Federal Perspectives on the Need for a Large Population Study
Ruth Brenner, M.D., M.P.H.

DR. TUCKSON: Now let us move to our next panel, which will inform us about federal programmatic efforts in this area and provide federal perspective on the need for a large population study. In this case, our panelists are under a little more pressure, because they only have 10 minutes to do their presentations. We appreciate, though, very much their involvement.

Let us start with Ruth Brenner from the National Institute of Child Health and Human Development to update us, Ruth, on the National Children's Study. Thank you so much.

DR. BRENNER: Thank you. I'll try to go through this briefly and stick to the time frame.

I'll be providing first a background about the National Children's Study, an update on the current status, and the future timeline.

The National Children's Study was authorized in the Children's Health Act of 2000. In the Health Act, the language is here. It authorized NICHD to conduct a national longitudinal study of environmental influences, including physical, chemical, biological, and psychosocial influences on children's health and development.

This slide outlines the study concepts that were largely derived from the Children's Health Act, that it be a longitudinal cohort study beginning prior to birth, and continuing through age 21 years, that this study be national in scope, again, that it be a study of environmental influences on children's health and development with environment broadly defined, and that the study be designed to allow measurement of both chronic and intermittent exposures.

A number of additional study concepts have been defined from both the Children's Health Act, subsequent workshops, and work of the Federal Advisory Committee and the Interagency Coordinating Committee. These are outlined on this slide, that the study by hypothesis-driven with primary outcomes related to child health and development, that there be sufficient power to study the common range of environmental exposures, but less common outcomes.

That we look at both the effects of environment and gene environment interactions on child health outcomes, and that the study involve a consortium of multiple agencies, both in the planning and carrying out of the study. Finally, that the data collected serve as a national resource for future studies.

Focusing now on the rationale for the National Children's Study, why the focus on children? Well, first, children have increased vulnerability to a number of environmental exposures. There are also critical windows of vulnerability, particularly early in development in utero when many of the organ systems are forming.

Children have immature mechanisms for detoxification and protection. There are also differences in metabolism and behavior that may yield higher effective exposures when children and adults are exposed to the same environments.

This is a slide taken from Selevan and published by Selevan in Environmental Health Perspectives that looks at some of these factors. I won't go through all of them in the interest of time, but if you just look at the top row, you can see that looking at surface area to body mass

ratio, that ratio is higher in infants than in children, and higher in children than in adults. There are a number of other domains that you could look at and see how children actually have higher exposures to environments when placed in the same environment.

So why now? Why do this study now? First, there has been increasing concern about numerous exposures with suggestions that these exposures lead to adverse outcomes. The types of exposures range from changing social environments, to increased exposure to the media, to exposures to new chemicals that have been introduced in the environment.

Additionally, there is an increase in concern about diseases and conditions of children, some of which appear to be increasing, such as obesity and possible autism, and attention deficit and hyperactivity disorder. At the same time, there has been growing experience with the effects of exposures and how they affect child health outcomes, particularly exposures in pregnancy and early childhood, like lead and fetal alcohol. There have been advances in technological capabilities, many of which you've already heard about today.

Finally, why a longitudinal study? Again, most of this has already been discussed today. It allows inference regarding causality, it allows a study of multiple outcomes, and simultaneous and sometimes synergistic effects multiple exposures.

It allows study of mediating pathways between exposure and disease, recall bias decrease, particularly in relation to exposure. Particularly important for children, it facilitates the study of development trajectories and how environmental influences at a particular point in time can affect these trajectories.

This is just a schematic of the multiple levels of measurement that we anticipate in the Children's Study. There will be community level measures of neighborhoods, schools, and communities, measures of the social environment, friends, family, and organizations, a number of individual factors, and how all of these interact with genetics to affect health and development over the 21-year time period.

Now turning to the recent milestones and the current status of the project. After a number of meetings, including deliberations of an expert panel and recommendations from the Federal Advisory Committee in June of 2004, the decision to utilize the National Probability Sample was announced. Shortly after that, the study plan was developed, and this was first presented in September of 2004 to the Federal Consortium. Later in November of 2004, the study plan was made public as part of the request for proposals for the Vanguard Centers.

At the same time, a request for proposal for the Coordinating Center was released, and we published the "Growing Up Healthy" document, which I think was included in the packet. If it wasn't, I brought extra copies with me.

Briefly, the National Probability Sample, the first stage was drawn by the National Center for Health Statistics, 101 study locations, which are, for the most part, single counties, although in some rural areas, it involves multiple contiguous counties. We draw from the full list of all counties in the United States. Thirteen of these locations are self-representing locations. Those are locations with higher populations. We anticipate a large number of births per year. Sixty-two are metropolitan and 26 were non-metropolitan locations, primarily rural locations.

In the second stage of sampling, we will be selecting segments or groups of households from within the study locations. We anticipate a highly clustered sample to facilitate study of

community characteristics, as well as to increase the logistical efficiency of the study. Therefore, we anticipate a few number of segments within each location.

We will be soliciting input from the successful offerors to help define the segments. There are advantages and disadvantages to using traditional ways of defining segments which rely on Census boundaries versus less traditional ways like school areas. We will be asking offerors to help us in defining the segments and seeing what is possible within their locations. But to maintain the integrity of the sample, the offerors will not do the actual selection of the segments. That will be done by the data center in collaboration with the statisticians from the National Center for Health Statistics.

This is the study map. These are the 101 locations that were selected across the country.

The next step was the selection of the vanguard locations. From the initial list of study locations, eight locations were selected to potentially serve as the vanguard locations. The vanguard locations will start data collection a year before the other locations, and will serve to pilot our procedures and modify them before we have the full complement of study locations on board.

Two certainty and four metropolitan, but non-certainty and two non-metropolitan locations were randomly selected. This included two locations in each of the four U.S. Census regions, and this map shows the eight locations that were chosen to potentially be vanguard locations.

That's an important distinction. Offerors were asked about potentially versus actual vanguard locations. Offerors were asked to propose procedures for data collection in one of those eight areas.

However, the number of awards that is made is dependent upon availability of funds and the quality of the proposals that we receive. We anticipate a total of three to eight awards. Therefore, somewhere between three to eight vanguard locations.

There will be no more than one award for collection of data in a single location so we won't have two entities collecting data in the same county. If there are three awards, our goal is to make one award in each of the three categories of certainty, non-certainty, and non-metropolitan.

In addition, if there are four awards, our goal is to have one vanguard location in each of the four Census regions. The reason for this is so that we can get as broad of an experience as possible in the vanguard phase so that the experience can be applied to development of the procedures for the full study.

A few other aspects of the study plan. Again, we'll be enrolling women and, when possible, their partners, prior to or early in pregnancy, with follow-up of children until 21 years of age.

For the main locations, the enrollments over a 4-year-period in the vanguard phase, there is an extra year, so it is five years. Data will be collected in both face-to-face visits and remote data collections, and will include questionnaires, interviews, environmental samples, and observations both in the home and in the community.

Clinical and behavioral assessments, again, both in the home and in the clinical setting, and a number of biological samples.

This is the proposed schedule as it appeared in the study plan. There is a total of 15 face-to-face visits proposed, with additional visits for those who are enrolled preconception. You can see they are spread between home visits and clinic visits, and then one visit in the hospital at the time of delivery.

In addition to the challenges that were outlined in the previous slide, these are some of the challenges that we face in the data collection aspect. Certainly the combination of a probability sample with actual data collection conducted through the Centers of Excellence is a new design, and something that we're hopeful will be successful.

I think I mentioned the end date for receipt of proposals was a couple of weeks ago. It looks like this has fostered some interesting collaborations. We're hopeful that this will be a successful strategy.

We also propose to collect multiple levels of data in a variety of settings. I have just given an example of some of them, environmental specimens in the home, biologic samples at the time of delivery which are going to require relationships with multiple hospitals since we're using a community-based approach, versus the hospital recruitment, and a number of measures in the community.

We also want to capture both intermittent and chronic exposures, and we hope to capture those exposures during critical periods of development. It's the combination of these two challenges that led to the preconception component of the study, to get those very early intermittent exposures, those early exposures in pregnancy that are sometimes short lived.

The projected timeline. Again, the closing date for receipt of proposals for the Vanguard Centers and Coordinating Center were last month. We hope to select the initial centers, the Vanguard Centers, in late 2005, and to complete and pilot the initial protocol in 2006.

We hope to enroll the first participants in the initial centers in early 2007, and to select additional centers in 2006 and 2007. The first preliminary result should be available in 2009 to 2010, and we'll continue to analyze data throughout the course of the study.

Finally, we've had ongoing and will continue to have ongoing meetings, peer reviews, workshops, and consultations. I just wanted to mention one of those. In September of 2004, we had a workshop on the collection and use of genetic information. This brought together experts in the federal government to explore opportunities and challenges, and provide recommendations to the National Children's study.

The focus was on appropriate collection and storage of biologic samples. There is a workshop report that will be available at our website, probably at the end of this week. This is the website, if you want additional information. Again, I did bring, if anybody is interested, I brought some additional copies of the "Growing Up Healthy" document.

DR. TUCKSON: Thank you very much, Dr. Brenner. We very much appreciate that.