REQUEST FOR OMB CLEARANCE
Information Collection Request
Stress and Cortisol Measurement for the National Children's Study (NICHD)

Part A only

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A. Justification

A.1 Circumstances Making the Collection of Information Necessary

Legislative Mandate

The President's Task Force on Health Risks and Safety Risks to Children recommended in 1999 that a large study to define the actual risks associated with broad environmental exposures is the critical first step in addressing the potential risk factors that may affect the health and development of children in the United States (US). Following the recommendation of the task force, Congress passed the Children's Health Act of 2000 (Public Law 106-310) which authorized the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) to conduct a national longitudinal study of environmental influences on children's health and development. These environmental influences include physical, chemical, biological, and psychosocial aspects.

1. The Children's Health Act of 2000 (Sec. 1004) states that the Director of the NICHD shall establish a consortium of representatives from appropriate Federal agencies to: "Plan, develop, and implement a prospective cohort study, from birth to adulthood, to evaluate the effects of both chronic and intermittent exposures on child health and human development."
2. "Investigate basic mechanisms of development disorders and environmental factors, both risk and protective, that influence health and development that influence health and developmental processes. "

This national longitudinal study, termed the National Children's Study [NCS], is required by law to include three research imperatives justifying the collection of information:

1. "Incorporate behavioral, emotional, education, and contextual consequences to enable a complete assessment of the physical, chemical, biological and psychosocial environmental influences on children's well-being."
2. "Gather data on environmental influences and outcomes on diverse population for children, which may include the consideration of prenatal exposures."
3. "Consider health disparities among children which may include the consideration of prenatal exposures."

Purpose of Vanguard (Pilot) Study

The NCS Vanguard (Pilot) Study (OMB #0925-0593) was approved by the Office of Information and Regulatory Affairs within the Office of Management and Budget with an expiration date of 7/31/2013. The purpose of the Vanguard (Pilot) Study is to assess the feasibility, acceptability, and cost of the recruitment strategy, study logistics and operations, and study visit assessments that will be used in the second component, the NCS Main Study. "Feasibility" assessment refers to technical performance and reliability. "Acceptability" refers to the impact on the study participants and overall study infrastructure. "Cost" refers to the level of effort, personnel, resources, and money involved in a study development

and implementation. The NCS Main Study, currently in the concept phase, will run in parallel with the NCS Vanguard (Pilot) Study. Additional substudies and formative research projects will inform future NCS design and activities. Currently, the design of the Main Study is being informed by the experience obtained in the Initial Vanguard Study, combined with data from the Alternate Recruitment Substudy.

Purpose of this Submission

Some formative research projects related to the overall goals of the NCS Vanguard (Pilot) and Main Study have a larger scope and may provide more information on exposures and outcomes, in addition to informing the protocols and processes used in the Vanguard (Pilot) and Main Study. As such, these formative research substudies may require a larger sample size and more complex and varied data collections from participants. With this submission, the NCS seeks OIRA clearance to perform a multi-center substudy, called the Stress and Cortisol Measurement Substudy, aimed at developing a validated questionnaire that will reflect specific physiological measures of stress.

The overall goal of this substudy will be to replace the need for biospecimen collection, physiological measurements, and associated analysis of cortisol and other measures of stress, thereby reducing cost and NCS participant burden. This substudy will develop a common, core protocol for determining the most reliable, acceptable, and cost-efficient approach for assessing maternal stress. Developing an optimum measure of maternal stress is of particular interest to the NCS based on studies that have shown an association between maternal stress and still birth, low birth weight, preterm birth, problems in offspring brain function and behavior including lower IQ and impaired executive function, immune-related problems such as allergies and asthma, congenital malformations, infections, and numerous disorders of organ systems. Epidemiological studies suggest that maternal stress is significantly and independently associated with an increased risk of spontaneous preterm birth. Stress factors are also more prevalent in the population of socio-demographically disadvantaged women who are at an increased risk for preterm birth.

Stress increases corticotrophin-releasing hormone, which may result in increased uterine contractility. Stress also increases cytokine production, which may independently lead to preterm birth, or increase susceptibility to infection and thereby increase the risk of preterm birth. Additionally, stress may change health behaviors that lead to preterm birth and other adverse birth outcomes. Studies of the physiology of childbirth suggest that neuroendocrine and immune processes play important roles in the physiology and pathophysiology of normal and preterm birth. Pregnancy is a period of relative increase in cortisol, even among normal, healthy women; the activation of the hypothalamus-pituitary axis during pregnancy has been proposed to function as a biological clock. This model proposes that the placenta is a stress-sensitive organ and that placental corticotrophin-releasing hormone is a trigger to initiate labor.

However, not all women with high levels of stress or infection deliver preterm, and little is understood about factors that moderate susceptibility to the pathophysiology of the endocrine and immune systems during pregnancy. Not all studies support the association between stress and adverse birth outcomes; this inconsistency in study findings may be related to the diversity of tools and measures used to

quantify stress in pregnant women. Additionally, scales that tally the number of stressful life events that have been experienced may not account for internal stress responses to external events, and therefore, may not accurately assess chronic stressors that may be of specific importance to pregnancy outcomes. The link between chronic maternal stress experienced during pregnancy and low birth weight or preterm birth remains uncertain.

Therefore, the NCS seeks to develop an adequate measure of maternal stress in the form of a brief questionnaire that correlates with more invasive and burdensome approaches to the measurement of biological and physiological measures of stress. Birth outcomes have been selected for this substudy because they represent priority outcomes for the NCS, and they will be available and can be collected within the study timeframe. We expect that findings from this proposed Stress and Cortisol Substudy will improve the current state of risk assessment during pregnancy, and will assist in defining characteristics of pregnant women who are especially susceptible to stress. Identification of a standardized, validated approach to evaluate exposure to psychosocial stress during pregnancy will facilitate the measurement of stress as a variable of interest in the NCS by providing an efficient, low-burden approach to stress measurement.

Measures and assessments of maternal psychosocial stress currently included in the NCS protocol exclusively consist of participant self-reported, retrospective recall measures. Weaknesses of these traditional self-reported recall measures relate to biases associated with retrospective recall and failure to assess and account for individual differences in biological stress responsivity. In order to adequately collect data to empirically inform the selection of measures of maternal stress and stress biology for the NCS, this substudy will compare and contrast the reliability and validity of data using maternal self-report instruments currently in use by the NCS, as well as additional measures tested in this substudy against self-report and biological data collected using ambulatory assessments and biospecimens.

A.2 Purpose and Use of the Information Collection

The Stress and Cortisol Measurement Substudy will develop an optimized, item-reduced measure of self-reported stress that is supported empirically through convergent validity analysis of stress biomarkers. Key moderators of stress biomarkers will be evaluated to inform the efficiency and quality of measurements during pregnancy. Development of a scientifically robust maternal stress measure would measure chronic stress more efficiently, would not require biospecimen collection and biomarker analyses, and would thereby reduce participant burden and NCS Vanguard (Pilot) and NCS Main Study costs.

To this end, we will collect several types of information from 700 participants demographically similar to NCS Vanguard (Pilot) Study participants, but not geographically eligible to participate in the Vanguard Study:

1) Medical record abstraction;

2) Questionnaires (a series of validated stress measures);

3) Physiological measures (heart rate and self-reported stress) and

4) Several types of biospecimens (blood, saliva, urine, and hair samples.)

Visit Structure:

The visit structure is composed of three visits that are explained in detail below: (1) First in-person visit, (2) four-day ambulatory assessment period, and (3) Second in-person visit.

First In-Person Visit

At an initial in-person visit, after screening and consent, Study staff will collect blood and hair samples to be analyzed for cortisol levels. The addition of the measurement of cortisol levels in hair will provide a relatively non-invasive, complementary, and more cumulative biomarker of stress than what is currently available using salivary cortisol measures. At this time, Study staff will also demonstrate to participants the procedures for saliva self-collection, and will train participants on the ambulatory assessment procedures, including an explanation of the ActiHeart heart rate monitor and a review on how to complete an electronic time diary. At this time, participants will also be asked to complete a demographic and health interview (please see attachment 6: Demographic and Health Interview), a contact form (please see attachment 4: Participant Contact Information Sheet), and a series of stress surveys (please see attachment 7: Visit 1 Stress Questionnaire and attachment 10: Stressful Life Events Schedule).

Four-day Ambulatory Assessment Period

After the first in-person visit, participants will complete a take-home packet of additional stress measures and questions on family background (please see attachment 8: Take Home Packet). Participants will be asked to complete a time diary each day for four days. This electronic diary will be programmed on an Android smart phone; diary entries will be prompted by an on-board electronic diary that is pre-programmed to signal the participant an average of one time per hour (i.e., every 60 minutes + 10 minutes) during the waking hours of the four-day monitoring period. Diary items will appear one at a time on the screen, and participants will use the smart phone's touch screen to make response choices. Responding to the electronic diary will take approximately two minutes per entry, and participants will record 18 entries per day for four days. During this four-day period, participants will also be asked to wear an ActiHeart device on the chest by clipping two standard ECG pads onto a chest band. The ActiHeart does not cause discomfort and can be worn under any type of clothing. The ActiHeart battery is rechargeable using a built-in USB which can also be used to retrieve the data collected by the device.

Additionally, during the four-day ambulatory assessment period, participants will be asked to collect a set of saliva samples. Due to the diurnal nature of saliva cortisol, participants will be asked to collect saliva at several time points over the course of four days. Participants will be reminded to collect saliva samples with the alarm on the Android smart phone, and will be instructed to store the saliva samples at room temperature.

During the last evening of the four-day monitoring period, participants will be asked to collect an overnight urine sample. Participants will collect all urine excreted between 8PM and 8AM the following morning. Following the four-day monitoring period, participants will return to the Study Center to return the ActiHeart device, the Android smart phone, the saliva samples, the urine sample, and the take-home packet.

Second In-Person Visit

Approximately 12-14 weeks after the first in-person visit, we will schedule a second in-person visit with each participant. At the second visit, Study staff will collect blood and hair samples a second time. Participants will also be asked to complete a second set of stress questionnaires (please see attachment 9: Visit 2 Stress Questionnaire and attachment 10: Stressful Life Events Schedule).

Study staff will complete an enrollment survey (please see attachment 5: Enrollment Medical Record Abstraction Form) and a postnatal survey (please see attachment 11: Postpartum Abstraction Form) by way of medical record abstraction, with participant consent, outside of the in-person interview.

These collections will be performed and analyzed by a subset of NCS Study Centers. All participants at all Study Centers will follow the same protocol. For a summary of specific analytic activities undertaken by each Study Center participating in this substudy, please see Table A1, below. The overall goal of the Stress and Cortisol Substudy is to conduct a multi-center collaborative project that will be used for the empirical evaluation of maternal stress measurement for use in the NCS Main Study. The use of ambulatory assessments is not feasible for the larger NCS Vanguard (Pilot) and Main Study due to heavy participant burden; however, the use of these assessments as a gold standard against which self-report questionnaires and interviews should be accurately validated makes them useful for purposes of developing an optimized stress measure.

There are a wide range of approaches and protocols available to assess maternal stress and stress biology during pregnancy, with different opinions among experts regarding their relative feasibility and acceptability. Because cortisol is not secreted continuously and at the same levels, multiple approaches to its measurement are needed to estimate the trajectory of cortisol secretion over time, in the absence of continuous monitoring. Blood permits measurement of cortisol at a single point in time. Urine provides an estimate of cortisol secretion over an overnight or, in some cases, a 24-hour period of time. Hair provides for not only quantification of levels of stress over a period of approximately 30 days, but also for a measurement of cortisol levels at times up to six months prior to collection time, and of multiple exposures relating to cortisol. Saliva permits for cortisol collection at multiple time points within a 24-hour period, and allows for a relatively noninvasive estimation of the cortisol secretion trajectory for a given day. Specifically, replication of previous protocol demonstrations of cortisol measurement in hair is necessary for NCS biomarker prioritization. Information regarding a number of health, demographic, and other variables will be collected and analyzed to evaluate their role as potential covariates in the measurement of cortisol and stress, and relevance for the development of a reduced item questionnaire. Depending upon the results observed, further testing in a broader or more diverse population may be necessary to produce a standardized, validated, scientifically robust measure

of chronic stress. Further testing, if needed, would be accomplished by requesting a non-substantive change to the regular clearance once it is established. Approximately 2,100 burden hours are requested in A.12 for "follow-up studies."

The activities, Study Centers involved, and intended study outcome(s) are summarized below in Table A1.

Table A1. Stress and Cortisol Substudy Activities

Activity	**Study Centers**	**Analysis & Intended Outcome**
Developing Optimized Measure of Chronic Stress in Pregnancy	Tulane University University of California – Irvine University of Minnesota Brown University Northwestern University	Develop an optimized, item-reduced measure of self-reported maternal stress; subsequent validation against biologic measures of stress
Evaluating Psychosocial Stressors in Pregnant Women	University of California – Irvine University of Texas Health Science Center	Empirical evaluation of psychosocial stress measures and impact on biomarkers of health risk
Validation of Self-Report Measures of Stress	University of California – Irvine	Compare and contrast reliability and validity of data used in maternal self-report assessment against data collected using physiological assessments, to inform the selection of maternal stress measures for the NCS
Validation of Cortisol in Hair Samples	University of California – Irvine University of Washington	Optimization of use of hair samples for measuring stress biomarkers

A.3 Use of Information Technology and Burden Reduction

The Stress and Cortisol Measurement Substudy is designed to develop a more acceptable self-report measure of maternal stress, and may include computer-assisted interviewing, automated data collection, and other procedures designed to decrease participant burden, study costs, and to improve data accuracy. Other appropriate information technology solutions will be embraced to reduce respondent burden and improve data quality. Of particular note for this substudy, participants will be given an Android smart phone containing an electronic diary. Participants will be prompted with reminders to complete diary entries as required for this substudy, and will be able to answer specific questions using a touch screen. Using this type of electronic diary will reduce the amount of participant

burden during the four-day time period. Additionally, the electronic diary will increase the accuracy and reliability of diary results by enabling an analysis of participant compliance. Use of the ActiHeart device to measure heart rate and physical activity will also decrease participant burden while increasing the reliability of data collection and the ability to manipulate raw data in third-party statistical programs.

Title II of the E-Government Act of 2002 requires federal agencies to conduct privacy impact assessments (PIAs) before developing or procuring information technology (IT) systems that collect, maintain, or disseminate personally identifiable information (PII). In 2007, NIH released Manual Chapter 1745-1, "Privacy Impact Assessments (PIAs)," which reinforces the Department of Health and Human Services (HHS) requirement for PIA completion, and details NIH employee roles and responsibilities in support of this process.

PIAs provide a documented process, the purpose of which is to identify and protect employee and public citizens' PII; and it ensures that the government has considered necessary safeguards for the PII passing through or being collected, maintained, or disseminated in its systems. The NCS must effectively manage participant safety while preserving data integrity and availability to carry out NCS activities. To do so, privacy risks associated with NCS systems are documented by having field contractors (Study Centers) complete PIAs and include risks in the system plan of action and milestones (POA&M). The NICHD Chief Information Officer exercises appropriate oversight of contractors in carefully reviewing PIA information.

A.4 Efforts to Identify Duplication and Use of Similar Information

Prior to the planning and initiation of the NCS, an inventory and review of longitudinal studies was conducted. The review examined whether the study goals could be addressed without embarking on an entirely new study. The systematic review of all available longitudinal cohort studies found no study capable of answering the questions and concerns that led to the proposed National Children's Study regarding potential long-term effects in children from environmental exposures. Additionally, selected NCS Vanguard study visit assessment measures were revised based on data from the Initial Vanguard Study (OMB# 0925-0593, approved by OIRA on 09/22/2008). These measures now require testing before implemented responsibly in the NCS Main Study. User acceptance testing complements, but does not adequately replace, use and evaluation of measures in a large-scale data collection environment.

Substudies of this nature will be utilized by the NCS as a way to demonstrate proof-of-concept in a manner that minimizes participant burden and study costs, prior to testing in the NCS Vanguard Study protocol if results warrant. In this way, formative research projects and substudies will not duplicate, but rather, guide NCS Vanguard Study and Main Study information collection.

A number of NIH-funded research grants have investigated stress in pregnancy. The Pregnancy, Infection, and Nutrition Study (PINS) concluded that the relationship between measurements of reported stress and biomarkers is not straightforward in large epidemiological studies of pregnancy. Other studies have concluded that pregnancy-specific stress contributes directly to preterm delivery, and indirectly to low birth weight. In addition, international research has identified stress in pregnancy as an important area for scientific investigation. The Danish National Cohort Study concluded that maternal stress during pregnancy may be a common risk factor for impaired child health, suggesting

possibilities for new approaches to reduce childhood diseases. However, these studies have not sought to establish a standardized, validated approach to evaluate exposure to stress, including psychosocial stress, which correlated highly with more invasive and burdensome approaches to measurement of biological markers of stress. Measures developed by this substudy will be nonproprietary and available to all.

A.5 Impact on Small Business and Other Small Entities

The potential impact of the Stress and Cortisol Measurement Substudy on small businesses will largely include health care providers such as physicians, nurses, and others. Local NCS staff will work with physicians and other medical care providers or facilities to provide information about the study to their patients. With the consent of the participant, key medical diagnostic and treatment information on study participants will also be requested of medical providers. Where requested, the study will reimburse providers for any expenses incurred as part of filling requests for information.

A.6 Consequences of Collecting the Information Less Frequently

The Stress and Cortisol Measurement Substudy is a one-time collection of information. To obtain all of the information required, we will interact with participants at two time points during their pregnancy. The first interaction with participants will occur during early gestation (between 14 and 20 weeks), and the second will occur during late gestation (28-32 weeks). In between substudy visits, participants will be asked to complete a four-day ambulatory assessment. The purpose of multiple collections in this substudy is to provide an opportunity to evaluate early and late outcomes of stress during pregnancy.

A.7 Special Circumstances Relating to the Guidelines of 5 CRF 1320.5

There are no special circumstances that would cause this information collection to be conducted in a manner inconsistent with 5 CFR 1320.5.

A.8 Comments in Response to the Federal Register Notice and Efforts to Consult Outside Agency

The 60 day Federal Register Notice regarding the Provider-Based Sampling for the NCS Vanguard (Pilot) Study was published on pages 9666-9668 of Volume 77 of the Federal Register on February 17, 2012. One comment was received in response to that notice. The commenter questioned the value of the National Children's Study overall and suggested that the NCS be eliminated. The comment is reproduced below in its entirety:

our govt is getting entirely too nosy. the fat cat bureaucrats in skanky corrupt washinton dc. want to manage out kids bodies, instead of parents and now they seem to want to m anage our kids minds. it is time to downsize this out of control agency. this agency seems to find parents unacceptable. the budget for this proposal should be zero. this is invasive govt at work. the taxpayers of america do not want to be taxed to pay for this. this survey is not helping america, where l out of 2 americans are living in poverty. they are overtaxed to pay for the wastefulness of this agency.

Response to the comment: The National Children's Study was mandated by Congress through the Children's Health Act of 2000 (Public Law 106-310), which states:

(a) PURPOSE.—It is the purpose of this section to authorize the National Institute of Child Health and Human Development to conduct a national longitudinal study of environmental influences (including physical, chemical, biological, and psychosocial) on children's health and development.*
(b) IN GENERAL.—The Director of the National Institute of Child Health and Human Development shall establish a consortium of representatives from appropriate Federal agencies (including the Centers for Disease Control and Prevention, the Environmental Protection Agency) to—*
(1) plan, develop, and implement a prospective cohort study, from birth to adulthood, to evaluate the effects of both chronic and intermittent exposures on child health and human development; and
(2) investigate basic mechanisms of developmental disorders and environmental factors, both risk and protective, that influence health and developmental processes.
(c) REQUIREMENT.—The study under subsection (b) shall—
(1) incorporate behavioral, emotional, educational, and contextual consequences to enable a complete assessment of the physical, chemical, biological, and psychosocial environmental influences on children's well-being;
(2) gather data on environmental influences and outcomes on diverse populations of children, which may include the consideration of prenatal exposures; and
(3) consider health disparities among children, which may include the consideration of prenatal exposures.

A.9 Explanation of Any Payment or Gift to Respondents

To maximize response rate, many research studies, particularly those involving medical procedures, offer incentives for participants. For example, the National Health and Nutrition Examination Survey (NHANES) has offered their participants incentives since the 1970s. Incentives are effective in increasing response rates for in-person surveys and can help increase response rates especially for minorities and low-income households.

Participants in NCS substudies will receive monetary and non-monetary incentives for their time and effort. The incentive amount will be determined by the amount of time required of the participant, as well as the type of activities that will be required. Incentive amounts will be consistent with the approved incentive schedule for the NCS Vanguard Study, including the Initial Vanguard Study, the Recruitment Substudy, and formative research. Participants agreeing to provide biospecimen samples will be offered a monetary incentive or equivalent not exceeding $25. Small gifts of appreciation for participation may be provided to participants in lieu of cash incentives. These may include items such as t-shirts, tote bags, etc., and are intended as tokens of appreciation.

In the proposed Stress and Cortisol Measurement Substudy, data collection visits will feature data collection questionnaires averaging one to two hours in length. Additionally, at each visit, participants will provide a set of biospecimens, including blood, saliva, hair, and urine. For these in-person visits, participants will receive incentives not exceeding $50 ($25 for completion of questionnaires, plus $25 for biospecimens). Participants will receive incentives not exceeding $25 for each of two sets of participant-collected saliva samples sent to Study Centers. Total incentives per participant for this

substudy will not exceed $125.A.9 Table 1: Incentive by Visit/Activity		
	Assessments and Collections	**Incentive Provided**
Clinic Visit 1	• Screening • Blood • Hair • Saliva Self-Collection Demonstration • Ecological Momentary Assessment Training • Urine Self-Collection Instructions • Visit 1 Stress Questionnaire • Demographic and Health Interview • Participant Contact Information Sheet • Stressful Life Events Schedule Checklist	Up to $50
Ambulatory Assessment Period	• Take-Home Questionnaire • Time Diary • Heart Monitoring • Saliva • Urine	Up to $25 (non-monetary)
Clinic Visit 2	• Blood • Hair • Visit 2 Stress Questionnaire • Stressful Life Events Schedule Checklist	Up to $50
Follow-up Studies	• To be determined	To be determined

Table A2. Maximum NCS Incentives, by Study Activity and Impact on Participants				
Data Collection Activity Characteristics	**Initial NCS Vanguard Study**	**NCS Recruitment Substudy and Formative Research**		
		Phase 1	Phase 2	Formative Research
Time for encounter	3 hours	0.5 to 1 hour	0.5 to 1 hour	0.5 to 1 hour
Sensitivity of questions	Sensitive, including sexual activity	Few sensitive questions	Few sensitive questions	Few sensitive questions
Physical measures	Yes	No	No	Yes*
Environmental specimens	Yes	No	Yes	Yes*
Biospecimens	Yes	No	Yes	Yes*
Participant observation	Yes	No	No	No
Monetary incentive, per visit	$100	$25	$25 for the group of study questionnaires, plus $25, in total, for any bio-specimens collected during a contact and, where appropriate for environmental specimens	$25, in total, for any bio-specimens collected during a contact. For questionnaires, or any environmental specimens – up to $25 when deemed necessary
Non-monetary incentives (tote bags, post its, key chains, etc.)	In addition to the monetary incentive, non-monetary incentives valued at $25 or less may be offered to participants	As an alternative to the monetary incentive, NCS logo gifts valued at $25 or less may be offered to the participants in lieu of cash or local incentives not exceeding $25 in value and deemed non-coercive by local IRBs	In addition to the monetary incentive, NCS logo gifts valued at $25 or less may be offered to the participants if these are deemed acceptable by local IRBs	Instead of monetary incentives, NCS logo gifts valued at $25 or less may be offered to the participants if these are deemed acceptable by local IRBs

*Specific information proposed for formative research purposes will align with approved generic clearance mechanisms (that is, generic clearances for Recruitment and Retention projects (OMB #: 0925-0590, expiration date 09/30/2014) and Biospecimen and Physical Measurements projects (OMB # 0925-0647, expiration date 01/31/2015)), and the Generic Clearance Request for Environmental Science projects, in process.

A.10 Assurance of Confidentiality Provided to Respondents

The Stress and Cortisol Measurement Substudy will follow the same procedures and standards of confidentiality applicable to the NCS Initial Vanguard Study and Recruitment Substudy. Participants will be informed about the Certificate of Confidentiality granted to NCS to protect data from involuntary disclosure.

The study centers, under contract to conduct the NCS, will have policies and procedures regarding confidentiality and protection of study data which will be reviewed and monitored by the NCS Program Office.

In addition to their own confidentiality procedures and policies, study centers will implement all federally required study-related confidentiality and data security procedures. All NCS Program Office staff, NCS study center staff, and other NCS contracting staff with access to NCS data must receive data confidentiality and security training provided by the NCS Program Office or its agent. These include completion of the NIH Information Security and Privacy Awareness Training, completion of a Human Subjects Protection Training, and signing an Assurance of Confidentiality or similar pledge that NCS data will only be used for the intended scientific purpose. All NCS Staff are required to complete security background checks consistent with Office of Personnel Management requirements.

To further assure confidentiality of participant data, the study will employ rigorous methods to provide security for personal identifying information. Each study center and the NCS Program Office Data Warehouse will be required to submit an NCS Security Plan and Assessment that complies with the Federal Information Security Management Act (FISMA). This Security Plan will include: a) certification and accreditation of proposed data capture and case management software; b) configuration of those systems on study equipment; c) full disk encryption and two-factor authentication of study computers housing NCS data; and d) security assessment of the physical computing environment. After study centers complete the self-assessment of their security plans, the NICHD Chief Information Officer will review all study center security plans to determine study center's authority to operate. Frequent and regular monitoring visits will assist in compliance with these terms.

Specific NCS data and materials to be collected, disclosure review, and data access are described in detail in the Data Access and Confidentiality Committee Manual. Principles and policies are available at http://www.nationalchildrensstudy.gov/about/organization/dacc/Pages/PolicyManualandDataUseAgreements.aspx; the manual is available to the public upon request. Specifically, all NCS data files will undergo disclosure review for personally identifiable information, using procedures consistent with or exceeding those named in Working Paper 22 of the Federal Committee on Statistical Methodology, and steps will be taken to appropriately manage disclosure risk. For example, genome-wide scans conducted on NCS specimens will be considered personally identifiable information and treated as such. Some biologic analyses (for example, HIV status, exposure to specific toxicants), results of some mental health screening tests, and reports of abuse are also considered sensitive.

A.11 Justification for Sensitive Questions

There are a number of questions that may be contained in NCS questionnaires and in stress assessment questionnaires that could be considered sensitive such as pregnancy status, reproductive and medical histories, and income. As part of the informed consent process, women will be informed that their participation in the NCS is voluntary and that they may refuse to answer any question. All study questionnaires that are proposed for this substudy have been or will be reviewed by Human Subjects Review Boards at NICHD and participating institutions.

Each of these sensitive questions is necessary to allow comparisons between the substudy sample and persons potentially eligible for the Main Study, thereby informing whether proposed questionnaire items and biospecimen collections would warrant further testing in the NCS Vanguard Study.

A.12 Estimates of Hour Burden Including Annualized Hourly Costs

Estimates of annualized hour burden and annualized cost to respondents are laid out in Tables A.12-1 and A.12-2, respectively. The total number of estimated respondents is 2,100 annually. The total number of annual burden hours is 9,499. The estimated total annual respondent cost is $94,490.

The Stress and Cortisol Measurement Substudy is intended to be a one-time data collection; there may be follow-up studies that involve testing in a broader or more diverse population to produce a robust measure of chronic stress, as noted in A.2. The frequency of data collection differs by data collection activity, and is displayed in Table A3. In most instances, data are collected once. However, adult saliva (28) and time diary (72) collected several times.

Estimates of the total annual respondent cost for the collection of information use the wage rate of $10.00 per hour.

The cost of contracting out or paying outside parties for information collection activities is included in A.14.

A.12 - 1 Estimates of Hour Burden

Table A3. Estimated Hour Burden for Stress and Cortisol Measurement Substudy

Data Collection Activity	Type of Respondent	Estimated Number of Respondents	Estimated Number of Responses per Respondent	Average Burden Hours Per Response (in hours)	Estimated Total Annual Burden Hours
Clinic Visit 1	Members of NCS target population (not NCS participants)	2,100	1	83/60	2,916
Ambulatory Assessment Period	Members of NCS target population (not NCS	700	1	275/60	3,208

Data Collection Activity	Type of Respondent	Estimated Number of Respondents	Estimated Number of Responses per Respondent	Average Burden Hours Per Response (in hours)	Estimated Total Annual Burden Hours
	participants)				
Clinic Visit 2	Members of NCS target population (not NCS participants)	700	1	105/60	1,225
Follow-up Studies	Members of NCS target population (not NCS participants)	700	1	180/60	2,100
Total		**2,100**			**9,449**

A.12 - 2 Annualized Cost to Respondents

Table A4. Estimated Cost for Stress and Cortisol Measurement Substudy

Data Collection Activity	Type of Respondent	Estimated Total Annual Burden Hours	Hourly Wage Rate	Estimated Total Annual Respondent Cost
Clinic Visit 1	Members of NCS target population (not NCS participants)	2,916	$10.00	$29,160
Ambulatory Assessment Period	Members of NCS target population (not NCS participants)	3,208	$10.00	$32,080
Clinic Visit 2	Members of NCS target population (not NCS participants)	1,225	$10.00	$12,250
Follow-up Studies	Members of NCS target population (not NCS participants)	2,100	$10.00	$21,000
Total		**9,449**		**$94,490**

A.13 Estimate of Other Total Annual Cost Burden to Respondents or Recordkeepers

There are no other known costs to participants or recordkeepers.

A.14 Annualized Cost to the Federal Government

The proposed information collection is estimated to cost the federal government about $605,887 per year over the three-year period. The annualized cost to the federal government is based on budgetary

data for task orders that include costs of information collection, design, development, tests, printing forms, mailing list compilation and maintenance, mailing or enumeration, editing, coding, tabulation, analysis and publication of results. Salary and travel costs associated with project development, implementation, and monitoring are incorporated into the annualized cost to the federal government.

A.15 Explanation of Program Changes or Adjustments

This request proposes a new data collection.

A.16 Plans for Tabulation and Publication and Project Time Schedule

Statistical goals for the collected information are: 1) To identify constructs of psychosocial stress that correlate with biological and physiological measures of stress; 2) To use ambulatory momentary assessments of stress to identify standard physiological and biological measures of stress that reflect levels of psychosocial stress; and 3) To compare cortisol concentrations measured in hair with cortisol concentrations measured in saliva, hair, and urine.

A relational database will be established for this substudy. An ID number for each participant will be linked to data entered into the database. Detailed reliability checks of the data will be done, and double data entry for non-electronic questionnaires will be used to prevent data entry errors. Additionally, datasets will be checked for missing data, outliers, and ambiguous, incomplete, or otherwise invalid responses using SAS programs. Data analysis will be completed in three major steps: 1) Descriptive analysis; 2) Bivariate analysis; and 3) Multivariate analysis. All analyses will be carried out using SPSS (version 16.0) and SAS (version 9.2).

Descriptive statistics will be computed to evaluate the characteristics of the sample and to examine the distributions of each variable. Summary statistics will be computed to characterize the study population with regard to important demographic and biomedical dimensions. Cross correlation analysis will be performed to identify significant correlates of biologic and physiologic measures of stress.

During the second stage of analysis, bivariate analyses will be conducted to examine inter-relationships among predictor and outcome variables, and to create indices for selected substudy variables. An important part of the second phase of analysis will be assessing the extent to which constructs were adequately measured. Additionally, psychometric analyses of measures will be performed to determine the dimensional structure of instruments and to identify overlapping constructs.

Multivariate analyses will include testing relationships between psychological and biological stress and maternal and fetal DNA and birth outcomes (birth weight, length of gestation). Given that these models may include correlated predictors, measures of variance inflation will be used to assess potential problems of multicollinearity, and the appropriate scaling factors will be employed.

After necessary tests for unidimensionality, item response theory methodology will be used to examine how well individual items fit the latent trait being measured (e.g., severity of stress), estimate the difficulty and discriminability of items along the stress continuum, and estimate the amount of psychometric information provided by items or groups of items (scales). Differential item functioning

approaches also will be used to determine the extent to which item information varies between relevant population sub-samples.

Model fitting will be undertaken employing a variety of methods that have been developed to examine the item fit. Extensive evaluation of dimensionality to eliminate items that do not meet the IRT assumptions will be conducted. Misfitting items will be reviewed for clinical relevance. Item calibration and discrimination will be accomplished using a 2-parameter model to fit the data, in order to compare the discrimination power of the items, items with higher discrimination parameters will be preferred for inclusion in the optimized stress scale.

Item response theory models will provide item and scale information functions that can be used to examine precision of individual items or groups of items (scales). An information function indicates the precision with which a patient's stress is estimated along the stress continuum. Information functions of different items will aid in the selection of items for the final optimized scale.

Associations between self-reported stress (measured by the optimized stress scale) and (dichotomized) biomarkers will be identified using a multiple logistic regression model. Sociodemographic and clinical variables will be empirically evaluated as potential covariates. Using a conservative sample size estimate of 500, the estimated statistical power will be 80% to detect a change of 18% to 29% of women with elevated biomarker levels in the low stress group compared to the high stress group (odds ratio = 1.88).

Table A5: Project Time Schedule

Activity	Time Schedule
Participant Recruitment & Screening	1-2 months after OMB approval
Data Collection Activities	4-10 months after OMB approval
Validation	10-22 months after OMB approval
Analyses	10-22 months after OMB approval
Follow-up Studies	12-36 months after OMB approval

A.17 Display of Expiration Date of OMB Approval

The NCS is not seeking an exemption from displaying the expiration date of OMB approval.

A.18 Exceptions to Certification for Paperwork Reduction Act Submissions

The NCS is not requesting any exceptions.