, access the data and merge it with new information.

- Ms. Dubler noted that within the specific aims, there is a difference between chemical/physical/biological measures and psychosocial measures. She asked whether the collection and analysis of psychosocial data are sufficiently specific so that the data will be as valid as the other types of data.

- Dr. Lengua said the key constructs for psychosocial factors (for example, family, context, and parenting) are in place, but the specific measures have not been determined. It is not clear how thoroughly psychosocial factors will be measured. There needs to be more detail in the Research Plan and more thorough assessments.

- William D. Lyman, Ph.D., a member of the public, provided a comment. He agreed that a study's specific aims are a critical element. In his experience, it is better to write short declarative statements for the aims. Long and all-encompassing specific aims are difficult to read and respond to in a research plan. In a specific aim, it is difficult to determine the absence of something because the absence of evidence of something is not evidence of absence. Dr. Lyman suggested that the language be modified and that a few more short, specific aims be added.

- Dr. Currie asked whether the psychosocial assessments will be sufficient to include screening questions for conditions such as attention deficit-hyperactivity disorder, depression, or other specific mental health problems.

6-Is the balance of measures across the key exposure domains and the early outcomes appropriate and reasonable?

- Dr. Lebowitz—noting again his unfamiliarity with weight of evidence and the findings of working groups—considered the measures of both exposures and outcomes to be unbalanced. Does the weight of evidence indicate causal pathways? Does the weight of evidence suggest effect modifiers or mediators? Dr. Lebowitz believed there is a lack of clarity and sufficient thought about what is currently known about exposures that affect early outcomes. The breadth of the Study may preclude sufficient depth in its measures.

- Dr. Rozier described two unbalanced areas in the Research Plan. Use of health care is one of the major effect modifiers of exposures and outcomes. Given the disparities in health care, it is important that the Study sufficiently measure the use of health care. Dr. Rozier observed that nine self-reported questions will be used to assess use of dental care. He asked whether these questions are specific enough to measure this major effect modifier, which is thought to be important in the relationship between a woman's periodontal health and birth outcomes, and between a mother's infection level and tooth decay in her children. Dr. Rozier noted that the dental care system is much like the mental health care system. Both systems are specific enough and unique enough to require reasonable expert input to the Study. For example, dental insurance is a major determinant of the use of dental care. Asking questions about health insurance will not answer questions about dental insurance. Dr. Rozier asked what input the Study has received from dental epidemiologists and dental health services researchers.

- Ms. Dubler said that if the Study is going to measure access to and use of mental health and dental care services, then it also has to measure barriers to access and use. In previous meetings, the NCSAC discussed linking families and children with health care providers to contain the unintended effects of lack of access. In the current health care system, whether an individual uses or does not use medical care or dental care is not related to intent or level of disease. It is related to insurance status, which could be a confounder in the Study's data.

- Dr. Fleischman elaborated on comments by Drs. Currie and Lebowitz. Over the past several years, many individuals have been concerned that psychosocial factors were not being adequately addressed in the Study. There have been concerns about too much emphasis on measures of chemical exposures. Dr. Fleischman asked Dr. Lebowitz whether there are too many chemical measures in the Research Plan. Dr. Lebowitz replied that there are not too many chemical measures. Studies have shown that there are mediators of psychosocial outcomes and that the causal pathways are much more likely to include the chemical and physical environments. The weight of evidence is fairly strong for gene-environment (specifically chemical and physical) interactions that have a major impact from preconception, through pregnancy, to early childhood.

7-Are the plans for analysis adequate and able to fulfill the goals of answering the hypotheses and additional important questions that may arise in the future?

- Dr. Levin focused his comments on chapter 10, which offers a cursory presentation of statistical methods. Some areas of the plans are very specific, and others were not. He

said this question could not be answered without a detailed statistical analysis plan. Both the equations and the plans for modifying the equations need to be included. The Research Plan needs to state explicitly and with more specificity the statistical analyses that will be used. Dr. Levin said he would feel more secure about the plans when the next level of detail is added.

- Dr. Currie said the statistical plans fall short because several methods have been omitted.

- Dr. Long commented that the genetic analyses are consistent with approaches being used by other investigators and address the questions that are being asked in this type of study. Implementation of the most promising, current statistical designs will not be impeded by the Study's analysis plans. Although it is difficult for the Research Plan to be more detailed at this time, the lack of specificity allows latitude in using future analyses and in no way limits the quality of these analyses.

8-Are the human subjects concerns adequately addressed for a document of this type?

- Ms. Dubler said the human subjects concerns should have been addressed in more depth. The Research Plan's acceptability will depend on the community's perception that it is fair and just. There was not sufficient information to determine whether the Research Plan was fair or just. Ms. Dubler suggested the document include a human subjects protections analysis that is not limited to the specific regulations of 45 CFR, Part 46, but reflected more generally the ethics of research. The ethics of community-based research must address benefits, burdens, and obligations. The core issue of human subjects protection is whether Study participants receive health care for problems that may be identified—however they are identified—particularly for children who do not have health care. The provision of health care is a justice issue. Informed consent only may not be adequate for the Study. The Research Plan should begin with justice and fairness and address how, once participants are enrolled, problems that are discovered will be addressed. With regard to informed consent, the Study should strongly acknowledge that adolescents can consent on their own to minimal risk research. Although IRBs will have their own policies, the Study must send a message to reinforce its position on adolescent consent. Failure to address this issue could impact the data. Ms. Dubler expressed her concern for children who are in foster care and tend to be "discarded" from medical care and research. State agencies that serve as legal guardians for these children will most likely not give consent. Ms. Dubler noted that about 89 percent of people in prison had a history of foster care. If a state agency must give consent, the Study will probably miss this very needed population. Another concern is that the Study has no plans to follow biological mothers and fathers who have no contact with their children in foster care. Jurisdictions are more frequently terminating parental ties to these children. With regard to the Grimes v. Kennedy-Kreiger ruling and undue influence on participation in research, monetary reimbursement for time and expenses for study participants may not be appropriate in all communities. Food vouchers and nonmonetary reimbursement may be more appropriate in certain communities. Ms. Dubler commented that much has been learned since the AZT studies in San Francisco in the late 1980s. If communities that are going to be

studied are not involved from the beginning with the design of the study, both participation and design are affected and the resulting data are of lower quality.

- Dr. Corbie-Smith emphasized the need to exceed the standard regulations for human subjects protection. She suggested the Study examine the NAS report on this topic to raise awareness of all parties—children, parents, families, communities, health care providers—that need to be considered in the Study's human subjects protections. The Research Plan needs to address these issues more substantively and to more clearly articulate how communities could help the Study apply ethical principles. Dr. Corbie-Smith said the Research Plan is written from a "research-centric" viewpoint. Input on risks and benefits from other viewpoints would be valuable.

- Dr. Genel proposed the Research Plan include an appendix that discusses the ethical framework and myriad ethical issues for human subjects protections. The Research Plan's current description of human subjects protection is limited to an overview of how the Study will conduct human subjects protections in a programmatic manner.

- Mr. Guzman commented that a discussion of community engagement should include a community-based participatory model. The Research Plan hints at such a model but does not elaborate. It needs to strongly and specifically state the steps that must be taken to engage communities. Without clear directions, certain community groups and individuals will inevitably be left out of the process. The community must be engaged at the grassroots level for the Study to be successful.

- Dr. Lyman, as a public commenter, said he agrees with the concepts of fairness and justice for research participants. These concepts are critical to the development of the Study Protocol. He explained that the Study was devised as a probabilistic sampling of the American population. One of the Study's primary aims is to measure the timing, frequency, and duration of environmental exposure. This approach implies a natural history study, and by definition, such studies should not have interventions that affect outcomes and skew data. Dr. Lyman asked: Is this a natural history study? Is it an intervention study? Or is it a hybrid of the two? The Protocol must be carefully written to clearly address the type of study.

- Dr. Jarvis noted there have been long conversations about the Study being an observational study. He suggested justice issues with observational studies be addressed in an appendix to the Research Plan. The Study should explicitly state to future offerers that a specific community engagement plan needs to be included in proposals. Interpreting data will be dependent on intimate knowledge of the community (for example, on Indian reservations). Study Planners should add to the human subjects protocol a plan for community engagement and participation.

- Dr. Eaton commented that "community" should be broadly defined to include health care providers. The Research Plan should state how the Study will involve and keep engaged community-level providers delivering services to participants.

- Dr. Corbie-Smith confirmed that community-level providers are the stakeholders that the Research Plan does not address. There are several resources to serve as prescriptive guides for engaging communities. Dr. Corbie-Smith suggested the Research Plan and Protocol clearly describe what each Study Center must do for community engagement. One reason for community engagement is to ensure data validity.

- Ms. Dubler asked whether there could be a DSMB to monitor each risk or exposure. Present data show that not having access to medical care is a risk for children's health. Ms. Dubler explained that, given the experience of the Tuskegee Study and the Grimes v. Kennedy-Kreiger ruling, there can no longer be a clear natural history study with no obligations to intervene. The federal government cannot be involved in a natural history study. Therefore, the Study must be a hybrid of observational and interventional approaches. Ms. Dubler acknowledged that it will not be possible to track and intervene in all situations, but there is some basic level of access to medical care and the intervention that allows access, which needs to be designed as part of the Study.

- Dr. Genel recalled an NCSAC discussion on providing information about "clinically relevant and actionable items" to participants. Dr. Genel understood that such information would be shared with primary care physicians. This process is not stated in the Research Plan.

9-Is the level of burden placed on participants reasonable for a study of this scale and scope?

- Dr. Fleischman explained that because of the longitudinal and complex nature of the Study, the burden will be more intense early in implementation and less intense as it progresses. A substantial number of areas, with many variables and many questions, will be addressed by investigators. He asked NCSAC members whether they could tell from their review of the Research Plan whether participants' burden is reasonable, given the Study is a minimal risk, observational study with no prospect of direct benefit. Burden involves the Study's children, mothers, and families in general.

- Dr. DuPlessis said it is not known whether the burden is reasonable because the degree to which communities have been engaged is not known. Communities need to learn about and understand this kind of study and its long-term implications. Dr. DuPlessis wondered whether the types of specimens being collected and the types of questions being asked would cause anxiety about how the data were going to be used and what the data will show. As a health policy expert and pediatrician, Dr. DuPlessis supports the Study because of its potential to answer important questions and change public health policy on how child health and wellness are viewed. She said the potential benefits outweigh the burden.

- Dr. Lebowitz said the benefits outweigh the burden. He mentioned his experience with OMB and its review of the National Human Exposure Assessment Surveys, which had about half the burden of the Study. A more appropriate question is whether the Study can provide the motivation and rationale to overcome both bureaucracy and hesitancy of

participants' parents or guardians so that, through education and explanation of the benefits, the burden is perceived as not so great. Dr. Lebowitz said the Study's potential benefits are so enormous that it is worth the effort.

- Dr. Spengler asked whether the level of burden is so high that it will increase attrition. Minimizing attrition and preserving participation are very important objectives.

- Ms. Dubler remarked that, within the ethical context of research, no burden is justifiable if the scientific data collected are not valid and important. The ongoing existence of the cohort and guarding against attrition is so critical that it is not just the individual burden that is important but the burden on an individual within a community. If the community is aware of and supportive of and reinforces participation, then the burden is not disproportionate. However, if the cohort disappears because of the lack of community engagement and support, then the burden is unreasonable.

10-Does the general plan for an information management system appear to be clear and reasonable and able to meet the needs of the Study?

- Dr. Levin suggested the Research Plan include concrete examples, illustrations, and screens. There is a certain amount of skepticism about large-scale, network-based, multifaceted information systems. Demonstrating that such systems function as designed dispels skepticism. Dr. Levin asked for a demonstration of the IMS at a future NCSAC meeting. How will data be entered? Will immediate feedback be given? Is there edit correcting? It is important that the Research Plan address IMS functionality to diminish skepticism.

- Dr. Currie said both data entry and data access and extraction are important. The Research Plan needs to articulate how the data will be accessed and who will be able to use it.

- Dr. Lebowitz said IMS success often depends on contracting with a data coordinating center that has appropriate experience. The issue is whether the Study has worked with experienced data coordinating centers to demonstrate that the data can be managed or to provide examples of competency.

- Dr. Chapin said that, given the depth of the IMS detail in the Research Plan, the developers have a high-level grasp on what the general concepts should be. The next step is what the IMS will be in reality.

- Dr. Long found the IMS plan to be "disturbing" because it is so open-ended. Phrases such as the "IMS supports centralized" or the "IMS supports uniform consistent participant de-identification" lack specificity. There are no statements of what the IMS requires from Study Centers. The IMS plan would be more rigorous if it had less generality.

- Dr. Butenhoff agreed that, at a high level, the IMS plan is acceptable. Specific aspects of data architecture, security, data use, and data verification should have been addressed in the plan.

Closing Comments on the Research Plan

- *Dr. Chapin:* The authors have done a remarkable job distilling practicalities from the enthusiastic hand-waving of the Working Groups. They shed the hard light of reality on what is possible and distilled what is doable in the real world to address real problems.

- *Dr. Corbie-Smith:* Release of the document is a turning point in the Study. It is good to be able to respond to such a commendable document. The next step is refining the Research Plan.

- *Ms. Dubler:* It is a remarkable step in the process. Before the document is posted for public review, it needs an executive summary that eloquently and persuasively states the tremendous opportunity to do things for our children in the future. It is an obligation of the federal government to make the lives of children better. The document needs this kind of language to present itself in the most positive light. The NCSAC recognizes how critical and important the Study is. The Research Plan needs the best possible presentation to a diverse public audience that will convey the Study's critical importance.

- *Dr. Long:* The Research Plan reflects the Study's ongoing progress. The document would benefit from an "encapsulation" highlighting the importance and value of the Study.

- *Dr. Peck:* The work is impressive and exceptional. The Research Plan's authors should be praised. There are concerns with recruitment, retention, how communities and families are defined, children in foster care, and children in families with alternative lifestyles. The Research Plan would benefit from a preamble providing an overview of the Study.

- *Dr. Eaton:* The Research Plan is an outstanding accomplishment. It would benefit from greater detail on how to engage health care providers and inclusion of a preface. A well-known personality who appeals to family and children would be the ideal spokesperson to share the document's introduction.

- *Dr. Genel:* A preface would be useful and perhaps could serve independently of the Research Plan. It could serve multiple uses. The Research Plan will undoubtably be modified by the Vanguard Centers' experiences and, therefore, should be viewed as a "living" document.

- *Mr. Guzman:* The work has been impressive. Do not lose focus on the community. An executive summary is an excellent idea.

- *Dr. DuPlessis:* The Study needs to be comprehensively promoted to the Vanguard and Study Centers to ensure that they understand what the Study is all about and keep the entirety of the Study in mind as it is implemented.

- *Dr. Currie:* The Research Plan is a great document, and it is very informative. A selling point is that this is the first cohort study of this kind for the United States. Other countries have already conducted similar cohort studies. The information learned from these other cohort studies could be included in the Research Plan's introduction. The Study should be the best possible platform for a wide range of adjunct studies. Success of these adjunct studies depends on open data access and data sharing.

- *Dr. Jarvis:* Implementing the Study in American Indian communities will be challenging. Vanguard Centers will have to develop tactics for engaging these communities. Vanguard Centers that are savvy about indigenous Americans' special issues will be successful. Those involved with the Study should understand that the Research Plan outlines strategy and implementation.

- *Dr. Rozier:* The document's content is educational, and it is well written.

- *Dr. Lebowitz:* The Research Plan and the amount of work that has gone into it are impressive. The fact that it is incomplete or lacking in detail is somewhat unsatisfying. The document would benefit from more scientific information. The Research Plan should be a dynamic living document, which will improve with comments and input.

- *Dr. Levin:* Despite the difficult decisions that were made in determining the Research Plan's content, the end product is a high-quality document. Including concrete, real-life examples would improve the document, without adding undue burden. Examples would serve as communication and educational tools. Providing a clear charge will aid the NAS review process.

- *Dr. Butenhoff:* The Research Plan is the product of an exceptional effort. Although the document is informative, there are opportunities for improvement. The writers are to be commended.

Adjunct Studies: Enhancing the National Children's Study

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

The Research Partnerships Program is developing a program for adjunct studies to leverage the Study and spark ideas for additional research in both public and private sectors. Ideas for adjunct studies will come from the Study Protocol, links between exposures and outcome measures, and ongoing research findings as the Study progresses.

Adjunct studies are modular, focused studies that use the Study's infrastructure. They involve a subset of the Study cohorts (that is, all or some of the participants, their biological specimens, or environmental samples) at one or more Study Centers. Adjunct studies may be initiated by a Study Center, independent investigators, government scientists, industry, or research advocates. They will focus on a unique research interest/capability or a specific community concern; use, complement, or leverage upon the core protocol for mutual benefit; and rely on outside funding. By comparison, additions to the core protocol will involve the entire cohort.

Adjunct studies must support and maintain the Study's quality and integrity. Key review factors include scientific merit, significant public health importance, "fit" with the Study, and appropriate use of biological specimens and environmental samples. Other key review factors include burden on participants and Study infrastructure, human subjects ethical and legal considerations, peer review, IRB review, and funding.

There will be a uniform review and approval process for adjunct studies. It will be iterative and simultaneous to facilitate timely and supportive review and approval of proposals. Submitting a brief electronic preliminary application will be the first step. Approval of the preliminary application will be followed by a full electronic application. Electronic review forms will be used to assess proposals. An electronic tool to sort and track proposals is being developed. The Program Office will be responsible for coordinating the review and approval process. The ICC, Steering Committee, Coordinating Center, and NSCAC may all be involved in some aspects of proposal review.

Outside funding can include government grants such as R01s, public-public partnerships with key government agencies (for example, intramural funding and requests for applications for specific studies), and public-private partnerships (for example, industry, foundations, academia, and research advocacy groups). Funding could come from existing relationships, direct support, or in-kind support.

As of June 2007, Vanguard Centers are expected to conduct the pilot year from July 2008 to July 2009. In July 2009, nonpilot enrollment begins at Vanguard Centers and new Study Centers. Adjunct study proposals for preconception, pregnancy, delivery, newborn, and early infancy periods will be accepted in the near future, with studies to begin in July 2009.

Dr. Balsam concluded by noting that, for scientists in academia and government, opportunities will continuously arise for additional research by leveraging the Study. Adjunct studies will broaden and enhance the Study's contribution to children's environmental health. Opportunities exist for public-private and public-public partnerships (that is, other government agencies). An adjunct study overview and applications for proposals are available on the Study's Web site.

NCSAC Discussion and Recommendations/General Discussion

The discussion addressed the following topics:

- *Requirement for Study investigators to serve as adjunct study co-investigators.* Proposals to access and analyze Study data are not considered adjunct studies. Adjunct studies may use biological specimens or environmental samples and may require direct interaction with Study participants. Adjunct studies require a sponsoring person such as someone from the Program Office or ICC, or a Study Center principal investigator (PI). Sponsors will have an allegiance to the Study and a vested interest in preserving specimens and samples and protecting participants. Study Center PIs are needed for accountability and to ensure fidelity to the Study's overall mission.

- *Merging Study data with outside datasets.* The use of specimens, samples, and interacting with Study participants are considered adjunct studies. The availability and use of public datasets and other extant datasets linked with the Study data and the merging of datasets are not subject to the adjunct studies process. The issues involving the use of identified versus de-identified data, data-only access requests, and data use agreements need to be resolved. Mechanisms for accessing data that are not public-use datasets are not yet defined. It was suggested these mechanisms be outlined in the Research Plan and that a mechanism be in place to protect human subjects whose data is used in identified datasets.

- *Adjunct study review process.* This process may be needlessly cumbersome. It was suggested the process be simplified. Funding issues may complicate the process. A staged review process was recommended, as was head-to-head comparison of adjunct study proposals. Study Planners are advised to structure windows for application pertaining to specific phases of the Study, rather than open enrollment, in an effort to better protect and care for the biospecimens and environmental samples. RFPs could be released at specific intervals to facilitate a systematic review.

- *The Study's role in adjunct studies.* The Study will serve as a platform for adjunct studies. Communication among Study scientists and potential investigators will facilitate development of adjunct studies.

- *Funding partnerships.* The Study should clarify the mechanisms for developing funding partnerships with nongovernment entities, such as industry, academia, and private foundations. The Study provides a number of opportunities for industry partnerships, but the Study needs a clear message inviting participation. The Study could invite the top 10 foundations with interests in child health and well-being to set their goals and objectives to overlap with those of the Study.

- *Protection from excessive burden.* Adjunct studies may request additional visits, procedures, sample collection, and tests. Approval of such requests will involve practicality and the extent of additional burden.

Continued Discussion of the Informed Consent Process

Dr. Fleischman

Dr. Fleischman provided an update on informed consent activities since the December 2006 NCSAC meeting. A Human Subjects Working Team was created, with members from Vanguard Centers, the Coordinating Center, and the Program Office. Team members are all experts in human subjects protections. The team reviewed the human subjects strategy for the Study, reviewed site-specific issues, reviewed the video for informed consent, and developed a memo titled Information Relevant to Human Subjects Protections and IRB Review. With regard to video informed consents, the pregnancy and prepregnancy video consents have been revised, written analogues of video consents have been developed, a video for fathers' informed consent

is being developed and is close to completion, and an evaluation pilot study comparing video consent with written informed consent is being developed.

Dr. Fleischman reviewed the Information Relevant to Human Subjects memo. He reviewed the contents of several chapters of the memo. Chapter 5 of the memo describes the need for several ongoing areas of review. The proposed roles and responsibilities of a data and safety monitoring committee (DSMC) was described. The DSMC will be reviewing Study performance, scientific quality and validity of data, and safety of Study participants. It will report to the Director, NICHD; and through the Coordinating Center will provide aggregate reports on adverse events to local IRBs. Since participants will provide consent for future studies not yet conceived, an additional committee will be required to assure participants that all future studies and uses of stored specimens are consistent with the Study's goals and mission. This committee will need to have representation of community members. There will also be the need for a process to review adjunct studies that have human subjects concerns.

Dr. Fleischman reviewed chapter 6 of the memo, which relates to Study "risks." The chapter defines "minimal" risk and describes other risks including breaches of confidentiality and addresses future uses of specimens, reporting of child abuse or neglect, revealing findings to individual participants, and revealing aggregate findings to communities. Breaches of confidentiality involve IMS staff training and certification, certificate of confidentiality, data-sharing agreements, and public-use datasets.

Dr. Fleischman reviewed chapter 7 of the memo, which addresses specific issues of informed consent. The chapter describes the video consent tools for women 18 years old and older and women younger than 18. The Study will not engage women younger than 18 years old if they are not pregnant. Consent of pregnant adolescents, 15 years old and younger, will obligatorily involve families. Pregnant adolescents above the age of 15, will be assumed to have the authority to consent to the Study for themselves and their child unless this is not allowed in the local legal jurisdiction. There will be two points of assent for child participants, at about 7 years of age and at about 14 years of age. At the legal age of majority, a full informed consent will be obtained from participants. In regard to foster children, the Study will engage foster families and those with legal authority to help retain those participants.

NCSAC Discussion and Recommendations/General Discussion

The discussion addressed the following topics:

- *Examples of adverse events.* Even observational studies have adverse events. They may include breaches of protocol, problems with sampling such as mislabeling, misinformation to participants, and breaches in confidentiality such as stolen computers. Even a car accident while traveling to a Study Center may be considered an adverse event. Child abuse would not be an adverse event of the Study but would be reported to authorities and noted in the aggregate data.

- *Much of the materials from this memo should be integrated into the Research Plan.*

- *IRB acceptance of informed consent.* The consent outlined in the memo is generic, and it is hoped that the Study's informed consent will be universally accepted. Given that this is unlikely, mechanisms have been developed to allow the consent video to be tailored for local IRBs. The video can be edited, amended, or revised. For example, local pictures and identifiers can be added. In addition IRBs are being encouraged to defer review to another IRB through a collaborative, cooperative arrangement. The Study will encourage such collaboration, and cooperative agreements will be developed.

- *Translation of informed consent materials.* The informed consent video will be in English and Spanish. All written materials will be in English and Spanish. Translation to additional languages and the extent to which materials will be translated will be determined by site-specific needs. In some cases, interpreters may be needed.

Representativeness With Successive Waves of Sample Locations: Sequel

Dr. Scheidt

Dr. Scheidt reviewed the Study's multistage national probability sample of 105 locations. Contracts for seven Vanguard Centers for seven locations have been awarded. The remaining locations will be added incrementally. Awards for additional locations will occur in at least two, probably three, waves. The representative nature of the locations will be kept as intact as possible. Scientific and technical capability will be major considerations in the awards. All 98 remaining Study locations will be open in the next solicitation. Locations will be regionalized to centers with locations in the same or adjacent states. Multiple locations/centers with base and optional locations will be encouraged. This approach allows maximum competitiveness with given funding and will be as close as possible to representativeness. With this approach, there will be more upfront effort but less overall effort.

NCSAC Discussion and Recommendations/General Discussion

The discussion addressed the following topics:

- *Next steps.* It is anticipated that the current solicitation will result in awards for about 20 Study Centers that will include about 30 locations. During the contract negotiating process, the Study will identify, from the total 98 locations, a representative subsample that will approximate one-third of the Study's total remaining locations. With additional funding in fiscal year 2008 and beyond, there will be additional waves and competitions. By the end of 2007, there should be 27 Study Centers. The next solicitation should increase the number of Study Centers to 35, which may include 60 or more locations. There could be two or three subsequent solicitations to bring all 98 locations on board.

- *Study Center performance.* The Program Office will need to identify quality assessment approaches, regularly monitor Study Center performance, supervise and manage appropriately, and implement necessary changes. The Coordinating Center will assist Study Centers as needed. Recompetitions may be necessary. Study Center contracts are 5 years long. Performance requirements are explicitly stated in the contracts.

- *Variations in competition.* There will be intense competition at some Study locations but less competition at others. Variations in competition could affect representativeness. The Program Office will need to make every effort to ensure high-quality proposals for all Study locations. Solicitations can be structured to enhance competition at certain locations, if necessary, and the process can be modified to achieve representativeness of the full sample.

- *Coordinating Center oversight.* The Program Office is closely collaborating with the Coordinating Center and providing oversight. Program Office and Coordinating Center staff meet weekly to discuss Study activities. Outside expertise is brought in as necessary. As Study implementation expands, issues of adequate resources to monitor Coordinating Center performance may need to be addressed. Limitations of the Coordinating Center's resources may also need to be addressed.

- *Midwifery components at obstetric centers.* A public commenter asked if a special strength in midwifery was a stated requirement in the Study solicitations. This is not the case. Although the North Central Bronx Hospital in New York City has a large midwifery service and is willing to participate, the Bronx is not a Study location. Midwifery will be included at those Study locations where it exists but will be included only as it represents obstetric care. Additional issues related to midwifery could be studied in an adjunct study.

- *Vanguard Center eligibility.* Vanguard Centers are eligible to compete for additional Study locations.

- *Participants' mobility.* Participants who move from one Study location to another will be reassigned to different Study Centers.

- *Maintaining community engagement.* Community engagement is a critical element for the success of the Study. With the Study implemented in waves, the Study will have to maintain engagement with communities in non-active locations. Study Centers that are awarded contracts for more than one location may be directed to implement the Study in stages, and the communities will need to be informed.

Future Directions and Subcommittee Assignments

Dr. Fleischman

Dr. Fleischman described the NCSAC's roles and responsibilities including:

- Providing advice/recommendations to the Director, NICHD; Study Director; and ICC regarding general direction and conduct of the Study, ethical issues, community engagement and consideration, hypotheses, and other considerations of the Study
- Responding to specific requests for advice/recommendations by the Director, NICHD; Study Director; and ICC
- Serving as ambassadors for the Study to outside groups

- Providing a forum for considering requests from the public and scientific community, and providing advocacy and industry perspectives and representation.

Dr. Fleischman reviewed the roles, composition, and relationships of the various entities involved in the Study's governance and management. He presented his view of the relationship among the various entities in the Study in a slide:

The NCSAC has three standing subcommittees:
- Concept Review: provides advice and recommendations concerning pilot studies, scientific questions, and aspects of the Protocol, as requested by the Study Director
- Ethics: provides advice and recommendations concerning various ethical concerns
- Community Engagement: provides advice and recommendations concerning community involvement/engagement in the Study.

The role of the NCSAC is evolving, and it must focus on how it can optimize its role in the Study and determine how it can be most effective. The NCSAC needs to determine whether the standing subcommittees should continue or disband and whether new subcommittees need to be created.

NCSAC Discussion and Recommendations/General Discussion

The discussion addressed the following topics:
- *Communication among Study entities.* The description of the varying committees responsible for the governance and management of the Study was thought to be very helpful to clarify the complex relationships among them. Communication from the NCSAC to the Steering Committee and ICC should be enhanced. The NCSAC should inform the other entities that it is available as a resource. It was suggested that the NCSAC establish additional lines of communication with other Study committees..

- *NCSAC perspective.* The NCSAC provides a valuable perspective for the Study, offering multidisciplinary expertise and sage advice. The NCSAC will have opportunities to provide advice as the Study is implemented. Because the NCSAC serves as an independent body, with the absence of conflict of interest, its perspective is different than other Study entities' perspectives.

- *Community engagement.* A communication link between the Steering Committee's outreach and engagement subcommittee and the NCSAC's Community Engagement Subcommittee could facilitate the Study's community engagement.

- *Study Center quality control criteria.* An NCSAC subcommittee could be established to evaluate criteria that could be used to monitor Study Center performance. It was suggested that this issue be discussed at the next NCSAC meeting. The NCSAC could not be involved in the tracking of Study Center performance; however, the NCSAC could give advice on this topic.

- *Continuation of subcommittees.* It was suggested that the Ethics Subcommittee be retained as currently titled. The Concept Review Subcommittee may need to be renamed and its purpose broadened to reflect the maturing nature of the Study. It is likely that the NCSAC will be asked to be involved with some forms of Study review. Therefore, the Concept Review Subcommittee will be renamed The Scientific Review committee. NCSAC members will be solicited for interest in becoming a member of one of these subcommittees.

- *NCSAC future role.* The NCSAC can advise on the "state of the science" by monitoring developments in methods and the advent of new technologies. The NCSAC can help the Study keep its science and methods current. Such review is important to maintain awareness of developments to enhance the Study, keep costs down, and keep the Study on the right path.

- *NCSAC communication.* Subcommittees can deliberate privately under certain circumstances, but NCSAC deliberations are generally public. Subcommittee findings and recommendations must be made to the full NCSAC. NCSAC meetings must be publicly announced. It was suggested that questions for the NCSAC be provided in advance of its meetings. It was suggested that more time be given for open discussion at NCSAC meetings and that the NCSAC be given an opportunity to give input on agenda items, rather than being asked to simply react. It was also suggested that the NCS organizational chart be included in each meeting's briefing book as a reminder and reference for NCSAC members.

- *Protocol and Study Plan Review.* The question was raised as to whether the NCSAC is independent enough to review the Protocol and Study Plan. Dr. Genel recommended creating an independent body to review. An external review will be helpful in terms of credibility.

The Challenge of Clinical Event Data Collection

Dr. Balsam

Dr. Balsam reviewed the challenge of collecting clinical event data. Clinical events are diagnoses or interventions by a health care practitioner or in a health care setting of significance to children's health and development. They represent outcomes (for example, diagnoses), exposures (for example, procedures and immunizations), and confounders or mediators. Considerations regarding data collection methods include completeness, accuracy, cost, and burden of collection. Current data collection plans include interviews at home visits and clinic visits, telephone contacts, and paper diaries and logs to assist recall. Electronic data collections are available because of increasing electronic data capture within the health care sector and increasing computer access and competence. The Study has evaluated electronic options for practicality, usability, cost, reliability, accuracy, completeness, and confidentiality. There is a national momentum regarding electronic medical records and personal health records but

technical issues (for example, no significant interoperability) and privacy/confidentiality/security concerns remain.

Challenges Collecting Clinical Event Data

Mary G. Greene, M.D., M.P.H., M.B.A., Booz Allen Hamilton

Dr. Greene highlighted challenges to capturing clinical event data and provided an overview of the current state of electronic health records (EHRs) and personal health records (PHRs). A clinical event is defined as any interaction with the health care system that leads to a diagnosis and possibly to specific interventions. Interventions may include routine, acute, and chronic care visits. Interactions with the health care system do not include regularly scheduled home or clinic visits that are part of the Study Protocol. Although relevant clinical events and required data are yet to be fully defined, certain data elements may be of particular interest. Among the electronic data capture modalities considered for the Study, EHRs and particularly PHRs warranted further investigation. EHRs are increasingly looked to as a method for fostering greater connectivity within the health care community. Legislative initiatives led to the creation of the public-private health information technology "community" that drives the strategy for increasing EHR interoperability and adoption. Although EHRs have the potential to support clinical research from enrollment, to execution, reporting and collaboration, widespread use of them in clinical research has been constrained. Personal health records are an emerging technology that puts health information in the hands of the consumer. PHRs are distinct from EHRs but may share common data depending on who provides the PHR tool (sponsors). PHRs are growing in prominence due to the convergence of several factors, and legislative actions are enabling PHR proliferation and adoption. PHRs may have more privacy and security challenges than EHRs because vendors of free-standing PHRs may not be required to comply with Health Insurance Portability and Accountability Act (HIPAA) regulations. Yet, EHRs and particularly PHRs may become useful reservoirs of clinical event data for the Study.

NCSAC Discussion and Recommendations/General Discussion

- Dr. Balsam explained that a contractor (Booz Allen Hamilton) researched electronic methods for clinical event data capture to provide information on the relative merits of the various options that could be applied to the Study. This information will provide the basis for a pilot study on PHRs to compare factors such as completeness, accuracy, costs, and effectiveness with the Study's current data capture methods (interviews, telephone contacts, and paper diaries). The contractor is developing the pilot study design.

- Dr. DuPlessis said that, as the potential functionality of electronic clinical data options continues to improve, the Study must recognize the tremendous spectrum of sophistication along the functionality range. The Study must collect clinical data from a variety of sources in a variety of methods influenced by the need for complete and accurate data and cost. She strongly recommended that the Study pursue the PHR pilot study. In addition, she recommended that Vanguard Centers develop relationships with hospitals and clinical centers with clinical data repositories in an effort to more easily

access those data. Electronic data capture is both a challenge and tremendous opportunity for the Study.

- Barbara Anne Nabrit-Stephens, M.D., M.B.A., noted that many major health insurance companies are creating shared repositories of health information to facilitate portability of information between health care providers and health insurance companies. The Study's desire to use EHRs and PHRs provides an opportunity for public-private partnerships.

- Dr. Corbie-Smith commented that many NIH clinical translation science awards have focused on the use of EHRs to gather data and catalyze translational research. The data will be standardized across those funded entities. These entities provide another partnership opportunity for the Study.

- Dr. Chapin said the Study can serve as a tool to implement a vision about what health care and health care record tracking should look like in the future. The Study's participants, families, and other stakeholders can identify what this vision should be and then adopt that vision. Dr. Chapin agreed that partnerships should be developed to implement the vision, and he suggested that the NCSAC create a subcommittee to be involved in the development of the vision. The individual expertise of NCSAC members can be applied to this effort.

- Dr. Eaton said successful implementation of electronic data capture requires extensive training and a commitment by the health care provider to fully understand the use of EHRs.

- Dr. Lebowitz asked whether there will be an adjudication system for diagnostic events considered critical Study outcomes. He recommended that a system be developed or subcommittee created to examine the validity of clinical data and the specific diagnoses used in EHRs.

Relationships Between Health Care Providers and the Study

Kenneth C. Schoendorf, M.D., M.P.H., Member, Interagency Coordinating Committee, National Children's Study

Dr. Schoendorf listed three roles of community providers: (1) source of information about the Study for potential participants, (2) channel of communication from the Study to participants, and (3) channel of communication from participants to the Study. Health care providers are a potential important source of "secondary" data (for example, chart reviews or clinical event forms). He noted that health care providers will not be primary data collectors for core Study data. They can potentially be involved in location- or population-specific adjunct studies. Dr. Schoendorf offered three areas for discussion: (1) health care providers as a potential barrier because of a lack of provider familiarity with environmental health, (2) issues of communicating with the health care community, and (3) facilitating two-way communication between the Study and health care providers.

Engaging the Health Care Community

Nancy Fahrenwald, Ph.D., R.N., Associate Professor, College of Nursing, South Dakota State University

Dr. Fahrenwald provided an overview of health care community engagement at the Brookings County, South Dakota, and Pipestone, Yellow Medicine, and Lincoln Counties, Minnesota, (BPYL) Vanguard Center. She described the geographical layout for the Study location and compared population density and number of births in 2003 for the seven Vanguard Centers. The BPYL Vanguard Center has 21 people per square mile and had 621 births in 2003. It is composed of four rural counties in two states. The counties have a strong sense of community. The BPYL Vanguard Center will engage a variety of entities in the health care community, including primary care providers, obstetric/gynecologic physicians and nurse-midwives, nurses (hospital, clinic, public health), county and state public health agencies, school health officials, academic programs, the Indian Health Service, numerous professional organizations, and nonprofit and philanthropic groups. Health care community engagement will provide ethical access to Study populations and augment recruitment, establish partnerships, assist human subjects approval, help inform and evaluate the Protocol, support data collection, develop opportunities for adjunct studies, and provide referral and follow-up related to the Study.

Child Health Provider Engagement in the Study

Leonardo Trasande, M.D., M.P.P., Assistant Professor, Community and Preventive Medicine, and Assistant Professor, Pediatrics, Columbia University, Mount Sinai School of Medicine

Dr. Trasande reviewed the child health provider engagement activities at the New York City (Queens) Vanguard Center. Early activities included publication of a special article describing the Study, meetings with chairs of pediatric departments at hospitals affiliated with Mount Sinai School of Medicine and Columbia University, and outreach to local and state chapters of the American Academy of Pediatrics. Engaging providers in Queens requires engaging all New York City providers. Dr. Trasande listed the number of births and hospitals by borough: 20,600 births in 9 hospitals in Queens; 4,985 births in 15 hospitals in Manhattan; 1,559 births in 15 hospitals in Brooklyn; 123 births in 8 hospitals in the Bronx; and 51 births in 2 hospitals in Staten Island. The command center for the Queens Vanguard Center will likely be at Elmhurst Hospital, with possible satellite offices in the Rockaway Peninsula and eastern Queens. Engagement activities will involve staff pediatricians, nurse practitioners, family practitioners, and nurses; in-services; tokens of appreciation such as Study magnets and mugs; and educational opportunities at conferences and meetings. Study results will be mailed to providers, adjunct studies will be conducted, and results will be disseminated. Potential obstacles for engaging child health providers are providers' lack of knowledge about environmental health and lack of knowledge about the Study.

Relationship Between the Obstetric Community and the Study

Michael W. Varner, M.D., Professor of Obstetrics and Gynecology, University of Utah School of Medicine

Dr. Varner reviewed the relationship between the obstetric community and the Study at the Salt Lake County, Utah, Vanguard Center. Investigators at the University of Utah have been involved in a number of clinical research studies: the Maternal and Fetal Medicine Unit Network, the First and Second Trimester Evaluation of Risk of Aneuploidy Study, the Stillbirth Collaborative Research Network, and EAGR. The Study provides an opportunity to develop long-term academic/community relationships. For the providers, the Study is an opportunity to provide training and updates, trusted and accessible referral sources, and respect. Dr. Varner described these opportunities as "win-win" solutions. Dr. Varner listed several recommendations for preconceptional through first trimester recruitment: Never underestimate the attractiveness of "free" ultrasounds; endorsement of obstetric and pediatric care providers will be crucial; start building community relationships in all jurisdictions now. From an obstetrics perspective, the birth visit requires awareness of attendants, dedicated staff, knowledge of HIPAA, and involvement with sample collections.

NCSAC Discussion and Recommendations/General Discussion

- Dr. Nabrit-Stephens said the underlying power and leverage of the health care provider community is patient trust. The Study may be using too narrow a view of the health care provider community. Expanding this view will determine how the health care provider community should be engaged. Potential supporters and health care providers need to be better informed about the Study. The Study needs to engage residents in training to generate long-term involvement and support.

- Dr. Eaton described important elements of health care provider community engagement. Education over a continuum is a vital part of engaging and maintaining engagement. The definition of health care provider needs to be monitored, and all individuals and entities who are involved in the provision of health care need to be included as early as possible in the process. Community advisory boards should be included. Clinical involvement will play a major role in retention. Lack of access to care will impact clinical involvement, as will lack of provider reimbursement.

- Frank A. Chervenak, M.D., clarified the difference between pediatrics and obstetrics. He described obstetrics as "a profession under siege." The pressure on obstetricians to be efficient and productive and their fear of litigation will affect their willingness to be involved in the Study. There may be no grassroots enthusiasm among obstetricians.

- Dr. Varner countered that the Study provides an opportunity to prove which, if any, obstetric interventions affect meaningful outcomes and perhaps dispel certain medical myths.

- Dr. Jarvis asked whether there is an Indian Health Service service unit in the BPYL Study location. Dr. Fahrenwald replied there was not; the upper Dakota Sioux community does

not have a service unit. Births at the service may be minimal. Tribal issues of Study involvement have not yet been resolved.

- Dr. DuPlessis agreed that the Study needs to broaden its definition of health care provider. She emphasized the importance of establishing and maintaining trusted community contacts, knowing who the providers are, and informing the providers about the Study, which may require expertise in information dissemination (not general public relations). Study scientists may not have the necessary expertise and may have to partner with those who do.

- Dr. Corbie-Smith reiterated the importance of engaging and informing the health care provider community. A broad, simple message needs to be sent to raise awareness in this community. Study information needs to be disseminated beyond the academic press, perhaps at a more "retail" level.

- Dr. Genel said knowledge of environmental health can be both a barrier and an opportunity. There may be a misperception that environmental health is a "soft" science. Providers will have to understand that the Study can provide concrete answers on environmental effects on health outcomes. The Study will have to find multiple avenues for disseminating its message.

- Ms. Costella explained the Program Office is exploring ways the Study can be "retailed," including a designated spokesperson. Ogilvy Public Relations has been a Study contractor for several years and has been working to develop the Study's message to a variety of audiences.

- Dr. Levin commented on the importance of births in rural counties because of the weighting placed on those births.

- Dr. Trasande explained the process for publishing the article on the Study. The Program Office is very supportive of publications and reviews all manuscripts relating to the Study prior to publication.

- Dr. Peck said there are subgroups within the American Academy of Pediatrics that should be engaged with the Study: Pediatric Researchers in Office Settings, the Young Physicians Section, and the Residents Section.

- Dr. Eaton noted that advertising agencies have been known to do pro bono work and may be able to provide the Study with marketing expertise. Other sources of marketing expertise include Masters of Hospital Administration and Masters of Business Administration programs.

- Dr. Currie suggested engaging large food product retailers such as General Foods and McDonald's to create public-private partnerships.

- Dr. Fahrenwald said undergraduate students in mass media and communication at South Dakota State University have been involved in focus group research and information dissemination projects for the Study.

- Dr. Trasande said a major national media campaign for the Study should be an "easy sell" and it is never too early to start a national outreach program.

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

07/26/07

Date

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