



September 21, 2007

The National Children's Study  
National Institutes of Child Health and  
Human Development  
National Institutes of Health  
6100 Executive Blvd., Room 5C01  
Bethesda, Maryland 20892

Dear Sir/Madam:

The American Association for Clinical Chemistry (AACC) appreciates the opportunity to provide comments on the National Institutes of Health's National Children's Study 2007 Research Plan. As a strong supporter of this initiative, we are very pleased with the agency's efforts in advancing this study. In general, we believe the research plan is well crafted, clearly delineating the purpose of the study, its design, and the measures that will be employed. We urge the study planners, however, to consider a number of minor refinements to the study.

#### **Chapter 7: Selection of Outcome and Exposure Measures**

The research plan lists carbohydrate-deficient transferrin as the test that will be utilized to detect alcohol use. The use of carbohydrate-deficient transferrin is known to lack sensitivity in detecting mild to moderate alcohol use. This is a serious limitation given that many mothers may not be willing to admit to alcohol use. We urge that the plan be modified to include additional measurements of biomarkers that are sensitive to milder alcohol intake, such as fatty acid ethyl esters or phosphatidylethanol, which would more accurately assess alcohol use in the study population.

Also, there are a number of potential confounding issues that might impact outcomes. For example, the study may end up including up to 40 subjects who will have inborn errors of metabolism that will be detected by newborn screening and an undefined number of other metabolic diseases in addition to those cases with impact from maternal metabolic abnormalities (pregnancy associated diabetes etc). These cases could potentially skew such areas as neurodevelopment and mortality. The numbers are relatively small but the effects huge. The research plan should address how it will deal with this issue in the final document.

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### **Chapter 8: Rationale for Outcome Measures**

In 8.5.3, the research plan states that “Potentially relevant laboratory analyses can include assessment of ghrelin, leptin, adiponectin, and other adipocytokines” to determine if those compounds are causally related to increased weight and adiposity or are an intermediate phenotype.” These analytes are not on the list of specimens in Appendix G: Detailed Overview of Biospecimens. Will the list of analytes be continually updated as the study moves forward? Will there be opportunity for additional public comment if new tests are added?

### **Chapter 9: Rationale for Exposure Measures**

In section 9.5.6, NIH briefly discusses how information regarding illicit drug use will be obtained from the mother before and during pregnancy and after birth. We recommend that this section be expanded. Although the document mentions that “drug screening of biologic samples (blood, cord blood, and urine) can also be performed,” it does not mention what methods may be employed or what detection limits will be utilized. AACC would caution against using the Substance Abuse and Mental Health Services Administration (SAMHSA) cut-off limits for screening purposes as it would fail to detect many exposures that could potentially affect child development.

Section 9.6.6 describes the rationale for collecting PBMCs and establishing future cultures to augment genomic analysis. These cultures, in our opinion, will provide an invaluable link between genotype, phenotype and mechanism that is not adequately emphasized in the current document. We recommend that NIH clarify the intent of such studies by including a few specific examples of informative experiments that might be conducted using these cell lines. We also suggest that different forms of sample collection for genomic analysis be considered, including dry DNA storage technology.

### **Chapter 10: Statistical Analysis Plan**

The research plan states that NCS will obtain 100,000 participants from 105 geographical sites. In aggregate, the statistical power of 100,000 enrollees seems adequate. We are concerned, however, that the study design may not be sufficient to identify geographically isolated exposures. In each geographic region containing slightly fewer than 1000 participants, exposures that result in low frequency outcomes (<1%) will yield only a handful of cases. Thus, it appears that the design will not be sensitive to exposures restricted to a single geographic region. We urge that the document more clearly address this limitation.

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### **Chapter 15: Quality Assurance and Quality Control**

In 15.7, the research plan states that laboratory performance will be monitored on a continuous basis, including the use of “external QC,” such as proficiency testing (PT), and through routine inspections of staff and procedures. AACC agrees with this approach. However, it is not clear from the document whether NIH is planning to perform these duties in-house or contract with a private accrediting program. We believe it would be more efficient to contract with an existing CLIA-accredited organization, such as the College of American Pathologists, rather than to re-invent these mechanisms internally.

### **Appendix G: Detailed Overview of Biospecimens**

In Appendix G, NIH lists the biological specimens that will be collected from the parents and the child. We are concerned that a number of analytes in the study exhibit some geographic and/or seasonal variation (e.g., hematocrit, Vitamin D). Currently, the plan does not discuss how the researchers will control for these problems when they collect the specimens or how they will address them in the statistical analyses. We recommend that these issues be addressed in the final research plan.

Also, the research plan states that 31.0 mL of blood will be collected from the child at six and twelve months. We are concerned about total volume of collection in these infants. We recommend that the NCS determine total volume of collection based on the individual infant's weight and have a contingency plan for collecting fewer samples from smaller infants. A prudent limit to adopt is 5% of the patient's total blood volume. Further, we suggest that urine specimens from babies be collected by catheterization for females and bagging for males.

AACC is the principal association of professional laboratory scientists. Our more than 9,000 members develop and use chemical concepts, procedures, techniques and instrumentation in health-related investigations and work in hospitals, independent laboratories and the diagnostics industry worldwide. If you have any questions, please call me at (504) 568-4281, or Vince Stine, PhD, Director, Government Affairs, at (202) 835-8721.

Sincerely,



Larry Broussard, PhD  
President-Elect, AACC