

**National Children's Study
Federal Advisory Committee 33rd Meeting
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Bethesda, MD**

The National Children's Study (the Study) is led by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) of the National Institutes of Health (NIH) in collaboration with a consortium of federal government partners. Study partners include the National Institute of Environmental Health Sciences (NIEHS) of the NIH, the Centers for Disease Control and Prevention (CDC), and the Environmental Protection Agency (EPA).

Welcome and Introductions

Patricia O'Campo, Ph.D., Chair, National Children's Study Federal Advisory Committee (NCSAC), Centre for Research on Inner City Health, St. Michael's Hospital, University of Toronto

Dr. O'Campo welcomed the meeting participants, who introduced themselves.

Welcome from the Director of NICHD

Alan E. Guttmacher, M.D., Director, NICHD, NIH, Department of Health and Human Services (HHS)

Dr. Guttmacher expressed his regret that he could not attend in person because he was keynote speaker at another meeting in Colorado. He noted that this meeting of the NCSAC is clearly an important meeting for the Study in getting the committee's input on the design of the Main Study. Past input from the NCSAC has been valuable, and the topics of discussion for this meeting reflect input from prior meetings. He thanked the NCSAC members for their time and efforts on behalf of the Study.

National Children's Study Update

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

Dr. Hirschfeld welcomed the committee and expressed his appreciation for the valuable input the committee has provided over the years and continues to provide. He briefly reviewed the historical arc of these discussions to place them in a larger context. In 2009, the Study went into the field based on a design that used door-to-door personnel from the Study to recruit women. This enrollment approach was restricted to particular secondary sampling units (SSUs), which were small geographic segments within larger primary sampling units (PSUs); PSUs were generally at the level of a county. It was found that with this approach, the resources required, including time involved to recruit women, did not match the assumptions and expectations—there was a disconnect between what was observed and what was expected. In addition to being resource-intensive, the door-to-door approach involved strangers approaching families. Therefore, two additional recruitment approaches were designed: a direct outreach campaign and a provider-based approach. The three approaches were then tested at 10 locations each. Observations about the health care provider approach supported its use as an efficient

mechanism to recruit women into the Study. This approach gained certain efficiencies and resulted in a demographic profile of enrolled individuals that was consistent with American community survey data and natality data in areas where the Study was recruiting.

In April 2011, the NCSAC was asked to consider the concept of using health care providers as a primary mechanism to enroll women into the Study, and this topic was discussed during the July 2011 meeting. Subsequently, this question was revisited in many meetings with a variety of stakeholders, in workshops, and in consultations. The Program Office received two thematically general responses over the course of the past months: (1) the Study should use strategies that allow a sample design based on a national probability sample, and (2) enrolling multiple populations—women in the preconception period, pregnant women, and children just born—poses a difficult problem. The approach the Program Office has used to solve this problem involves splitting the larger problem into smaller problems to address the recruitment challenges for the Study. The Program Office has filtered and integrated the input received in the past from this committee and others in preparing the current proposal, and is looking for further input and guidance from the NCSAC.

The current proposal is based on use of a national probability sample for the majority of the sample. This national probability sample would recruit some women perinatally and some women during pregnancy; the sum of these two groups would equal about 90 percent of the cohort that would be enrolled into the Study. No decisions have been made yet about relative proportions of those two groups. About 10 percent of the cohort would be women recruited before conception, as well as any subpopulations that might be underrepresented for any legitimate scientific reasons, such as demographic underrepresentation or particular characteristics or exposures. These set-asides to target preconception women and underrepresented populations would not be a national probability sample. There would be multiple waves of recruitment for the Main Study. Once a Study location begins active recruitment, the recruitment window is expected to be approximately 2 years.

The broad scientific goals of the Study have been and remain the effect of environmental exposures, including an examination of genetic contributions, on health outcomes. To ascertain environmental exposures and the feasibility of this entire approach, a pilot study will soon be launched. This pilot will examine at least two components of the proposal—recruitment at hospitals and birthing centers, and recruitment through clinics and office-based practices. Several questions will be posed, many of which are outlined in the briefing document. Prior public documents contain some examples of scientific questions the Main Study should address; these questions serve as placeholders for similar questions that might arise.

Questions for the NCSAC to discuss include whether there are aspects of the proposed design that will not allow certain types of questions to be posed, whether this design has sufficient flexibility to allow the Study to address the types of questions being proposed, and whether the compromises in the design are scientifically acceptable. If the design is appropriate for further development, the next step will be preparation of a more detailed proposal for review by this committee and all the Study's stakeholders.

Discussion of National Children's Study Main Study Design

Discussion Championed by NCSAC Member

*Randall J. Olsen, Ph.D., Professor and Director, Center for Human Resource Research,
Department of Economics, Ohio State University*

Dr. Olsen said he developed several questions to help start the discussion. The starting point in this discussion should not be solely in terms of sampling. Sampling is done because there is a scientific agenda and a purpose for the data collection. Therefore, the merits of the sampling plan must rest not only on the statistical properties of the sample and its ability to support sound analytic work, but also on its ability to deal with the range of research topics the Study is meant to support. Dr. Olsen suggested focusing the discussion on what the Study can possibly provide, whether the sampling plan is consistent with the goals, and what will have to be given up with the proposed design. Something has to give, so much of the discussion should center on exactly what that will have to be.

Dr. Olsen raised the following question for discussion: *Assuming the probability sample is drawn using a birth-center list from sampled PSUs, is there any reason to mount a door-to-door respondent recruitment effort?* He noted that that door-to-door recruitment was the original plan and the assumption was that the sample would be a valid probability sample.

- Jennifer Madans, Ph.D., said that she thought shifting to this approach would cause the Study to lose a lot. The best thing the design provides is a birth cohort. Her preference would be to go back to the original design if there were unlimited time and money, but that is not the case. A provider-based design is reasonable but would miss a lot. Getting prenatal information on a nonrandom subset of people who happen to be at birthing centers should be discussed because that approach costs money and may not provide what is really needed. Issues include the generalizability of the data to another population. Without the assurance that the Study can do something with the prenatal information obtained and generalize it, she is skeptical about this approach.
- Joseph Andrew Kostan, Ph.D., commented about the relative proportions of women being enrolled at delivery versus those enrolled in the prenatal period. The thrust of the proposal document suggests that recruitment at delivery would be the primary way to recruit and no longer the 5 percent of women the Study could not pick up before delivery—a massive change in the emphasis of the Study. This would change the information the Study can get about prenatal exposures in many ways. He was interested in the guidance that prompted the proposal to recruit a substantial number of women who theoretically could have been recruited well before then. Perhaps the rationale was cost.
- Dr. Hirschfeld responded that the Study was challenged by trying to recruit a continuum from preconception to pregnancy to birth. A tactical decision was made to separate those populations because each would require somewhat different logistics. With recruitment at birth, the first encounter would occur during the perinatal period and would focus on collecting birth specimens. Any information about prenatal exposures would be retrospective, but the Study would not have to invest in the resources for those prenatal visits and follow-

ups. It was decided to try to project a model by asking how many women would be needed with as complete a prenatal history as possible to answer questions of scientific interest. The thinking was that having tens of thousands would generate sufficient information for the resources involved, particularly if the thousands were selected using the national probability sampling approach. This would allow the Study to make inferences and analyze relationships in ways that would justify answering those questions related to prenatal exposures.

Compared with how national cohorts in other countries were approaching questions of prenatal exposures, the Study seemed to be the only one with a strong bias for getting prospective data. Thus the idea was to get some balance by having some, but not all women have prospective prenatal data collection, and then recruiting other women at the birth visit. There would be some internal controls and adjustments as needed. The Study is going into the field to learn whether recruiting some women in the perinatal period and other women in various stages of pregnancy results in differences in the profiles of those recruited and differences in the quantity and quality of information. The splitting of the perinatal and prenatal recruitment was viewed as a mechanism to conserve resources, save costs, and address some important questions about the quantity and quality of data. Whatever the n is for the prenatal cohort, the Study would want to be assured that it is a sufficient number of women to address key questions.

- Dr. Konstan said this change could cause some significant statistical power issues because of effectively halving the number of women for whom the Study would have prospective prenatal information. For many potential health outcomes, this would be problematic.
- Dr. Madans noted that the earlier in pregnancy women are recruited, the smaller the percentage of pregnant women on whom data can be obtained. She described a compromise in which the Study would not focus on the early part of pregnancy, because it would be a biased sample and the numbers small, and instead focus on getting information closer to birth. It is not possible to generalize to women at 8 weeks of pregnancy, but as one gets closer to birth, one can do a better job. If the Study wants to say something about preconception and early exposures but cannot do that, considerations include where the critical line is and whether the design can be modified to get at least that information. If the Study really wants to do prospective data collection, given how women receive prenatal care, the issue is how to get a generalizable sample without doing questionable modeling and losing a lot of power.
- Dr. Konstan said that even if the Study were to go back to household sampling, data from the use of that approach show that of the pregnant women reached, only 62 percent enrolled. That seems to be a threat to generalizability by itself. He asked whether there are some standard percentages needed to ensure a representative sample and whether certain percentages indicate that a particular approach will not produce a sample representative enough to be a viable option, thus requiring consideration of alternatives.
- Dr. Olsen noted that political polling actually deals with completion rates in single digits and can be predictive; however, for a scientific study the criteria are more stringent. The question Dr. Konstan posed focused on the immediate—the ability to get women to enroll at birthing

centers or through perinatal providers, versus the household approach. However, this is a study that's 2 decades in length, and what is important is what can be obtained over the 20-year period. One of the things learned from long-running panel studies is that attrition due to recalcitrant respondents is heavily front-loaded. Some will do a survey no matter what, some will not participate no matter what, and the middle group might or might not participate. When sampling at the household level, those who will not remain in the Study for 20 years will label themselves early on in this way. Higher enrollments can be obtained in birthing centers. Dr. Olsen asked what the sampling size was that the Study could afford with that original model and how much the Study would have to give up in terms of sample size to stay with that approach.

- Dr. Hirschfeld said there are some other factors that go into estimating what that sample size might be, including overall resources and the time it would take to recruit. Initial recruitment was expected to be a 4-year window, but the projections indicated it would take twice that long. That would result in quite a spread in the cohort, and a tighter cohort was desired. The proposed current design would involve roughly a 2-year recruitment window, resulting in a fairly tight cohort. Further testing would be needed, but the size of the cohort would probably be on the order of 30,000—that is, half a log lower than the original 100,000—based on a 4-year enrollment period. After the data from the original approach were available, broad public discussion was used to answer critical questions about environmental exposures and outcomes using provider-based sampling.

In other locations around the globe, recruitment is usually done through a directive to the national health care system, but the United States does not have that option. Using health care providers is a mechanism with much precedent and experience that would be consistent with other large national cohorts. The question is what precisely the Study would sacrifice and what questions the Study would not be able to answer with this approach. It may be possible to obtain some prenatal exposure data on people enrolled at birth by looking at medical records, history, and exposures that accumulate, but it is not clear what would be compromised going forward. The current proposal would have an internal control because there would be some women with prenatal data collection and others with none, and this will be piloted to determine what can be obtained. What will not be obtained includes biospecimens and near-time evidence of very short-term exposures. The Program Office is looking for input about important questions that cannot be answered with a smaller number.

- Peter Grevatt, Ph.D., asked whether these approaches have been tested in the Vanguard Study.
- Dr. Hirschfeld replied that they were tested indirectly, not systematically. The proportion of women enrolled in the Vanguard Study who were captured at birth is less than 5 percent. More than 1,000 women were recruited using health care providers. Because no field test has been done that provided sufficient information on a provider-based sampling method, the Study is going into the field now to test this approach in three locations: Harris County, TX; Jefferson County, KY; and Worcester County, MA. There are a few differences, because in the earlier design, a woman had to live in the PSU and a selected SSU; and in the design to be tested, the health care provider will provide service to women residing in the PSU. This is

a technical issue. The hope is to have robust data from this pilot when this committee meets again.

- Dr. Grevatt commented that it is a little difficult to say what the Study will lose. Things that happened in the Vanguard Study are being compared with things not yet tested. The prenatal component of the Study is tremendously important to understanding the relative contribution of factors that play out prenatally versus perinatally in some of the disease outcomes, and some of those play out very early in life. Not being able to understand as much as possible about the prenatal component will make it difficult to answer some of the key questions.
- Dr. Hirschfeld responded by asking how many women would need to be in that cohort and where the resources should go.
- Joan Y. Reede, M.D., M.P.H., M.B.A., asked how changing the sampling frame from women living in the sampling areas to providers in the sampling areas would affect prenatal versus perinatal recruitment in terms of who gets recruited and how. Concerns are the effects of health manpower shortages, differences in women's access to health care providers, and what information would be lost from women who do not go to these providers. The women who go to these providers may be quite different from those who do not.
- Dr. Hirschfeld replied that these questions are part of what will be tested. The data from a few sources show that a high percentage of women deliver in hospitals—97 percent or higher. A supplemental approach would target populations that are missing or underrepresented. The proportion of pregnant women who get prenatal care varies but is always a majority. The logistics of targeting missing or underrepresented groups will be a local function of the Study locations, which have not yet been selected.
- Dr. Madans said a key issue is what prenatal information can be gotten from this design. Assuming a worst-case scenario, the Study will miss exposures to a certain point for a significant number of women, who would be inherently different from those on whom data are collected. How to deal with that problem is still open. It may be possible to adjust statistically or through modeling, or so much may be missed that the ability to draw conclusions is inhibited. There will certainly be attrition in the sample. The Study will do better getting women to sign on using health care providers, but there is a question about who is going to the providers and whether they are different from other women. She is concerned about where and when the contact will occur.
- Adda Grimberg, M.D., said she appreciated the logistical appeal of going to a provider-based model and agreed with what had been said so far related to generalizability of data. Another matter is looking at data for the birth cohort retrospectively and the quality of the retrospective data. If the data are not useful, the Study might have essentially foregone that population of women in terms of prenatal exposures. She noted that relying on recall is problematic for several reasons and wondered about the use of electronic health records, which might bias the providers being used. Unless certain questions are fields that the health care provider fills in, it may not be possible to get the answers retrospectively. Even training providers to get the data into the record can be problematic. In her experience working with

providers to use electronic health records, even though providers volunteer and buy in, certain practices are more overwhelmed than others and cannot absorb more work. This can introduce bias because data are not captured for women in those practices.

- Bruce Gelb, M.D., commented about the potential loss of data on the chemicals to which people are exposed. Part of this study is to determine which chemicals have an impact on children's health. It may be possible to go back and collect dust in a house after the fact, for example, but a pregnant woman will mostly be exposed at home or at work, and both are liable to change over time. The farther from the time of exposure, the more things change in the home and workplace. Getting early exposure information would be great, but even the second trimester can give information that delivery will not give. Another point is that some compounds are volatile, and there is no way to get that information retrospectively—the biological samples are needed. Dr. Gelb gave examples of data collected at birth that would not be helpful, such as determining blood glucose levels at the time of birth. The Study would be giving up what could be learned about exposures before birth. He would prefer to get data about exposures early in the second trimester.
- Dr. Grevatt said that the proposal document discusses the birth cohort first and acknowledges that it is the simplest and lowest cost strategy compared to others. This gives the impression that as many women as possible would be recruited that way. He suggested that the Study should place emphasis on getting as many as possible early in pregnancy, and then the birth cohort could fill in some numbers, as opposed to the opposite approach.
- Dr. Hirschfeld responded to Dr. Grimberg's technical comment by saying that the Study would hire a contractor who is competent to do the data collection, which would be separate from the information that health care providers collect routinely. Regarding Dr. Grevatt's comment, the numbers can be dialed up or down depending on what will be gained or lost. Currently the birth cohort is about 5 percent, so dialing up or down has different resource implications. Everyone would say that the best study would identify women before pregnancy and enroll and follow them, but this is not an option. He described the process as "trying to thread a needle" by proposing several specifications—one using health care providers as the default mechanism to bring women into the Study. The goal also is to generate a national probability sample. Focusing on each of the populations and being as efficient as possible for each population is the framework being proposed. One of the open questions the Program Office would like to test is the quality and nature of what can be learned retrospectively versus prospectively. The intent is to have tens of thousands of women followed prenatally.
- Dr. Madans said that investigators have no control over when women show up at providers' offices. If the birth cohort is small, there will be more nonrepresentative data on the prenatal cohort. Assuming that all members of the prenatal cohort become a birth, and the two cohorts can be put together, the Study will have a larger birth cohort. Enrolling women late in the second trimester would get a much higher proportion based on the percentage of women getting prenatal care at that time.

- Dr. Gelb asked a logistical question about how consent would be obtained from women giving birth and how biologic specimens would be obtained around the time of delivery. Would hospitals and birthing centers be asked to save desired samples on all women that deliver?
- Dr. Hirschfeld responded by describing a hypothetical situation in which women would be recruited at birth in some systematic fashion, such as using certain days of the week or selecting one out of some number of women, or another system. Some places routinely take blood on the mother, so in that setting there would be blood samples, and most likely there would be some urine samples. Some locations routinely collect and keep the placenta for a while. The Study would ascertain the local practice and request the collection of specific specimens, and if the woman consents for the Study, there would be access to those specimens. There would need to be a logistical arrangement so the Study could collect what is important. Currently, cord blood, placenta, blood, and urine are collected. The woman would be asked whether she would agree to let field staff come to her home, collect dust samples, take pictures, and so on.
- Dr. Konstan commented that with regard to scheduling of cesarean sections, his experience is that the day of the week scheduled is not a random distribution. People do not want to schedule the surgery on a Friday and be cared for by weekend hospital staff. Also, women who schedule cesarean sections are not representative of the population generally, and those who are aware of the scheduling issues have a different socioeconomic and educational status. Taking every *n*th delivery does not have that problem.
- Jeffrey Krischer, Ph.D., commented about the fundamental issues of representativeness and generalizability. He would be more comfortable that bias would not be introduced with a prospective cohort from birth centers and hospitals, because the intersection of those places and the population is high (more than 90 percent). The point has been made that the intersection between a cohort of pre-pregnant women and health care providers has the possibility of introducing bias, but one cannot really test for bias. It is hard to back away from bias. Numbers are a secondary concern. Dr. Krischer asked whether the design that involves identifying a prospective cohort of women in their child-bearing years and following them is off the table.
- Dr. Hirschfeld replied that the challenge with such a design is efficiency and resources, and it would be a very different kind of study. A spectrum of proposals was discussed in April, and other discussions have addressed the numbers. It was concluded about a year ago that aiming for 100,000 participants at the end of the Study would be beyond available resources. The Study was interested in conditions that would have a prevalence of between about one-half percent up to 5 percent, which includes many conditions that would have the attention of public health, insurance companies, and researchers. With a number much below 100,000 and with attrition, the number of individuals overall with those conditions would be small at the end of the Study. The Study would need to start with at least 100,000 to have enough people with a variety of conditions of interest within the cohort to provide information on those conditions.

- Dr. Krischer said that the tradeoff was efficiency relative to the targets and the questions. To maintain representativeness, it may be necessary to limit the lower limit of prevalence of conditions that can be studied adequately for the dollars available. It may not be practical to go down to .5 percent incidence, for example, with a sample size of 100,000. A prospective cohort study like this is not the design to use if studying rare diseases.
- Dr. Olsen suggested focusing the discussion on the major issue—the question of the birth cohort versus prospective enrollment and the implications for collection of data early in pregnancy, and whether a substantial amount of effort should be focused on that part of the Study. A birth cohort primarily pivoting around the delivery providers is a sampling scheme that can be executed most feasibly and rigorously because births get channeled mostly through hospitals. Rolling back to less-central providers who provide prenatal care is a different matter. Another issue is what is gained and lost between the two primary competing sampling designs—the hospital/birthing center approach versus the household approach. The household approach would definitely be more costly and the sample size smaller. In terms of getting prospective data other ways, the sample would be smaller and the sampling process would have unrecognized properties, and there is no guarantee of getting all the covariances right. He asked whether the Study will be able to validate its data when it ultimately has a data set with hundreds of thousands of variables.
- Yolanda Padilla, Ph.D., M.S.S.W., suggested going back to the theory and hypotheses behind the Study in order to determine what would be gained or lost. She asked what past studies have provided the hypotheses on prenatal environmental exposures that the Study will test and when more focused studies can be carried out. She discussed immigrant mothers; about 30 percent of Mexicans Americans and Latinos are immigrants. The issue of prenatal exposure in this group is confusing because the children seem to do well.
- Dr. Konstan said that the discussion was really about tradeoffs among certain inflection points. So far, everyone has accepted that environmental assessment at the time of identification of pregnancy would be a good thing. The other point being discussed is an environmental assessment presumably within weeks after delivery. The question is whether there are systematic deviations that might correlate with things that would affect any of the hypotheses that will be studied. For example, it was pointed out that women may leave work, which may correlate to socioeconomic status or health issues, and a suggestion was made to look at the end of the second trimester. There was some discussion that overall environmental factors change little, but when they change, they can change dramatically. There may be information available about when people move prior to childbirth or leave jobs and so on.
- Dr. Hirschfeld responded to Dr. Padilla’s request by summarizing information about exposures and outcomes that were included in the briefing document. Exposures of interest listed included industrial chemicals and byproducts of industrial chemicals in air, water, and soil; commercial products and natural products in air, water, and soil; pharmaceuticals; radiation; effects of proximity to manufacturing, transportation, and processing facilities; living with animals, insects, and plants; media and electronic devices; noise; access to health care; learning opportunities; diet and exercise; family and social network dynamics; and

cultural and geographical context. Outcomes of interest include premature birth, birth defects, growth and development, interpersonal relationships and bonding, inflammatory processes, allergies, asthma, infections, genetic and epigenetic status, epilepsy and other neurological disorders, cardiovascular screening and function, childhood cancer, multidimensional aspects of sensory input, autism and other neurodevelopmental disorders, learning and behavior, and precursors to chronic diseases such as obesity, asthma, hypertension, and diabetes.

- Dr. Padilla said that she was looking for one hypothesis, for example related to autism, to see the connection between predictors and outcomes.
- Dr. Hirschfeld explained that a few assessments were selected to serve as surrogates for the many to determine whether a particular design could address a particular question; if so, the design should be able to address other questions. On that list of assessments, linear growth rate and body mass serve as a surrogate for general health issues. Other surrogates include a metabolic screen for nutrition and dietary exposures, frequency and duration of health system encounters for respiratory illness and pulmonary health, and timing of standard neurodevelopmental landmarks or deviations from trajectory for cognitive and social development. There are four domains—four specific quantitative assessments—and these in turn are representative for broader classes. Also, there are specific examples for environmental exposures, including heavy metals, pesticide residue, and semivolatile organic compounds, as three core assessments. Household dust, blood, and urine are surrogates for more specific environmental exposures.
- Dr. Padilla said that with conditions of interest, there is a need to know the hypothesis in order to determine which exposures matter and when.
- Dr. Hirschfeld noted that the Study's mandate is to look at health, and growth is a surrogate. Defining health is complex to do across the life course.
- Dr. O'Campo said that for certain outcomes—birth defects and premature delivery—birth is definitely too late. Although it would be ideal to get information prior to conception to be able to look at the period of organogenesis, doing so does not seem to be feasible due to cost. The question is what time period during pregnancy would be a reasonable time to target to capture information about exposures and be able to answer questions.
- Dr. Hirschfeld stated that the data so far do not indicate that going door to door identifies women earlier in pregnancy than other recruitment methods.
- Dr. Grevatt said that in his view, looking at the Children's Health Act of 2000 that kicked this study off, a move primarily to a birth cohort would be a different study than originally conceived of and would be a mistake. He believes the Study was meant to get the earliest possible exposures, and a practical way should be found to do that, keeping in mind that the Vanguard Study's experience suggests that door-to-door recruitment is not feasible.

- Sheila Newton, Ph.D., said from the perspective of the NIEHS, she wanted to echo what others were saying about birth being too late. Everything in research since the Children's Health Act was passed leads to the inescapable conclusion that earlier is more important. She urged a focus on finding ways to get to the earlier information and not leaving it for birth recruitment.
- Dr. Konstan suggested that there may be a mismatch related to what a hypothesis is and how to use hypotheses. He discussed two examples; in one example, it would be possible to retrospectively obtain pretty good data, but in the other example, it would be much more difficult to get the data later. If the message is that birth is too late, it is really too late only for certain important questions. The rest of this is a tradeoff between how early, how much things are likely to have changed, and how much it costs. So then what matters most? Is it more important to make sure the sample is really representative, even if it is not necessarily taken at the preferred time? Or is it more important to get the sample really early even if that requires making statistical adjustments and adding specific cohorts to deal with underrepresentation in the early sample? Regarding the option that everyone is assuming is off the table, the Study could say it needs more money to do it right.
- Dr. Madans said she thought the Children's Health Act called for a birth cohort and, if possible, gathering prenatal and preconception data. There was a lot of interest in getting at exposures early on. There is still much to learn from a good birth cohort followed for 20 years. A cohort of women very early on probably cannot be obtained on a probability basis. The Study would have to find providers with access to that population. It might be possible to identify certain exposures that are important by using different methods, and if there is similar data collection across various cohorts, the data can be cross walked (but not merged). Rather than trying to look at every hypothesis and when the data should be collected to address it, it would be better to look at broad areas in the prenatal period and where the Study can hone in through this mechanism.
- Everett Rhoades, M.D., said he had gotten the impression the discussion had moved to a point where the assumption was being made that provider-based recruitment was the establishment of a birth cohort rather than also recruiting women in the prenatal period. He noted that in table 3 in the briefing document, the proportion of pregnant enrollees with pregnancy less than 14 weeks of gestation was 23 percent for the provider-based approach, 23 percent for the enhanced household approach, and 22 percent for the direct outreach approach. This suggests that early pregnancy information might not be lost with the provider-based approach. The best compromise may be to use a provider-based approach with modifications.
- A member of the audience asked whether the provider definitions used in the Vanguard Study were the same as those used in the proposed sampling plan under discussion. Dr. Hirschfeld replied that the definitions were the same because a broad definition of provider was used. However, the type of provider can be adjusted. In the definition, a hospital or birthing center is a provider, and people with offices or clinics are also providers although they provide somewhat different services such as prenatal care and advice. Dr. Madans was right that the Children's Health Act says to do a birth cohort; the Act also has two

requirements in a subsection that says to get prenatal information if feasible. There has also been advice from this committee and other groups that the Study should have a national probability sample. Regarding how to fold in the prenatal exposures, a compromise is being proposed. It is difficult to do a probability sample on a prenatal cohort because people are enrolling at all stages of pregnancy. There will be biases, and however participants are recruited, it will not be a probability sample from which one can generalize about every stage of pregnancy. If the Study does a birth cohort and a prenatal sample and brings in a substantial number of women with prenatal exposures, the Study will use what is learned in the birth cohort to make inferences and draw relationships. Not every question can be answered or every mandate addressed. Given the limited resources, the question is what the Study can do that will give credible scientific information and the best return on investment.

- Dr. Reede expressed concern that recruiting through a narrow set of hospitals and birthing centers would miss out on women who only come to hospitals at the time of delivery and have their prenatal care elsewhere, resulting in more bias. Certain populations would be left out.
- Dr. Hirschfeld agreed that this is a troubling issue. The law calls for enrolling diverse populations to address health disparities. The supplemental approach proposed is meant to address those issues and allow the Study to address questions related to the health of different populations, particularly underrepresented or vulnerable populations. That is the compromise being proposed.
- Dr. Olsen asked how different the 23 percent of women enrolled prior to 14 weeks gestation in the earlier Vanguard experience would be for provider-based recruiting if the definition of providers was limited to hospitals and birthing centers. Dr. Hirschfeld replied that the answer was not known, but there is a proposal to go into the field to look at this question. Dr. Olsen said that the question was, if the sample is drawn based on sampling at hospitals or birthing centers, whether the Study would still be getting 23 percent of enrolled pregnancies that are 14 weeks of gestation or less. Would the Study pick up the same fraction of early gestational age no matter what?
- Dr. Konstan said he did not think there was reason to believe the amount would be less rather than more. The proposal indicates that women would be recruited through prenatal providers who have privileges at the hospitals. It seems likely that more educated and wealthier patients are more likely to seek prenatal care early and to seek out providers with privileges at particular hospitals, which would suggest a higher percentage, but it would be an unrepresentative sample.
- Dr. Olsen said if the sampling was done using providers who have privileges at hospitals, which could be a long list and may be difficult to sample from, there is the question of whether that will be a feasible sampling strategy. As people present to these other care providers, there will be a lot of socioeconomic and demographic information in terms of when they present, and some people may just deal with their local general practitioner until the day of delivery.

- Dr. Reede asked whether providers are defined as those that have admitting privileges in hospitals and birthing centers.
- Dr. Hirschfeld said that the definition is an intentionally vague point in the proposal because this is something the Study will be getting input on. Providers are on the staff list or referral base for the facility, but the level of detail has not yet been resolved. He considers this a critical issue that needs to be addressed.
- Dr. Reede said that capturing who is referring to a particular hospital is important. In a shortage area, deliveries may occur in one place but the women are coming from many providers. Providers defined as staff are not the only providers that women are seeing for their care. The definition of providers needs to be broader. Being able to understand social determinants will be critical, and the Study will not be able to capture this information unless it enrolls a broader range of women who receive care from providers other than hospitals and birthing centers.
- Dr. Hirschfeld responded that one mechanism that has been discussed is working through HHS regional administrators, who have the pulse of what is going on in their regions. They can provide information about who is going where for care, and they are interested in including women who are in the Women, Infants, and Children (WIC) program and those who go to Title V clinics, for example. There have been regular meetings with maternal and child health staff from the Health Resources and Services Administration. The plan is to work through those channels to learn as much as possible about these populations.
- Dr. Rhoades said he thought there was some preliminary information from the Vanguard Study indicating that the initial effort to seek providers, which targeted a wide array of providers including those that might not deliver, seemed to not be feasible due to low yield.
- Dr. Hirschfeld said that the data indicated the provider-based approach had the ability to recruit from a broad range of providers. There are options in this multilayered approach as to what channel to use, and the selection will need to be made with the understanding that it will not be part of a national probability sample.
- Dr. Madans said that there are no preexisting lists of birthing facilities to sample from. There are good lists of hospitals and doctors, but an issue is how to get a list of other providers that does not include every provider licensed to do something. There have been some proposals about how to create those lists within the PSUs. It is difficult because there is no clear, easy way to do it. A population-based sample is attractive because the Study could go straight to the women and would not have to worry about all the providers. The Study could get a pretty good national representative sample of women early in pregnancy, but that would be expensive. Making sure everyone has a non-zero probability of selection in a study is very challenging, but it is possible to do that with births. There is no guarantee beyond that. It is kind of a balancing act.
- Dr. Gelb said he thought for Vanguard sites that tried the provider-based approach, recruitment was restricted to women within portions of the PSU. They did not pick providers

within a PSU and take all women who go to them, but it was an expensive approach. He asked for confirmation that the other approach has not been tried yet.

- Dr. Hirschfeld confirmed that the other approach has not yet been tried—it is the one the Study is going into the field to test. The segment approach was frustrating because of the need to screen so many people, and it added confidentiality requirements and expectations. It was then decided that this approach should be put aside, and rather than using the geographic area as the secondary sampling unit, the approach that will be tested will use the clientele of the provider.
- Dr. Konstan said that one of the key questions is whether, based on what the committee had heard so far, the committee members buy in to the idea that given the tradeoffs, the right approach is dividing up the sample to have a group of a certain size that is nationally representative and whether it is acceptable to have other groups to tweak and manipulate to get data that cannot be gathered in an economical way. He said he had not heard a consensus on that approach, so it seemed that it might be a useful point to revisit this question explicitly with the assumption that the sampling will be done as well as it can be done.
- Dr. Olsen said he assumed that for the different tiers of the sampling, there might be slightly different questions at the baseline interview for women picked up prospectively than for those picked up just after delivery. With that exception, these different tiers would converge at some point and would be treated with exact same instrumentation going forward so there would not be the problem of multiple substudies based on the uptake strategy.
- Dr. Madans noted that some data can be combined and some cannot. Some data from the supplemental approaches cannot be combined, although if the same data collection is used, there could be a cross comparison.
- Dr. Konstan said the data collected can be the same after birth, but the data cannot be combined for analysis because of uncertainty about whether the prenatal cohort is representative. Analyses could be done over a period of years to determine whether there are in fact statistical differences. It is very important that the data collected are the same to be able to answer that question.
- Dr. Olsen commented that this issue does seem to be a downside of the proposal. As data are collected earlier and earlier in pregnancy, the sampling procedures become more distant in rigor from the hospital-based provider survey, and therefore the characteristics are more uncertain. Also, the idea of pooling samples becomes questionable because of not knowing what the statistical properties of some of these early prenatal samples might be. Combining them into one grand sample could be quite speculative.
- Dr. Konstan said he would argue that is also a strength in that it allows the study of questions that could not otherwise be studied, including the question of whether health outreach efforts through prenatal care providers are likely to reach the people who need it most. There are two possible extremes of the outcomes; one is that 15 years later it becomes clear that the different groups still cannot be combined because there is no convergence. The decision to

seek prenatal care early is a decision that correlates with factors that last well into adolescence or beyond in impact. The other possibility is that the Study would learn over time that with some statistical adjustments, these populations are moving in nearly identical ways, so there would be the benefit of additional power for studies.

- Dr. Krischer suggested using a design that would enroll children in the birth cohort and enroll the mothers at same time. The mothers would be followed for subsequent pregnancies, and the Study would collect preconception data and outcomes in that group. Obviously this would not be the same as selecting people through provider sampling strategy looking for pregnancy exposures.
- Dr. Hirschfeld said the Study actually wanted and intends to do that. However, the proportion of women who would have a second child within the timeframe of recruitment would probably not be a large enough sample that the Study should dismiss the opportunity to recruit other women and do prospective prenatal data collection. That approach is viewed as a critical internal control on the validity of some of the other data collection. Women who have multiple births within the recruitment window are a population the Study does not want to lose, and there are some plans in that regard.
- Dr. Krischer suggested extending the recruitment window in the subsequent birth cohort and also possibly reducing the follow-up period to, for example, 15 years.
- Dr. O'Campo described a multi-site study she is involved in that is doing something similar. The investigators were interested in the interconceptional period, so women were enrolled immediately postpartum. The researchers' real interest was in subsequent pregnancies, so they tried to enroll women who were very likely to give birth again. The expectation was that around 35 percent of the women might have a subsequent birth in a period of a little more than 2 years, but the actual number turned out to be closer to 10 percent. If the data gathered on women who do not get pregnant again are not used, that is a huge expense for data that are not used. Dr. O'Campo also noted that it was challenging to follow and keep track of the women; contact every 6 months was not sufficient.
- Dr. Krischer said he thought that follow-up every 6 months would be a minimum. He asked whether the study followed the first pregnancies and about extending the period for a subsequent pregnancy to 4 years instead of 2 years. Dr. O'Campo agreed that there would be more pregnancies if the timeframe were extended. The incidence would not be 10 percent per year. The study did not follow the first pregnancies because the interest was mainly in the interconceptional period and prepregnancy exposures. The study was done in five sites in the United States.
- Dr. Konstan said he was in favor of following subsequent pregnancies, but doing so does not solve the issue of prenatal exposures. Only looking at prenatal exposures in pregnant women who already have a child is limiting. One would hope the process of having a first child would lead a person to reduce risky exposures, such as use of tobacco, exposure to lead, a dangerous housing environment, and alcohol use. To study prenatal exposures effectively, the Study would need to look at exposures of women who, ideally, did not know they were

pregnant, as well as women who may have made changes based on knowing they were pregnant.

- Dr. Grevatt agreed about the issues of relying on subsequent pregnancies. A subsequent pregnancy may or may not be the second pregnancy—it could be a later pregnancy. Some women will have already made adjustments in their lives due to a prior pregnancy. Returning to the importance of prenatal factors, the Children’s Health Act talks about birth to adulthood as one aspect of what needs to be carried out and also talks about investigating basic mechanisms of developmental disorders and environmental factors, both risk and protective, that influence health and developmental processes. No one could argue that not including prenatal data meets that requirement of the Act. The Study may get valuable data from subsequent pregnancies, but there needs to also be a focus on prenatal data. It is important to try to have both, with one key focus area of trying to get a cohort as early as possible in the prenatal process. It may be possible to do this through health care providers. Some issues will arise about how representative that sample will be, but a prenatal cohort has to be a focus of the Study.
- Dr. Hirschfeld responded that the Program Office was quite aligned with this view and takes “prenatal if feasible” as a mandate for the Study to broaden the scope of its investigations. A formative research program was developed, and there are 300 different projects to help understand the methods and logistics of doing the Study or to examine aspects of influences on growth and development including stress, markers of stress, and so forth.

Public Comment

Dr. O’Campo opened the period for public comments.

- Teresa Morris, Ph.D., M.S.L.S., California State University, San Bernardino, said she was from a county that was part of Wave 2 in the original Study plan. Regarding the geographical rationale for selecting the PSUs in the new proposal, she asked whether it is based on the original counties or whether there is some other rationale for selecting the PSUs based on geography.
- Dr. Hirschfeld replied that the Program Office has not yet made any decisions as to locations. The determination of the locations will be made based on design parameters and other factors in about a year or so.
- William Lyman, Ph.D., Michigan Alliance for the National Children’s Study, Children’s Hospital of Michigan, made several comments. He has attended many NCSAC meetings over about a 9-year period, and it seems that the same questions are being asked after 9 years. He commented about having a hypothesis-driven sample design and gave examples of the incidence of autism and pediatric leukemia and the implications for the number of children in the Study. More common conditions would not require as large a sample. The issues of number and sample design should be driven by the hypotheses. Finally he commented about the importance of retention in the Study. There will be a difference between women enrolled at birth and those enrolled prenatally. The relationship to the Study will be different and

presumably longer term for women recruited before they give birth than for those recruited at the time of birth. Retention is the critical element.

- Sharon Wyatt, Ph.D., University of Mississippi Medical Center, said she spoke on behalf of the principal investigators at a previous NCSAC meeting. She was delighted with the sampling plan that retains the two most important elements, the primary necessity for a national probability sample and the creation of a prenatal cohort, which most likely can be sufficiently obtained through a provider-based approach despite introducing a certain set of biases. Both prenatal care providers and birthing center providers are difficult to engage, but hospitals will be far more difficult. She described her experience with a midsized county with six hospital birthing centers. Five of the six were difficult to engage, and the process took a year. In hospitals, unlike in offices, the investigators were dealing with multiple shifts and multiple changing staffs and the inability of staff to remember that cord blood was to be collected. Whether data are to be collected for every *n*th birth or on certain days, expecting the staff to recall what data to gather retrospectively after the mother is enrolled is fraught with difficulties.
- Dr. Olsen asked Dr. Wyatt whether, if the Study were to adopt the provider strategies she suggested, the Study would not just be postponing the difficulties she outlined because when the woman goes to the hospital to deliver, the Study would face the same problem of securing the cooperation of the hospital to get biospecimens around the time of birth. If hospitals are harder to sign up, that suggests one would want to deal with as few hospitals as possible.
- Dr. Wyatt said she thought that was a piece of the provider-based sampling design being tested in the field. The provider-based recruiting method that was tested was based on where a woman lived, so every hospital had to be engaged. But when that is flipped, providers are randomly selected in an area and any woman who comes into the practice can be selected. It is still necessary to engage the limited number of hospitals the providers deal with, but the investigators can develop protocols with the hospitals to collect samples explicitly needed for this study, not relying on what might be collected anyway, and can work with hospital staff carefully to assure that those samples are collected. It is the provider one must get on board to get the samples; providers do the deliveries. With the proposed prenatal cohort, the issues will already have been worked through with the woman, her provider, and the hospital staff before delivery. With the woman's commitment obtained in advance, she will make sure that cord blood is collected at delivery.

National Children's Study Federal Advisory Committee Discussion

- Dr. Gelb said that based on the robust discussion during the morning, the tradeoff was getting a highly representative sample around a birth cohort versus a less representative sample with a provider-based approach, which would provide real-time prenatal data. He asked whether a field experiment could determine how close recruiting through the provider-based method would come, when taken out to birth, to recruiting just at birth in terms of representativeness. The prenatal data would not be representative, but at least the Study would have it. Moving

forward, the Study would have everything that would have been obtained with the birth cohort anyway.

- Dr. Hirschfeld responded that the Program Office had been intrigued with the same question and could not find data to address it, so that is what is going to be done in the field. The nomenclature gets complicated. The experience in the field that Dr. Wyatt described was provider-based recruitment that used geographic segments that turned out to be a problematic filter. The next iteration is called provider-based sampling, where the sampling unit at the second level is a provider, but there is some ambiguity about providers. The field testing will show how many people are referred by different types of providers so the Study can get some idea of who will need to be engaged. The experiment will be done in three locations and will put providers into two large strata, those in institutions (hospitals and birthing centers) and those in offices and clinics. This experiment will provide information about the efficiency of recruitment methods, acceptability of the methods, the demographics of the two populations, and the quantity and quality of data collected. The Program Office can inform the NCSAC how the experiment is going at the next meeting and can provide more robust results at the meeting after that.
- Dr. Konstan said he thought that he heard agreement that there are two different ways to look at this. One is that the frame is provider-based sampling. Another way is getting a nearly representative sample at the time of birth. If the goal was to recruit the first time a pregnant woman saw an obstetrician within the frame of what the Study is looking at, that is the point at which prenatal data collection would begin; it might be at delivery or at various points during pregnancy. With this scenario, the problem is how to identify the obstetricians, allocate the sampling among them, deal with migration patterns, and so on. How to include or exclude women is solvable. The result would be a nearly representative sample, which has some subset of women for whom earlier environmental data are obtained. How broad can the definition of provider be and still track things upwards so that one ends up with a total cohort that can be generalized from?
- Dr. Hirschfeld said that the design Dr. Konstan described is close to what the Study is doing. Women will not be given multiple opportunities to enroll. The paradigm has been set up to first generate a list of providers. A measure of size will be applied by determining the number of births the provider is involved with or the number of clinic visits and amount of services provided. Providers will then be ranked on the basis of how busy they are. Women would only be selected at their first encounter; in the case of an office or clinic, the encounter would be a prenatal visit. The cohort will be divided into two groups: those who see providers selected from the list and those who see no providers or other providers not on the list and just show up at the hospital. In that design, women will not be double counted.
- Dr. Reede asked who the individual provider is. Dr. Hirschfeld replied that the provider is determined at the practice level, not the individual level. Agreement has not been reached about the terminology. He personally favors calling an institution a “hospital” or “birthing center” and calling a practice “practice-based sampling” or “prenatal care sampling.”

- Dr. Madans said that the only reason for going to providers is to enroll pregnant women. One can recruit pregnant women at birth or somewhere else, usually through a provider. The key here is getting the list of the providers—and that list does not exist. It must be created, and a question is how one can determine that it is a good list. As long as the Study can get to the woman at the desired time and identify her with some measure, then it is okay. The other key is to be sure it is all right to have incomplete coverage on the prenatal variables. If the Study is willing to spend the money and effort and collect all the variables, and then live with a biased 22 percent of the target cohort, it is not an issue. But the question is what kind of conclusions can be drawn from things measured on 22 percent of the target cohort. By the time one gets to measures at the end of the second trimester, the percentage will be much higher. By the week before birth, which is when the other women would be enrolled, it might be only 5 percent. For that group, one would only have things at the latest point in time.
- Dr. Gelb said the answer on the 22 percent is more than one would get with 11 percent. Dr. Madans is right that it would be a biased 22 percent. If the Study can get to the unbiased group by the time of birth, it is no worse off, except for money issues. Dr. Madans replied that the 22 percent may be worse than 11 percent because it is biased. Dr. Gelb said that the 11 percent will be biased too.
- Dr. Madans said that the possibility of spending the money in a better way, for example, to increase the total sample or do something else that would allow generalizing, would need to be weighed when making a decision. She is worried about the early prenatal data. Why put all the eggs into a biased sample?
- Dr. Hirschfeld said that the value of the committee’s discussion was in raising the points that need to be considered moving forward. There is not yet a finished plan. The Program Office is trying to see what the strengths and weaknesses are of the proposed plan, where compromises can be made, and where further work should be done.
- Dr. Reede asked whether there will be oversampling for certain populations or whether they are to be picked up in the supplemental approach. The issue is how to deal with questions regarding disparities, where certain groups may be at more risk than other population groups.
- Dr. Hirschfeld replied that the Study wants to reach the goal of getting information from those populations, but the right technical approach needs to be determined empirically as to whether this should be done through supplemental sampling or adjustments. There will need to be enough people and enough informative events to do analyses on. The Program Office recognizes that it will not have a national probability sample for some populations and needs to come up with a plan that will specifically address the issue that Dr. Reede posed.
- Dr. O’Campo said there is a difference in whether the approach is to oversample or to go after some convenience sample to supplement the probability sample with these populations of interest. She thinks the Study will want to oversample in the context of the probability sample. She suggested that the tables the committee reviews in the future could include some information on the proportion of the low-income population that can be accessed through the

recruitment methods. This information will show how feasible the different methods of enrollment are.

- Dr. Hirschfeld responded that in prior briefing documents, there have been preliminary data showing that reaching out to the public through a general announcement tends to favor people who have higher education, are married, and are older. With the provider-based approach, one tends to get more women who are less educated, less likely to be married, and are lower income. That information was another factor considered. In some cases, certain types of clinics went into the field early and provided early data, but the process took longer with others. The next experiment will provide clearer data because it will take away some limitations with the geographic segments. The Program Office will continue to examine the data going forward and will report the data back to the NCSAC.
- Dr. Konstan asked whether there is a list of difficult-to-sample populations, such as Amish communities, reservation-dwelling Native Americans, Alaska natives, and so forth. It would be nice to know there is an inventory of such hard-to-reach groups that could be cross-checked against the methods.
- Dr. Hirschfeld said the general reference frame was Census data—two forms of American community survey data and natality data. There are heat maps that show where births occur, populations in those areas, and so on. There may not be a specific list of populations that are less likely to fall into the sample, but there are data that provide a reference frame and can provide guidance on where to do oversampling or supplemental sampling. There have been some surprises in terms of who has come forward and enrolled in the Study, so he is uncomfortable labeling some populations as difficult to reach. While doing the next pilot, the Study will keep a dynamic approach to that issue.
- Dr. Konstan said he could see wisdom of that, but he thought that the Census, with the possible exception of reservation-dwelling Native Americans, does not have questions that regularly capture densely isolated communities, such as the Hasidic communities in Brooklyn. There are isolated groups where there are environmental factors that may lead to later health impacts. It may be important to make sure these isolated groups are studied.
- Dr. Hirschfeld thanked Dr. Konstan for that insightful point and said that it is an item to put on the list of considerations.
- Dr. Olsen said that in the morning discussion, there was an implicit proposition that perhaps the preconception effort ought to be dropped because it would be difficult to execute and costly. On the other hand, interesting data would come from it. He asked for discussion of this issue.
- Dr. Krischer asked whether, if he seconded the idea to drop the preconception effort, the committee could vote on it. Dr. Olsen said the vote might not have any impact. Dr. Krischer said he seconded the motion. Dr. Olsen asked, with the motion having been made and seconded, whether there was any discussion. [Note: The motion was not accepted or voted on.]

- Dr. Reede returned to the issue of capturing subsequent pregnancies. She asked why there was a limitation on the period within which the repeat pregnancy had to occur. Dr. Hirschfeld replied that the limits on the time period were logistic and part of the design; there will be start and stop dates to define the limits of the cohort.
- Dr. O'Campo noted that the Study would also be following a lot of women who will not necessarily stay in the Study simply because they are going to have a subsequent pregnancy anytime soon. If there is an unlimited enrollment period, the Study would be following a lot of women for a long time.
- Dr. Reede said she thought only the women who were already enrolled would be followed for subsequent pregnancies.
- Dr. O'Campo said a woman would be followed for two reasons: because she is the mother and because she has a child in the Study. The Study would follow her because she might have another child.
- Dr. Olsen noted that Dr. Reede had suggested earlier that the women be followed for a limited number of years for subsequent pregnancies.
- Dr. Hirschfeld commented that he has frequent conversations with people who have proposals about what the Study ought or ought not to do. It is important to keep circling back to what Congress asked for—a birth cohort on children. He thinks the Study is pretty committed to following women for subsequent pregnancies, and he is willing to listen to suggestions on implementing approaches to do that.
- Dr. Reede asked whether there is a way to get some of those preconception variables. Is there somewhere in between a vote to eliminate something completely after a brief discussion and saying this is an important area to capture data?
- Dr. Hirschfeld replied that they were in agreement that preconception is a wonderful time in which to do data capture.
- Dr. Konstan said that in addition to issues of the subsequent child potentially being a different environmental frame to sample from, there is another issue with gathering prenatal data from subsequent children only. These would be women who have chosen to have another child and in relatively close proximity to the previous child, which he assumes is another biasing factor. The opportunity to follow siblings provides chances to do studies that compare different children raised in a similar environment with similar genetics. But if the Study is trying to gather prenatal data, he would rather do that right with fewer people instead of starting with something as biased as close-interval subsequent children.
- Dr. Olsen noted that that analytical experience shows that having data on siblings in studies provides considerable analytic advantages, especially if the study is looking at social, emotional, and cognitive development.

- Dr. Madans said that the idea of studying subsequent pregnancies has more promise even given the bias. This approach would be very efficient because the Study would already be in contact with the families. The additional cost would probably be reasonable. It is difficult to get a good sample of preconception any other way. In the hierarchy of things the Study is trying to do, preconception is the hardest and most expensive so is probably on the bottom. Dr. Madans recommended expanding the timeframe to catch subsequent pregnancies to 4 years.
- Dr. Konstan added that the Study should gather data on the older siblings at the same point when data are first collected on the birth cohort sibling to allow the Study to look at comparative data. When the child enrolling is the second or third child, it seems sensible to get comparative data on siblings.
- Dr. Gelb said that, from an efficiency point of view, to the extent the Study would be undersampling some groups for the prenatal cohort at early time points, the subsequent pregnancy approach would augment the data. Presumably that bias would not be inherent in the data from subsequent pregnancies.
- A participant commented that it would be interesting to get data about DNA. Dr. Hirschfeld said there is a formative research project to learn whether there is the option to get information from grandparents. The Program Office is following some of the DNA sequencing competitions that have gotten media attention with keen interest. Having DNA not only for sequencing and genomic information but also for looking at epigenetic and other types of information will be extremely useful. The Study has not abandoned the environment in favor of genetics; genetics will be an important augmentation to help interpret the environment.
- Dr. Olsen raised a final point for discussion: the issue of what the Study's n should be and whether the sample size should be one of the things that should be compromised on in terms of looking at factors that have small impacts, where large samples could be an advantage. If the Study cannot get the needed environmental covariates, perhaps the case for having power for some rare things is attenuated. Secondly, in terms of cost, this is a project over 20 years, and the larger the initial sample size, the higher the cost of maintaining the quality and intensity of the effort over time and in the out years. So if one goes for a smaller initial cohort size, when the time comes that financial resources are limited, the sacrifice may not be as painful. Alternatively, perhaps this is a study that will focus and hang its hat on a large sample size or at least in part on the depth of the data collection mounted. The larger the initial sample size, the more difficult it will be in the future to say that some things will be interesting add-ons later. His question for discussion was whether that n is something that needs to be looked at for a compromise to be made.
- A participant asked whether it has been determined that there is going to be an issue with resources that would necessitate looking at this type of compromise in order to reduce costs.
- Dr. Hirschfeld said that everything is a balance among multiple priorities, but the rationale for 100,000 is based on the desire and the input received to have enough informative

participants with certain conditions in the 1 percent or slightly lower range. It is also based on projections for attrition over 21 years. It is important for the Study to have the opportunity to ask not only about onset and origins but also find out delayed and long term effects of some health conditions. The ones that seem to generate much interest, based not only on familiarity but also public health impact, are in that range, which guides the overall sample size. If resources were not an issue, a much larger sample size might be considered. The compromise for going to a smaller sample size, as Dr. Krischer said, is that the bar is moved up to things that affect 10 percent. Premature birth is in the 8–11 percent range. If a platform is built for doing the Study that is scientifically rigorous and people are made aware of the opportunities, the Study may be able to engage partners going forward that will help bring resources and add additional studies and substudies. Part of the idea of this multilayered plan is that the Study could have partners come in at different points and focus on things that align with their priorities. Those are the drivers, but there is no definitive answer yet on the question of the number.

- Dr. O’Campo said she thought the committee had gone through the questions that were raised in the sampling strategy document and perhaps the meeting could end early. She thanked everyone for all their thoughtful comments. The committee will continue discussion and talk about pilots that are under way at the next meeting.
- Dr. Hirschfeld commented about the issue of who “we” are. From his personal perspective and the Program Office perspective, it is an inclusive “we.” Everyone involved with the Study is part of the same team. He thanked the meeting participants.
- Dr. Olsen asked whether there were any requests from the committee members for materials they would find helpful to view in the intervening months to get up to date. He suggested seeing the draft sampling plans for how the experiments in the field are being conducted to help appreciate the processes and protocols and understand how this is going to work. It would help the group in future meetings to have an in-depth view of how things are going to be executed and perhaps see instrument drafts as well.
- Dr. Hirschfeld said that information can be easily provided. For the record, all this information is made public and published in the *Federal Register* every time a submission is made to the Office of Management and Budget. These instruments and proposals are all in the public record. The Program Office can offer the convenience of assembling and sending a package with PDFs of the documents to the NCSAC. Also, all the *Federal Register* notice links are available on the Study’s Web site at www.nationalchildrensstudy.gov. The Program Office will send the committee these links right away.
- Alma M. Kuby, M.A., M.B.A., requested a listing of metrics to help the committee evaluate the next pilot. This information will also be provided to the NCSAC.

Dr. O’Campo thanked Dr. Olsen for being a great champion, and the meeting was adjourned.

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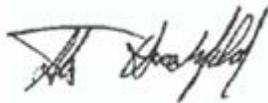
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I hereby certify that, to the best of my knowledge, the foregoing minutes are accurate and complete.



October 10, 2012

Patricia O'Campo, Ph.D.
Chair
National Children's Study Federal Advisory Committee



October 10, 2012

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