National Children's Study
Federal Advisory Committee 15th Meeting
December 5, 2006
NICHD 6100 Executive Boulevard, Room 5A01
Rockville, MD

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

The death of Warren Galke, Ph.D., was announced prior to the meeting. Dr. Galke, an environmental epidemiologist, was a member of the scientific staff in the National Children's Study Program Office. Dr. Galke was remembered for his many contributions to the development and progress of the Study.

Welcome and Introductions

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

Dr. Fleischman welcomed the National Children's Study Federal Advisory Committee (NCSAC) members and other participants to the 15th meeting of the NCSAC. He thanked Marion J. Balsam, M.D., NCSAC Executive Secretary, and Jessica Sapienza, M.H.S., NCSAC Committee Liaison Officer, for their work organizing the meeting.

Dr. Fleischman briefly reviewed the functions of federal advisory committees as defined in the Federal Advisory Committee Act and noted that the meeting was open to members of the public, who were invited to participate at appropriate times during the meeting. Dr. Fleischman reviewed highlights of the previous meeting. He assured NCSAC members that their work was important to the Study. NCSAC recommendations are taken seriously and are the template upon which discussion begins in deliberations of all organizational components of the Study.

Dr. Fleischman noted the strong support for the Study from major collegial organizations. Antoinette P. Eaton, M.D., commented that she was pleased to see the recognition given to the Study at the October national conference of the American Academy of Pediatrics (AAP). She circulated meeting materials referencing the Study and its importance and described an AAP workshop that focused on the Study.

Dr. Fleischman reviewed the meeting's agenda and highlighted upcoming presentations. With regard to the outgoing members to be recognized, he explained the rotation of members on and off the NCSAC and noted the outstanding caliber of the members.

Dr. Balsam asked that any member who might have a conflict of interest with regard to any topic of discussion during the meeting notify the Executive Secretary. Members were also asked to respond within a week to a survey about the functioning of the NCSAC that they will receive via e-mail after the meeting.

National Children's Study Video

Dr. Fleischman

Dr. Fleischman introduced the Study promotional video. The 8-minute video is intended to introduce the Study to communities but is not yet available for public use. Dr. Fleischman said that comments about the video were welcome, and NCSAC members will be informed when access to the video is available.

Welcome and Update of the National Children's Study

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

Dr. Scheidt discussed the Study's funding status, reviewed Study activities and progress since the last NCSAC meeting held May 31 and June 1, 2006, and described plans for the future.

The Study's Funding Status. Dr. Scheidt noted that:

- The President's budget for 2007 stipulates that no funds will be spent on the Study.
- Other agency funding is uncertain, and no funding will come from NIEHS this fiscal year.
- House and Senate Appropriations Committees indicate strong support for the Study.
- A continuing resolution is ongoing, and the budget may be passed in mid February or there may be continuing resolutions for the duration of fiscal year 2007.

Special Notice for Additional Study Centers. A copy of this notice, which is also available on the Federal Business Opportunities Web site, was provided to meeting participants. It acknowledges the intent to post a request for proposals (RFP) for award in 2007, conditional upon funding. The requirements are similar to those of the 2005 RFP for Vanguard Centers. Locations must be in a Center's state or a contiguous state, and multiple locations per Center are encouraged. Dr. Scheidt noted that current Vanguard Centers will be eligible to submit proposals. Specific questions regarding the RFP should be directed to Elizabeth Osinski in the Contracts Management Branch.

Steering Committee Notable Activity. The Steering Committee met in July and November. With regard to community representation on the Steering Committee, which was proposed by NCSAC in January 2006, two interim full members were appointed, and the policy for including two community representatives was approved at the November meeting. Other activities and actions include the following:

- The Publications Committee is drafting a publications and data access policy.
- Principles for revealing findings from the Study were considered and approved, following NCSAC recommendations. Clinically critical findings will be revealed to participants, and routine data will be revealed as an incentive.
- Guidelines for releasing details about sample segments were developed that recognize the need to protect communities during the implementation and recruitment phase of the Study.

Awareness and publicity of information will be minimized to protect knowledge of participation in the Study. Confidentiality of participant data will be assured through design of public use datasets.

- Jacques Rossouw, M.D., Director of the Women's Health Initiative (WHI) discussed his experiences and lessons learned while implementing a long-term study. Advice was provided on the use of a performance monitoring committee of peer investigators, strategies for communications and revealing findings to participants and communities, and incorporating the large number of ancillary study proposals with the core WHI study.

Interagency Coordinating Committee (ICC) and Lead Agencies. The Director of NIEHS asked to maintain membership on the ICC. No additional support for the Study will be provided by NIEHS in 2007, but future support is a possibility. Participation of the Department of Education was proposed in response to the Children's Health Act modification of 2004. A series of meetings were coordinated with Lynn Okagaki, Ph.D., Commissioner for Science, of the Institute of Education Research to explore the possibility of involving the Department of Education in the planning and implementation of the Study. Further discussion is expected.

Presentations and Events. Presentations related to the Study since the last NCSAC meeting occurred as part of the following meetings:

- North American Congress on Epidemiology (June 2006)
- 46th Annual Meeting of the Teratology Society (June 2006)
- American Association of Clinical Chemists Annual Meeting (July 2006)
- International Council of Chemical Associations Biomonitoring Workshop (July 2006).

Future Activities. Dr. Scheidt cited several events and activities anticipated over the next few months, including completion of the protocol through 18 months, peer review of the protocol, and procurements—pending fiscal year 2007 funding—through an RFP for additional centers. Presentations are planned for several meetings, including the Maternal and Child Health Epidemiology meeting in December 2006; the Pediatric Academic Societies meeting in May 2007, and the American Statistical Association meeting in July 2007. With regard to funding, a continuing resolution for the 2007 DHHS budget into February 2007 is expected.

Announcements. Dr. Scheidt closed with two announcements:

- Elizabeth Osinski, Contract Officer, will lead contracting activities for the Study and will make comments prior to one of the afternoon discussions.
- Dr. Marion Balsam will end her tenure as Executive Secretary of the NCSAC after this meeting to more actively assist with protocol development and other critical issues in the Study. Ms. Kate Costella has been appointed as Executive Secretary for the NCSAC commencing after this meeting.

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

- *NIEHS activities related to the Study.* Allen Dearry, Ph.D., NIEHS, commented about the role of NIEHS with regard to the Study. He reaffirmed that the agency still is very supportive of the Study. It has contributed financially to directly support the Study in the past. Dr. Dearry described recent NIEHS activities including leading, with the National Human

Genome Research Institute (NHGRI), development of a gene-environment initiative across NIH. Within that initiative, NIEHS is leading an exposure biology effort designed to develop better sensors and methods to assess biological indicators of environmental exposures and has contributed $6 million to that effort. This work is critical and fundamental for implementation of the Study as well as other cohort studies. Such tools are essential to assess the environmental etiologies of disease. Dr. Dearry hopes this work will allow NIEHS to play a more significant role with the Study in the future. Dr. Scheidt responded that this kind of initiative could provide an enormous opportunity to advance and expand the measurement capability of the Study.

- *Revealing data to Study participants' physicians.* Myron Genel, M.D., asked Dr. Scheidt to comment about the plan for revealing data to participants' physicians. Dr. Scheidt explained that the Study will provide clinically critical data, but not routine data, to participants' physicians when the physician can be identified and with the permission of the participant. In response to a question about the definition of clinically critical data, Dr. Scheidt explained that for data to be considered clinically critical, there must be a high level of certainty about the significance of the data.

- *Activities and funding level under a continuing resolution.* Under a continuing resolution, Study activities will continue at the 2006 funding level, but no awards can be made for additional centers.

Report from the Director, NICHD

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

Dr. Alexander thanked NCSAC members for their participation and said that the NCSAC's advice was valued and essential to the Study. He had hoped to announce good news about funding, but unfortunately could not do that. He praised the Study staff for their dedication and continuing hard work in the face of uncertainty.

The Study is needed as much as ever. Children's environmental health remains a major question in pediatrics. Dr. Alexander gave several examples of children's health issues, including autism, obesity, asthma, and learning disabilities, for which research is needed. He mentioned other NICHD activities including those carried out under the Best Pharmaceuticals for Children Act and through several research networks. He noted that none of these efforts have the magnitude of the National Children's Study.

Dr. Alexander discussed several recent developments:

- **Scientific peer review of the Study protocol.** Language in the Senate Appropriations Committee called for scientific peer review of the protocol.
- **NIH Collaborations.** Francis Collins, M.D., Ph.D., NHGRI Director, and David Schwartz, M.D., NIEHS Director, were invited to continue working with the Study to develop the protocol, and Dr. Collins named Alan Guttmacher, M.D., to work with the Study. Dr. Schwartz wants to continue involvement with the Study as well and is interested in new measures development.

- **Department of Education involvement.** Grover J. Whitehurst, Ph.D., Director of the Institute of Education Sciences, named a senior staff member (Dr. Okagaki) to be involved with the Study.
- **Study funding.** Both the House and Senate have indicated a preference that the Study should continue. Two continuing budget resolutions have been passed and a third is expected to be extended to February or March. There is much speculation and uncertainty about what the new Congress will do with regard to the budgets for 2007 and 2008. For the Study, until the budget is resolved, the Vanguard Centers and the Coordinating Center will continue activities, and work will continue on the protocol.

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

- *Budget discussions for fiscal year 2008*. In response to a question from Dr. Genel about discussions at NIH and DHHS on the 2008 budget, Dr. Alexander said that budget requests go forward to DHHS, but it is clear that the Study is a competitor for funds.

- *Framing of the scientific peer review.* Alan Zaslavsky, Ph.D., asked how the direction for a scientific peer review was framed. Dr. Alexander explained that the decision of how the review will be carried out has not yet been made. The direction received was general and only specified an outside scientific review, which allows for great latitude. He mentioned several examples of review options, such as turning the review over to the NICHD Division of Scientific Review or asking another group to put together a review group. The mechanism and process for the review have not yet been determined.

- *Opportunities for saving the information and work in the event that long-term support for the Study does not develop.* Fernando Guerra, M.D., M.P.H., asked about the possibilities for salvaging the work that has been done. Dr. Alexander said that scaling back the Study or salvaging the work would still require resources. Additional support from industry, advocacy groups, and foundations could be sought if federal funding for the Study is not received. Only federal government resources would be adequate to fund the core of the Study.

Recognition of Departing Members

Dr. Alexander

Dr. Alexander presented certificates of appreciation to the following NCSAC members rotating off the Advisory Committee: Linda M. Burton, Ph.D., Duke University; George Daston, Ph.D., Procter and Gamble; Fernando A. Guerra, M.D., M.P.H., San Antonio Metropolitan Health District; Loretta F. Jones, M.A., Healthy African American Families; and P. Barry Ryan, Ph.D., Emory University.

Protocol Update

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

Dr. Brenner said that there had been much activity related to protocol development since the NCSAC's last meeting.

Sampling. Dr. Brenner presented a chart depicting the sampling design for the Study. Most Study locations are single counties, although several sites are composed of multiple counties. The current focus is on selection of neighborhoods within counties or clusters of counties. Dr. Brenner illustrated hypothetical segment selection in a rural and an urban site using maps. Proposed segment boundaries are shared with local communities to see whether the boundaries are reasonable. Once the final boundaries are determined, the segments are selected. An extra step in urban areas involves sampling GUs within strata. One GU in a stratum will be divided into segments.

The following issues regarding the release of information about segment boundaries were presented at the July 2006 Steering Committee meeting:

- With whom can the information be shared?
- How much information can be shared?
- What is the most appropriate time to share this information?

Competing needs of the Study were identified, including outreach and engagement, operational aspects, and confidentiality, particularly with respect to identification of individuals in public data files through potential linkage of data. Guidance was developed by a small subcommittee and was reviewed by two working teams and the Steering Committee, and a revised document is under review. Key elements of the proposed final guidance are as follows:

- Information about segments will be released as needed to support community outreach and engagement and Study operations.
- No information about segments will be released at the national level.
- Confidentiality will be protected through additional measures such as release of partial datasets, for example, randomly selecting a portion of participant records or releasing some but not all of the variables.

Outreach and Engagement. The team includes members from each of the Vanguard Centers, the Program Office, the Coordinating Center, and the community representatives to the Steering Committee and is chaired by Chris Cronk, Sc.D., co-principal investigator for the Waukesha, WI Vanguard Center. The team's goal is "to ensure that participant and community interests, perspectives, and needs affecting recruitment and retention are represented and used in planning and implementation of the National Children's Study."

Recent activities of the team include compiling information about Community Advisory Boards assembled in each of the Vanguard Centers, developing a process for communicating community perspectives to other groups working on the Study protocol (such as other working teams), and developing a participant recruitment brochure.

Contacts and Data Collections. Dr. Brenner reviewed the original schedule of face-to-face and telephone contacts prior to pregnancy and the contacts following pregnancy. The process of protocol development involved:

- Specifying details for data collections from preconception through one year, based on input from working teams

- Combining all recommendations into a single framework allowing better estimates of costs and burden
- Trimming the protocol to meet constraints when it became clear that the measures would be too burdensome and costly.

The working teams felt that the most important elements of the Study were the size of the sample, the longitudinal nature of the Study, and the breadth of measurements. Other important elements included the preconception component, the measures during pregnancy, cord blood collection, and repeated visits during childhood.

The initial approaches to trimming costs were (1) to defer analyses of biological and environmental samples to spread costs over time and to take advantage of new technologies and lower analytic costs in the future and (2) to bring on new locations in a staggered fashion to spread out the initial high-cost years. The next step was to examine the proposed measures within specific visits. The following is the revised plan for preconception visits:

- Low risk of pregnancy group—no visits
- Moderate risk of pregnancy group—no visits
- High probability of pregnancy group—a single visit supplemented with phone follow-ups and self-collected specimens.

Additional changes were made to the visits following pregnancy, including eliminating the oral glucose tolerance test (OGTT) and several visits. The OGTT will be replaced with a less burdensome measure of glucose metabolism. Efforts were also made to reduce the length of face-to-face visits, because most of the time burden was in the interviews. Shorter options were selected and questions that were too extensive for an epidemiologic study were eliminated. Some constructs were moved to a telephone interview or to a self-administered approach.

Other issues include the use of fertility monitors, collection of semen and saliva, and ultrasound exams. The current plan for ultrasound examinations is to obtain an ultrasound in each trimester of pregnancy. For the first trimester ultrasound, which is being obtained primarily to confirm gestational age, results from a routine clinical ultrasound will be used, when available, in lieu of performing a separate Study ultrasound. Second and third trimester ultrasounds will be included as components of the Study visits.

The summary of preconception and pregnancy contacts is as follows:

- Household screening
- Preconception
  - High probability of pregnancy group: Home visit, telephone call 1, 2, and 4 months following visit
  - Moderate probability of pregnancy group: Telephone every 6 months
  - Low probability of pregnancy group: Telephone every year
- First trimester—home visit
- First trimester—dating ultrasound if not available from clinical records
- Second trimester—telephone phone interview, ultrasound
- Third trimester—full clinical visit.

The summary of visits through age 18 months is as follows:

- Visit at the place of delivery
- 3 month phone interview
- 6 month visit in the home
- 9 month phone interview
- 12 month visit in the home
- 18 month phone interview.

Participation of fathers/partners. Biological fathers will be invited to participate in the Study, but if the mother does not want to reveal information or does not want the Study to contact the father, her wishes will be respected. Fathers need not live with the mothers to participate. The first approach will be during the first trimester of pregnancy, and interview data, biologic samples, and weight and height will be collected. Partner interviews are planned at 6 months (face to face), 9 months (telephone), and 12 months (face to face).

Childcare-related data collection. Data collection related to childcare settings will be challenging, because a single child may have multiple types of childcare and frequent changes in childcare. The approach will be to collect childcare usage at each contact and to conduct a substudy of 20,000 children with more direct measures, such as collection of data from providers, environmental samples, and observations. This topic was addressed at the May 2006 NCSAC Meeting.

Development of the protocol document. Dr. Brenner reviewed the development of the protocol document, which will undergo outside scientific review. A charge to the review committee has been drafted and a first draft of the document has been developed. The final version will be distributed to the review committee. Dr. Brenner noted that the need for ongoing scientific review is also recognized. The first iteration of the protocol will provide background and scientific justification for the Study, provide an overview of the entire Study, and document detailed measures through 1 year of age.

NCSAC Discussion and Recommendations/General Discussion

Following Dr. Brenner's presentation, the following topics were discussed:

- *Concerns about transferring face-to-face contacts to telephone contacts.* In response to a comment by Dr. Eaton, Dr. Brenner said this was a valid concern that has been discussed. The frequency of contacts has actually been increased to every 3 months after the child is born to help keep participants engaged; telephone contacts are scheduled between face-to-face visits.

- *Nuchal translucency ultrasound.* Frank Chervenak, M.D., urged that a first-trimester nuchal translucency measurement be considered for inclusion. Dr. Brenner noted that a first trimester ultrasound was not included in the original plan and was added since the last NCSAC meeting. Dr. Fleischman suggested that Dr. Chervenak discuss this issue further with Kenneth Schoendorf, M.D. Dr. Scheidt suggested that some thought be given about what hypotheses that measurement would test.

- *Measurement of socioeconomic status.* Janet Currie, Ph.D., asked about the measures of socioeconomic status. Dr. Brenner said that this information will be collected as baseline data and then will be updated at each interview.

- *Childcare substudy.* David Schonfeld, M.D., questioned whether the proposed sample size for this substudy would limit its statistical power. Dr. Brenner said that this plan was in development and that collecting data on all participants would be cost prohibitive. Dr. Schonfeld suggested that some less costly methods of gathering information, such as phone interviews, would enable the Study to collect at least some data on the entire sample.

- *Community outreach.* Peggy Shepard asked how communities will be identified for outreach. Dr. Brenner responded that the process for community outreach is the responsibility of the Vanguard Centers. Activities have been delayed somewhat due to the funding situation. A plan for evaluating community outreach is being developed; it includes examining the use of community advisory boards. Dr. Fleischman noted that an article has been accepted for publication in *Ambulatory Pediatrics* by Jessica Sapienza, M.H.S.; Giselle Corbie-Smith, M.D., M.S.; Sarah Keim, M.A., M.S.; and himself about how to engage the community before the community is defined. Amelie Ramirez, Dr.P.H., advised the Study to consider the lessons learned from other studies such as the NIEHS Sister Study on Breast Cancer or the Women's Health Initiative.

- *Protocol document for peer review.* Dr. Brenner stated that the current protocol document includes details through 12 months, but it will also include a section to justify the timing of later visits and describing the domains that the Study intends to capture. No specific measures or instruments beyond 12 months will be included. She would welcome input on how best to present this information in the document.

- *The term "biological father."* Ms. Jones suggested that referring to "identified father" would be more appropriate than "biological father." Jeffrey Long, Ph.D., commented that when a woman is specifically asked who the biological father is, her answer is usually correct. Dr. Fleischman noted that the NCSAC has recommended in the past that the Study keep acquired information about biological fathers confidential.

- *Sharing information with health care providers.* Nigel Paneth, M.D., M.P.H., commented that there are confidentiality issues about sharing information with health care providers. Dr. Brenner said that much thought has been given to this issue and that there is an operational need to identify women who later present to health care providers.

- *Posting of documents on the Study Web site.* Dr. Brenner said that the protocol is not yet ready for posting. Dr. Scheidt noted that the protocol will receive agency review as well as peer review, and availability for public comment will occur after the documents are ready.

- *How information on prenatal care and health problems will be obtained.* Bernice Pescosolido, Ph.D., asked how information will be collected about prenatal care and the women's perceptions of health problems and health care. Dr. Brenner said this type of information will be collected through interviews.

- *Recruitment and training of staff responsible for collecting data.* Helen DuPlessis, M.D., M.P.H., asked how recruitment and training will be done. Dr. Brenner said that the "train the trainer" model will be used. The Coordinating Center will train the trainers, and in-person training and some Web-based approaches will be used. The quality management plan addresses training and performance of staff. Dr. DuPlessis encouraged getting feedback from the Study Centers and having a vehicle for translating best practices, and Dr. Brenner assured her that an evaluation component will be included.

Genetic Aspects of the National Children's Study

Moderator: Alan R. Fleischman, M.D.

Report from the September Meeting on Gene/Environment Interactions

James M. Swanson, Ph.D., Co-Principal Investigator, Orange County Vanguard Center; Director, Child Development Center, Department of Pediatrics, School of Medicine, University of California, Irvine

Dr. Swanson reported on the Genes, Environments and Human Development, Health and Disease (GEHDHD) Meeting that took place on September 7–8, 2006 in Orange County, California. The meeting was a great success:

- It showed that eminent geneticists are quite interested in the Study.
- It generated excitement about the potential of the Study and the Study's strengths, including repeated measures over time.
- Discussions revealed potential advances in areas of genetics that may emerge from the Study.

The meeting included eminent scientists who had not previously been involved with Study planning, because new expertise was desired to build upon the work of the past 5 years. Presentations were on scientific topics rather than based on Study hypotheses. The focus was on development and gene-environment interactions that occur over time.

Many of the scientists who participated were not familiar with the Study and were impressed with its "large and thick" nature. They recognized many important strengths of the Study, including:

- The representative and large sample
- Prospective assessment starting early
- Repeated observations over time
- Reciprocal relationship based on feedback
- Comprehensive exposure and outcome measures in all participants.

Participants thought that genetics should be part of every hypothesis and recognized many opportunities that the Study would offer to the field of genetics, such as the repository of stored samples for future use and the opportunity to test "proof of principle" studies.

Dr. Swanson discussed examples of research and summarized six themes from the meeting:

- Technology and biology (Hood and Hartwell)
- Epigenetics and mitochondrial genetic change (Feinberg, Meaney, Jirtle, Cheverud, Wallace)

- Genetics and maternal-fetal environment (Gillman, Wadhwa, Simhan, Cheverud)
- Genetics and evolutionary biology (Ayala, Moyzis, Haig, Procaccio, Templeton)
- Considerations for design and analysis of genetic studies (Sing, Cox, Murray, Kramer, Wadhwa, Gillman, Lanphear)
- Genetics and infant and child development (Cooper, Lanphear, and Posner).

Dr. Swanson described several presentations in detail. For example, a visionary presentation by Lee Hood, M.D., Ph.D, on "Technology and Biology" illustrated Dr. Hood's systems biology approach, which involves identifying networks of genes and perturbed pathways in the networks that lead to disease. This approach generated excitement among meeting participants about its application in the Study to assess the onset and progression of many different disorders. Dr. Swanson described Dr. Hood's approach of using change over time to "reduce dimensionality" of data due to individual differences in genotype and phenotype.

Dr. Swanson discussed other presentations from the meeting related to epigenetics and mitochondrial DNA that addressed topics relevant to the Study. For example, the work of Michael Meaney and colleagues concerns the molecular effects of mother-child interactions, and the work of Randy Jirtle concerns epigenetic changes associated with maternal diet during pregnancy. A presentation by Andy Feinberg discussed mechanisms that may be affected by assisted reproduction techniques.

The meeting concluded with the questions that must be considered to advance science in the context of the Study:
- Which genetic factors should be evaluated?
- Which environments should be targeted?
- Which developmental processes are most critical?
  - At what periods of time?
  - In which tissues?

Comments

Jeffrey Long, Ph.D., NCSAC member; Professor of Human Genetics, University of Michigan School of Medicine

Dr. Long commended Dr. Swanson for an excellent and inspiring presentation and said that the Study does have great advantages for genetics. He noted that the complex relationships between genes and phenotypes can come about for reasons besides interactions, such as age and sex effects. Age effects and maturation will be something the Study is ideally situated to address, and the Study's large sample is important. Some complexity arises from uneven distribution of environmental risk, and that is something else the Study will contribute to.

There is also a need to look at the correlation of genes with environments—which is different from the interaction of genes and environments. Sometimes a particular genetic variant coexists with a particular environment, and presumably genotypes seek environments. Genotype-environment interaction implies something more: that the total phenotype is different from the sum of its parts. Dr. Long mentioned an article by Francis Collins and colleagues that provides

an example involving lipids and discusses the importance of large sample size. He said there was a "snake under the rock" when it comes to interactions. One thing the Study can do is to examine whether a change in environment has a more or less consistent effect on different genotypes and whether a change in genotype has a consistent effect on environments. Dr. Long is interested in whether theoretical or empirical rules can be developed to predict where interactions will be found and to help guide some hypotheses.

NCSAC Discussion and Recommendations/General Discussion

After Dr. Swanson's presentation and Dr. Long's comments, several issues were discussed:

- *Responsible use of Study data.* Dr. Schonfeld said that he was concerned about the possible iatrogenic cost to society that may arise from the enormous amount of data that the Study will produce and that will be part of the public use dataset. People will look for associations, and when associations are found, people will go to doctors wanting to be tested. Dr. Schonfeld noted that how the Study will help people use this information responsibly and how it will handle other information about environmental exposures are issues of concern. Dr. Swanson said that Dr. Schonfeld's concerns were insightful, and he has found through his own experience that people will want to use genetic information as a test and will try to commercialize such testing. Dr. Fleischman said that Dr. Schonfeld's question is a broad challenge for the NCSAC and for the Study—there is a responsibility to think about the impact of how the research is done and the use of data over time.

- *How to encourage interdisciplinary science.* Dr. Burton asked what mechanisms can be put into place to encourage interdisciplinary science among individuals who take a more genetic approach to outcomes and people in the social science domain. She commented about the high rates of multipartnered fertility and serial relationships, which are much higher in the United States than in other developed countries, and referred to the "social address model" as a method of linking biology with social analysis. Dr. Swanson noted that the issues she cited are addressed in a report about social environment from the National Academy of Sciences that will be released soon; he has a preprint of the paper. Also, the report of a conference convened by the National Institute on Drug Abuse on social environment is available.

- *Epigenetics.* James N. Jarvis, M.D., said that a seminal observation of epigenetics was that genetically identical twins may be discordant for phenotype. It is difficult now with existing methodologies to "shotgun approach" epigenetics. A study about a genome-wide scan of DNA methylation was recently published in *Cell*, and methylation will turn out to be very important because it will determine gene expression. Dr. Jarvis noted that epigenetic changes are heritable—one generation can change the methylation pattern, which can be inherited. This is reminiscent of what is said in Mohawk culture, that what a mother does reverberates to seven generations of her offspring.

- *Dealing with advancements over time.* Barbara Anne Nabrit-Stephens, M.D., M.B.A., asked how the Study will handle advancements over the course of the Study and about the process for making sure that the right people are aware of the Study and help keep the Study current and appropriate. Dr. Scheidt responded that the Study planners have tried hard to have an open, inclusive planning process that has involved about 3,000 scientists, and this process

will continue. The planners are aware of the evolving nature of the science and are giving thought to the design and process to accommodate changes including ongoing peer review of the protocol as it develops. The expectation of scientific change is why the planners are not seeking to lay out the details of later exams at this time. Dr. Scheidt said that the Study would appreciate hearing about ideas for improving this process.

- *Multidimensional task of understanding gene-environment interactions.* Bruce Levin, Ph.D., said that even with strategies for reducing dimensions, there are too many dimensions and that dealing with the multidimensional task of understanding gene-environment interactions in 100,000 participants is a daunting premise. Dr. Levin proposed using a subsample of 10,000 participants and then validating this data with the other 90,000 participants' data.

The Science of Representativeness: Successive Waves of Sampling

Dr. Scheidt

Prior to his presentation, Dr. Scheidt invited Elizabeth Osinski, Contracting Officer, to comment. Ms. Osinski cautioned that because of federal rules concerning contracting, the discussion should be limited to high-level aspects of sampling. Advice was needed from the NCSAC about successive waves of sampling, but specifics of sampling and the anticipated RFP for additional Study centers described in the special notice should not be discussed.

Dr. Scheidt reviewed the process of development of the national probability sample, which included pilot study reviews and analysis, Westat's analysis of sampling strategies, NCSAC recommendations, an expert panel meeting on sampling and study design, the preparation of several white papers by Battelle Memorial Institute, and input from the ICC and from the NICHD Director. The result was the decision to use a national probability sample for the Study.

A national probability sample was chosen because such a sample will:

- Ensure that exposure/outcome relationships are valid and apply to the children of the United States
- Avoid selection biases that could lead to invalid inferences
- Capture the diversity of the U.S. population
- Represent the range and diversity of exposures and outcomes and help ensure that key exposures are not missed, given uncertainty regarding their distribution.

Dr. Scheidt described the process of drawing the national probability sample. The National Center for Health Statistics led development of the multistage probability sample of primary sampling units. The sample includes 105 locations roughly corresponding to counties, or clusters of adjoining counties; 78 sites are metropolitan and 27 are rural. Seven Vanguard locations were chosen and seven Vanguard Centers were established in four geographic regions.

A center-based strategy for implementation was chosen because of centers' scientific expertise and facilities needed to carry out the Study's measures. The Study requires flexibility and adaptation of the centers to the scientific design and requires support and guidance by a coordinating center.

Dr. Scheidt explained the plans for adding locations to reach the full complement of 105 Study centers. The remaining locations will be added incrementally. This approach is logistically advantageous and will flatten the cost bubble from recruitment and pregnancy-infancy data collection. At least two and probably three waves of awarding contracts for additional locations are anticipated.

The questions for NCSAC consideration regarding this incremental process for adding Study locations were:

- What does this do to the national probability sample?
- Does expanding the recruitment window by several years reduce or eliminate the value of a probability sample?
- How important is it for the total locations at each wave to be as representative as possible?
- Given fewer locations, how pure does the probability sample need to be?

NCSAC Discussion and Recommendations/General Discussion

The NCSAC discussion included clarification of several points and discussion of the questions posed. The following issues were clarified:

- *The meaning of the wording of the fourth bullet regarding fewer locations.* Dr. Nabrit-Stephens asked for clarification, because she understood that eventually there would be 105 locations. Dr. Scheidt said that this reference was to the intervals before the full number of sites was reached. The question is how important it is to be as representative as possible with fewer locations.

- *Changes to the locations and population over time and how they will be documented.* Dr. Jarvis asked whether, given that locations can change, Census data would be able to help follow changes. Dr. Scheidt said that changes will be experienced in Study locations to the same degree that changes occur across the country. The sample will experience similar variation over time. Ms. Shepard asked how changes in areas over time will be documented. Dr. Scheidt said that the Study planners anticipate documenting changes both by the data collected and extensive use of the datasets outside the Study. One pilot study examined administrative datasets and found about 130 datasets without individual identifiers and 30 with identifiers that are available to use.

- *The sampling frame for the probability sample.* In response to a question from Dr. Currie, Dr. Scheidt clarified that the sampling frame was based on live births per sampling unit, and an analysis showed that such a sample would be similar to a population-based sample.

- *The recruitment window.* In response to a question from Dr. DuPlessis, Dr. Scheidt clarified that each center will have a 4-year recruitment period, and the startup of new centers will be staggered.

- *Identification and inclusion of pristine and degraded communities.* In response to a question from Ms. Shepard, Dr. Fleischman explained that the primary sampling units (105 locations) have been chosen, but adjunct studies could focus on issues of relevance to other communities of interest. Dr. Scheidt added that within any random sample, there are clusters

and voids. The Study could decide to "tinker" to get geographic distribution and representativeness of different attributes. That is one of a number of possible approaches.

Much of the discussion focused on maintaining the probability sample over time:

- Dr. Levin said that his answer to the questions would depend on plans for interim analysis of data and dissemination of those results. If the Study waited to analyze the data until all data were collected, the order that subjects were recruited in would not matter. But if, for example, the Study recruits about 20 sites a year over the next 5 years and would like to do interim analysis of data, if the data are released, the Study must respect and maintain the probability sample or face the risk of disseminating results that will change.

- Dr. Nabrit-Stephens expressed concern about the difficulty of maintaining representativeness with the approach of phasing in centers and wanted to know more about the consequences and scientific implications of this approach.

- Dr. Zaslavsky said that what concerns him most was that the Study in 8 years will be different from the Study today, so any relationship between the sequence in which areas are brought into the Study and the timing will be a potential source of confounding. This will be partly due to changes in sampling and testing methods. He said that the conclusion might not be that the sequence of sites must be chosen randomly, and he suggested stratifying the areas and ensuring the representativeness of those strata over time, but not necessarily in a purely random way. Dr. Zaslavsky noted that this was a tricky approach, however; and there are certainly risks in doing that. If the changes in Study are expected to be substantial but not excessive, it may be possible to adjust away some effects of the lack of pure randomization, but some degree of representativeness should be maintained. Dr. Scheidt asked how the stratification would be done, and Dr. Zaslavsky said that would be difficult because of the need to anticipate differences among the Study areas. The approach would involve revisiting the same issues that were considered when the sampling strategy was chosen.

- John Butenhoff, Ph.D., said that if a goal is to look at the influence of the environment on children's health, keeping the representative nature of the locations as intact as possible would be important.

- Dr. Currie noted that significant demographic changes can occur within a single ZIP code in 10 years and that the Study should not rule out such changes but try to keep the Study as representative as possible at any given point in time.

- Dr. Genel said that an essential factor will be the capability of applicants to do the work that they are expected to do. Scientific and technical capabilities of the applicants must be a major consideration—that is, quality counts. Dr. Zaslavsky commented that if the Study has difficulty achieving representativeness in the first wave due to the lack of qualified applicants, the study design will be in trouble.

- Dr. Schonfeld said that the Study should be visualized as a national study with sampling from communities, and everything will change—environments will change, families will change, people will move, and so on. The Study needs expertise in following populations over time.

Dr. Schonfeld thought that skill sets other than those being asked for in the RFP will be more important for meeting the long-term challenges over the course of the Study, such as the ability to collect data in schools or to network with other centers across the country.

NCSAC Recommendations

The NCSAC recommendations were summarized as follows:
- Representativeness makes sense but cannot be accomplished completely given the incremental process for establishing Study locations.
- Various ways of stratification should be considered.
- The Study will need to address the varying challenges that will surface over time, and there may be changes in what becomes critical down the road.
- The Study Centers will need to be of high quality and have the requisite scientific and technical capabilities to handle the critical tasks of the Study.

The E-Consent Tool

Dr. Fleischman

Dr. Fleischman presented the Study's strategy for institutional review board (IRB) review:
- The Study will not create a central IRB.
- To facilitate uniform review of protocol and acceptance of informed consent process, the Study has convened IRB "thought leaders" from Vanguard Centers prior to IRB submission.
- The Study will provide a comprehensive memo to IRBs explaining Study policies and approaches.
- The Study will obtain IRB approval from NICHD, Coordinating Center, and Vanguard Center IRBs.
- The Study will encourage use of "Cooperative Agreements" (§46.114) among regional IRBs.

Dr. Fleischman said that the E-Consent tool is in the process of development and that the version being presented is intended for pregnant women. Two others will be developed, one for women prior to conception and one for fathers/partners. Both Spanish and English versions have been developed.

Dr. Fleischman reviewed the following issues related to the human subjects aspects of the Study:
- No "prospect of direct benefit" claimed
- Collateral benefits of participation exist
- Participant burden "moderate"
- Level of risk "minimal."

Other human subjects issues include genetic sampling and biobanking, observing children in imminent harm, revealing findings, confidentiality, and informed consent/assent.

Essentials of informed consent, from federal regulations (§45CFR46.116) include the following:
- Study involves research
- Purpose of the study
- Number of participants

- Duration of participation
- Description of procedures
- Risks and discomforts
- Alternatives
- Voluntary nature of participation
- Confidentiality of records and data
- Revealing individual findings to participants
- Compensation and incentives
- Reporting of suspicion of child abuse or neglect
- Revealing aggregate new findings of importance
- Sample storage and future testing.

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

The intent is that a recruiter will be with the participant as she reviews the E-Consent video. He added that the Ethics Subcommittee had already seen the video, and the video will be evaluated by 18 women chosen for cultural, ethnic, and geographic diversity; their responses will be used to modify this version of the consent. All input will be used in preparing the next version of the video by January 2007.

The 38-minute video was screened for meeting participants and its interactive aspects were demonstrated. The video can be paused at any time, and specific interactive questions are embedded in the video to ascertain the level of understanding of critical elements of the informed consent from the participants. After 35 minutes, there is a formal pause during which potential participants are asked if they have any questions.

At the conclusion of the E-Consent video, Dr. Fleischman noted that Mildred Solomon, Ed.D, who was involved in conceptualizing the video, was on the telephone to listen to comments.

Report from the NCSAC Ethics Subcommittee

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

Dr. Genel said that the Ethics Subcommittee of the NCSAC reviewed the video, and Dr. Schonfeld gave him extensive and helpful comments about his reactions. The subcommittee's overall impression was that the video was very well done and adequately covers the relevant issues for informed consent. The expectation is that the tool will be field tested. One concern was the length of the video. He thought the opening segment with the "talking heads" could be shortened, but that would not save much time. He was interested in others' comments about that.

One possibility raised was to split the video into two parts, but that would likely add to the total length rather than shorten it. Dr. Genel made the following comments:

- Providing participants with a stamped, addressed envelope to mail if they want to withdraw from the Study might be a better approach than just giving them the address of the Study coordinator.
- The statement about storage of samples for possible future medical interventions seems somewhat far-fetched. Dr. Genel suggested the statement could be removed.
- There was laughter about the statement in one of the distracter responses to a question about tax records, but government intrusion into people's business is a serious issue.
- The statement that the Study will help determine why some children do well in school may not be valid.

Other comments from Dr. Schonfeld were:

- People may not know what the reference in the risk section to "imminent harm" means. The risk section is rather vague, and Dr. Schonfeld suggested saying that if a child is being abused or seriously neglected, the Study team would have to report it to the authorities to protect the child.
- The information about the Certificate of Confidentiality is vague and giving concrete examples would be helpful.
- The statement that a person "might decide to undergo additional tests, or additional expense," should be changed to say that "You might decide to undergo additional tests that may result in additional expense."

NCSAC Discussion and Recommendations/General Discussion

NCSAC members discussed the following topics with regard to the E-Consent tool:

- *Overall positive impression of the E-Consent tool.* Many NCSAC members commented favorably about the tool and were impressed with its approach. Dr. Chervenak said that the tool elevated informed consent to a new level and did what it is intended to do. Dr. Pescosolido said that the tool surpasses previous methods for obtaining informed consent. Dr. Dearry described the tool as comprehensive and commendable.

- *Length of the E-Consent video.* Many members expressed concerns about the length of the video and thought that it was too long. Several members suggested that the introductory portion of the video could be shortened or omitted entirely. Dr. Dearry noted that holding people's attention for 7 to 12 minutes—the average time between television commercials—is a challenge.

- *Whether to break up the consent process into shorter segments.* Views on whether to split the video into two parts or break up the process in some other way were divided. Dr. Chervenak said that he thought the tool should be used at one sitting, and Dr. DuPlessis said she did not think it should be split into two parts. Dr. Ryan noted that the pause built into the video occurs late in the process and suggested that the recruiter could pause after each question and answer. Dr. Zaslavsky suggested that the recruiter could break up the process with social interaction to establish a relationship and noted that there were some natural break points to

pause, such as after the introductory video and after the discussion of risks and benefits. The total time is likely not as much of an issue as the sense of time. An interactive video may better retain the attention of the viewer and could improve acceptability.

- *Allowing the opportunity to talk with family or friends about consenting for the Study.* Ms. Jones suggested offering women the option of taking some time to talk to family or friends about the Study before signing the consent. The person could be told: "You have the opportunity to sign now, or if you want to talk with your family, we will come back later."

- *Literacy concerns.* Dr. DuPlessis expressed concerns about terminology used in the introductory video not being understood. Dr. Jarvis commented that the introduction's language would be incomprehensible to many people in Oklahoma and that the introduction was directed to the wrong audience. The tool should be field tested at a lower literacy level. Dr. Chervenak suggested referring to "diabetes" and not "type 2" because the types of diabetes are not general knowledge.

- *Discussing risks and benefits earlier in the video.* Dr. Pescosolido said that the discussion of costs, benefits, and risks and issues of confidentiality should follow the introductory information to address people's concerns up front. Dr. DuPlessis agreed that the discussion of risks occurred too late in the video.

- *Spanish language version of the tool.* Dr. Guerra said that the Spanish language version would be even longer than the English version because explanations of complex issues take more words in Spanish than in English.

- *Description of incentives.* It was suggested that a word such as incentive, reward, or gift card be used instead of "payment." A member commented that the reference to a music CD as an incentive was already dated.

- *Ways to improve the tool.* A number of suggestions were made for changes or improvements to the tool, including making the tool more interactive; adding more diversity to the images of communities in the video and including an image of a city; including a better description of the certificate of confidentiality; and adding local, site-specific information and pictures to the tool. Dr. Levin suggested having the buttons with possible answers to questions light up as the voice reads what is written on the button.

- *Opting out of portions of the Study.* Dr. Long commented about the reference that a person need not consent to the genetics portion of the Study to participate in the Study and suggested that this might apply to other aspects of the Study.

- *Whether relatives of a person could be recruited.* In response to a question about whether it would be appropriate to recruit relatives, Dr. Long strongly recommended against doing this because of the effect on the genetics components of the Study.

- *What was missing from the tool.* It was noted that the tool did not inform people that they may have to give consent more than once and that the term "research" was not used. Dr.

DuPlessis commented that disease was mentioned in the introduction but not in the part of the tool relating to the purpose of the Study. Kevin Teichman, Ph.D., noted that not many older children were included in the images of children.

- *Other suggestions for the tool.* Other suggestions included saying that the Study will not report undocumented individuals and making it clear that the Study will not be giving participant any drugs or medications, not only experimental ones. Dr. Chervenak liked the tool's vagueness in some areas because it allows for covering some issues without turning people off and suggested leaving in the statement about possible future discoveries from Study samples. Dr. Nabrit-Stephens suggested replacing the "talking heads" in the introductory video with children talking about what they want to do.

Additional comments included the following:

- Drs. Butenhoff and Eaton addressed the statement about participants' health insurance not being affected and questioned whether coverage might be refused in the event that a disease was discovered.
- Dr. Eaton said that mothers of young children might find it difficult to not be distracted by the child when trying to focus on the E-Consent tool.
- Dr. Burton suggested that the introductory video would benefit from having a woman and/or Asian physician represented.
- Drs. Currie and Eaton commented about the video seeming somewhat negative at times, such as references to things that could go wrong and people being on their own to follow up on findings.
- Drs. Eaton and Chervenak expressed differing views about the depiction of a child smiling during a blood draw; Dr. Eaton was pleased to see the positive image, but Dr. Chervenak thought the depiction could be modified somewhat. Dr. Jarvis noted that blood draws need not be painful with the use of topical anesthetic.
- Dr. Ryan noted that there will be some concerns about drug testing of the samples.

Dr. Genel said that the comments reinforced his impression of the wisdom of the NCSAC. He noted that some of the portions of the informed consent are required and must be included to obtain IRB approval.

Comments during the general discussion addressed the following points:

- Large portions of the primary sampling units (counties) will not be included in the Study; therefore, referring to neighborhoods might be more accurate.
- Nothing was mentioned about the child's assent. The child must be a willing participant.
- Mentioning nongovernmental organization endorsements might be helpful.
- For the woman who asks what is in it for her, make it clear that the Study is meant to help people in the future.
- The images of women and families suggest that participants have to be part of a nuclear family. More diversity in the depiction of environments would be good.
- A sophisticated mother might ask about confidentiality of genetic information and whether her and her child's data will be part of a public use dataset.

Dr. Fleischman said that this was an extremely helpful discussion. Regarding the length of the E-Consent tool, it is a challenge to be responsive to the federal requirements and achieve a high standard of quality without overdoing it. The tool is now being field tested by women with diverse demographic characteristics.

Peer Review of the Protocol

Dr. Scheidt

Dr. Scheidt reviewed the rationale for scientific peer review, which was first called for by Donna Shalala, former Secretary of DHHS, and the 2000 President's Task Force on Environmental Health and Safety Risks to Children. The ICC and the Study Program Office have consistently said that there would be peer review, and peer review is expected by the scientific community. Peer review is needed to address congressional concerns and to "assure the Study is scientifically rigorous and being carried out with the best available methods." Peer review is also required by the NICHD IRB.

Challenges for peer review of the protocol include:

- Not typically done as with individual grants
- Extraordinary breadth of study
- Appropriateness for this type of study
- Independence and credibility of review
- Absence of bias for or against the Study
- Time and expense of the peer review.

Given the Task Force recommendation, the Congressional Directive, the underlying concerns regarding the possible effects of environmental exposures, and the concerns about diseases and conditions with possible environmental causes, Dr. Scheidt presented a summary of what will be the charge to the peer review group as follows:

- Responds to the Children's Health Act, 2000?
- Addresses necessary exposures and outcomes?
- Identifies hypotheses to frame and guide the Study?
- Employs appropriate measures?
- Addresses gene-environment interaction as state-of-science?
- Capitalizes on the Study to efficiently and economically address the multiple separate concerns?
- Provides an effective platform for future study?

The Program Office is working to complete the protocol and determine the process for scientific review.

NCSAC Discussion and Recommendations/General Discussion

The discussion addressed the following topics:

- *The nature of the peer review group.* Dr. Genel asked whether the peer review group would be a free-standing group or an existing group. Scheidt said the group will not necessarily be a free-standing group. He anticipates that an *ad hoc* review group will be convened specifically

to review the Study, but the group must be convened by some entity. A number of options have been discussed, including convening the group through the scientific review branch of NICHD. Credibility would be an issue if the group were convened through the Program Office or the NCSAC. Dr. Fleischman noted that Drs. Scheidt and Alexander will determine under whose auspices the review should be done.

- *Utility of the charge.* Dr. Jarvis commended Dr. Scheidt for the charge and the bullets with concrete questions that could be addressed by the reviewers. He thought the charge would work well to focus the review and help to keep the reviewers on task. He recently participated in a review in which the reviewers were helped by having a charge similar to this one. Dr. Scheidt noted that thanks were due to the Steering Committee for asking that a clear charge be developed and to the ICC for its input into the charge.

- *Whether to ask about efficiency of the Study in addressing multiple concerns.* Dr. Dearry said that the list of criteria was excellent, but he would not ask a review group about efficiency. He thought that the plan to review the overall program and not the individual contracts was a good approach.

- *Adding a question about the use of results.* Dr. Teichman agreed that the set of questions was very good and suggested adding a question about the plan for the use of Study results.

- *Keeping the questions as concise and well-formed as possible.* Dr. Butenhoff agreed that the charge was a good approach and would work. He suggested keeping the questions as concise and well-formed as possible to ultimately get yes/no answers. He noted that such reviews can be a difficult process when a group of people with diverse backgrounds is convened.

- *What is missing and what the group is charged not to do.* Dr. Levin raised this question and noted that in some reviews, budget issues are not supposed to be addressed. He wondered whether the review group would be told what it is not supposed to do. Dr. Scheidt said that this was an interesting comment. A major concern is that some awareness of budget factors and limitations is critical for the review. Dr. Zaslavsky commented that the review group will need to know what the assumptions are and that the group is not being asked to answer the bigger questions, such as whether enrolling 100,000 children is the right thing to do. He noted that gene-environment interactions are mentioned in the charge, but other areas, such as social exposures, are not specifically mentioned. Care should be taken to avoid language that would bias reviewers to focus on certain objectives and not others.

- *Suggested rewording of "gene-environment interaction."* Dr. Long suggested changing the wording to: "roles of genes and environments in development" (or in maturation).

Dr. Fleischman thanked NCSAC members for their deliberations and advice. He thanked Dr. Balsam and Ms. Sapienza for their work, Circle Solutions for managing meeting logistics, and other meeting participants.

NCSAC Members and Ex Officio Members

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**Did not attend.*

ICC Members in Attendance

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

02/06/07

Date

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