

**National Children's Study  
Federal Advisory Committee 25th Meeting  
July 21, 2010  
Natcher Conference Center, National Institutes of Health  
Bethesda, MD**

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

**Welcome and Introductions**

*Carol Henry, Ph.D., Acting Chair, National Children's Study Federal Advisory Committee (NCSAC), School of Public Health and Health Services, George Washington University*

Dr. Henry welcomed the participants and introduced herself as the Acting Chair of the NCSAC.

Dr. Henry highlighted the agenda topics from the April 27, 2010, NCSAC meeting's open session, which included the following:

- Update from the Director's Office, NICHD
- Study update
- Study data update
- Legislative update pertinent to pediatric research
- Study communication plan
- Study visit assessments evaluation.

In a subsequent closed session, the NCSAC discussed several issues and made recommendations to the Study's Program Office that included:

- Clarifying the roles of the various advisory groups (for example, the NCSAC, the Interagency Coordinating Committee [ICC], and the Independent Study Monitoring and Oversight Committee [iSMOC])
- Structuring the NCSAC meetings to allow for adequate discussion time
- Presenting detailed Study data updates
- Addressing study recruitment challenges
- Focusing on study participant retention at future meetings
- Summarizing the Study's document translation policy
- Identifying ways in which the NCSAC can publically support the Study.

Dr. Henry reviewed the July meeting agenda, and referred the group to the discussion questions which were previously distributed and posted on the National Children's Study website.

## **National Children's Study Update**

*Steven Hirschfeld, M.D., Ph.D., Acting Director, National Children's Study, NICHD, NIH, HHS*

**Alternate Recruitment Launch Status.** The establishment of alternate recruitment strategies has been discussed since October 2009 with the goal of improving recruitment for the NCS Main Study. Field data indicated that the costs, time, and resources involved in the initial household recruitment strategy would be unsustainable and not affordable. A series of discussions and workshops identified three specific strategies: provider-based recruitment, enhanced household recruitment, and a two-tiered high intensity/low intensity (HiLo) recruitment strategy. Ten Study Centers are implementing each alternate recruitment substudy. At this time, these 30 Study Centers are developing informatics systems, hiring staff, establishing infrastructure, and developing communications and community outreach plans for the NCS Vanguard Study. The kickoff meeting for the provider-based substudy was held in San Antonio on July 15. The kickoff meeting for the HiLo substudy will be held in Chicago on July 29. The kickoff meeting for the enhanced household substudy will be held in St. Louis on August 6. Initial data collection efforts for the substudies will focus on questionnaires. More complex questions, robust instruments, and specimen and sample collection will be phased in over the coming months. There is no timeline for completing the alternate recruitment substudies. Each substudy will be conducted until sufficient data have been collected to adequately evaluate its feasibility, acceptability, and cost. There should be sufficient data to begin analysis when each strategy reaches a steady-state recruitment rate.

**Informatics Systems Development.** Data fields, structure, relationships, and data tables are being developed centrally to address specific operational questions. The focus of this development is on operational data elements to study feasibility, acceptability, and cost for the Vanguard Study. Data collection and transmission standards have been conveyed to Study Centers. The Study Centers will be responsible for identifying, developing or adapting if necessary, and deploying case management and data acquisition systems. All required data will be transmitted per specifications to a central database at the NICHD.

**Formative Research.** Formative research is an essential component of Vanguard Study's data-driven, evidence-based strategy. Formative research projects are focused, time-limited activities for Study contractors to address specific technical or methodological questions. The first round of formative research projects is ready to begin. The second round of formative research projects will begin in August 2010.

**Transition of the Original Seven Vanguard Centers.** The seven original Vanguard Centers have contributed important and essential data to bring the Vanguard Study to its current status. With the deployment of 30 additional Study Centers and a new informatics structure, the seven original centers will transition to a new system and new data collection specifications to align their processes and instrumentation with the other 30 Study Centers. During the transition period, there will be a short-term scaling back in visit intensity. More intense visits will be phased in as the transition period ends and the decentralized facilitated informatics system is implemented.

**Federated Institutional Review Board (IRB) Launch.** The federated IRB model, previously discussed at the January NCSAC meeting, was approved for implementation in July 2010. Three documents were made available to the Study Centers: Compact for Federation of Study IRBs,

which outlines the principles, processes, and performance goals; a Memorandum of Understanding; and Questions and Responses. The NIH Deputy Director for Intramural Research is the designated official and will sign bilateral agreements with participating Study Centers. The level of participation in joining federated IRB is currently at the discretion of the Study Centers. For those who choose to join, the NICHD IRB can be the IRB of record, or responsibilities can be shared between the NICHD IRB and the local IRB or the local IRB can be the IRB of record. Other NIH programs and studies have expressed interest in adapting the federated IRB model.

**Office of Management and Budget (OMB).** The OMB received the Program Office's submissions for the alternate recruitment substudy as well as the proposed modifications of the questionnaires. There have been successful and collegial discussions with the OMB and the Office for Information and Regulatory Affairs in particular regarding the Vanguard Study protocol and the alternate recruitment substudy. The OMB has provided many helpful suggestions and is motivated and supportive of the Study. Formal clearance is expected prior to the end of July 2010.

**Program Office Reorganization.** The Study is transitioning to engage dedicated Project Managers to provide guidance and oversight for the contracted Study Centers. Six new Project Manager positions were established, of which four have been filled with start dates in August 2010. Program Office activities will be aligned in four areas: planning, operations, analysis, and communications.

**Study Investigator Activities.** The Steering Committee will meet on August 10, 2010, to discuss, among other topics, the Federated IRB, Vanguard Study status, informatics, and compliance with the Federal Information Security Management Act (FISMA). There will be satellite meetings on topics such as communications and outreach, original Vanguard Center transitions, and the alternate recruitment substudy schemas.

## **NCSAC Discussion and Recommendations**

- Thomas Ten Have, Ph.D., M.P.H., asked how the Study sites were allocated to the three alternate recruitment strategies. He also asked whether the 30 Study Centers conducting the alternate recruitment substudies will participate in the Main Study. Dr. Hirschfeld said the 30 new Study Centers will participate in the Main Study. He explained that requests for letters of interest soliciting volunteers to conduct the alternate recruitment substudies were made to the Study Centers, all of which have contracts with the Study. The Study sites for the substudies are, in general, distributed geographically and balanced within the 10 locations for each strategy. There are urban and rural locations as well as northern, southern, eastern, and western locations. However, the participating locations do not make up a statistically valid, nationally representative sample. The Vanguard Study, which includes the 30 Study Centers participating in the alternate recruitment schemas and the seven original Vanguard Centers, will operate ahead of and in parallel with the Main Study for 21 years. Dr. Hirschfeld explained that the 30 new Study Centers will recruit participants for the substudies. These participants will be followed for the duration of the Study as Vanguard Study participants. In the future, the 30 Study Centers and seven original Vanguard Centers will recruit for the Main Study while maintaining a separate Vanguard Study cohort and protocol. Vanguard

Study participants will not be part of the Main Study but will continue as Vanguard Study participants.

- Benjamin S. Wilfond, M.D., asked whether a family with a child enrolled in the Vanguard Study will be able to enroll a second child in the Main Study. Dr. Hirschfeld said a family can have one child enrolled in the Vanguard Study and another child in the Main Study.
- Ana Diez-Roux, M.D., Ph.D., M.P.H., asked whether all Study Centers will be using the same data forms and informatics software. Dr. Hirschfeld said the Study Centers may use different software for data acquisition and case management and the specific forms may vary in format and modality, but they must all use the same data fields in the same sequence with the same patterns and logic and the data must be transmitted to the Program Office in the same format according to NSC specifications. Study Centers can use or adapt existing data collection systems and platforms for Study informatics related to case management and data acquisition. The 30 Study Centers that are conducting the alternate recruitment substudies are currently comparing their data collection systems with an option to collaborate in their data collection efforts.
- Jonas H. Ellenberg, Ph.D., asked how informatics systems quality control will be assessed. Dr. Hirschfeld said they will be assessed centrally. They must conform to data transmission standards. The Program Office provides quality assurance guidelines to the Study Centers and evaluates the quality and consistency of the data. There are three levels of review: local, program, and central. Data specifications, data collection instruments, and required data fields are the same for all Study Centers. Jessica Graber, Ph.D., commented that the quality of the local data collection has not yet been assessed. The Program Office has not yet developed a detailed plan to look at the raw data.
- Melissa Tassinari, Ph.D., asked how many proposals (that is, letters of interest) were submitted for formative research projects. Dr. Hirschfeld said about 35 proposals were submitted.

### **Vanguard Study Recruitment Update**

*Jessica Graber, Ph.D., Senior Scientist and Coordinating Center Project Officer, National Children's Study, NICHD, NIH, HHS*

Dr. Graber provided an update on Vanguard Study recruitment and retention. Dr. Graber also provided information on prepregnancy, prenatal, and birth data collection. As of the end of June 2010, recruitment status was as follows:

<b>Recruitment Stage</b>	<b>Total</b>	<b>Response Rate</b>
Total listed households	83,716	
Household enumeration completed	66,971	86%
Age-eligible women identified	34,016	
Pregnancy screening completed	29,599	91%
Study eligible women identified	1,999	
Consented/enrolled women	1,157	63%

Dr. Graber presented graphs and charts showing the following:

- Cumulative recruitment rate trend—Recruitment reached a steady state by March 2010.
- The monthly number of Study-eligible women by consent outcome—There were lower consent rates in August and December.
- Consent rate by race and by ethnicity—White women had the highest consent rate (66 percent). Asian women had a lowest consent rate (47 percent). However, only 50 Asian women have consented compared with 617 White women and 764 non-Hispanic women.
- Consent rate by ethnicity and survey language—Hispanic, non-English-speaking women had the highest consent rate (76 percent). Non-Hispanic, non-English-speaking women had the lowest consent rate (44 percent).
- Prenatal data collection—The highest data collection completion rate was for the first trimester first mother visit (70 percent). The lowest data collection completion rate was for the prenatal father visit (42 percent).
- Prepregnancy visit completion—Of 322 women, 212 (66 percent) have completed the full or partial visit, and 57 (18 percent) have visits scheduled but not yet initiated.
- First pregnancy visit completion (eligible for either a first or third trimester visit)—Of 860 women, 652 (77 percent) have completed the full or partial visit, and 81 (9 percent) have visits scheduled but not yet initiated.
- First pregnancy visit completion rates by demographic characteristics of mother—Of the women who completed the first pregnancy visit, the highest percentage (54 percent) were age 26–35 years; 90 percent of these women completed the visit. Of the women who completed this visit, the 86 percent had the interview conducted in English; 89 percent of these women completed the visit.
- First pregnancy visit completion rates by demographic characteristics of mother—Of the women who completed the first pregnancy visit, 56 percent were White and 64 percent were non-Hispanic.
- Cumulative number of enrolled women and births—The graph included women enrolled before conception. About 1,200 women have enrolled. About 80 were pregnant when enrolled. There have been 412 births.
- Differences between expected and actual births of enrolled women—Expected births were calculated from due date obtained during the pregnancy screener. In June 2010, there were about 50 expected births and about 30 actual births.

Dr. Graber listed the following next steps:

- Identify strategies to improve enrollment rates, overall and for non-Hispanic non-English speaking women
- Explore barriers to completion of Study visits
- Further examine missed birth visits and identify strategies to reduce passive refusals
- Monitor alternate recruitment strategies for changes in demographics of enrolled women, with continued focus on improving access to Asian populations.

## **NCSAC Discussion and Recommendations**

- Patricia O’Campo, Ph.D., asked whether the 83,000 households were the final list or whether Study staff would attempt to list more households in the case of families moving in or out the

primary sampling units. Dr. Graber said that during enumeration field staff identify “hidden dwelling units.” Once identified, these dwellings are rolled into the sample file. In addition, there is continuous tracking of residential turnover. Each Vanguard Center has a continuous enumeration strategy.

- Joan Y. Reede, M.D., M.P.H., M.B.A., asked whether any of the 480 pregnant women who were identified as Study eligible had contacted the Vanguard Centers. Dr. Graber said all of these women were identified through telephone follow-up. Dr. Reede also asked how many of these eligible women have consented. Dr. Graber said she did not know how many had consented.
- José F. Cordero, M.D., M.P.H., asked what the “Other” category is on the Consent Rate by Race and by Ethnicity graph. Dr. Graber said this is a catch-all category for women who do not self-identify with the OMB race categories.
- Maria Cancian, Ph.D., asked what is known about the nonconsenting women other than race and ethnicity. Dr. Hirschfeld said the data systems used in the original Vanguard Centers did not collect this type of information. However, this information will be collected in the alternate recruitment substudies.
- Bruce Gelb, M.D., asked what is known about the recruitment variability across the seven Vanguard Centers. Dr. Graber said the standard variability is as expected. There are differences in recruitment between urban areas and rural areas. It is more difficult to recruit in urban areas. Among the Vanguard Centers, there is variability in staffing models, use of subcontractors, and organizational infrastructure. These factors may play a role in recruitment variability, but at this time there are not sufficient data to make any conclusions.
- Dr. Reede asked whether data were collected on socioeconomic status (SES) and whether SES played a role in consent. Christina H. Park, Ph.D., said that the highest consent rates are in rural areas where the populations tend to be more homogeneous. SES data are not being captured in a consistent, systematic manner. Dr. Hirschfeld said SES data could not be compiled for presentation at this meeting, but there is intent to compile and analyze SES data for the alternate recruitment substudy.
- Dr. Ellenberg asked whether the Vanguard Study is considered a success so far. Dr. Graber said it is. The household enumeration process has worked well. However, the recruitment rates are lower than expected, and the number of pregnant-eligible women is lower than expected.
- Dr. Henry asked that the Program Office summarize the accomplishments of the Vanguard Study so far. She noted the importance of Vanguard Study experience in informing the alternate recruitment substudies and the next phases of the Vanguard Study. Dr. Hirschfeld commented that the multiplicity of data platforms used by the Vanguard Study in its initial phase made analysis technically challenging, so while the intent to provide additional analyses exists, the technical issues must be addressed prior to completing those analyses .  
Elena Gates, M.D., asked about the identification of prenatal fathers. Dr. Graber said the 868

fathers who are eligible for the data collection visit were identified by the pregnant women, who gave permission to contact the fathers.

- Michael F. Greene, M.D., said it makes a difference when people are interviewed in terms of exposure and outcomes. He noted the larger data collection window for the prenatal father visit. The unreliability of memory over time may affect the quality of the data collected from this visit. Dr. Graber explained that one of the constraints of the current information management system is the sequence of events and how it is processed. Once a woman is identified as pregnant, she completes a first pregnancy visit, in which she can identify the father and give permission to contact him. The visit data are transmitted to a central database and processed, which creates a case identification for the father. Once the case identification is established, the prenatal father visit can be scheduled. The information management system was not designed to collect prenatal data from the mother and father at the same time.
- Dr. Gates commented that the Study reports should focus on the positive aspects and successes of the Vanguard Study so far.

### **Real-Time Specimen and Sample Analysis for the National Children's Study**

*Steven Hirschfeld, M.D., Ph.D., Acting Director, National Children's Study, NICHD, NIH, HHS*

Dr. Hirschfeld presented a brief overview of real-time specimen and sample analysis.

**Real-Time Data Analysis.** To date, an assumption has been that the vast majority of samples and data would be analyzed in the future over an unknown timeframe when motivated and qualified investigators were identified and when additional funding was available; The prospect of real-time analysis for a subset of the samples and specimens collected may change this approach. Real-time analysis is currently being explored through formative research. Real-time analysis may or may not become routine throughout the Study.

**Relevant Considerations.** Personal health information may be important to participants even if analyses are conducted sometime in the future. Some types of analysis for the evaluation of samples are known at the time of collection; others are not yet determined. Some research results require lab analysis; others can be reported immediately. Some tests could inform current or future medical care; others have unknown implications. The timeliness of availability for some test results, as well as the salience of analysis for these tests, can change over time. In context of children's research results, not only availability of research results, but children's age and developmental stage, are relevant to decisions about returning results.

### **Implications of Real-Time Analysis for Human Subject Protections in the Study.**

Dr. Hirschfeld listed the following questions for the NCSAC to consider and discuss:

- Does the timeframe in which research results become available have implications for which research results should be reported to participants?
- Does the prospect of real-time analysis and real-time availability of individual research necessitate a change to our return-of-results policy?
  - What may not be clinically relevant today may become relevant in the future.

- The concept of “clinical relevance” may not be uniformly applicable across geographic regions, across communities, and across time.

## **Return of Individual Research Results to Study Participants: Implications of Real-Time Analysis for the National Children’s Study’s Policy and Practice**

*Jennifer Park, Ph.D., Senior Scientist and Study Center Project Officer, National Children’s Study, NICHD, NIH, HHS*

*Julia Slutsman, Ph.D., Bioethicist, National Children’s Study, NICHD, NIH, HHS*

Returning Study results is salient to many stakeholders, including participants and their communities. When considering the return of individual research results from real-time analysis, the following questions should be considered:

- Does the timeframe in which research results become available have implications for
  - Which research results should be reported to participants?
  - A change to the Study’s return-of-results policy?
  - A change to the Study’s human subject protections procedures, such as informed consent forms?

Although the return of results to participants is a key issue, the Study acknowledges the importance of returning results to communities through a transparent and rigorous process. The process identified by the Study to return results to participants may inform the development of strategies to return results to communities.

**Current Process for Developing the Study’s Return-of-Results Strategy.** The independent Study Monitoring and Oversight Committee (iSMOC) determines which, how, and when findings will be reported to affected individual participants and in aggregate to communities. When the iSMOC identifies an analysis or a standard and determines whether results are clinically actionable, a recommendation is made to the Study Director. The Study Director, in consultation with others, determines whether and how the recommendation should be implemented. This may include returning results to participants, consulting with and reporting to oversight bodies, revising the Study protocol, and revising the Study’s design. If the Study’s return-of-results policy is revised, this information would be incorporated into Study visit, consent and other materials.

**Current Study Return-of-Results Strategy: Informed Consent.** The consent process is designed to tell participants:

- What data the Study would like to collect
- Why and how the Study would collect the data
- How the Study would protect the data
- The research results that can be shared with the participants at the time of a given visit
- When and under what circumstances the Study may contact participants to ask whether they would like to receive their individual research results.

**Current Study Return-of-Results Strategy: Considerations.** The current Study practice of returning results to participants is informed by:

- Identification of analyses to be conducted with Study samples

- Source of analysis (for example, Clinical Laboratory Improvement Amendments [CLIA]-certified lab versus non-CLIA-certified lab)
- Available clinical and regulatory standards and current practice
- Timeframe in which some research results can be analyzed and made available for potential reporting
- Potential health impact of research result based on clinical significance and medical actionability.

**Categories of Health Impact of Individual Research Results.** The categories are as follows:

- Descriptive health information (for example, height and weight)
- Clinically nonsignificant health information (for example, sex and routine copy number variations in genomic DNA)
- Clinically significant health information, which can be medically actionable or not medically actionable
- Unknown clinical significance (for example, levels of environmental analytes with no agreed-upon critical values).

**Reassessment of Current Study Return-of-Results Strategy.** Drs. Park and Slutsman listed the following questions for the NCSAC to consider and discuss:

- Does the prospect of real-time availability of research results necessitate revision to the Study's return-of-results strategy?
- Are there particular analyses currently not being reported due to lack of immediate availability of results?
- Which of these would be addressed by real-time analyses?
- If real-time analysis were to become part of the Study design, would it apply to Vanguard Study and Main Study data?

## **NCSAC Discussion and Recommendations**

- Dr. Ten Have asked for clarification on the types of analyses. One type of analysis would be routine CLIA-approved lab reporting with normative values. Results for this type of analysis may be actionable. Another type would be research results where there are no critical values and no clinical consensus on what constitutes an actionable value. Research results would be peer reviewed and validated by peer review before being reported. The Study may be expecting too much from research results to determine what constitutes actionable values. Dr. Hirschfeld said the types of results that would be considered potentially actionable would have to have accepted reference standards. The Study's infrastructure for real-time analyses may not be CLIA certified. Values that are considered out of range may have to be reanalyzed and validated by CLIA-certified labs.
- Steven K. Galson, M.D., M.P.H., asked whether there would be a provision to ask participants what type of results they want to know versus what the Study thinks they should know. Dr. Hirschfeld noted that communities are also interested in knowing Study findings. Community advisory boards (CABs) may be used to help determine the types of findings that should be reported. Dr. Slutsman said that the visit information sheets clearly explain what research activities will be conducted during the visit and ask for permission to collect data.

This mechanism could be used to inform participants the types of results and analyses that could be shared and asking whether the participants would like to be informed of the results. IRBs or other groups may override an individual's decision if there are compelling reasons to report the findings to the participant. Dr. Park noted that participants have an option to decline a particular test, specimen collection, or analysis.

- Dr. Reede said that although there may be situations in which there is a compelling reason to share results, the participant may not necessarily understand the results or know the options for acting on the results. Dr. Hirschfeld said results may be shared with a health care provider or a regulatory or political authority (for example, for certain environmental findings) to provide participants with additional support and clearly communicate research findings. There are multiple scenarios for the reporting of findings; it is a complex issue. Dr. Slutsman commented that some participants are getting ultrasounds. These participants are asked for permission to contact a health care provider or may be offered a referral to a qualified provider through the local Study Center if there are abnormal ultrasound results.
- Dr. Gelb noted that there are issues of when results are medically actionable. He cited an example of a genetic disorder. Genetic results do not necessarily have to be shared with parents. Some can be shared when a child is of age of consent. Dr. Hirschfeld said it is important that the Study have an appropriate structured process for the reporting of findings. The process would involve a number of advisory groups. Dr. Gelb cited a legal decision about reporting genetic findings from a study funded by the National Heart, Lung, and Blood Institute (NHLBI). The NHLBI legal decision was that genetic results from non-CLIA-approved labs were not reportable. Determining which genetic results are meaningful and which should be reported will be a challenge for the Study.
- Dr. Ellenberg said that the reporting of findings may interfere with the observational nature of the Study. He asked: If clinically actionable findings can be defined, how does this impact the Study? Dr. Hirschfeld said the focus at this time is developing an acceptable process for when and how findings will be shared and with whom the findings should be shared.
- Dr. Greene commented that the reporting of findings has the potential to change the fundamental nature of the Study from an observational study to an interventional study. He noted that potentially actionable findings from a non-CLIA-certified lab can be referred to a CLIA-approved lab for reanalysis. Results from a non-CLIA-certified lab could still be provided to participants and health care providers.
- Dr. Galson said that although there are legal issues about reporting findings, there are IRB-mandated reporting requirements and ethical obligations to report certain findings.
- Dr. Gates said it is important to be transparent about the criteria for the decisions to report findings. She also said the Study needs to be clear to participants that research observations such as ultrasounds do not take the place of regular prenatal care. Dr. Slutsman said NCS ultrasound findings are not routinely provided to health care providers. There are criteria (for example, dysmorphologies) for referring or providing findings to health care providers.

- Elena Fuentes-Afflick, M.D., M.P.H., said the Study must be clear in communicating to participants how data are supposed to be used and why the Study cannot report every finding back to them. The Study must be consistent in explaining the consent process to participants. There must be uniformity in the consent process.
- Dr. Wilfond said there is an opportunity for the Study to take a leadership role in developing a process for returning research results to participants. He cited an example in which findings regarding variations in sex chromosomes may have clinical relevance even if the findings are not actionable. Such findings should be reported. For reporting certain findings (for example, rare disorders), reanalyses can be performed at CLIA-certified labs outside of NIH before returning results to participants.
- Dr. Reede commented that there are risks in assuming that a participant has access to health care and the resources and capacity to act on the findings (for example, follow-up tests and health care). Dr. Park said that the Study has provisions for reporting certain findings to participants through health care providers. If a participant does not have an identified health care provider, the Study Center is responsible for identifying a health care provider.
- Everett Rhoades, M.D., said that in considering the return of results to participants, the Study should also consider which findings will not be returned. It may be better to give participants too much information rather than not enough. An exception might be genetic findings. Dr. Rhoades said there should be a distinction between conducting research and practicing medicine: Researchers should not practice medicine. The Study should consider having communities involved in making decisions about what results should be returned.
- Dr. O'Campo asked to what extent communities are involved in discussions about returning results. She cited a study of biomarkers in which the community was very clear about the types of information that should be provided to participants.
- Dr. Henry said several return-of-results scenarios have been discussed. She said it might be worthwhile for the Study to write up several scenarios to describe how results would be returned in each scenario. She noted that there are issues about returning results of environmental findings that must also be addressed. She cited the example of real-time analyses of house dust and the reporting of findings for things such as pesticides, heavy metals, and endocrine disrupters. There are restrictions in which labs are capable of conducting real-time analyses of these types of chemicals. Dr. Henry described the use of a lay panel on biomonitoring. The panel's concern with biomonitoring involved the insurance ramifications for a person who is found to have high levels of, for example, PCBs. This person may not be able to get insurance.
- Dr. Reede said it is important that the public realize that the Study has their best interest at heart. She also said the Study should not assume that the public knows what is meant by "research" and "an investigation."

- Dr. Henry commented that the long-term storage of specimens and samples may be detrimental to the Study in that measurements are not known or published, and results can not be returned to the participants or the community.
- Dr. Gates said there may be challenges in returning results to 100,000 mothers and children, given the scope of the issue. There may be a financial burden for participants (for example, copays) to follow up on their results.
- Dr. Rhoades said there is some ambiguity in the consent language. The Study must be as specific and transparent as possible in communicating to participants about the timing of tests, the types of tests, and the timeframe for returning results. Dr. Park commented that the information about how and when the Study will return results will be stated in the visit information sheets. The process for conveying information to participants will continuously improve.
- Dr. Wilfond said one of the reasons for returning results is to maintain a reciprocal relationship with the participants. There is a potential for ancillary care obligations.
- Edwin Trevathan, M.D., M.P.H., noted the importance of archiving samples and specimens for future analyses. The Study should be clear that better technologies and methodologies will be available in the future and that the types of future analyses are not known. He said the language about returning results should be clear.
- Dr. Galson cited an example of using a health information technology (IT) system for real-time data reporting of adverse events. The IT system generated a great deal of data that were difficult to compile, process, and analyze. He cautioned against having real-time analysis being technology driven, with decisions made by IT professionals.
- Dr. Hirschfeld commented that real-time analyses will not be implemented for most of the samples and specimens collected, primarily due to cost constraints. Most, if not all, samples and specimens will still be stored for future analyses.
- Dr. Tassinari asked about the process for selecting the real-time analyses. Dr. Hirschfeld said that 30 proposals were submitted for formative research on real-time analyses. Selection of the real-time analyses will be data driven. The formative research will provide data on the types of samples that can be analyzed in real-time. The real-time analyses will be selected on the basis of their feasibility and cost-effectiveness.
- Dr. Diez-Roux commented that one of the criteria for selecting the real-time analyses should be the type of results that the Study would like to return to participants quickly.
- Dr. Wilfond asked how frequently the iSMOC will meet. Dr. Hirschfeld said the frequency of the meetings has not yet been determined. The process for returning the results to participants needs to be developed, and that process will affect the frequency of iSMOC meetings.

- Dr. Reede asked about determining the quality of the samples. Dr. Hirschfeld said there are multiple mechanisms. Formative research projects are looking at different types of samples for different types of quality. Specialized contractors with expertise in certain types of samples are also providing feedback on the reliability of samples and analyses.

### **National Children's Study Environmental Methodologies**

*Mike Dellarco, Dr.P.H., Senior Scientist and Project Officer, National Children's Study, NICHD, NIH, HHS*

The goals of the Vanguard Study are to determine feasibility, acceptability, and cost of recruitment strategies, Study operations and logistics, and Study assessments. These goals are to be achieved by (1) rigorous objective data-driven evaluations of the current protocol procedures and (2) testing and evaluation of alternative methods and procedures to improve the efficiency and economy of Study data collection and evaluation and participant satisfaction. Two of the major cost drivers of the Study are the number of visits and the complexity of each visit. The Study visit assessments will include environment exposure methodologies. These methodologies should be reliable, reproducible, have informative value, and lack redundancy. They should also be feasible, acceptable, and cost-effective.

Existing exposure information is fragmented with no uniform terminology or standard methodology. There is a lack of validated exposure measurement and modeling methodology for public health applications, and there are no centrally accessible databases for exposure data. Validated environmental exposure measurement is important because of (1) emerging contaminants of concern, (2) increasing complexity to estimate exposure in terms of spatial and temporal variability, and (3) public health consideration for susceptible periods of development and vulnerable population segments.

There are several Study visit challenges for collecting environmental exposure data. A single monitoring design cannot address all of the environmental issues for the Study. Study visit measurement methods must be of high quality, documented, accessible, and transparent. The Study visit schedule must be flexible and adaptable to meet the unanticipated future needs of the Study. Vanguard Study environmental methodologies to date will be evaluated for performance. Formative research projects will be used to expand and optimize visit measurement methodologies.

Opportunities for the Study include the following:

- Developing exposure nomenclature and terminology for longitudinal cohort studies
- Developing a database of environmental exposure instruments used in longitudinal cohort studies
- Conducting validation studies for environmental exposure instruments
- Fostering adoption of consensus standards and methodologies to ensure consistency, scalability, adaptability, and interoperability for environmental assessments.

## **NCSAC Discussions and Recommendations**

- Dr. Ellenberg asked about the meaning of “dynamic flexible structure and schedule” with regard to evidence-based approach to Vanguard Study evaluation. Dr. Dellarco said the Vanguard Study will develop a baseline collection of information for characterizing the environment, and, based on issues such as locality, behavior, and other parameters, the Study will zero in on a selection of additional measurement methodologies to provide greater clarity about particular types of exposure. This approach will help focus on what the ambient conditions are and what the behavior of the participants is and will help identify the contaminants of greatest concern and then verify their presence in the particular concentrations of concern. Dr. Hirschfeld explained that the Study uses an evidence-based approach to environment methodologies.
- Dr. Diez-Roux said that as the Study develops its protocols, it is important to keep in mind that if one of the goals of the Study is to look at causal effects of environmental exposures, the Study must be careful of introducing biases when investigating selected subsamples. Dr. Hirschfeld said the Study will have a systematic approach for identifying sources of bias.

### **Drinking Water Quality: Findings of the U.S. Geological Survey (USGS), Challenges for Future Monitoring Activities, and Thoughts on Collaboration with the National Children’s Study**

*Michael Focazio, Ph.D., Senior Hydrologist, Office of Water Quality, USGS*

The USGS serves the Nation by providing reliable scientific information to describe and understand the Earth; minimize loss of life and property from natural disasters; manage water, biological, energy, and mineral resources; and enhance and protect American’s quality of life. The USGS has several water-specific programs, including the National Research Program, the National Water Quality Assessment Program, and the Toxic Substances Hydrology Program. The USGS also has a National Water Information System.

The USGS has monitored ambient, source, and drinking waters across the nation in various environmental settings for decades from thousands of sites. It has collected hundreds of analytes using nationally consistent methods and procedures. USGS monitoring networks are designed to test hypotheses related to study objectives. In general, there are four study types: reconnaissance, targeted, probabilistic, and retrospective.

Challenges to linking contaminant occurrence in drinking water to human health risk in the Study include national consistency, targeting the “right” contaminants, developing the “right” laboratory analytical methods and occurrence models, and asking the “right” questions.

An area for potential collaboration and application to the Study are USGS Health-Based Screening Levels (HBSLs). They were designed to provide a nationally consistent metric to help interpret water quality data within a human health context. HBSLs are nonenforceable benchmarks that were developed by the USGS in collaboration with the EPA and others using EPA methodologies for establishing drinking water guidelines and the most current EPA peer-reviewed, publicly available human health toxicity information.

## **NCSAC Discussions and Recommendations**

- Dr. Galson asked about the process for folding the USGS data into the Vanguard Study. Dr. Focazio said the process is currently under discussion.
- Dr. Henry noted that an important issue is monitoring the contaminants of tap water versus the contaminants of water from treatment plants. Dr. Hirschfeld said there are a number of methodological issues in collecting water samples, depending on the source (for example, schools versus homes). The information from the samples needs to be informative and not just provide isolated data at one time from one source.
- Dr. Fuentes-Afflick commented that the Study should collect kitchen tap water samples even though the types of analyses have not yet been determined. The Study's kitchen tap water data could then be linked to other database such the USGS water quality databases.

### **Workshop on Optimizing Exposure Metrics for the National Children's Study**

*Roy Fortmann, Ph.D., Acting Director, Human Exposure and Atmospheric Sciences Division, National Exposure Research Laboratory (NERL), EPA*

Dr. Fortmann reviewed the proceedings and outcomes of a Workshop on Optimizing Exposure Metrics for the National Children's Study. The workshop was held on April 12–13, 2010, in Research Triangle Park, NC. The goal of the workshop was to explore and propose innovative exposure metrics and exposure classification schemes for relating environmental exposures during critical windows of development to better understand potential health outcomes of interest.

Three separate workgroups were formed to address three areas with clear exposure-to-health outcome linkages. The areas were (1) air pollution and asthma, (2) insecticides and neurological development, and (3) endocrine-disrupting chemicals and reproductive endpoints. The workgroups identified and discussed chemicals of interest; sources, routes, and pathways of exposure; critical time windows of exposure; necessary biological and environment samples; and nonmeasurement approaches. The workgroups made recommendations for protocols and research.

All three workgroups identified house dust as the highest priority environmental sample to be collected. They noted the need to measure dust loading in the home, not only concentration, and they noted the need for standardized collection methods. A protocol needs to be developed to address collection of a single sample for multiple analytes.

The workgroups made general research recommendations on measurement approaches for house dust, air exposures, blood, and urine. The workgroups made several recommendations for nonmeasurement approaches. Overall recommendations were as follows:

- Consider house dust as a high-priority environmental measurement in the Study, conduct evaluations of existing data, develop protocols, and evaluate protocols in the Vanguard Study

- Develop and evaluate workgroup approaches recommended for exposure metrics for the asthma hypothesis (potential collaboration with EPA-NERL)
- Conduct analyses to better understand urinary variability for nonpersistent chemicals (potential collaboration with EPA-NERL).

## **NCSAC Discussions and Recommendations**

- Dr. Galson asked why naturally occurring steroids and metabolites of pharmaceuticals did not meet the threshold for being considered chemicals of interest. Dr. Fortmann said the workgroups focused on consumer products and materials. He noted that collecting house dust allows analyses of a range of chemicals. Dr. Henry said pharmaceutical metabolites in water is an issue of concern. Dr. Hirschfeld clarified that one of the Study's areas of interest is pharmaceuticals, which will probably be discussed in a future workshop. However, the Workshop on Optimizing Exposure Metrics workgroups identified house dust as a high-priority environmental sample. The workgroups were asked to identify potential shortcomings in available methods and needs for methodologic research. Some of the recommendations were used to develop questions and areas of interest for the second round of formative research.
- Dr. Ellenberg asked whether the USGS is collecting enough water contamination data from the Study's 105 locations such that the data could be used instead of taking samples from homes. Dr. Ellenberg also asked whether the USGS data would be representative of household consumption and exposure. Dr. Focazio said the USGS and the Study are currently trying to find out where the USGS data overlap with the Study locations. He noted that in many areas the primary water sources are wells, not treatment plants. The water from treatment plants would not be representative.
- Dr. Rhoades asked Dr. Fortmann whether house dust is heterogeneous and to what extent exposure to such things as mites, insects, and indoor smoke can be measured. Dr. Fortmann said house dust is heterogeneous and provides a good archive of chemicals in a home. House dust is a good indicator of persistent chemicals as well as some nonpersistent pesticides. The workshop did not discuss exposures to mites, insects, and indoor smoke relative to asthma. Dr. Henry commented that exposure to mites and insects would be included in allergens and endotoxins.
- Dr. Henry said she was interested in the value of questionnaires in predicting exposures. Dr. Fortmann said extensive analysis of questionnaires has shown them to be poor predictors of exposure. The answers on the questionnaires do not correlate with household samples or biomonitoring data (for example, urinary concentrations). People who answer questionnaires generally do not know the contents of particular consumer products such as insecticides. If there are effective tools such questionnaires for exposures, the Study would want to test them to ensure that they are appropriate for the Study. Dr. Hirschfeld explained that if the Study found that there were no questionnaires for a particular situation, the Study might be justified in developing new instruments. Dr. Fortmann said the workgroups recommended that if questionnaires are used, they should be very focused in order to reduce burden.

- Dr. Tassinari said the Study should explore the use or development of gated questionnaires and should explore collaborative activities with federal agencies such as the EPA and the USGS. The Study should identify where activities overlap. Dr. Hirschfeld said that because the Study does not have the wisdom, knowledge, or resources to develop de novo environmental questionnaires, it needs to collaborate with other federal agencies and leverage the available tools.
- Dr. Henry asked whether scripted studies would be predictive. The goal is to relate a biological measurement to an environmental exposure. Dr. Fortmann noted that the available exposure metrics are fragmented and limited. The EPA is trying to improve exposure metrics as the Study moves forward. The EPA's work will contribute to exposure metrics for the Study, and the Study will improve exposure science. The EPA's goal is to conduct research that is relevant to the Study.
- Dr. Ellenberg said his understanding is that exposure is best measured by body burden, that is, taking specimens and measuring what is in the body. The second level for exposure is to measure chemicals, contaminants, and pollutants in the environment (for example, the house or school) as an approximation for what is in the body. The third level for measuring exposure is questionnaires. He asked how an environmental study could proceed without knowing how to measure the ultimate predictor variable of outcome. Dr. Fortmann explained that if a good biological measure is available (for example, measuring lead levels in blood), a surrogate exposure measure is not necessary. However, in situations for which there is not a good biological measure, a surrogate measure of exposure is needed. For outcomes such as asthma, there are no good biological measures of exposure. In this situation, good environmental measures such as dust are needed. The Study will measure many exposures and attempt to draw correlations with various outcomes.
- Dr. Reede commented that because of the diversity of the Study's participants, it would be challenging to capture the different types of exposures with questionnaires. Dr. Fortmann said that surrogates of exposure are also used because of their lower burden. Surrogate measures such as house dust have a low burden and do not have the challenges of questionnaires. Dr. Henry noted that there are only a few exposures with known relationships to outcomes. The health relevance for many exposures is not known.
- Dr. Hirschfeld said the operational challenge for the Study is collecting credible environmental data and linking to a source or health outcome. The Study needs to know which environmental methodologies are credible and cost efficient for the Study. At this time, the Study is focused on operational hypotheses and methodological research. It is also focused on feasibility, acceptability, and cost of methodologies.
- Dr. Ten Have asked whether the Study has looked at the precedence in other fields such as food measurements and questionnaires. Dr. Hirschfeld said several formative research projects are looking at food questionnaires, and the Study is collaborating with the National Cancer Institute to develop tools for dietary measures.

- Kevin Y. Teichman, Ph.D., said that the Study and lead agencies are interested in going from source of environmental exposure to health outcome and understanding all the steps in between. Different agencies have different responsibilities in investigating the different steps. Each agency has something to benefit from the Study. The Study's interest in environmental exposure methodologies is to understand what gets into the body. However, there are trade-offs between cost and burden.
- Dr. Galson said the Study needs to do more work in the areas of centrally accessible databases and consistent terminology in order to achieve the necessary scientific consistency and reproducibility.

## **Discussion on NCSAC Operations**

The NCSAC discussed how to improve efficiencies and maximize benefit to the Study. The possibility of reconstituting the subcommittees to address certain topics and issues, and the process for making formal recommendations was discussed.

- Dr. Henry said that if the NCSAC is going to make formal recommendations, it needs a different process. The NCSAC would need to understand what it is going to recommend and would need to be prepared to have a discussion of the pros and cons of a recommendation. If the NCSAC chooses this approach, it will have to devote more time and preparation before its meetings.
- Dr. Wilfond said there needs to be a better understanding of the boundaries between the various advisory groups and how the Program Office views the NCSAC's role. There needs to be an understanding of how the ICC, iSMOC, and NCSAC interact. Each group should be aware of the others' activities. Dr. Hirschfeld said the advisory groups need to respond independently and objectively. However, the Program Office could provide regular reports from the ICC and iSMOC to the NCSAC.
- Dr. Reede asked whether the Program Office is getting its questions answered. Dr. Hirschfeld said the questions are meant to stimulate discussion at the meetings. The Program Office is getting valuable input from every NCSAC meeting and the question topics are addressed during the discussions.
- Marshalyn Yeargin-Allsopp, M.D., commented that the roles of each group are distinct. The ICC's role is to ensure the Study remains aligned with the mission of the lead federal agencies. Dr. Yeargin-Allsopp proposed increased communication among the various advisory groups.
- Jessica N. DiBari, M.H.S., reminded the group that the NCSAC's meetings and subcommittee meetings must be open to the public to be compliant with the Federal Advisory Committee Act.
- Dr. Ellenberg said that he preferred that the NCSAC not make decisions, vote, or formal recommendations to the Program Office. The NCSAC role should be advisory.

- Dr. Henry commented that the NCSAC should have a better understanding of the Study's current challenges, which would require more information and input from the Program Office. There will be opportunities in the future for the NCSAC to make recommendations or give endorsements. The NCSAC needs feedback from the Program Office about its evolving role as the Study moves forward.
- Dr. Tassinari noted that the NCSAC did not address the specifics of the questions regarding real-time analyses and did not answer them. The NCSAC needs to determine how it can answer such questions during the meetings. Dr. Hirschfeld said formal responses or votes are not necessary, that the questions are intended to guide discussion and the Program Office is receiving the input it seeks. For the future he suggested that perhaps an individual on the NCSAC could be designated as an advocate for each question or topic area, review the issues before the meeting, and provide a summary following the committee discussion.
- Dr. Cancian proposed eliminating slide presentations at the meetings to allow more time for informed discussion. Dr. Hirschfeld said that presentations help to align the terminology and concepts for discussion and inform the general public. The presentations are intended to be more than just what is on the slides. The slides should simply help frame the discussion.

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



August 17, 2010

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Date

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Carol J. Henry, Ph.D.  
Acting Chair  
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