

**Questions Posed to the NCSAC from the ICC
August 26, 2003**

For the purpose of developing the protocol for the NCS, the ICC would like to pose these questions to the NCSAC for response, with the assumption that the NCSAC will in turn pose them to the Working Groups to research the responses. Once the responses meet the expectations of the NCSAC, the ICC requests that the NCSAC compile the responses and provide them as advice or recommendations to the ICC.

The ICC would like to strongly recommend that the Working Groups focus on making their responses as specific as possible and that they rely to the fullest extent on the expertise and judgment contained within the groups. As always, inter-Working Group interactions are encouraged.

The ICC hopes to receive progress reports, outlines, or clarifying questions from the NCSAC from the December 2003 meeting, with final responses at the NCSAC's March 2004 meeting. This will facilitate the continuing development of the protocol by incorporating this new information, as it is prepared. The attached list of current core hypotheses will help guide the Working Groups. While this list is continually being re-evaluated, it remains a good reference point for answering these questions.

Physical Environment Working Group:

PE1. Assuming measurement of the built environment is important to assessing a range of exposures and outcomes in the NCS (e.g., physical activity patterns, social and behavioral outcomes), what specific measures would you propose to address the current list of proposed core hypotheses? What methods might be most appropriate?

PE2. Given limited resources and subject burden, for the measures you have proposed in the above question, can you propose specific criteria to be applied for choosing which might be selected for the NCS? Assuming that criteria may be in conflict or mutually exclusive, what is the relative priority for each criterion?

Fertility and Early Pregnancy Working Group:

FEP 1. Assuming that some of the participants in the cohort are enrolled before pregnancy, what methods or measures would you recommend be used to determine that a couple is infertile or subfertile?

FEP 2. Is subfertility or its treatment likely to be an important confounder or effect modifier for any of the core hypotheses? If yes, what information on subfertility or its treatment would you recommend be collected in the Study and when?

FEP 3. What practical methods or measures do you recommend for assessing early pregnancy losses as accurately and reliably as possible in the Study?

FEP4. Given the Working Group's evaluation of collection methods for biological samples and other information from couples at or before conception, which logistically and economically feasible measures are most highly recommended? These can include identification of pregnancy, or assessment of exposure. If couples are followed for an extended time prior to pregnancy, how often, and at what intervals would you suggest repeating measures? If there are different recommendations for use at home versus in a clinical setting, please describe these separately. Please consider responses in terms of ease of use, compliance, and participant burden.

FEP5. For the measures you have proposed in the above questions, can you propose specific criteria to be applied for choosing which might be selected for the NCS? Assuming that criteria may be in conflict or mutually exclusive, what is the priority for each criterion?

FEP6. What practical methods or measures would you recommend for assessing the development of secondary sexual characteristics during puberty and adolescence in a standardized manner? How accurate and reproducible are such measures? What are the critical windows for exposure? At what ages should such measures be taken? (Work with Nutrition, Growth, Pubertal Development Working Group on this.)

Asthma Working Group:

A1. What methods would you recommend be utilized in the NCS to measure asthma and early life indicators of asthma development? What time periods are critical?

A2. Given limited resources and subject burden, for the measures you have proposed, can you propose specific criteria to be applied for choosing which might be selected for the NCS? Assuming that criteria may be in conflict or mutually exclusive, what is the priority for each criterion?

Chemical Exposure Working Group:

CE1. What chemicals or biological (e.g., allergens) agents would you recommend be measured in order to test the current set of core hypotheses? Please consider both exposure measures directly related to the hypotheses, and major confounding factors.

CE2. What techniques are available to measure these at different life-stages in the development of the child? Please identify the advantages and disadvantages of using these methods in residential or other settings, and identify likely costs and subject burden limitations associated with the collection, processing, and analyses of these samples. Please provide specific criteria to be applied in selecting measures for the NCS. Given

that criteria may be in conflict or mutually exclusive, what are the relative priorities for these criteria?

CE3. When and how often do these samples need to be collected, given possible relationship to health outcomes and temporal variability in concentrations or exposures?

CE4. How can existing monitoring data (e.g., for air pollutants and allergens) and information obtained from questionnaires/diaries or other methods be used to help estimate exposures for time periods and for individuals that are not directly monitored? Please provide information on the specific questions that can be used, and the utility of these questions in other studies.

CE5. What approaches can be used to collect newborn and infant urine samples?

Gene-Environment Interactions Working Group:

GEI1. What genetic polymorphisms would you recommend be considered in relation to each of the core hypotheses?

GEI2. What are the frequencies of such polymorphisms?

GEI3. How much statistical power will the study need to have to adequately examine gene-environment interactions given the expected frequencies of the health outcomes and respective polymorphisms and exposures?

GEI4. Are there accurate and reproducible measures of and instruments for collecting family history to enhance evaluations of gene-environment interactions? When during the course of the study would it be optimal to collect such information?

GEI5. Given the genetic heterogeneity of certain ethnic groups likely to be part of the study (e.g., Latinos) and the diversity in cultures and diets within such groups that may impact on the health outcomes of interest in the Study, how would you recommend that race/ethnicity be taken into account in evaluations of gene-environment interactions?

GEI6. Given limited resources and subject burden, for the measures you have proposed in the above questions, can you propose specific criteria to be applied for choosing which might be selected for the NCS? Assuming that criteria may be in conflict or mutually exclusive, what is the priority for each criterion?

GEI7. How should biologic samples be collected in a logistically and economically feasible manner to best allow for addressing current and future hypotheses involving genetic data?

Nutrition, Growth and Pubertal Development Working Group:

NGPD1. What methods or measures would you recommend for assessing the development of secondary sexual characteristics during puberty and adolescence in a standardized manner? What methods or measures would you recommend to evaluate manifestations of early sexual development? How accurate and reproducible are such measures? What are the critical windows for exposure? At what ages should such measures be taken? (Work with Fertility WG on this.)

NGPD2. Are there candidate genetic polymorphisms that you recommend be considered when evaluating premature or delayed sexual development?

NGPD3. What methods or measures would you recommend for measuring height, weight, body composition, and fat distribution during pregnancy, infancy and early childhood, puberty and adolescence? What are the advantages and disadvantages of such methods?

NGPD4. What methods or measures would you recommend for characterizing dietary intake and level of physical activity during pregnancy, infancy and early childhood? What are the advantages and disadvantages of such methods?

NGPD5. Given limited resources and subject burden, for the methods and measures you have proposed in the above questions, can you propose specific criteria to be applied for choosing which might be selected for the NCS? Assuming that criteria may be in conflict or mutually exclusive, what is the priority for each criterion?

Pregnancy and the Infant Working Group:

PATI1. What are the specific measures needed for your two candidate hypotheses, beyond the ones that are likely to be collected as general pregnancy-related data?

PATI2. Are there any candidate genes that you would recommend be studied because they might either aggravate or mitigate the effect of the exposures in question (infection and stress)?

PATI3. What are the appropriate sources for these measures (e.g., vaginal swab, vaginal wash, cervical swab, serum, plasma, etc). Which measures are generally available (e.g., commercial assay kits)? Which are only available in selected research labs? And, which need to be developed?

PATI4. Given limited resources and subject burden, for the measures you have proposed in the above questions, can you propose specific criteria to be applied for choosing which might be selected for the NCS? Assuming that criteria may be in conflict or mutually exclusive, what is the priority for each criterion?

Community Outreach and Communications Working Group:

COC1. Based on all of your deliberations to date, the December 2002 workshop, etc., what specific incentives for *communities* would be most appropriate and recommended for this Study during:

- a) the period before recruitment begins
- b) recruitment
- c) the rest of the Study?

COC2. Based on all of your deliberations to date, the December 2002 workshop, etc., what procedures and methods of communication would you most strongly recommend be implemented for reporting study results to a community?

COC3. Under what conditions is it most appropriate and sufficient to report study results to participants in aggregate form (e.g., through a newsletter)?

Medicines & Pharmaceuticals Working Group:

MP1. What are the criteria for determining when an in-depth evaluation of medicines and pharmaceuticals exposures should be triggered? For example, a hospitalization would likely involve multiple pharmaceutical exposures. What other circumstances would warrant such a probe?

MP2. What methods exist for capturing data via questionnaires on new medicines and pharmaceuticals (including herbals and supplements) as they become available?

Early Origins of Adult Health:

EOAH1: Looking at the current core hypotheses, what would you recommend for specific measures for fetal and infant growth and development (e.g., certain measures available through 3-D ultrasound to assess fetal growth as it might pertain to adult conditions)? What methods would be most appropriate, in your opinion?

EOAH2. Given limited resources and subject burden, for the measures you have proposed, can you propose specific criteria to be applied for choosing which might be selected for the NCS? Assuming that criteria may be in conflict or mutually exclusive, what is the priority for each criterion?

Health Services:

HS1. Propose a standard list of measures and associated methods for basic assessment of access to and utilization of health services, relying on the current list of core hypotheses as a guide for exposure and outcome areas of interest. Then, propose a more expansive “wish list” of measures and methods for health services variables that the Working Group feels are important but are not necessarily implied in the current list of core hypotheses.

HS2. Given limited resources and subject burden, for the measures you have proposed in the above questions, can you propose specific criteria to be applied for choosing which might be selected for the NCS? Assuming that criteria may be in conflict or mutually exclusive, what is the priority for each criterion?

Repository Working Group:

No questions at this time.

Immunity, Infection and Vaccines Working Group:

IIV1. What specific cytokines or inflammatory markers would you recommend be measured to test the hypotheses concerning infection?

IIV2. Define the specific advantages and necessary requirements (especially during pregnancy and the first year of life) for using a pre-conception cohort to test the infection, inflammation and preterm birth hypothesis.

IIV3. Given limited resources and subject burden, for the measures of infection, immunity and inflammation, can you propose specific criteria to be applied for choosing which might be selected for the NCS? Assuming that criteria may be in conflict or mutually exclusive, what is the priority for each criterion?

Injury Working Group:

INJ1. Given a hypothesis: exposure to a range of potentially harmful chemicals in the environment during pregnancy and early life may be associated with increased rates of injury at later times, what are the injury measures necessary to test this hypothesis?

INJ2. In order to study injury in a study like the NCS, what specific candidate genes would be necessary to examine in order to study the interactions between such genes and the environment?

INJ3. How would this Working Group recommend the Study measure child maltreatment while sustaining participation, protecting confidentiality and protecting the child?

Development and Behavior Working Group:

DB1. Given limited resources and respondent burden, what are the most appropriate measures and critical time periods to capture the cognitive, physical, psychosocial, communication and behavioral aspects of children's development in the NCS?

DB2. Can you propose specific criteria to be applied for the types and specific measures of child development and behavior to be considered for use with the NCS? Assuming that criteria may be in conflict or mutually exclusive, what is the priority for each criterion?

DB3. The proposed hypothesis on positive development notes many aspects and components of development across various domains. The hypothesis states that environmental factors will interact with genetic determinants to affect the resultant developmental outcome. Specific models of how these interactions will be determined are needed to plan the study. What are the leading (approximately five to ten) candidate genetic polymorphisms to be studied for environmental influence on genetic expression of child development? What is their frequency (if known)? What are the types of development outcomes most likely or possibly associated with these polymorphisms?

DB5. What are the major polymorphisms for possible genetic and environmental expression that could affect or contribute to the cause or severity of autism spectrum disorder? What are the frequencies of these polymorphisms?

DB6. How often should neuro-psychological assessments be made in order to test the hypothesis concerning schizophrenia?

DB7. What types of neuro-psych tests should be used in assessing the possible development of schizophrenia and at what intervals would you recommend applying them? What other measurements should be taken to assess the possible development of schizophrenia?

DB9. What are the specific neurotoxicants that have been shown to be associated with deficits in attention and how can we measure attention in children in the NCS?

DB10. Developmental regression is reported to occur in up to 30% of children with autism and environmental causes have been attributed to this subtype. Retrospective reporting of regression is often not reliable. Should we try and capture regressive autism in children in the NCS? If so, how should we do it and are there any environmental exposures that should be considered as prime candidates for a possible causal association?

Ethics Working Group:

ETH1. Based on your work to date, the recent workshop you conducted, etc., recommend appropriate informed consent for the various stages along the 21+ years of the study. (Highlight considerations based upon recent HIPAA guidance.)

ETH2. Recommend a process to facilitate IRB approval for both the onset of the study, as well as throughout the course of the study as new elements become incorporated.

ETH3. What kind of incentives would you recommend as most appropriate to consider for potential participants in the study?

- a. At enrollment
 - i. Women
 - ii. Partners
- b. During follow-up
 - i. Child care provider
 - ii. child

ETH4. Are sample consent forms from other longitudinal studies adaptable to the NCS? Which would be most useful and where can they be accessed?

Birth Defects Working Group:

BD1. What methods are available for conducting standardized examinations of growth and development of the fetus, newborn, and infant within the context of the NCS? What criteria should be used to select or develop the optimal method?

BD2. For which measures of growth and development of the fetus, newborn, and infant should data be collected to allow for prenatal and postnatal comparisons (i.e., longitudinal assessment) of growth and development?

BD3. What methods are available for conducting examinations of the fetus, fetal deaths, newborns, and infants for the presence of internal and external structural malformations? For a standardized diagnostic classification of affected offspring? What criteria would you recommend be used to select or develop the optimal method in each case?

BD4. Which candidate genetic polymorphisms may enhance or attenuate the association between impaired glucose metabolism and the risk for birth defects?

BD5. What additional information would you recommend be collected to take into account potential confounding effects or effect modification by maternal conditions or exposures before or early in pregnancy?

BD6. Given limited resources and subject burden, for the measures you have proposed in the above questions, can you propose specific criteria to be applied for choosing which might be selected for the NCS? Assuming that criteria may be in conflict or mutually exclusive, what is the priority for each criterion?

Health Disparities and Environmental Justice Working Group:

HD1. Given Dr. Camara Jones' presentation at the June 2003 NCSAC meeting, what specific testable hypotheses would this WG like to propose, in light of the comments received at the meeting? What variables would need to be measured to test these hypotheses? And/or, would this WG propose integrating these measures into existing hypotheses instead of creating new ones?

HD2. In order to launch the NCS and begin testing the above hypotheses, what pilot or methods development studies would need to be conducted to overcome gaps in knowledge that would significantly impede the success of the NCS?

HD3. What are the specific areas (exposures and outcomes) related to health disparities that are most important to capture in the NCS within the other core hypotheses, and how can they be measured? Given limited resources and subject burden, for the measures you have proposed, can you propose specific criteria to be applied for choosing which might be selected for the NCS? Assuming that criteria may be in conflict or mutually exclusive, what is the priority for each criterion?

Study Design Working Group:

SD1. Please provide specific thoughts on initial list of core hypotheses put forth by ICC. If there are gaps, what exactly is missing? If the current study questions are too broad, please give targeted examples to improve specificity. If some are inappropriate, please specify, along with the reasons for those thoughts.

SD2. What is the Study Design WG's response and comments to the sampling strategies workshop recommendations (to be held in approximately December 2003)?

Social Environmental Working Group:

SE1. Regardless of the inclusion of specific "social environment" hypotheses in the NCS, the assessment of a child's and family's social environment will be an important component of the Study. Please compile/present findings on methods of measuring social position, family environment, and other related topics appropriate for various stages of the NCS. For example, assessments of social environment during pregnancy, infancy, childhood, and adolescence will likely differ. Please provide detailed information regarding different measurements obtained via interview, observation, or other methods.

SE2. Given limited resources and subject burden, for the measures you have proposed in the above question, can you propose specific criteria to be applied for choosing which might be selected for the NCS? Assuming that criteria may be in conflict or mutually exclusive, what is the priority for each criterion?

General Questions that could be assigned to multiple Working Groups:

Are there key measurements that should be made (exposure and/or health) during the early childhood years (age 2-4) as part of a general environmental health assessment, to support hypotheses in the major NCS theme areas? If key measures are known, what would they be and when would we make them?