

**National Children's Study  
Federal Advisory Committee 20th Meeting  
November 5–6, 2008  
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 \(HHS\)](#), the National Institutes of Health (including the [Eunice Kennedy Shriver National Institute of Child Health and Human Development \[NICHD\]](#) and the [National Institute of Environmental Health Sciences \[NIEHS\]](#)), the [Centers for Disease Control and Prevention \(CDC\)](#), and the [U.S. Environmental Protection Agency \(EPA\)](#).

**Day 1**

**Welcome and Introductions**

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

Dr. Fleischman welcomed the NCSAC members, ex officio members, and other participants to the 20th meeting of the NCSAC. He reviewed the functions of federal advisory committees as defined in the Federal Advisory Committee Act and the NCSAC's roles and responsibilities, which include:

- Providing specific advice and recommendations to the NICHD Director, the National Children's Study (the Study) Director, and the Interagency Coordinating Committee (ICC)
- Responding to specific requests for advice and recommendations by the NICHD Director, 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.

Dr. Fleischman reviewed the minutes of the 19th NCSAC meeting on August 7, 2008. This meeting focused on the National Academy of Sciences (NAS) report on the Study's Research Plan, the Study's response to the report, and the NCSAC's advice and recommendations regarding the report and the response. The NCSAC provided advice and recommendations regarding funding, Study Centers, data access, the Study's conceptual framework, ethical issues, and health disparities.

**Informed Consent**

*Sarah Keim, M.A., M.S., Associate Study Director for Operations and Logistics, National Children's Study*

Because the Study is a longitudinal study, there will be an ongoing need to inform participants about data collection and use. Components of the informed consent process currently include a general consent booklet, a biospecimen and environmental sample consent booklet, signature forms, visit information sheets, and consent video.

It is planned that the general consent booklet will be administered once at enrollment. It is a hard copy booklet in question-and-answer format. There are two versions, one for women and one for fathers. The general consent booklet describes the purpose of the Study, the information to be collected, how the information will be used, the possible risks and benefits of the Study, the incentives, and what information can be shared with the participant and when. The general consent booklet states that a participant is free to refuse any item at any time and still be part of the Study. The booklet is meant to be a general introduction to the Study and agreement in principle. In addition to English, the booklet will be available in Spanish, Chinese (traditional script), Korean, Russian, Urdu, French, Punjabi, and Bengali. These languages are prevalent at the Duplin County, NC, and Queens, NY, Vanguard locations. Other languages will be added as needed, and interpreter services will be provided as necessary.

The biospecimen and environmental sample consent booklet will be administered once after general consent at the time of the first anticipated collection of biospecimens and/or environmental samples. There are versions for women and fathers. The booklet reintroduces the Study and describes in greater detail the kinds of biospecimen and environmental samples to be collected. Participants are reminded that they can refuse any item at any time and still participate in the Study.

The general consent and biospecimen consent signature forms are on paper. Again, there are versions for women and fathers. The signature form is one page and includes telephone numbers for the local Study Center as well as the national office. Study Centers can append the signature forms with other information as required by their local institutional review boards (IRBs). Supplemental site-specific information can be added to the consent folders, but otherwise the consent booklets will be consistent across all Study locations.

The visit information sheets will be administered at every visit. The sheets will be tailored for each visit, and separately for women and fathers. The sheets will describe in detail the information to be collected at that visit, how the Study would like to collect it, how it will be used and protected, and which information the Study can give to participants and when. Participants give verbal consent for the data collection and use processes. The visit information sheets will remind the participant that she/he can refuse any item at any time and still participate in the Study.

The informed consent video will be designed to parallel the general consent booklet. Participants who view the consent video will use the same hard copy general consent signature form. The pilot phase of the consent video will tentatively be implemented in spring 2009 at the five Vanguard Centers in Group 2. It is planned to revise the video's language based on the feedback from use of the hard copy booklets.

The pilot phase research plan of the Study has been approved by the Office of Management and Budget (OMB) and the following IRBs: NICHD, University of North Carolina, Mt. Sinai School of Medicine, South Dakota State University, and Westat (the Coordinating Center). The pilot phase plan is under review by IRBs of the University of Utah, the University of Wisconsin-Madison, the University of California-Irvine, and the Children's Hospital of Philadelphia. Both

local and subcontractor IRBs will review the pilot phase plan. IRBs have not yet approved the informed consent documents.

A prototype of the English and Spanish versions of the general consent booklet for women was circulated to the NCSAC during the meeting. A prototype of the biospecimen and environmental sample consent booklet was also circulated.

## **NCSAC Questions and Comments**

- Benjamin S. Wilfond, M.D., proposed that the visit information sheet change “verbal consent” to “verbal authorization.”
- David J. Schonfeld, M.D., asked whether participants who move from one Study location to another will have to go through the informed consent process again due to some of the site-specific variations and supplemental materials. The Study should discourage this activity if the local modifications are minor. Ms. Keim replied that the Program Office is looking at the details of how participants transfer among locations, including the managing of the consent process. Some issues may depend on the requirements of local IRBs.
- Nancy Neveloff Dubler, L.L.B., asked what the Study will do if there are disagreements between parents about enrolling their child into the Study. She also asked about the strategy for adolescent engagement and retention. Ms. Keim explained that the woman has the authority to give general consent for herself and her eventual child. The Study will not ask the father to give consent for his child’s participation. The details for adolescent engagement, retention, and consent at the age of assent have not been worked out. Dr. Fleischman noted that children are not enrolled in the initial phases of the Study, only women and men. Issues may arise if the father does not want his child enrolled. Details for addressing these issues will have to be discussed further.
- Myron Genel, M.D., asked whether the Study is gathering information about experiences with the IRB review and approval process. Given the many IRBs involved in the process, many issues are sure to arise. Describing the issues and how the Study dealt with them will be of interest to many people in the research community. The description could be published. Ms. Keim said that because most of the IRBs involved so far have judged the Study to be of minimal risk, most issues have been minor.
- R. Gary Rozier, D.D.S., M.P.H., asked about the process of developing and testing the consent materials’ effectiveness with low literacy populations. Ms. Keim said the language has not been formally evaluated for literacy level; the language has been evaluated from a technical standpoint to lower the literacy level as much as possible. The Vanguard Centers will conduct formal evaluations of the consent materials.
- Dr. Wilfond asked whether IRBs have stipulated any limitations in data collection or other Study activities in the supplemental materials. It is important that the language be consistent from site to site. Ms. Keim noted that only three IRBs have reviewed the consent materials. The Study will track the language of supplemental materials.

- Helen M. DuPlessis, M.D., M.P.H., asked whether the IRB process was part of the procurement application process. Ms. Keim replied that the IRB approval is not required for contracts. The pilot phase research plan was not submitted to Vanguard Center IRBs until it was approved by OMB and the NICHD IRB.
- Dr. Fleischman asked whether the three IRBs that have approved the pilot phase plan (University of North Carolina at Chapel Hill, Mt. Sinai School of Medicine, and South Dakota State University) are using the cooperative agreement approach. According to Ms. Keim, the approaches have been variable. For example, many of the birthing hospitals at the Queens Vanguard location have cooperative agreements with their university affiliates. Columbia University (a subcontractor) will not review the pilot phase plan, but a number of birthing hospitals will. The Program Office will track IRBs' responses and assess how the approval process affects the Study timeline. Dr. Fleischman commented that the federal regulatory framework allows affiliated research centers such as birthing hospitals to defer to health care research institutions to review and approve a protocol. For example, at the Queens Vanguard Center, the Columbia University IRB deferred to the Mt. Sinai School of Medicine IRB. It is important to track the Study's IRB experience in an effort to help streamline the process for multicenter studies.
- Ms. Dubler commented that the director of the Office for Human Research Protections (OHRP) might be asked to convene a meeting of Study Center IRBs and mediate a common language for informed consent. She said that the local supplemental materials that list specific inclusion and exclusion criteria would not benefit the Study. She proposed that the Study take an active approach in negotiating consent across Study Centers.
- Dr. Genel said the Study's consensus process presents a unique opportunity to work through consent issues, as well as IRB processes, in real time. One possible outcome would be models that could be developed through the Clinical and Translational Science Awards network.
- Dr. Fleischman noted that the Study presented its informed consent process to OHRP during the tenure of Bernard Schwetz, D.V.M., Ph.D., as director. Dr. Schwetz, who strongly supports the Study, convened two symposia for stakeholders concerning centralized or alternative models of IRB review. Dr. Fleischman recommended that the Program Office engage and inform the new OHRP director about the Study. He noted that despite national efforts toward centralized IRBs, many local IRB and institutional leaders have been unwilling to develop centralized processes, even with the support of OHRP.
- Ms. Dubler clarified that she was not proposing a centralized IRB review process for the Study but a negotiated process among local IRBs.
- Dr. Wilfond agreed with the idea of a negotiated process. Convening an in-person meeting with IRB leaders would remove the barriers to developing a consensus.

- Dr. Fleischman reminded the group that the Study held a meeting of Vanguard Center IRB leaders in 2005.

## **NCSAC Recommendations**

- The NCSAC recommended testing the brochures with potential participants or focus groups.
- The Committee recommended that the local IRBs meet to discuss the language of the informed consent materials and come to a group consensus to ensure consistency.
- The need for consistency in local language was emphasized.

## **Data Access Principles, Process, and Progress**

*Jennifer Park, Ph.D., Senior Scientist and Study Center Project Officer, National Children's Study*

There are four key groups with specific data access requirements:

- **Participants/subjects.** Study data will be gathered from participants through the informed consent process. The informed consent process is designed to tell participants what the Study would like to collect, why, how the Study would like to collect it, how the Study would protect it, and when and how the Study can give participants test findings. Personal health information will be important to participants even if tests are conducted sometime in the future.
- **Communities.** Study data will be of interest to communities for several reasons including advancing local public health activities generally and informing public health intervention strategies. A strong rapport with communities is integral to successful Study recruitment and enrollment.
- **Investigators.** Study investigators have a responsibility to data quality control. Responsibility is shared among Study Center investigators, the Coordinating Center, and the Program Office in every aspect of the Study, from design, implementation, data cleaning, data set production, and publication. Successful data quality control requires immediate access to raw and analytic data as appropriate.
- **Researchers.** The purpose of the Study is to answer scientific questions put forth in the Children's Health Act. Prompt access by members of the scientific research community to analytic data is required to answer these questions and address the Study's hypotheses. The research community comprises federal and nonfederal (affiliated and unaffiliated) scientists. Access must be clearly established for all members of the research community.

The context of answering key data access questions for participants and communities is balancing the right to know with the intent of doing no harm. Such issues will be addressed by the Study's Human Subjects Working Team and the Independent Study Monitoring and Oversight Committee. For investigators and researchers, the balance is between advancing science and protecting confidentiality. Issues of data access to investigators and researchers will be addressed by several Study groups and committees, including the Data Access and Confidentiality Committee and the Independent Study Monitoring and Oversight Committee.

Several principles for data access for participants and communities have been developed:

- Planned tests should be communicated to respondents clearly.
- Known environmental and health risks should be clearly communicated to respondents throughout the course of the study.
- Means to limit exposure to known environmental and health risks should be conveyed to respondents.
- Findings should be reported to individuals and communities in a scientifically and ethically responsible way.

In their review of the Research Plan, OMB staff noted that the use of “clinically actionable” or “medically relevant” as a decision tool for determining which findings should be conveyed to participants should be considered as difficult for the respondent to understand. Such a decision tool does not address how lags and delays may affect current and subsequent health care decisions of participants. In response to OMB staff concerns, the Study developed a new approach for the pilot phase. The “proximity to visit” decision tool tells participants that the Study will only report those findings that can be discerned and reported at a given visit. This approach is designed to minimize perceptions that Study tests replace regular health care and that any lags or delays in test reports indicate in any way the absence of health concerns.

With regard to revealing findings to participants and communities, decisions are made with consideration to the standard of the science, disclosure awareness, and human subjects protections. The Study’s scientific groups are involved with revealing-findings decisions. A schedule of testing, clinically actionable values, and a protocol informing respondents will be developed. Decisions are made in an iterative and evolving process as data collection is planned, scientific standards are adopted, and results are complete.

Principles for data access for investigators and researchers are to (1) maximize data quality and access to advance science and (2) limit disclosure of personally identifiable information. Study data users will include affiliated investigators and unaffiliated researchers. Affiliated investigators will have access to raw data for quality assurance/quality control (QA/QC) purposes only. The QA/QC process will transform the raw data into analytic data. Analytic data will be used for statistical estimation, inference, and hypotheses testing. These data will be shared without preference to affiliation. Final analytic files will not be withheld from unaffiliated researchers. Given their enhanced understanding of the Study’s design and operations, affiliated researchers will likely publish first. The analytic data will be used to test the Study’s hypotheses. Analytic data files can be constructed as separate public use and restricted use forms.

Monitoring use and/or content of data files is the central method of disclosure limitation. Therefore, by definition, all Study analytic data files will undergo some form of disclosure limitation. Disclosure is limited for several reasons. The Study views the protection of confidentiality of data a high priority. In the consent, data use is described as intended for scientific purposes only. Federal guidelines require limitations to disclosure, and OMB and IRBs require adherence to federal guidelines for their approval. A variety of options to monitor use and/or change data are available. In general, the more data access is monitored, the less the degree of data changes is required to limit disclosure.

## NCSAC Questions, Comments, and Discussion

- Dr. Fleischman asked the NCSAC and other meeting participants to initially focus their comments on data access to investigators, revealing findings to individuals, and revealing findings to communities. He asked the NCSAC ex officio members to comment on whether investigators from their respective lead federal agencies (NICHD, NIEHS, EPA, and CDC) should be given priority data access. Dr. Fleischman noted that the NCSAC at its last meeting reconfirmed its agreement with the Study that Study investigators should have priority access for data analysis and publications. Based on Dr. Park's presentation, there appears to be a change in this perspective. Dr. Fleischman also asked for an explanation of NIH data sharing rules, justification for the change in perspective, and the basis for the change.
- Peter C. Scheidt, M.D., M.P.H., explained that the community of Study investigators has privileged data access by virtue of their affiliation. Those investigators who are actively engaged in the Study have an inside track to the planning for, access to, and use of the data. Because the Study is publicly funded, the data will be publicly available to all investigators. There will be no withholding of data to the public. In addition, Study investigators will not withhold data as they are prepared for public use.
- Edwin Trevathan, M.D., M.P.H., commented that the key is to balance the need to give data access to the Study investigators that have invested their time, personnel, and careers with the need for public use data sets. One of the challenges of studies with multiple investigators across multiple sites is sustaining the commitment of key investigators. If Study investigators do not have advantages because of data access, it may be difficult to keep them engaged in the long term.
- Dr. Scheidt said there are two advantages for Study principal investigators (PIs). First, as members of the steering committee and working teams, PIs are an integral part of planning the measures and methods for data collection. Second, because of their intimate involvement with the Study, PIs are well positioned to analyze the data. However, the PIs' priority contractual obligation is to collect high-quality data for the Study. Study data should be considered a national resource and should be available to all.
- Allen Dearry, Ph.D., agreed that Study investigators should have priority data access. The Study and its investigators must adhere to NIH data access guidelines. NIEHS adheres to these guidelines and makes data publicly available as soon as possible. Public use data sets are posted on the NIEHS Web site.
- Mary Mortensen, M.D., M.S., asked whether the Study would use a data access model analogous to the one used by the National Health and Nutrition Examination Survey (NHANES), in which cleaned, deidentified data are uploaded to a Web site. The data sets and all related survey materials can be downloaded by investigators. Dr. Park said the Study will tentatively follow a similar model. In addition, different types of public use data sets will be released.

- Dr. Scheidt commented that the Study is different from NHANES in the fact that it is a multicenter, hypothesis-driven, observational study. The Study has a core analytical framework to collect data to test the hypotheses. Study investigators will analyze data to test hypotheses and publish their findings. NHANES data are centrally collected and do not address hypotheses. Once made public, NHANES data can be analyzed by any investigator for any purpose.
- Janet Currie, Ph.D., asked whether the Data Access and Confidentiality Committee will make decisions about who has access to restricted use data sets. She expressed concern that the committee could have too much power. Dr. Park said decisions on data access will not be made on an individual level. The Data Access and Confidentiality Committee will ensure maximum access to and use of the data. She noted that several social scientists are on the committee.
- Michael D. Lebowitz, Ph.D., asked whether investigators have rights of ownership in which they are allowed a certain amount of time to analyze data before they are publicly available. Dr. Scheidt replied that Study investigators gathering the data do not have exclusive ownership. The data are collected under contract, and by virtue of the contract, the federal government owns the data. However, the federal government will not restrict investigators who collect the data from using them. Because of NIH-funded investigators' low compliance with its data access guidelines, NIH is reviewing and revising the guidelines to enforce compliance and improve data access and use by the public.
- Ms. Dubler asked for clarification on OMB's role in data access and use. Dr. Park said there are federal disclosure limitations rules (for example, what constitutes personally identifiable information), and OMB's role is to ensure that these rules are followed. Ms. Dubler commented that there are different rules for "do no harm." She cited an example of HIV incidence in an identifiable population and asked whether the Study had a mechanism to address such an issue. Dr. Scheidt said the Independent Study Monitoring and Oversight Committee is the first step in the mechanism and will be explicitly charged with monitoring these issues. Ms. Dubler commented that notions of data ownership prioritization of access and use can be divisive. The Study should develop a very clear set of guidelines explaining fair usage of data.
- Dr. DuPlessis asked who is responsible for creating the analytical data files and ancillary materials and whether there are required timelines in the contracts for preparing and analyzing the data. Dr. Park said raw data will be cleaned by Study Center investigators and Coordinating Center personnel and then converted to analytic files according to variables determined by the working teams. Study Centers will not have access to raw data from other Study Centers. Ancillary data materials will be created by the working teams with help from Study investigators, Program Office members, and Coordinating Center personnel. Dr. Park noted in the National Childhood Longitudinal Study, it took about 2 years from time of data collection to create final analytic data files representing 10 percent of the sample.
- Dr. Schonfeld said that in addition to individual-level data and aggregate community-level data, there may be individual-level data of interest to non-Study participants. For example,

participants may be giving permission to collect environmental samples from homes they rent, and the home owners/landlords may be interested in Study findings (for example, lead in drinking water, radon). There may be issues about disclosing health risk findings to health departments and third parties.

- Dr. Genel said that he did not expect the terms “clinically actionable” or “medically relevant” to be used verbatim in the consent language, but this concept should be operationalized by staff and the Steering Committee by defining and clarifying these terms for the informed consent. He asked to what extent the Study agrees with the NCSAC’s recommendations concerning revealing findings to participants and whether, if the Study does not agree, there is a mechanism to inform the NCSAC and explain why the Study does not agree.
- Elena Gates, M.D., asked whether “proximity to visit” is a criterion for sharing findings or more of a guiding criterion for sharing. She asked how obstetric ultrasound would fit under the criterion.
- Carol Henry, Ph.D., commented that the Study will inform participants about the biospecimens and environmental samples that will be collected but will not inform about the types of analyses that will be performed. Because the specimens and samples will be banked, it will be difficult to explain to participants that the Study will share findings that are “clinically actionable” or “medically relevant.” Dr. Park said that the Program Office is aware of these issues and is exploring how to address them. Most likely, the Independent Study Monitoring and Oversight Committee will be involved with resolving some of these issues.
- Dr. Park clarified the role of OMB in reviewing the consent process and reporting findings to participants. OMB approval of the pilot protocol is necessary for the conduct of the Study. OMB contacts indicated concern with the proposed concepts of “clinically actionable” or “medical relevant” as not providing clear guidance to participants regarding which test results would be made available to them. Without this clear guidance, OMB contacts were concerned that participants would be mistakenly encouraged to believe that participating in the Study would replace regular health care. This was closely related to the concern that some test results (including the actual tests to be performed) would not be known for some time, perhaps when no longer as useful to the participant. Those delays might also dissuade the participant from seeking regular health care. Because the actual tests, expected completion of results, and available guidance for interpretation of those results will vary across Study measures, and are not known at the time of the initial consent, OMB asked for clearer guidance to be provided to participants about which test results would be made available to participants and when. An agreement was reached between the Study Program Office and OMB contacts that, for the pilot phase of the Study, proximity to visit would be the guideline used to report findings to participants. This means that if a test is known, performed, and scored during a visit, those results are given to the respondent at that visit. In this way, the Study can clearly state at each visit which test results will be given to the respondent and which will not. This does not preclude the Independent Study Monitoring and Oversight Committee from recommending that additional test results be reported to respondents, when known (and actionable).

- Dr. Wilfond commented that, given the weight of Independent Study Monitoring and Oversight Committee decisions, the number and composition of its members are critical. Five members may not be adequate, and community and participant representation may be important. The role of the committee (that is, routine guidance versus resolution of disputes and controversies) may affect its membership.
- J. Ricardo Guzman, M.S.W., M.P.H., commented that the role of community-based organizations is critical in the discussion of data sharing. Mr. Guzman asked for a definition of public use data files, and asked what restrictions or limitations are imposed on the use of the files. Dr. Park said a public use data file has been reviewed and determined that there is minimal risk of disclosure of individual participants and is consistent with federal guidelines to protect personally identifiable information.
- Dr. Currie noted that local and regional data are not useful for testing national hypotheses. However, local or regional data could be used to evaluate local or regional interventions. Dr. Scheidt clarified that data from Study locations are designed to be nationally representative but are not designed to represent a county or state.
- The one copy of the consent booklet being circulated reached Ms. Dubler, and she commented that the material looks intimidating, with lots of print in small font size. She said the booklets are not user friendly.
- Wilma Brakefield-Caldwell, R.N., said the consent booklet presents too much material for consumers to read.
- Ms. Keim said the print will be larger in the actual materials; the booklets are prototypes. She explained that Study personnel will be trained to walk participants through the materials, clarifying and answering questions in the process. The consent video will complement the booklets. The utility of the video and booklets will be evaluated in the pilot phase of the Study.
- Ms. Dubler said that because the consent booklets are one of the most important interactions with Study participants they should be accessible and user friendly.
- Gary Q. Peck, M.D., asked whether OMB's purview will change with the new administration. Dr. Scheidt replied that the implications of a new administration are not yet known. OMB's political perspectives may change. OMB's Office of Information and Regulatory Affairs, which reviewed the pilot phase research plan, is not political and is concerned with only scientific issues.
- Dr. Trevathan asked whether there are data for the recruitment/enrollment education process in communities. He also asked about the Study's plans to pilot test recruitment/enrollment materials. Ms. Keim said a number of focus groups with hypothetical and potential Study participants have met to discuss these materials. Dr. Scheidt said there will be an evaluation

of the pilot phase consent process. Vanguard Center PIs have been sharing details of their experiences with community education and engagement.

- Dr. Gates commented on the potential impact of environmental sampling on participants, their neighbors, and communities. She noted that potential impacts are not mentioned in the present version of the consents. This includes the legal obligation to reveal known environmental hazards when selling or renting a home.
- John L. Butenhoff, Ph.D., commented on the process of revealing findings that are of significance to participants. He asked how the Study will ensure appropriate promptness, consistency, and continuity of the Study Centers' providing findings to individual participants.
- Dr. DuPlessis said the pairing of the consent video with the consent booklets could be effective. Ms. Keim said that the original video was considered to be too long. The language in the video is being modified to parallel the language in the written materials. The new video will not be ready to use at the Duplin County or Queens Vanguard Centers but will be ready for the remaining five Vanguard Centers. The video will be formally evaluated in the pilot phase.
- Dr. Park explained that much information regarding data collection and data sharing will be explained in the visit information sheets, not in the general consent booklets. Working teams and the Independent Study Monitoring and Oversight Committee will help develop mechanisms for ensuring prompt and consistent reporting of findings to participants across Study Centers. It is likely that OMB will have a continuing role in the informed consent and data access processes.

### **NCSAC Recommendations**

- The Committee reiterated the recommendation that the Study allow Study investigators priority access for data analysis and publications.
- The NCSAC recommended that the Study reveal medically important findings to participants and develop clear and understandable language about this process for the informed consent materials.
- The NCSAC is interested in the criteria and timing of revealing findings to participants and communities and would like to be kept informed about this important part of the Study.

### **National Children's Study Program Office Report**

*Dr. Scheidt, Director, National Children's Study*

In 2007, the Study received \$69 million in funding. In 2008, funding increased to \$110.9 million. The projected funding need for 2009 is \$192.3 million. No funds were specified in the President's proposed budget for fiscal year 2009. However, the House Appropriations Committee set aside \$192.3 million for the Study, and a member of the Senate Appropriations

Subcommittee expressed his intent to fund the Study. The federal government is currently operating under a continuing resolution, which is in effect until March 6, 2009. There are three scenarios: the 2009 budget could be passed before March 6, the budget could be passed at end of the continuing resolution, or the continuing resolution could be continued for 2009.

Since the April 2008 NCSAC meeting, one Program Office scientist has departed to academia and five scientists have joined the staff. The Program Office is recruiting for additional staff in several specific areas: community engagement, genetics, bioethics, and maternal–fetal medicine. The Program Office has been allotted additional office space to accommodate its growing staff. In a move that will benefit the Study’s procurements and existing contracts, the Contract Management Branch returned from the National Institute for Diabetes and Digestive and Kidney Diseases to NICHD.

Other recent events and milestones include OMB certification for (1) a generic bank of hours for formative research, including community assessments, and (2) a pilot study of the full protocol at the Vanguard Centers; IRB approvals; designation of repository contract award in 2009; designation of environmental laboratory capacity award in 2009; and completion of a memorandum of understanding with CDC’s National Center for Environmental Health for biological specimens laboratory and biomarker assays.

In August 2008, the NCSAC met to review the NAS report on the Research Plan and the Program Office’s response to the report. The NCSAC provided comments, advice, and recommendations, which were posted on the Web and provided to OMB, Congress, IRBs, and many others.

The Study’s Steering Committee and Executive Steering Committee have been expanded, and a Vanguard Center subcommittee has been constituted for the pilot phase. The Data Access and Confidentiality Committee is preparing policies, and the Adjunct Studies Review Committee will convene in the near future. The Specimen Oversight Committee has not yet been constituted, and the Independent Study Monitoring and Oversight Committee (which will function similar to a data and safety monitoring board) is seeking nominations.

In July 2008, a delegation of Japanese officials and environmental scientists visited the Program Office and the University of Utah seeking input on plans for a Japanese birth cohort study with 60,000 subjects. A full Steering Committee meeting was held August 13–14. On the day the Wave 2 contract awards were announced (October 3), NICHD Director Duane Alexander, M.D., and Dr. Scheidt briefed the Congressional Working Group on the National Children’s Study. Later that same day, separate telebriefings for the media and stakeholders were held.

Upcoming events include the beginning of enrollment and data collections at Vanguard Centers in 2009 and presenting at important meetings and symposia. Significant ongoing activities include establishing key entities and committees, preparing for first Study enrollment, and planning and refining the protocol.

## NCSAC Questions and Comments

- Dr. Schonfeld asked why constitution of the Independent Study Monitoring and Oversight Committee is being expedited. Dr. Scheidt said that the NICHD IRB asked to see the roster of committee members before data collection begins in January 2009. Because the Independent Study Monitoring and Oversight Committee, like a DSMB, is not a federal advisory committee, its deliberations do not have to be public.

## Vanguard and Wave 1 Activities

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

The full Study will be implemented in three waves from 2010 to 2012, with about one-third of Study locations in each wave. The intent is for each wave to be reflective of the full sample. There are 105 designated Study locations. In general, a Study location is a county. In some sparsely populated areas, however, adjacent counties have been joined to form a single Study location. The Study has 110 primary sampling units (PSUs). These units are used in the first stage of sampling. In general, a PSU comprises a county that is a Study location. However, three very large counties (Los Angeles County, CA; Harris County, TX; Cook County, IL) have been divided into more than one PSU, yielding a total of 110 PSUs.

The following outlines both the contracts that have been awarded and the unawarded locations to be included in a future procurement:

- 36 Study Centers plus Coordinating Center
- 105 Study Locations
  - 36 Wave 1 Locations (includes 7 Vanguard locations)
  - 36 Wave 2 Locations
  - 15 Wave 3 Locations
    - Wave 3 locations awarded as contract options, to be exercised in the future, pending availability of funds.
  - 18 Locations un-awarded

Locations to be included in a future procurement, pending availability of funds.

The Vanguard locations have been placed into two groups. Data collection for Group 1 (Duplin County and Queens) begins in January 2009. Data collection for the five Group 2 Vanguard locations begins in April 2009. Wave 1 locations are scheduled to begin data collection in July 2010. Contingencies for data collection are OMB clearance for the full study (based on evaluation of the pilot phase experience) and continued funding.

There are four main Study Center tasks:

- **Sampling.** The Vanguard Centers have completed tasks related to the second stage of sampling and have listed all households. Wave 1 Centers have submitted geocoded birth data and stratification variables. These Centers are finalizing segment boundaries and are in the early process of selecting segments. The Vanguard Centers have learned that it takes at least

a year to complete these initial tasks. Although there are some general issues comparable across locations (for example, invisible boundaries, the need for guidance about release of information about boundaries), many issues are unique to the specific location. Community input has been useful, even at this early stage.

- **Community Outreach and Engagement.** The Vanguard Centers, which have active community advisory boards (CABs), are developing expansive community outreach activities and materials. The Vanguard Centers are finalizing local Web sites and are beginning targeted formative research efforts (for example, focus groups). Wave 1 Centers are in various stages of forming and meeting with CABs. Outreach is at the level of organizations. These Centers are beginning plans for formative research. The Vanguard Centers have learned that community outreach and engagement should start early. It is a complex but important process. In general, the Study has been well received by local communities. General issues are comparable across locations, but many issues are unique to the specific location.
- **Field Site Readiness.** Vanguard Centers are leasing and building out of field office space, establishing local call centers, shipping and testing of computer equipment, conducting physical security checks, purchasing supplies, finalizing materials that require local modifications, and preparing for their site-readiness visit.
- **Data Collection.** The start of data collection requires a number of IRB approvals. It also requires security clearances and the hiring and training of staff. There will be locally required trainings as well as training for enumeration and pregnancy screening (EPSC) and the first trimester visit overview.

Future Study milestones and timeline are as follows:

- 2009           Begin pilot cohort at Vanguard Centers
- 2009           Repository and laboratory procurements
- 2009–2010\*   Additional Center and location awards (Wave 3)
- 2010\*†       Begin full study for Wave 1 locations
- 2011\*       Begin full study for Wave 2 locations
- 2012\*       Begin full study for Wave 3 locations
- 2016         Full data set for outcomes of pregnancy

*\*Pending funding*

*†Pending OMB approval*

## **NCSAC Questions and Comments**

- Bruce Levin, Ph.D., asked whether the Study waves are connected to the release of interim findings. Dr. Scheidt said the intent of the Study design was to have each wave as representative as possible of the entire national sample. The similarity of strata among Study locations in a wave allows comparisons across those locations.
- Mr. Guzman asked how the Study is assessing active community participation. Dr. Brenner explained that each Vanguard Center has an active CAB. Wave 1 Study Centers have submitted their plans for community outreach and engagement. Juanita Sims Doty, Ed.D., reviewed and evaluated all community engagement plans and discussed her preliminary

findings with Program Office staff. The evaluation and lessons learned from the Vanguard Centers will be compiled and reported to the Program Office on November 17, 2008.

### **Waukesha County Vanguard Center: Vanguard Center Perspectives Prior to Recruitment**

*Maureen Durkin, Ph.D., Dr.P.H., Waukesha County, WI, Vanguard Center Co-PI; Professor of Population Health Sciences and Pediatrics, University of Wisconsin-Madison*

The University of Wisconsin-Madison is the prime contractor and provides overall scientific oversight for the Waukesha County Vanguard Center. Subcontractors include the Medical College of Wisconsin, Marquette University, the Children's Service Society of Wisconsin, and NORC at the University of Chicago. Eleven protocol development and working groups are involved in planning activities. The phase 1 teams include co-PIs, the core management team, an internal advisory committee, community outreach and medical engagement teams, the sampling and segment characterization team, and the field operations team.

Planning phase activities from October 2005 to November 2008 have included:

- Protocol development
- Sampling, listing, and segment characterization
- Community needs assessment
- Community engagement
- Hospital negotiations
- Medical community outreach and engagement
- IRB approvals
- Staffing and field office planning.

The first steps in sampling were determining the number of births by birth hospital and collecting and geocoding birth data. A CAB provided some input on important variables for stratification. Subject matter experts and environmental epidemiologists provided additional input. The result was 17 strata that included geographic diversity, water source, poverty, housing age, and education. Each stratum was divided into about 10 segments, with about 25 births per year per segment. One segment was randomly selected per stratum, yielding 17 segments. Listing within segments involved counting of dwelling units to confirm which doors will be knocked on during the EPSC. Listing was done on paper, not electronically. Five part-time listers and one supervisor listed 12,803 dwelling units between July 28 and mid-September 2008. Segments were characterized by making onsite observation and using publicly available data (for example, EPA data were linked with aerial maps).

Community needs assessments were conducted through community discussions, by reviewing and summarizing existing data, by determining relationships between community needs and Study core hypotheses, and by focusing on costs and economic impacts of child health concerns in Waukesha County.

Plans for community participation and engagement are being developed. For potential participants, media and communication efforts are designed to raise awareness, inform the public, and promote the Study. The plan is being developed in collaboration with a local

Waukesha County marketing firm. The goal of medical community outreach is to raise awareness and generate support. Activities will include a practice partners' plan, newsletters, continuing medical education conferences, and CAB participation. Hospitals and prenatal care providers will be engaged.

A CAB was established to provide community perspectives on the Study and support for the Study within Waukesha County. The CAB is an exceptional resource whose advice and advocacy is highly valued in carrying out the aims of the Study. The CAB provides advice on outreach and recruitment strategies; communicates community concerns; assists with training, media relations, and outreach; and holds quarterly meetings.

Field operations staffing currently includes a project coordinator, about 30 EPSC interviewers, three field supervisors, two project assistants, six in-home data collector teams, and a yet-to-be-determined number of birth data collectors.

Challenges so far have included delays in federal approvals for data collection, funding uncertainties, and data security and confidentiality.

### **Duplin County Vanguard Center: Leading the Way**

*Nancy Dole, Ph.D., Duplin County, NC, Vanguard Center Co-PI; Deputy Director of the Carolina Population Center, University of North Carolina at Chapel Hill*

The Duplin County Vanguard Center was funded in fall 2005. It is designated as a Group 1 Vanguard Study location. Fieldwork will begin in January 2009. The Vanguard Center team includes the University of North Carolina at Chapel Hill, Duke University, and Battelle Memorial Institute. In addition, this team—together with McMillan and Moss Research—will serve as the Study Center for six Study locations in North Carolina (five are funded, with one option). There is a diversity of expertise and research focus among the Study Center investigators.

The Duplin County community was actively involved in refining the strata and segments. A community advisory group included specific components of the community that were representative of Duplin County. Social services, Partnership for Children, key businesses, the cooperative extension, the health department, prenatal care providers, and hospitals were represented, but it was challenging to involve parents and individuals not representing an organization. Since fall 2005, it has been challenging to keep the community engaged in Study activities. Community engagement has included developing community partnerships (for example, with local community colleges). Much of the outreach has been to the medical community, which is particularly important for ultrasounds and birth visits. There have been negotiations with birthing hospitals, several of which are outside of Duplin County.

Study activities required IRB approval from each of the three Vanguard Center team institutes. Approvals or deferrals were also required from two nonhospital ultrasound providers and seven birthing hospitals. The Vanguard Center will hire a compliance coordinator to facilitate IRB approvals, as well as memoranda of understanding with participating entities, in Duplin County and the other five North Carolina Study locations.

Preparing for fieldwork requires establishing a field office, hiring and training staff, and planning for biospecimen and environmental sample handling. Field work will begin with listing activities in a rural setting. It will include developing local publicity, maintaining visibility as the Duplin County Study, and retaining community outreach and engagement for the long term. Because Vanguard and Study Centers operate under contracts, there are many conference calls, meetings, and working teams; many formal and informal deliverables; and much effort tracking that is unlike that for a grant.

### **Questions and Comments from New Study Center Investigators and NCSAC**

- James Robbins, Ph.D., asked how the Study Centers will handle community engagement for an entire county while enrolling women in only certain portions of a county. Dr. Dole replied that the sampling approach needs to be explained. It is an educational process for the community. People who are not part of the sample need to understand the Study's approach. Dr. Durkin said that there may be broad engagement in a community with more intense engagement within the segments and outreach to those who are most likely to enroll in the Study.
- Dr. Robbins asked who has priority access to data. Dr. Scheidt explained that the goal is to be maximally productive in producing findings and reports that can answer the many serious questions regarding children's health. The Data Access and Confidentiality Committee is developing policies to guide this process. Dr. Scheidt further explained the data access process for Study-affiliated investigators, nonaffiliated investigators, and the public. Analytic data files will be released as soon as they are available.
- Jeffrey C. Murray, M.D., asked whether Vanguard Center investigators have promised deliverables to communities. Dr. Durkin said aggregate data will be made available, but no promises have been made about the type of data and timeframe for release. Dr. Scheidt commented that one of the Study's goals is to provide information for the benefit of participants and communities as much as possible, while protecting confidentiality. He clarified that a precise formula for data sharing has not been crafted, only the intent and goals guiding the process.
- Dr. Lebowitz commented that aggregate data may not be representative of a community, county, or state. Dr. Durkin said that the sample in Waukesha County will be representative by design.
- James D. Wilkinson, M.D., M.P.H., asked about IRB strategies to inform Study providers (for example, ultrasonographers, birth hospital personnel) on the need to protect participant confidentiality. Dr. Durkin replied that this issue has been challenging and is still being worked out. It will be important to educate providers on confidentiality.
- Ms. Dubler noted that there could be measurable differences in potential participants that are contacted depending on the methodology used. She asked whether the Vanguard Centers will evaluate their recruitment strategies. Dr. Brenner replied that recruitment strategies and

success will be evaluated. The goal is to collect quantitative and qualitative data. The evaluation plan is under development, which involves the community engagement team and Program Office staff. The next OMB submission requires such an evaluation. Experiences of Group 1 Vanguard Centers will inform the strategies of Group 2 Vanguard Centers. Each phase of the Study will inform the next. Interactions among Study Center investigators and project officers will continuously expand the knowledge base for the Study.

- Dr. Henry asked whether both local and national (that is, Program Office) recruitment and promotional materials will be used and whether the Vanguard Centers are aware of Program Office efforts. Dr. Durkin said focus groups to evaluate these materials will begin in December. She said that the Study's success will depend on the ability to engage local communities and it is essential to have some leeway in tailoring recruitment materials to communities. Dr. Brenner clarified that there are both national and local materials. The Program Office will review and approve all materials to ensure consistency of messages and accuracy of information. Although the consent materials will be consistent across all Study locations, IRBs may require location-specific supplemental materials.
- Dr. Wilfond asked about confidentiality during community engagement and recruitment, that is, the extent to which communities are concerned about confidentiality versus IRB concerns. Dr. Durkin replied that communities have not been concerned and that the importance of confidentiality has to be explained. Dr. Dole commented that about one-third of pregnant women in Duplin County will be recruited. The Study must protect the confidentiality of participants even at the recruitment stage. The more that is known about where recruitment is taking place, including details of the community, the easier it becomes to identify participants. Dr. Scheidt explained that it is important to protect the confidentiality of an individual's participation, and it is very important in protecting the confidentiality of the data, but some community entities (for example, health departments, police) may need to know the Study segment. These entities will be informed as necessary, and they will be instructed on maintaining confidentiality.
- Mr. Guzman asked who the interviewers are. Dr. Durkin replied that interviewers have not yet been hired; NORC will manage this process. Interviewers will be community members and mostly women. Social workers will serve as participant advocates. Dr. Dole said the Duplin County Study Center is actively recruiting interviewers, enumerators, and other staff, many of whom will be bilingual.
- Dr. Schonfeld commented that recruiting a large number of participants and retaining them for 21 years requires some pride in participating in the Study. Because of this, confidentiality in an observational study seems inappropriate. Children should be able to proudly identify themselves as Study participants. Dr. Schonfeld proposed objective evaluations of the success of community engagement across Study location. Dr. Brenner said an evaluation plan is being developed.
- Michele Forman, Ph.D., asked whether there is a plan to engage, recruit, and retain recent or undocumented immigrants. Dr. Brenner said there is an early formative research proposal

from the Duplin County Vanguard Center to address this issue. The results of early formative research and focus groups will be shared among Study Centers.

- Ms. Dubler expressed concern about the Study's ability to recruit participants in the upper socioeconomic tiers. She asked if there is a mechanism to evaluate recruitment across socioeconomic tiers. Dr. Brenner noted that Duplin County's population is mostly in the lower tiers, whereas Waukesha County's population is mostly in the upper tiers. Dr. Dole said one of the deliverables is a sample coverage evaluation, for which birth certificate data and geocoding will be collected. This information will help identify the neighborhoods in which Study births are occurring. Knowing the neighborhoods will provide some insight into the socioeconomic status of participants. Local statisticians will monitor birth information, and adjustments in recruitment may be necessary. Dr. Durkin said the high-income population of Waukesha County has a history of high participation in longitudinal studies.
- Dr. Levin asked about information that will be gathered on individuals who are recruited but choose not to enroll in the Study. The challenge will be psychosocial factors that may affect enrollment, that are not or cannot be measured, and that are not entered into a database. Lack of knowledge of these factors may affect adjustments in recruiting. Dr. Levin noted that nonrepresentativeness can affect bias in statistical analysis, and factors such as job loss may skew results. Dr. Scheidt said there are plans to study individuals who decline to participate.
- Dr. Wilfond commented that distinguishing between individuals who decline participation because they simply refuse to talk to a recruiter and those who hear the recruiter's pitch and then decline participation would provide valuable information. Jessica E. Graber, Ph.D., said multiple attempts will be made to recruit an individual and visits will be dispositioned with as much information as possible. Recruiters will be trained to probe for details about why an individual declines participation.

## **NCSAC Recommendations**

- Several Committee members believe that being a participant in the National Children's Study should be a point of pride and that participation need not be kept confidential. Individual-level findings should be kept confidential but the fact of participation need not be protected from public knowledge.
- Committee members emphasized the need to track why individuals choose not to enroll in the Study as well as whether this decision was made before or after hearing general information about the Study goals. The Study should explore social factors that may influence one's decision to enroll or decline enrollment in the Study.

## **Report from the Director's Office, NICHD**

*Duane F. Alexander, M.D., Director, NICHD*

The watchword in Washington, DC, and across the nation is *change*. Within the context of the Study, changes have occurred or are occurring. New Study Centers have been added and contracts have been awarded for Wave 2 Study locations. The composition of the NCSAC is

changing as members rotate off and new members come aboard. The advice of the NCSAC is greatly valued, and the NCSAC has played a major role in shaping the Study. The time and effort of the NCSAC members whose tenure has ended is greatly appreciated. New staff members have been added to the Program Office as a result of excellent recruitment. These new staff members are committed to the Study but are taking somewhat of a gamble with their careers given the nature of federal funding. The quality and expertise of the new staff members will help ensure continuing success of the Study. New leadership has come to NIH. Elias A. Zerhuni, M.D., has stepped down, and Deputy Director Raynard S. Kington, M.D., Ph.D., will serve as interim director. Dr. Zerhuni served as NIH director for more than 6 years and during that time was a champion for the Study. Dr. Kington has experience with national longitudinal studies, and he has been a staunch supporter of the Study.

There have been changes in the Study Plan as a result of reviews by NAS and the advice and direction of OMB staff, who acted in a scientific and professional manner. OMB provided excellent comments and recommendations that will improve the Study and pave the way for positive interactions in the future. The Study will need OMB approval for each phase. Since August 2008, there have been changes in the economy. In addition, changes in Congress and a new administration create uncertainties for Study funding. The federal budget will operate under a continuing resolution until March 2009. There is, however, strong Congressional support for the Study, as reflected in the increased funding over the past several years. The NCSAC, the Study community, and advocacy groups have advocated for the Study and helped to increase Congressional support.

Although there are uncertainties, there is hope. The Wave 2 awards were announced at a Congressional briefing of the National Children's Study Caucus, headed by Congresswoman Doris Matsui (D-CA) and Congressman Chris Smith (R-NJ). This is a congressionally initiated interest group supporting the National Children's Study. Drs. Alexander and Scheidt reported on the Study's status, its plans, the significance of the Wave 2 awards, and upcoming requirements. A strong case was made for continuing support of the Study. On days that the NCSAC members are not serving as Special Government Employees, they are encouraged to advocate for the Study to elected officials in their states.

The Study continues to operate at the fiscal year 2008 funding level of \$110.9 million. In 2009, recruitment and enrollment will begin at the Vanguard locations. Lessons learned from the first year of the pilot phase will be applied to the next year's activities, and the experiences of the Vanguard Centers will be applied to the Wave 1 Study Centers. The current changes in the Study are preparing for field work in 2009 and learning how to recruit and successfully enroll participants. Issues such as consent, data access, information technology, and confidentiality must be addressed. Issues regarding laboratory work and the biospecimen and environmental sample repository must also be addressed. Many challenges lie ahead. There have been critical times for the Study, and there will probably be critical times in the future. Many challenges lie ahead, and valued input from the NCSAC will help meet these challenges. The NCSAC has played, and will continue to play, an important role in the Study.

## Day 2

### Welcome and Recap of Day One

*Dr. Fleischman*

Dr. Fleischman welcomed participants to the meeting's second day, reviewed the highlights of the first day, and noted the following observations:

- The Study is developing a comprehensive approach to data access, including access of participants to their own data.
- The NCSAC considers issues of revealing findings to individuals and communities as part of the ethics and informed consent discussion.
- The presentation from Study staff demonstrates a new direction for informed consent that is different from the NCSAC's previously discussed and recommended direction.
- There is an inherent tension between analyses not being performed in real time and participants' expectations of learning about their children's health and potentially benefiting from Study findings.
- With regard to revealing findings to communities, there is a tension between the meaning of findings in terms of representativeness and the analytic capacity to use the findings and the Study's relationships with and commitment to a local community.
- There is a tension between the Study locations "owning" the Study (that is, identifying with it but using site-specific and/or culturally sensitive materials) and the desire for uniformity with national materials such that recruitment will not be affected.

### Autism as an Outcome in the National Children's Study

*Gitanjali Taneja, Ph.D., Senior Scientist and Study Center Project Officer, National Children's Study*

The Study has four broad hypotheses related to neurodevelopment and behavior. They involve:

- Nonpersistent pesticides and poor neurobehavioral and cognitive skills
- Prenatal infection and neurodevelopmental disabilities
- Gene-environment interactions and behavior
- Impact of media exposure on child health and development.

Studies of autism will fall under a broader umbrella of neurodevelopment and behavior and environmental exposures.

Concerns about autism are increasing because the prevalence of autism is increasing. The estimated prevalence is less than 1 percent. In the United States, 1 in 150 children are diagnosed with autism spectrum disorder. The etiology of autism is unknown, and autism has significant economic and social burdens. The Children's Health Act of 2000 stipulates the "expansion, intensification, and coordination of activities at NIH with respect to research on autism."

Because of its large sample size, the Study provides an opportunity to study autism. It is expected that there will be 670 autism cases in the Study. The Study's longitudinal design allows collection of data on early exposure and at multiple time points. The Study will collect exposure data, including biospecimens, environmental samples, and neurodevelopmental status of mothers

and infants. Autism is generally diagnosed before 3 years of age, but there is increasing evidence that it could be diagnosed at younger ages. The American Academy of Pediatrics (AAP) recommends autism screening at 18 and 24 months of age. The Study plans on conducting telephone interviews at these ages. Autism screening will be included in the interviews.

There are several approaches to studying autism in the Study. As part of the core protocol, the entire sample will be screened using the 23-item Modified Checklist for Autism in Toddlers (M-CHAT). Information on medical procedures and vaccines will be collected. Nested case-control studies will be used to compare children diagnosed with autism with children not diagnosed. Several genetic studies are being considered, including association, epigenetic, and genome-wide studies. Through adjunct studies, it will be possible to follow identified cases throughout the Study. There may be adjunct studies using increased screening for a segment of the population.

Autism Speaks, a not-for-profit corporation, has expressed interest in hosting a series of expert panel discussions to enhance and support the Study. Autism Speaks is dedicated to increasing awareness about the growing autism health crisis and raising funds for critical autism research. In 2007, it funded \$30 million in scientific research.

### **Autism Spectral Disorders and the National Children's Study**

*Geraldine Dawson, Ph.D., Chief Science Officer, Autism Speaks; Research Professor,  
Department of Psychiatry, University of North Carolina at Chapel Hill*

The mission of Autism Speaks is to change the future, fund global research, raise awareness, and bring hope. Autism Speaks provides about \$30 million annually for investigating the etiology, biology, and epidemiology of autism spectrum disorders; developing diagnostic and screening tools; improving treatment, and disseminating findings.

Autism spectrum disorders are characterized by impairments in social interaction and communication and restricted range of activities and behavior. The disorders are more common in males (4:1). Autism spectrum disorders occur in about 1 in 150 children. This prevalence is higher than the prevalence of type 1 diabetes (1 in 400), childhood cancer (1 in 2,000), and cystic fibrosis (1 in 3,500). According to the World Health Organization, autism's "burden of disease" is greater than that for type 1 diabetes, childhood leukemia, and cystic fibrosis. In the United States, the annual burden of autism is \$90 billion. The public health challenge is early diagnosis and early intervention because they are critical in reducing these costs. The average lifetime cost-savings for each individual who receives early intervention is about \$1 million.

Genes play a role in autism. Heritability is greater than 90 percent, and there is a high likelihood of epistatic effects involving interaction among several genes. Genetic liability extends to a broader phenotype. About 15 percent of syndromic autism has an identifiable genetic etiology. However, about 85 percent of cases are idiopathic. Environmental factors may play an etiological role, and some autism research is focusing on gene-environment interactions. Environmental factors include prenatal exposures to chemicals (for example, organophosphate pesticides and pyrethrins) and drugs (for example, thalidomide and valproic acid), maternal infection, and maternal antibodies to fetal protein. In addition, there are associations with paternal age and birth in urban areas.

Screening tools for infants and toddlers include the First Year Inventory (a parental questionnaire that assesses behaviors at 12 months of age) and the M-CHAT. The M-CHAT is a parent questionnaire combined with follow-up telephone calls that assess behaviors at 18 and 24 months of age. Diagnostic and assessment tools for infants and toddlers with autism spectrum disorder include the Autism Diagnostic Observation Schedule–Toddlers (12–24 months of age), the Autism Interview–Toddlers (12–24 months of age), and the Autism Observation Scale for Infants (6–24 months of age). New approaches to detection in infants at risk include biological, behavioral, and electrophysiological measurements.

Intervention in autism spectrum disorder is designed to alter trajectory of brain and behavioral development. Empirical evidence supports the success of early intensive behavioral intervention. Five randomized controlled trials demonstrated significantly accelerated development in treated children, increased IQ, and reduced autism symptoms. Although there are large individual differences in treatment response, 30–50 percent of children perform within normal limits at the end of treatment. Best practices in autism early intervention include:

- Earliest possible start to intervention
- Individualized to child
- Designed and overseen by trained, professional, interdisciplinary team
- Autism-specific curriculum
- Ongoing assessment and adjustment
- Children engaged throughout the intervention
- High intensity of intervention (more than 25 hours per week)
- Family training and involvement.

The Autism Speaks Toddler Treatment Network is a collaborative network committed to developing interventions for infants and toddlers at risk for autism. The network is conducting several clinical trials exploring new early intervention approaches. The discovery of autism-susceptibility genes and other biomarkers will allow alteration of early risk processes, thereby reducing or preventing emergence of autism symptoms.

The partnership between the Study and Autism Speaks began with the formation of an expert panel comprising experts in clinical sciences, autism diagnosis and screening, and epidemiology; current Study directors; and Study and Autism Speaks leadership. The advisory group's first meeting was a teleconference mid-November. The group will continue its dialogue for the next 3–4 months and meet in spring 2009 to develop specific ideas, identify logistical issues, and determine feasibility. The advisory group's goals are to:

- Create a plan to enhance autism screening and diagnosis in the Study
- Support and advise Study researchers
- Use the Study as a platform to study autism and improve the lives of Study families affected by autism
- Support targeted adjunct studies
- Test specific hypotheses about genetic and environmental risk factors
- Support the continuation of the Study through legislative and advocacy efforts.

## NCSAC Questions and Comments

- Dr. Peck noted that the autism expert panel lacks members with a medical perspective, including clinical research. The group would benefit from broader expertise. Dr. Dawson agreed that the expert panel would be strengthened by members with a medical perspective and expertise in genetics. Autism Speaks supports a medical perspective of autism through its autism treatment network. This network comprises 15 hospitals that serve children with autism. The network is modeled on the cystic fibrosis network.
- Dr. Jarvis commented on complex traits. The genome is much more complex than previously imagined. Many linear models of gene–environment interactions are too simplistic. Now that researchers know more about epigenetics, disorders that appeared inherited are not genetic at all. This new knowledge should influence conceptions of twin studies. For example, identical twins share the same amnion and chorion (that is, the same prenatal environment), and outcomes associated with this environment may not necessarily be genetic. All that is inherited is not genetic. Because of its unique opportunity to study complex traits of health outcomes, to fully take advantage of this opportunity, the Study needs to employ systems biologists and complex systems modeling specialists. The Study needs to be more comprehensive in its research approaches.
- Dr. Gates asked whether the Study would potentially be interventional if it is including early autism diagnoses. Dr. Fleischman said routine diagnoses of autism are not part of the Study. However, he suggested that because some screening tools provide real-time information, the Study may be obligated to reveal findings to participants, which may result in interventions. Dr. Taneja explained that the M-CHAT is a screening tool, not a diagnostic test. Although it is one of the best autism screening tools available, it has a high rate of false positives and false negatives. Some behavioral information (for example, mother–child interactions) will not be analyzed in real time. Individuals who administered the M-CHAT for the Study will be trained field staff; the M-CHAT will be administered in a telephone interview. Therefore, the Study will not be making diagnoses of autism. The Independent Study Monitoring and Oversight Committee will address issues of referral and intervention.
- Dr. Dawson said it is important for the Study to have well-developed protocols for children with positive autism screens. The AAP recommends that all children be screened with the M-CHAT at 18 months of age. AAP publishes practice parameters that may help the Study develop autism screening protocols. Researchers who have been conducting studies of high-risk infants have been grappling with ethical issues of communicating risk information, and their knowledge could inform the Study.
- Dr. Wilfond said that whether the Study should reveal findings may depend on how the information is provided to participants. The Study faces a broad challenge concerning when to analyze data. Even though the Study will tell participants that the information is being collected for research only, they may have expectations about the use of data. Dr. Wilfond proposed that diagnostic analyses be conducted at the same time the Study is collecting observation data.

- Dr. Schonfeld commented that delaying the scoring of the M-CHAT does not make sense because it is not difficult to score. Based on the score, obvious concerns would be noted, and the Study would need to act in an ethically responsible manner. It will be important for the Study to follow-up children who score positive to confirm subsequent diagnoses. Dr. Schonfeld also commented on one of the autism advisory group’s goals: “improve the lives of Study families affected by autism.” Improvement would require intervention, which would impact the ability to observe the natural history of conditions such as autism. The critical issue then becomes balancing the Study’s observational nature with its ethical responsibility and obligation to deliver timely information to families.
- Dr. Fleischman noted that language was added to the original consent video stating that families might learn things that they might then pursue in diagnostic workups and that might cost them money and make them concerned. The Study would not be paying for the diagnostic workups. Dr. Fleischman noted the example of HIV and AIDS in the 1980s as justification of natural history studies, at a time when clinicians did not have the knowledge or ability to successfully intervene. These studies changed when interventions became available and nonintervention could not be justified. The Study needs to be thoughtful of potential criticism if observations are made and participants are not informed. Although the Study should inform, it may not be obligated to intervene.
- Dr. Forman proposed using a nested case-control study without the M-CHAT; that is, the Study would identify through observation only those children who are diagnosed as autistic and compare these children with a set of controls. There would be observational data but no confounders from a screening tool that has a high rate of false positives and false negatives.
- Jeffery C. Long, Ph.D., said the Study needs to be cautious interpreting data from twins. The data from twins in autistic studies highlight the complexity of variables, suggesting some level of gene–gene interaction or gene–environment interaction. One challenge for the Study will be sorting out complex variables with state-of-the-art technology.
- Dr. Chapin said the speed of technological advancements will be logarithmic, not linear.
- Dr. Lebowitz commented that autism spectrum disorder probably involves multiple phenotypes and may involve other concurrent disorders. Researchers should pay more attention to *in utero* transformations due to environmental exposures. The Study will be able to address a number of these issues and will be able to address many more as technology advances. Dr. Dawson agreed that there are many autisms in terms of their etiology. She noted that there is a high prevalence of social and communication impairments in families with an autistic child. There is a 15–20 percent risk that siblings of autistic children will have some social and communication impairments, which may be less severe autism phenotypes.
- Dr. Durkin noted that Norwegian Birth Cohort Study of 100,000 has been using a Norwegian version of the M-CHAT for screening at 18 months of age. The autism expert panel may consider including a scientist from the Norwegian Birth Cohort Study.

- Dr. Henry commented on the issue of informing versus intervention. There are emotionalism and expectations associated with any childhood diseases observed in the Study. The Study needs to inform participants of screening, and they should be revealed as expeditiously as possible. Dr. Henry agreed that the expertise of the autism advisory panel should be broadened. The panel would benefit from an ethical perspective. Dr. Fleischman said the NCSAC Ethics Subcommittee could be a resource for the panel.
- George Lister, M.D., said there is a need for alternate thought on the research design. There are uncertainties in screening; uncertainties in the number of disorders; and uncertainties about whether the disorders are genomic, epigenetic, or environmental. In addition, the tools are changing. To the extent that there is intervention, the natural history of the disease may change. To the extent that there are known interventions, there are some ethical imperatives. The Study is not in control of these. Creative strategies will be needed because there are so many factors and variables out of the Study's control.
- Amelie G. Ramirez, Dr.P.H., asked Dr. Dawson about the prevalence of autism spectrum disorder across racial and ethnic groups. Dr. Dawson replied that there is no evidence that there are differences in prevalence across different ethnic groups. There are poor prevalence data in a lot of other countries, but data from Japan and Europe and from different ethnic groups within the United States do not support differences. There are, however, differences in the age of diagnosis, access to care, and so on. Dr. Ramirez asked whether health disparities play a role. Dr. Taneja said there are concerns about environmental exposures, access to health care, and the ability to diagnose and treat children with autism spectrum disorder.
- Dr. Schonfeld commented that the proposed use of a nested case-control study ignores the strength of the Study, which is that it is a longitudinal, observational, prospective study. Because of this, the Study will never be able to avoid the dilemma of careful observation and the need to act when it is ethically mandated. The science and ethics will have to be balanced responsibly. Dr. Schonfeld encouraged careful prospective observations, particularly of those outcome measures of highest concern. When a child screens positive, appropriate diagnostic testing should be performed not only for treatment but to ensure proper characterization of the phenotype. There is a critical need to define the phenotype. Dr. Scheidt said some nested case-control studies will be conducted because of cost restrictions to analyze complicated and expensive exposures.
- Dr. Dawson explained that, so far, there is no evidence to support a connection between vaccines, including preservatives such as thimerosal, and autism. There are questions that have not been adequately addressed concerning increased adverse effects due to multiple vaccines at one visit. Immune issues may be involved in autism. Mitochondrial disorders may play a role. A study of the prevalence of mitochondrial disorders in autism is under way.
- James Robbins, Ph.D., proposed that the Study protocol should address health, treatment, social, and educational services for children with autism spectrum disorder to clearly understand their affects on outcomes through the teenage years. Dr. Dawson agreed with the importance of tracking the effects of these services and said measures have been developed

for this purpose. Dr. Taneja noted that a Study working team will focus specifically on these issues.

## **NCSAC Recommendations**

- The Committee emphasized the need to share real-time test results with participants. There is an expectation that Study findings of potential medical importance will be revealed to participants in a timely manner.
- The autism expert panel would benefit from a broader representation of expertise.
- The Study is encouraged to integrate scientific and technological advances with the Study protocol to improve efficacy.

## **Review of the Study's Research Plan as It Relates to Preterm Birth**

*Siobhan Dolan, M.D., M.P.H., Consultant to the March of Dimes; Associate Professor, Department of Obstetrics, Gynecology, and Women's Health, Albert Einstein College of Medicine, Montefiore Medical Center*

The mission of the March of Dimes is to improve the health of babies by preventing birth defects, premature birth, and infant mortality. The March of Dimes carries out this mission through programs of research, community services, education, and advocacy.

After reviewing the Study's Research Plan, the March of Dimes' Scientific Advisory Committee's Subcommittee on the National Children's Study recommended the following:

- Pregnancy dating should be uniform and based on first trimester ultrasound.
- All pregnancy outcomes should be ascertained.
- Biologic specimen collection and storage should be more comprehensive and better described.
- Two hypotheses concerning birth outcomes (role of inflammation and maternal hypothyroidism) should be updated to reflect the state of the science in this rapidly evolving area of inquiry.
  - Hypothesis 1: There is an increased risk of preterm birth from intrauterine exposure to mediators of inflammation.
  - Hypothesis 2: Maternal subclinical hypothyroidism is associated with neurodevelopmental disabilities/adverse pregnancy outcomes.
- Maternal stress as a contributor to preterm birth, including the influence of racial and ethnic disparities, needs to be more comprehensively studied. The Study represents a perfect venue for such a comprehensive assessment.
- More data should be extracted from medical records, especially records for labor and delivery and the postpartum period, for both mother and newborn.
- Brief operational recommendations, including
  - A few pregnancy visits should be retimed to correspond with common clinical practice.
  - The usage of the term *nuchal fold* versus *translucency* should be clarified.
  - Data should be collected on sexual history and sexual activity during pregnancy.

- Data should be collected about family history of preterm birth, birth defects, and infertility.
- Newborn screening test results should be integrated into Study.

### **Ascertainment of Pregnancy Outcomes**

*Ken Schoendorf, M.D., M.P.H., Director of Protocol Development and Study Center Project Officer, National Children's Study*

The Study's primary means for determining gestational age will be first trimester ultrasound. Results will be obtained from clinical scans, if available. Otherwise, ultrasounds will be scheduled under Study auspices. Other relevant information will be collected: last menstrual period (LMP; maternal report at first trimester visit), prenatal care estimate, and possibly postconception urine from "prepregnancy" cohort. Gestational age will be defined for operational and analytical purposes. For scheduling visits, early ultrasound dates will be used; maternal LMP will be used if an ultrasound is not available.

For analytic purposes, the Study recognizes that early ultrasound, especially in concert with "good" LMP, is the current standard. There are, however, ongoing concerns with using "size" to measure "time." There is early variation in fetal growth measured during first trimester. This variation is associated with later pregnancy outcome. Mandating a study-defined gestational age may limit research. The Study's Publications Subcommittee will vet analyses conducted by the community of Study investigators, when appropriate. Making all variables available to the research community will enable a broad research agenda not limited by preconceived ideas.

The occurrence of miscarriages and stillbirths will be ascertained at each contact during pregnancy. If reported, the Study will gain permission to contact hospital or other care provider to collect additional information. The content of data collection is evolving. Study Center expertise will provide input, as will experience from the Stillbirth Collaborative Research Network.

Birth defect data will be obtained from prenatal records, neonatal records, parental reports, and medical care logs. This approach enables targeted follow-up or potential adjunct studies for more detailed data collection. Standardized examination was discussed at length with many people and ultimately deemed impossible to appropriately standardize and administer in the Study's setting. Standardized full-body photos were considered intrusive or "sensitive." Such photos are difficult to standardize. However, the Study will obtain facial photos at the birth visit.

The following biospecimens will be collected during pregnancy and at birth: blood; urine; vaginal swabs; saliva; hair and nails; placenta, cord, and membranes; and cord blood. The strategy for optimal use of biospecimens is to maximize potential of limited material. The Study will (1) balance between exciting in-depth analyses of early outcomes and the importance of early-life exposures to later outcomes; (2) assure adequate samples for future, as yet unrecognized, analyses; and (3) gain efficiency and utility from ongoing advances in analytic technology. The tactics for optimal use are to (1) minimize immediate analyses on total Study population; (2) store the majority of specimens in a repository; (3) process, aliquot, and store in flexible formats; and (4) focus on nested case-control studies.

Maternal serum and whole blood will be collected at preconception, first trimester, third trimester, and labor. Maternal blood has the potential for “gene expression” studies and the potential to immortalize cells. Vaginal swabs will be collect at preconception, first trimester, and third trimester. Vaginal swabs are considered less invasive, are self-obtained, and are well accepted. Vaginal and cervical samples have similar analytic utility.

The Study plans to collect placenta, cord, and membranes from all births. These plans may be constrained by limitations of delivery hospitals (for example, laboratory space, hoods). Whole placentas may be shipped to a central site for fixing and sectioning. Local pathology laboratories may be used for fixing tissue sections. The potential advantages of flash frozen specimens are recognized and have been considered, but this approach is not possible given the Study’s sample size. The possibility of adjunct studies is being discussed. Other biospecimens such as placental bed biopsy and amniotic fluid have been discussed but were deemed unsuitable or present logistical barriers.

The Study will abstract medical record data. Currently planned abstractions include prenatal records as available; labor, delivery, and postpartum records; and neonatal hospitalization records. Forms are being developed with input from prior and ongoing studies, Study Center obstetricians and pediatricians, consultants, and Program Office experts. The Study will assess the completeness and accuracy of medical care logs during the pilot phase. Plans may change with future developments in standardized electronic records.

## **NCSAC Questions and Comments**

- Dr. Gates said preterm birth is one of the major obstetric outcomes that require additional research. There has been little scientific advancement in this area over the past decade or so. Obstetricians who provide care to women in the Study will be interested if preterm births are highlighted. With regard to medical records, there may be differences in the variables listed on hospital records for physicians compared with those variables of interest to the Study. There are three indications for delivery, and the physician must select one but is not given an opportunity to give a written description. A Study questionnaire would be of value. With regard to issues of immortalized cells and informed consent, dialogue in the current stem cell research arena may be informative for the Study. There are consent issues for materials donated for stem cell research as well as immortalized cells from somatic tissues such as skin cell biopsies.
- Dr. Jarvis complimented Dr. Dolan for her presentation and recognized the March of Dimes’ progress in addressing complex traits. He noted that specimen collection issues are going to be “thorny” for the Native American population. Dr. Jarvis asked Dr. Schoendorf whether the Study could collect two PAXgene tubes in the specimen collection. A second tube would add 2.5 ml of blood that is drawn. He also asked whether PAXgene tubes will be collected from cord blood. The fetal contribution to immunological “conversation” at the maternal–fetal interface is an important area for research. Dr. Jarvis said there should be a plan to collect placental tissue specimens from some subset of mothers and preserve the specimens for gene

profiling. With regard to materials for proteomics, if the Study has good gene expressions or DNA extractions, it will have ready-made source of protein for many women.

- Dr. Schoendorf replied that PAXgene tubes in the cord blood are included in the protocol. He asked for clarification on the collection of two PAXgene tubes from mothers. Dr. Jarvis explained that it would be better to collect one tube at two different times, not two tubes at one time.
- Dr. Schonfeld asked about the Study's plans for monitoring maternal stress. Psychosocial variables are important for children's health outcomes but are difficult to assess. The Study will not reach its full potential if it does adequately address these critical but more difficult areas to study. Dr. Scheidt said there are modules of questions about stress in the interview questionnaires for pregnant women and mothers. Saliva will be collected to determine cortisol levels.
- Dr. Chapin commented that researchers with specific areas of interest would like the Study to collect as many samples as possible for their areas of interest (for example, preterm birth and pregnancy outcomes), but the collection of vast numbers of samples and specimens are constrained by the reality of the costs.
- Dr. DuPlessis encouraged the Study to assess maternal stress, including broader risk assessments that are necessary and important during the interconception and preconception periods.
- Dr. Long noted that, from the perspective of the infant, prematurity is not as critical as the consequences of prematurity. Outcomes measures of prematurity are important. He said a stool sample collected during pregnancy would inform on the gastrointestinal microbiome. Assessment of postpartum depression (for example, 1 or 2 weeks after birth) would also be informative. Dr. Long asked how the Study will handle fetal abnormalities discovered during ultrasounds. Dr. Schoendorf replied that the Vanguard Centers and their IRBs have been discussing this issue. Ultrasound response will vary by site, depending on who is conducting the ultrasounds and how they are conducted. The ultrasounds are not anatomic surveys; they are research ultrasounds that will look at measures of fetal growth. If an abnormality is observed, an algorithm will be invoked to ensure the women have adequate referral to a provider.
- Dr. Wilkinson asked how the Study will achieve its aims while still being realistic about the challenges of collecting specimens and measures during labor, delivery, and postpartum exams. He noted that the Baker, Hillsborough, and Orange counties, FL, Study location has 30 birthing hospitals and will rely on those hospitals' labor and delivery personnel.
- Dr. Butenhoff asked about the practical and logistical aspects of obtaining and shipping samples to appropriate locations. Dr. Schoendorf replied that it depends on the relationships among the Study Centers and birthing hospitals. Because these relationships vary, individual arrangements will have to be worked out. How well Study Center personnel and birthing

center personnel interact will be one of the Study's challenges in obtaining and handling samples.

- Dr. Lebowitz noted that some of the issues overlooked in preterm births are physical abuse and substance abuse, which may be related to stress and depression. He asked whether the Study will be measuring physical abuse. Dr. Schoendorf said the Study will, in a questionnaire, ask pregnant women and mothers about physical abuse.
- Dr. Scheidt noted that several of the March of Dimes' recommendations conflict with the Study's representative sample and the Study's cost constraints. In addition, it is challenging to consistently conduct the more detailed specimen collections across highly varied hospitals and birthing centers. The Study recognizes that hypotheses will evolve as the science evolves. Revisions of hypotheses take work, and the Study could benefit from the March of Dimes' expertise in developing new hypotheses.
- Dr. Durkin said that one of the issues at the Waukesha County, WI, Vanguard Center is handling adverse pregnancy outcomes, particularly in terms of how interviewers will interact with families. The Center's IRB has asked for scripts or standard protocols that demonstrate sufficient sensitivity and recognition of retaining the women in the Study, either for workup of pregnancy loss or future pregnancies. Dr. Durkin asked whether the March of Dimes had materials or recommendations for these situations.
- Dr. Henry asked how the Study will address recommendations to increase or improve measures of maternal stress, as well as incorporate new measures as they are developed. Dr. Schoendorf acknowledged that maternal stress is an evolving field of study. Its importance has been long recognized. Several recommended instruments to assess maternal stress have been incorporated into the protocol.
- Dr. Dolan commented that there need to be better markers of maternal stress and more validated instruments to measure it. The Study provides an opportunity to validate instruments to measure stress.
- Dr. Long cautioned against using genetics as a unifying theme in preterm birth. Genes clearly contribute, but there may be many genes that contribute in different ways. There must be care in thinking of preterm birth in genetic terms. Dr. Long also cautioned against grouping races or race admixtures genetically. Such groupings are problematic and lend themselves to misinterpretations.

### **NCSAC Recommendations**

- The Study should administer questionnaires that pertain to preterm birth to improve understanding of the relationship between preterm birth and specific confounders such as stress, depression, physical abuse, and substance abuse.
- The Study must thoughtfully develop a plan for specimen collection in the Native American population.

- A Committee member recommended that the Study collect two PAXgene tubes at two different times during specimen collection.
- It would be useful to collect placental tissue specimens from a subset of mothers and preserve the specimens for gene profiling.
- The Committee recognized the fact that the Study is limited by cost restraints and reiterates its recommendation that the Study develop a list of important measures that are not being obtained because of cost with the estimated incremental costs. The Committee also supports Dr. Scheidt's recommendation that the March of Dimes assist the Study in developing new hypotheses.
- The Study was advised to not group race admixtures genetically.

## **Process for Scientific and Protocol Development**

*Dr. Scheidt*

Scientific and protocol development is an evolving process that involves interactions among many teams, groups, committees, and Study personnel. The protocol for the pilot phase has been developed only from enrollment through birth and the early postpartum phase. Development and refinement will continue for subsequent phases. A variety of sources and documents identified a number of issues and provided a series of recommendations for the pilot phase protocol. The Program Office considered the issues and recommendations and revised the protocol as appropriate. The Program Office receives thoughtful proposals and recommendations for the protocol on a regular basis, and a mechanism to facilitate the protocol development process has been created.

The current scheme for protocol development begins with working teams, whose expertise comes from various Study Center investigators and Program Office personnel. The working teams will develop the various Study methods, protocol proposals and revisions, and scientific domains as the science evolves. Ad hoc subteams that include outside experts will provide input to the working teams as necessary. The working teams will submit proposed protocols to the Program Office Protocol Integration Team, which will then collaborate with the Executive Steering Committee and the Steering Committee to refine the proposed protocol. The Executive Steering Committee will address any design issues. The protocol is then submitted to the Study Director and Associate Director for Science for approval. The ICC and NCSAC will provide comments and recommendations. NCSAC recommendations will be communicated directly to the working teams. The NICHD Director provides final approval for all protocol modifications.

## **Development of the Data Collection Protocol: Working Teams**

*Dr. Schoendorf*

Protocol development is an iterative but parallel process that occurs in 2-year increments. OMB approval is required for each step. The first pilot phase protocol is from enumeration through 2 years of age. When completed, this protocol will be reviewed, revised as necessary, and

implemented for the first phase of the main Study (enumeration–2 years of age phase). As this step takes place, the second pilot phase begins for children 3–5 years of age. When piloting of this phase is complete, it is implemented as the second phase in the main Study. Piloting of the third phase begins ... and so on. This 2-year “pilot first, main Study second” process continues.

The Program Office is responsible for protocol development. The Steering Committee makes recommendations regarding scientific content of a study component, proposes changes to the protocol, and provides scientific expertise to support decision making. The ICC reviews the protocol for relevance to lead agency priorities and Study mission and goals.

The needed scientific expertise of the Study Centers is incorporated into the development process. Study Center involvement in the process improves appreciation of Study structure—both the opportunities and the constraints. Involvement increases scientific ownership within Study Centers and academic communities. To date, Vanguard Center staff and scientists have been intimately involved in pilot-phase protocol development. Topic-specific working teams were recently created to incorporate Wave 1 Study Center personnel. Wave 2 Study Center personnel will be incorporated as well.

Working teams are composed of a small core group of Program Office, Coordinating Center, and rotating Study Center members. There are two types of working teams: (1) operational and overarching and (2) scientific domain. Operational and overarching teams address operational areas relevant to all Study Centers, including policies, procedures, and communication between Study Centers. Other responsibilities include outreach and engagement, sampling, specimen and sample handling and storage, human subjects/IRBs, information management system users, and health informatics and linkages to extant data. Each working team has an identified point of contact from every Study Center to ensure effective communication.

There are currently about 12 scientific domain teams. Each team has a specific area interest. The general responsibilities of these teams are to revise existing protocols as appropriate, develop subsequent data collections, and consider the Study’s longitudinal nature to ensure coherence of measures over time, the fit into overall Study protocol, burden, and cost.

The starting point for the working teams is Vanguard pilot protocol. The experience and results from the Vanguard phase will inform the working teams as they revise and refine the protocol. Input will come from the review of the Research Plan by the NAS, lead federal agencies (CDC, EPA, NICHD, and NIEHS), and the NCSAC. In addition, public comments on the Research Plan have been noted. Ad hoc proposals will also be considered. The current working team structure involves a core standing working group comprising one Program Office representative, one Coordinating Center representative, and about six rotating Study Center members. Ad hoc subdomain teams will be formed for specific issues. These teams will report back through the core group. In early 2009, two people from Wave 2 Study Centers will be added to each working team.

## NCSAC Questions and Comments

- Dr. Schonfeld asked why the protocol was being developed in 2- to 3-year increments. He said it would be advisable to list a protocol development timeframe for the overall Study. Protocol development could be considered in 7- to 8-year increments because it is important to look forward, to begin planning now for what should or could be done in the years ahead. Working teams would determine what needs to be measured now for later analyses (for example, during adolescence). Dr. Schoendorf agreed and noted that the working teams are tasked with keeping track of the longitudinal nature of the Study. Dr. Scheidt commented that the written charge to the working teams is to maintain a broad view of the Study and protocol development. The 2- to 3-year increments are driven by the OMB approval process. Dr. Schonfeld clarified that what may be needed is earlier engagement of outside groups to develop strategic linkages and partnerships for future protocol development. These groups would be involved in the process and not simply asked for input after the fact.
- Dr. DuPlessis agreed that strategic linkages and partnerships should be developed between the working team and outside groups. She said there needs to be communication among the working teams to prevent overlap or duplication of effort. Dr. Schoendorf agreed on the importance of this communication; he noted that the process is still developing. Much of the communication among the working teams will initially be coordinated by the Program Office. Project Officers have been meeting weekly to discuss Study Center activities. They will also be meeting as working team chairs as the teams are formed. Dr. Schoendorf acknowledged that there will be overlap and gaps in the working teams' efforts. The Program Office will work to reduce the overlaps and fill the gaps.
- Dr. Currie agreed with Dr. Schonfeld on the importance of reaching out to professional organizations. Two organizations to consider are the Population Association of America and the American Society of Health Economists. It is important to include organizations that focus on psychosocial issues.
- Dr. Lebowitz noted that the environmental measures working team chaired by Michael J. Dellarco, Dr.P.H., held a closed meeting in October at the International Society for Environmental Epidemiology and International Society of Exposure Analysis joint meeting. Dr. Dellarco described the team's activities in a presentation at the meeting.
- Dr. Fleischman asked whether peer review would be part of the protocol development process. Dr. Scheidt replied that a peer review process is needed. The Program Office does not plan to have another NAS review. The NCSAC could play a role in peer review. Dr. Fleischman said the NCSAC's Scientific Review Subcommittee could conduct a peer review and provide advice and recommendations to the full NCSAC. The level of detail of peer review would have to be determined and agreed upon.

## **NCSAC Recommendations**

- It was recommended that the Study consider developing the protocol 7–8 years ahead to better prepare for later analyses. If this is not possible, strategic linkages and partnerships with outside groups could be developed early.
- Continual peer review will be necessary throughout the course of the Study, and the NCSAC can provide that function through its Scientific Review Subcommittee.

## **International Childhood Cancer Cohort Consortium (I4C)**

*Rebecca C. Brown, M.P.H., M.E.M., Health Scientist, National Center for Environmental Assessment, Office of Research and Development, EPA*

Childhood cancers are rare, and their etiologies are poorly understood. Researchers have investigated childhood cancers with retrospective case-control studies and longitudinal cohort studies. Both approaches have their respective benefits and limitations. Because of the low incidence of childhood cancer, a large cohort size is required to identify a sufficient number of cases, and a long study length is required to allow for cases to occur. Longitudinal cohort studies also allow prospective environmental and biological sample collection.

Another approach for studying childhood cancers is a consortium of cohort studies. There are two benefits of this approach: Pooling data across cohorts increases power to detect an association, and an international design increases information on human variability (for example, exposure, genetics). Limitations include: Collaboration is needed, funding sources are needed, and pooling data may be difficult.

In addition to the Study, a number of countries have recently commenced large infant/child prospective cohort studies to study common childhood diseases. Total enrollment for the current eight studies is about 570,000. Prospective cohort studies are being planned in six countries. Total enrollment for these studies will be about 510,000.

The first I4C workshop was held in 2005 to determine whether a collaboration of these cohorts could be brought together to examine childhood cancer and other rare outcomes. Representatives from 11 cohorts from four continents attended the workshop. It is expected that 700,000 subjects across the cohorts will result in 450 cases of childhood leukemia. The I4C was established, and a steering committee formed.

The second I4C workshop was held in 2007 to demonstrate the ability to pool data across cohorts and discuss a common core protocol across cohorts. A policies and procedures manual was discussed, as were strategies for funding and research support mechanisms. A number of committees were established.

I4C researchers have proposed several hypotheses related to acute lymphoblastic leukemia (ALL). Among them are the relationships of ALL to maternal folate intake, paternal age, chromosomal translocations at birth, pesticides, infection, birth weight by gestational age, and birth defects and childhood cancer. A feasibility and proof of concept study has been

implemented at the Murdoch Children's Research Institute in Melbourne, Australia. The initial hypotheses for analysis involve maternal folic acid level and ALL, and paternal age and ALL. Other research is focusing on chromosomal translocations and ALL.

Future directions for the I4C include publishing results of initial hypotheses, studying additional hypotheses related to childhood cancer, planning the next consortium meeting, and considering using the consortium for investigating other rare outcomes.

## **NCSAC Questions and Comments**

- Dr. Jarvis commented that the I4C model is at the cutting edge of research. Standard ROI mechanisms are no longer sufficient to study diseases in children with severe life-threatening illnesses or chronic illnesses. Consortia of longitudinal cohort studies are needed to study complex, relatively rare traits. Now that there are tools to model complexity, these types of international collaborations are the future of child health research. Dr. Scheidt said the NIH Roadmap is beginning to percolate through the Institutes and Centers; in small increments, the word about international consortium studies is being spread in bits and pieces.
- Dr. Fleischman asked about the comparability of the different international cohort studies in terms of measures that might be of interest to sorting out causation or epigenetic factors, particularly environmental measures and ascertainment of children's phenotypes of different disorders. Ms. Brown said none of the cohort studies were designed to study childhood cancer. Not all of them have measures similar to the Study's measures. Because data from all the studies cannot simply be pooled and analyzed, investigators are formulating certain hypotheses and evaluating previously collected data that are related to the hypotheses. The evaluations include comparability of tools and instruments, wording and language, cultural issues, and timing of questionnaires. Outcome data must also be evaluated. Many details for pooling the data need to be worked out.
- Carol Kasten, M.D., noted that Nordic and Scandinavian countries have complete electronic capture of children's medical data. Linkages between data sets (for example, birth defects and childhood cancer) can be quickly determined. Those countries with socialized medicine and electronic medical data capture can easily answer a lot of children's health questions. The cohort for the Chinese folate intervention study still exists and being followed. The Study offers another large database to investigate children's health issues. The National Cancer Institute is exploring collaboration with the Chinese to study childhood cancer.
- Dr. Scheidt clarified that all of the other large cohort studies are "thin." Much of the data come from questionnaires, not extensive biospecimens and repeated examinations. The real richness for these types of studies comes from blood samples, which offer the opportunity for genetic and biomarker studies. Ms. Brown said the other studies would have to agree to collect and preserve biospecimens and share them with the Study.
- Dr. Schonfeld commented that the size of the U.S. cohort (that is, the Study) could be increased by including more than one child per family. Nested case-control studies of health outcomes in siblings would provide valuable information. Dr. Scheidt explained that a

second child born during the enrollment period will be included in the Study. Twins will also be included. Studies of the Human Genome Project may include parents, grandparents, and older siblings of Study participants. The Study may be used as a control for other case-control studies.

- Dr. Henry asked whether Canada is conducting a national study of its children. Ms. Brown said such a study was planned but was not funded. Dr. Scheidt said several efforts have been made for a national longitudinal study. A smaller, environmentally focused study with about 8,000 children has been implemented.

## **NCSAC Recommendations**

- The Committee recognizes the need for international collaborations to maximize the benefit of research. These types of collaborations enable the cohorts to educate one and other on best practices based on their respective experiences.

## **NCSAC Members**

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### **New Study Center Attendees**

John Bancroft, M.D., Cumberland County, ME, Study Center; Maine Medical Center  
Bettina M. Beech, Dr.P.H., Davidson County, TN, Study Center; Vanderbilt University Medical Center  
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*I hereby certify that, to the best of my knowledge, the foregoing minutes are accurate and complete.*

12-30-08

Date



Alan R. Fleischman, M.D.

Chair

National Children's Study Federal Advisory Committee