

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

Part B only

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B. Collection of Information Employing Statistical Methods

B.1 Respondent Universe and Sampling Methods

Inclusion and Exclusion Criteria

The following groups are eligible for participation in the Stress and Cortisol Measurement Substudy:

- English-speaking women of the age of majority (typically, age 18) with a singleton intrauterine pregnancy, who are less than 20 weeks pregnant
- Children born to enrolled women

Women who have any prior or previous obstetric risk conditions such as systemic maternal disease, placental or cord abnormalities, uterine anomalies, infection, congenital malformations, chromosomal abnormalities, previous preterm labor or low birth weight will be excluded from this substudy. Women with any conditions that may interfere with neuroendocrine or cardiovascular function such as endocrine, hepatic, renal, or autoimmune disorder, hypertension, or use of corticosteroid medications in the last month, will also be excluded.

Participants for this substudy will be recruited as a convenience sample of women attending visits at clinics and hospitals associated with Study Centers. Persons demographically similar, but not geographically eligible, to participate in the NCS Vanguard Study will be invited to join the Stress and Cortisol Measurement Substudy using local advertising methods. Enrollment will continue until project-specific recruitment targets have been met. Invitations to join the Stress and Cortisol Measurement Substudy will clearly indicate the separate and distinct nature of NCS substudies from the NCS Vanguard Study. Invited participants will be reminded that their participation in NCS substudies is voluntary.

To achieve a sample of 700 participants for this substudy, we anticipate the need to screen approximately three women for each enrolled participant, or 2,100 women total.

B.2 Procedures for the Collection of Information

Medical Record Abstraction: Study Center staff (under contract to the NCS) will obtain information on participants' current gestational age, height, weight, and anticipated due date from prenatal charts, with permission granted by participants (please see attachment 5: Enrollment Medical Record Abstraction Form). This information will be used to determine eligibility and baseline information on participants' pregnancies. Birth outcomes, including pregnancy complications, preterm birth, birth weight, total days in the hospital following birth, infant feeding methods for the first 24 hours following birth, and presence of birth traumas, will be collected via medical record abstraction (please see attachment 11: Postpartum Abstraction Form). These birth outcomes will be collected to support analyses of the associations between maternal stress, as measured by participant self-report, cortisol levels, and physiological symptoms, and adverse birth outcomes.

Questionnaires: At two separate visits to Study Centers, Study Center staff will administer interview instruments in person. At their first visit, participants will also be given a take-home packet of self-administered measures (either paper and pencil administration or secure Web administration). Detailed reliability checks of data that has been entered into databases will be performed at each Study Center, with follow-up with participants to clarify potential errors or other issues. Questionnaire data will also be double-entered and cross-checked to prevent data entry errors. Datasets will be checked with SAS programs for missing data, outliers, and ambiguous, incomplete, or invalid responses. Several commonly-administered and validated stress scales will be administered to Stress and Cortisol Measurement Substudy participants. The stress measures selected will provide information on key domains of chronic stress, including:

- 1) *External stressors* as measured by the Home Hardships Scale (Illinois Families Study—Child Well-Being Supplement), a measure of hardship events that have occurred in the past year; the Childhood Trauma Questionnaire; the Sarasons Life Experiences Survey; self-reported emotional, physical, and sexual abuse as assessed by the Abuse Assessment Screen (McFarlane 1992); and the Stressful Life Events schedule, which measures stressful life events occurring in the past year;
- 2) *Perceived stress* as measured by the Cohen Perceived Stress Scale; the Prenatal Distress Questionnaire (Yani and Lobel, 1999), a measure that assesses worries and concerns related to pregnancy; and the Williams Discrimination Scale;
- 3) *Buffers of response to external stress*, as measured by the Medical Outcomes Study Social Support Survey (Sherborne & Stewart, 1991), a measure of the availability of emotional, information, tangible, and affectionate social support and the Rosenberg Self-Esteem Scale, a measure of one's attitudes about themselves;
- 4) *Enhancers of stress*, including the Center for Epidemiological Studies—Depression Scale (Radloff 1977) and the Sleep Quality Index, a measure of the quality of sleep in the past month.

Responses to questionnaires will be evaluated in the context of the presence of biological and physiological markers of stress. Data will be used to narrow the number and type of questions in order to produce an optimized measure of chronic stress that is highly correlated with more invasive methods of measuring stress in pregnant women.

Physiological Measures: We will use ambulatory monitoring to measure participants' heart rate, physical activity, location, social interactions, eating patterns, and other behaviors. Ambulatory monitoring will involve real-time assessments over a period of four days of the natural day-to-day settings of respondents' psychological states, behaviors, physiologies, and the use of statistical approaches using time-series hierarchical regression models to compute the degree of association between psychological and biological states.

At the first visit, participants will be given an ActiHeart device and instructed how to wear it. The ActiHeart device is the first truly lightweight (10g) and waterproof self-contained logging device which allows physical activity to be recorded synchronously with heart rate. The participant will wear it

continuously (except when bathing) for the entire four-day ambulatory monitoring period. Once returned by the participant, data from the ActiHeart can be downloaded and manipulated by third-party statistical programs. The ActiHeart has been shown to be a valid and reliable method of collecting ambulatory physical measurements and has been standardized across many settings (Brage, et al., 2005). The raw data is held in a database and can be edited with full traceability without compromising the integrity of the original data. Data can also be exported for manipulation in third-party statistical programs.

Participants will also be given an Android smart phone containing an electronic diary. Participants will be instructed in how to use the electronic diary during the first visit. The smart phone will remind participants to fill out an electronic diary entry approximately 18 times per day for the four days that participants are also wearing the ActiHeart device. This frequent monitoring will ensure that the sample of moments assessed is representative of participants' daily experience and that there will be an adequate amount of data to be assessed by each participant. Participants will use the touch screen to select responses to specific questions regarding their location, activity, social interaction characteristics, mood and affect, pregnancy-related symptomology, physical climate, and consumption of foods, liquids, and/or drugs. Each electronic diary response will be time-stamped so that compliance can be evaluated. Additionally, the electronic diary will record times when participants are reminded to complete an entry but do not do so.

We will compare data obtained from the ambulatory monitoring component of the Stress and Cortisol Measurement Substudy with responses to maternal self-report instruments to inform the selection of measures of maternal stress. Power and precision of this analysis is enhanced over typical survey data because the ambulatory monitoring component will allow the measurement of multiple conditions and/or exposures in each participant. Additionally, variability in exposure-response relationships due to between-subject characteristics is controlled for by design because of a reduction in the variability of the response variable, without reductions in the magnitude of the exposure-response relationship.

Biospecimen Collections: This substudy will take multiple approaches to cortisol measurement with the collection of saliva, blood, hair, urine. To investigate salivary cortisol levels, saliva samples will be collected over a period of four days, with participants self-collecting a total of seven saliva samples per day. Saliva samples will be collected Immediately upon awakening, 30 minutes after awakening, 45 minutes after awakening, and 60 minutes after awakening; at 12 PM; at 4PM; and at 8 PM. Participants will be instructed to place a cotton roll in their mouths until saturated with saliva, and then to reseal the swabs in a plastic salivette tube that has been pre-labeled with the date and time. During the last day of this four-day period, participants will be instructed to collect all urine excreted between the hours of 8 PM and 8 AM. Participants will be trained on these self-collection procedures during their first visit to the Study Center.

To assess glucocorticoid sensitivity and glucocorticoid binding, Study Center staff will take a venous blood sample with a needle at each of two participant visits. To assess cumulative cortisol production, Study Center staff will use fine scissors to cut hair strands as close to the scalp as possible.

Approximately 20 strands of hair will be collected from each participant. Participants will be asked to self-collect an overnight urine sample and return to the Study Center.

B.3 Methods to Maximize Response Rates and Deal with Nonresponse

Data from related studies and the pre-OMB pilot recruitment confirm that we expect to achieve an 80-85% response rate.

This response rate is calculated based on the following data:

- A.** Pre-OMB Pilot Recruitment: Study research assistants collectively approached 11 women to participate, and enrolled 9 of these 11 women, resulting in a response rate of 82%.
- B.** The Stress in Pregnancy (SIPS) Study is a prospective cohort of 114 pregnant women, carried out by Dr. Ann Borders at Northwestern University, using the same recruitment protocol, and similar patient burden. Similar to the this study, the SIPS Study protocol included 2 research visits in the prenatal clinic over the course of pregnancy requiring both self-reported and maternal blood collection along with a take home saliva collection. The response rate data from this preliminary study are an excellent predictor for the response rate expected. The SIPS Study recruitment was very successful with enrollment of 114 women out of 140 women approached, with an overall response rate of 81%.
- C.** The Ecological Momentary Assessment (EMA) Study is an observational, population-based cohort study of 103 pregnant women, led by Dr. Pathik Wadhwa at the University of California, Irvine. The EMA Study uses comparable protocols to this study with similar participant burden. The EMA Study protocol includes an assessment that covers a consecutive 4-day period of time (2 weekdays + 2 weekend days). During each assessment period, electronic diaries are used to collect approximately 15 measures/day (over waking hours) of subjects' psychological state, social interaction, activity and behavior. Continuous (24-hour) ambulatory measures of maternal heart rate and physical activity are collected, and seven saliva samples over the course of each day are obtained for indicators of autonomic and endocrine activity, respectively. At the end of each ambulatory monitoring session, a maternal blood sample is collected for measures of maternal-placental-fetal (MPF) endocrine processes (CRH, cortisol, E3), a urine sample is collected for biologic verification of self-reported health behaviors (smoking, illicit drug use), and traditional (retrospective recall) measures of maternal psychosocial stress and related constructs are administered. Biophysical, biomedical and birth outcome data are abstracted from the medical record. Similar to the SIPS and pilot study, the EMA Study enrolled 103 out of 128 women approached, and had an overall response rate of 80.5%.

Again, based on our experience with recruitment of 9 participants during the pre-OMB approval study period and data from our preliminary studies that employed similar recruitment and retention strategies, we expect a retention rate that is 95% or higher. This estimate was calculated with the following data:

- A.** Pre-OMB Pilot Recruitment: Of the 9 pre-OMB approval pilot participants, 6 participants have reached the window to complete a second study visit (Visit 2). All 6 eligible

participants have completed all Visit 2 self-reported stress measures and biospecimen collections and demonstrated 100% retention.

- B.** The Stress in Pregnancy (SIPS) Study: Of the 114 SIPS Study participants, only 3 participants were lost to follow up and did not complete their second study visit. We feel this level of compliance with protocol was a tribute to the rigorous patient retention strategies employed. This attrition rate of 3% supports the preliminary data from the pilot pre-OMB approval participants and further reinforces our expected retention rate for the study of 97% or greater.
- C.** Ecological Momentary Assessment (EMA) Study: Of the 103 EMA Study participants, only 4 participants did not wish to continue involvement in the study, yielding a 96% retention rate. Since the EMA Study used similar methods of communicating with and engaging participations as the pre-OMB pilot and SIPS studies, we are confident that this high attrition rate is reflective of what we can expect.

Given the preliminary studies and the Pre-OMB Pilot Recruitment phase, we have a tested and successful methodology established for recruitment and retention. We also have established excellent communication, training and oversight across the Study Centers to ensure understanding and adherence to these recruitment and retention protocols across all sites. We have established a Manual of Operations that details our recruitment and retention strategies. We held a national training meeting to assemble all research assistants for training on recruitment and retention methodologies as well as all study protocols. Our central study coordinator maintains communication with all Study Centers to ensure protocol is followed and any issues are addressed. Each Study Center has completed Feedback Forms after the enrollment of each subject in order to facilitate the review of any issues in recruitment, retention or overall protocol. Specific methods utilized to maximize participant response rates and compliance includes:

- A national in-person training in San Antonio for all Research Assistants to ensure full understanding and compliance of participant recruitment, survey administration, and biospecimen collection;
- Multiple trainings held with each Study Center on FISMA compliance and entering data into the centrally housed Research Electronic Data Capture (REDCap™) database to ensure high quality data submission;
- Monthly conference calls with all study Principal Investigators and Research Assistants to provide a forum of discussion and updates;
- The development of a Manual of Operations to detail all aspects of the study including recruitment, survey administration, biospecimen collection, and entering data into the REDCap™ database;
- A clear and concise explanation of all study requirements is given to potential participants prior to signing a consent form, to ensure they are knowledgeable about what participation entails;
- Participants have the option to do study visits immediately upon consenting, or at a later time point based on the patients schedule, as long as they are still within the Visit 1 window;
- If at all possible, we obtain study biospecimen samples at the same time prenatal labs are drawn for routine pregnancy visits;

- We request multiple methods of communication (phone and email) and communicate with participants using their preferred method;
- Scheduling study visits to correspond with prenatal visits for the convenience of participants;
- Remain in ongoing communication with participants and return calls or emails as soon as possible;
- Reminder phone calls are made the night before study visits to remind participants of the upcoming study visit;
- Reminder phone calls are made to participants to remind them to return saliva packets and/or answer any saliva collection-related questions;
- Reimbursement is provided for each component of the study when that component has been completed;
- Patients will receive a study newsletter with updates on study recruitment progress and eventually overall study outcome data;

B.4 Tests of Procedures or Methods to be Undertaken

As a result of the various pilot studies conducted in preparation for this substudy, we have learned that our recruitment and retention strategies, coupled with our study protocol and well-established study network, allow us to expect that we will successfully enroll, consent, and keep women engaged in the study. We have experienced success to date in communicating with participants and keeping them involved in the study. We have also received feedback from participants who participated in the Stress in Pregnancy Study or Pre-OMB Pilot Recruitment phase that participation has been a positive experience and they report very positive experiences with study staff.

We utilize the following strategies for quality improvement to ensure that our collaboration learns from all Study Centers' experiences regarding recruitment and administration of study protocol.

- Biweekly conference calls with study lead Principal Investigators, Project Coordinators and Research Assistants at lead sites;
- Monthly conference calls with all study Principal Investigators and Research Assistants to provide a forum of discussion and updates;
- Feedback Form that Research Assistants complete after each study visit, which reports any challenges encountered with the study protocol and recommendations for improvement;
- Study Coordinator maintains communication across all sites and oversees the Manual of Operations, training of all research staff across sites and maintenance of protocols.

B.5 Individuals Consulted on Statistical Aspects and Individuals Collecting and/or Analyzing Data

This research team is supported by a designated NCS Program Office subject matter expert and NCS statistical and field support staffs. Additionally, Study Centers continue to consult with federal agency representatives, advisory, and research groups, as well as individuals from statistical agencies on issues related to the NCS, including formative research and pilot testing.