

Johns Hopkins Medicine - eForm A

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1. Abstract

The NCS Vanguard studies have revealed concern that participant burden regarding biospecimens in the larger NCS project (100,000 participants to be followed from birth to age 20) might impact recruitment and retention. Poor recruitment and retention in the massive project will result in significant cost overruns and potential compromise the scientific value of the information obtained. Total project cost is estimated at approximately \$3 billion dollars (without overruns). The use of saliva in the NCS has the potential to increase participation and retention in the larger study.

Saliva sampling is viewed as having potential to increase participation and retention in the National Children's Study. However, saliva sampling techniques have never been employed on such a large scale. Prior to initiation of the larger study, it is imperative that the feasibility of saliva sampling techniques already employed in small scale studies with mothers and children are evaluated and refined. This study will determine the simplest, most time efficient way to collect saliva samples from mothers and small children (ages 3 months through 3 years). In this project, a prototype sampling protocol will be created based on information already in the literature, the protocol will be pilot tested and feedback will be collected about feasibility and acceptability from 66 mother-child dyads. That feedback will be incorporated into a revised protocol, and the revised protocol will be pilot tested in a second group of 66 mother-child dyads.

2. Objectives

The main objective is to understand the advantages and limitations to saliva sampling from the perspective of study participants. To enable the team to make evidence-based decisions about how we approach the design of the collections, sampling scheme, instructions and packaging to maximize success.

Approach:

The approach is to obtain key information about the feasibility of collecting saliva from a representative sample of families (mother-child dyads) similar to NCS participants. Discovering obstacles at the interface with the participants will enable investigators to avoid/address/overcome any such issues during the main study and increase perceived acceptability, reduce missingness due to noncompliance, increase participation rates, educate participants on correct techniques and procedures to reduce error, and reduce drop out.

Actions Items:

1. **Prototype Sample Collection Kit:** The JHU team will create a prototype saliva sample collection kit and train the JHU and Emory data collection teams in how to use the kit. JHU and

Emory will obtain IRB approval, and regional NCS subcontractors will administer these sample collection kits to 66 mother-child dyads (33 at each site).

All kits will be returned postage-paid from the participants' homes to the JHU Site. Compliance and performance of collection steps will be monitored, as well as adherence to collection schedule. After receiving the sampling containers back from participants, each site will employ a post-event questionnaire to debrief and determine which special issues need to be resolved.

2. **Final Sample Collection Kit:** The JHU team will use data from step 1(above) to refine the sample collection kit, retrain the three study centers' field staff and to administer the kit to another 66 mother-child dyads (33 at each site). Feedback will again be solicited using the post-event questionnaire.

Summary: JHU is lead center for compiling materials and conducting analyses. Emory will contribute to instrument development. Like JHU, the Emory site will administer surveys and prototype collection materials. Both sites will then work together to refine approach.

Action Plans:

- 1) All contact with participants from recruitment (“NA_00046970_Recruitment-TelephoneScreeningScript”) through study implementation will be conducted by NCS regional subcontractors.
- 2) Prototype collection kit will enable sample collection from mothers and young children. It will contain commercially available foam swabs (1 x 4 cm for adults; 1 x 12 cm for children); short drinking straws, and 15 mL and 2 mL collection vials.
- 3) **Day 1:** A home visitor will guide participant through consent process (“NA_00046970_Consent Form”), conduct a brief demographics questionnaire (“NA_00046970_Home Visit Demographics Questionnaire”), demonstrate the saliva collection, storage, and shipping procedures in person, and then give the participants and illustrated instructions and materials concerning the procedures. **Day 2:** Mothers will collect saliva 4 times at specified times of day from themselves and their child. Samples will be stored overnight in a small insulated box in the participants' freezer. **Day 3:** The samples will be mailed to JHU via FedEx or UPS. **Day 4:** The participants will receive a phone call in order to complete a follow up interview (“NA_00046970_Follow Up Telephone Interview”).
- 4) At JHU, the material received will be evaluated for the number of complete specimens, the sample volume generated, whether instructions were followed, how samples were packaged and shipped, and the maximum temperature the specimens reached during transport by.
- 5) The saliva collection kit will be revised based on feedback provided in the follow up interview (“NA_00046970_Follow Up Telephone Interview”) from the first cohort of 66 mothers. This may involve, for example, changes to the instructions and/or the size or shape of the swab material.

- 6) The revised collection kit will be deployed in same manner as the prototype to another 66 mother-child dyads.
- 7) The mothers of the second cohort will be also interviewed as above (NA_00046970_Follow Up Telephone Interview”)

3. Background

Advances in biotechnology, coupled with the recent characterization of a vast array of analytes and biomarkers in saliva, have created the opportunity to measure components of biological systems in oral fluids and apply knowledge gained from those measurements to a diverse spectrum of research. More than 25 years of basic research documents that many analytes can be measured in oral fluids. Much of this empirical work has focused on establishing the reliability, precision, and validity of the measurement of salivary analytes and biomarkers. In the past decade, the focus has shifted away from measurement issues to describing phenomenon. As a non-invasive and relatively inexpensive alternative to other methods of biological assay, salivary diagnostics may increase participation/compliance in both research and clinical settings.

This study is being done to further develop understanding of saliva as a research specimen with the specific goal of increasing recruitment/retention levels for the NCS study by decreasing burden on the subjects involved while accurately measuring relevant analytes. By aiming to develop and test a prototype of saliva collection methods for mothers and small children (ages 3 months through 3 years), accompanied by feedback from the mothers about the process, this study seeks to identify the simplest, most time efficient way to collect saliva samples from this population during the NCS study.

This is a multi-site project coordinated through the National Children's Study sites at JHU and Emory. A total of 132 mother-child dyads will be recruited, with 66 consented at each site. The first 66 dyads (33 at each site) will receive the initial prototype system of saliva collection demonstration/instructions, and then be interviewed for feedback about the process. Modifications will be made to the saliva collection system, then deployed to the next 66 dyads (again, 33 at each site).

The consenting process and data collection will be conducted by National Children's Study subcontractors (Battelle) in each region. As a full service professional data collection organization, Battelle will be conducting home visits, consenting, interviewing, and the data collection at Hopkins and Emory sites for this portion of the formative study. All the data will meet the FISMA requirement. Battelle has its own IRB process and conducts its own compliance/human subjects research training for its staff. Battelle's IRB approval will be forthcoming pending the submission of our approved documents and procedures, and staff compliance /human subjects research training will be complete in the near future as staff are still being hired at this time. **Therefore, sub-contractors will be added to our study team as their hiring and compliance/human subjects research training is completed.**

Procedures will involve the following basic steps: (Day 1) a short home visit by an interviewer to obtain consent, collect demographic data, and demonstrate the collection, storage, and shipping procedures and deliver instructions and materials for collection and shipping, (day 2) mothers will self-collect 4 saliva samples from themselves and 4 saliva samples from their child, (day 3) samples will be returned to JHU via

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UPS or FedEx, and (day 4) mothers will complete a short phone interview. All samples will be de-identified using bar-codes, and on return to Hopkins volumes and sample integrity will be assessed and destroyed. Samples will not be stored or assayed for any biological markers. Subjects are informed during recruitment (“NA_00046970_Recruitment-TelephoneScreeningScript”) and consent (“NA_00046970_Consent Form”) that no data based on their samples will be available to them.

4. Study Procedures

Overview:

This is a multi-site project coordinated through the National Children's Study sites at JHU and Emory, with JHU acting as the lead site. The project is coordinated via biweekly conference calls, and over the course of the 14 month project period there will be 3 in person meetings. The first such meeting was in January 2011 to launch the project planning phase. Each site will be responsible for consenting, collecting data, and having samples returned to JHU. Emory has received copies of the project protocol and the consent form submitted as part of this application to the JHU SOM IRB. Each site will be applying for IRB approval for the project at their respective study sites. Sampling will be coordinated by a PI at each site, but implemented by a subcontractor specifically working with that NCS study site. All data will be returned to JHU for integration into a master data set. The master data set, stripped of any potentially identifying data records, will be distributed to each site for statistical analysis and discussion.

At both NCS study sites (Atlanta and Baltimore/Washington Metropolitan area) there are extensive recruitment procedures already in place for the larger NCS study that include announcements in a variety of public media (radio ads, print ads on in newspaper, posters). These announcements direct interested participants to local subcontractors (e.g., Battelle in Atlanta and Baltimore/Washington Metropolitan area) responsible for consenting, and implementing data collection. The subcontractors are provided with inclusion/exclusion criteria for participation in the larger NCS study. Potential participants who respond to these advertisements but who do not qualify for the larger NCS study will then be screened (“NA_00046970_Recruitment-TelephoneScreeningScript”) by sub-contractors for inclusion/exclusion criteria in our NCS project: English-speaking from 18 to 35 years old with children between 3 months and 3 years of age) will be invited to participate. Sub-contractors will provide each subject with Hopkins study coordinator contact information in case she has further questions, but the sub-contractors themselves will arrange home visits with each participant directly. A total of roughly 132 mother-child dyads will be recruited, with 66 recruited at each site. The first 66 dyads (33 at each site) will receive the initial prototype system of saliva collection demonstration/instructions, and then be interviewed for feedback about the process. Modifications will be made to the saliva collection system, then deployed to the next 66 dyads (again, 33 at each site).

Consent (“NA_00046970_Consent Form”) will be obtained from each subject by a home interviewer in-person on day 1. The participant will have 5-10 minutes read and review the consent form and ask any questions he/she may have. The home interviewer will then conduct a brief demographics questionnaire (“NA_00046970_Home Visit Demographics Questionnaire ”) before providing verbal and written instructions of how and when to collect saliva samples (4 saliva samples from mother and child: upon waking, 30 minutes after waking, midday/noon just before lunch, and in the early evening just before dinner), store them in the freezer, package them appropriately, and prepare for pick up or delivery of the package the next day. The home interviewer will also demonstrate the two collection approaches to be employed (1) collecting passive drool by forcing saliva through a straw-like device into a collection

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container, and (2) absorbing saliva using state of the art foam swabs. These practice samples will be collected from the mother and child, and then discarded. The home interviewer will leave materials with the participant so that the participant can collect and freeze the samples on day 2. The samples will be mailed on day 3, and on day 4 they will respond to a follow up questionnaire (“NA_00046970_Follow Up Telephone Interview”) over the phone concerning the sample collection process, instructions, packaging, and performance indicators such as whether sufficient sample volumes are actually collected, whether the specimens as collected on schedule, whether the samples are packaged and returned in the manner necessary to maintain sample integrity. All samples will be de-identified using bar-codes, and on return to Hopkins volumes and sample integrity will be assessed and destroyed. Samples will not be stored or assayed for any biological markers.

Subjects are informed of the following during recruitment and consent: Participant removal criteria include failure to follow instructions, cancellation of studies, or other reasons unforeseeable at the time of recruitment. If participants stop participating, they may receive partial compensation depending upon level of participation. Subjects are informed during recruitment (“NA_00046970_Recruitment-TelephoneScreeningScript”) and consent (“NA_00046970_Consent Form”) that if researchers witness any abuse, neglect, or criminal activity, it must be reported to local authorities.

(Blinding, placebo, therapy, etc. are not applicable to this study.

5. Inclusion/Exclusion Criteria

Participants must be English-speaking mothers between 18 to 35 years old, with a child who is between 3 months and 3 years of age.

6. Drugs/ Substances/ Devices:

According to the JHMI IRB Guidelines, a serious risk device poses a “potential for serious risk to the health, safety, or welfare of a subject.” A device is a serious risk if it: is intended as an implant; is purported or represented to be for a use in supporting or sustaining human life; is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health; and/or otherwise presents a potential for serious risk to the health, safety, or welfare of a subject. Non-significant risk devices are devices which do not meet these criteria. None of the devices used in this study meet the above criteria for serious risk, therefore all devices used in this study are “non-serious risk devices”.

Saliva sample collection kits: Please note that we use the term "collection kit" within our study in a manner that is not the same as how the FDA is using this term. Our "collection kits" include research tools that are used to facilitate saliva collection. It is not required for these tools to be reviewed by the FDA. We are neither using them in clinical trials, nor using them for diagnostics, nor linking them to an FDA approved/cleared IVD. They are for research use only, not diagnostic use. They are for 2 methods of saliva collection: (1) drooling saliva through a straw, or (2) putting a foam swab under the tongue. The foam swabs have been qualified by the FDA as “Food Grade Substance”, but the other collection kit materials have not been reviewed by the FDA. These tools are not sold commercially. We are in the process of creating the parameters to optimize their acceptability and utility in the field. Medical, physical, psychological, emotional, and/or social risks to which participants in our study will be exposed due to “devices” used in this study do not have a

greater probability and magnitude of harm or discomfort than those ordinarily encountered in daily life or during the performance of routine physical examinations or tests.

No assays will be performed on the samples collected. All samples will be destroyed.

7. Study Statistics

The JHU team will evaluate the material received for the number of complete specimens, the sample volume generated, whether instructions were followed, how samples were packaged and shipped, and the maximum temperature the specimens reached during transit. Follow up questionnaires (“NA_00046970_Follow Up Telephone Interview”) will be evaluated qualitatively. All findings will be utilized to modify the entire process appropriately.

8. Risks

Medical

There is a minimal risk of choking hazard during saliva collection. A choking hazard warning sheet is given to the mothers to emphasize child safety. There may be other discomforts that are not yet known. Any unanticipated medical problems will be immediately reported to the medical doctor of our study team. A group of designated JH faculty/staff will have responsibility for monitoring, oversight of adverse events and other protocol events for this research and reporting them to the IRB.

According to the JHMI IRB Guidelines, a serious risk device poses a “potential for serious risk to the health, safety, or welfare of a subject.” A device is a serious risk if it: is intended as an implant; is purported or represented to be for a use in supporting or sustaining human life; is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health; and/or otherwise presents a potential for serious risk to the health, safety, or welfare of a subject. Non-significant risk devices are devices which do not meet these criteria. None of the devices used in this study meet the above criteria for serious risk, therefore all devices used in this study are “non-serious risk devices”.

Legal/Breach of Privacy/Confidentiality

There is a small risk that others could see sensitive personal information about the subject, which could cause embarrassment or have legal penalties. The staff working on the study and at times others working at Hopkins will see information collected from the subject. This includes people who review the research studies, their staff, lawyers, or other Johns Hopkins staff. The information may also be viewed by people outside of Johns Hopkins, such as government groups (such as the Food and Drug Administration), safety monitors, other hospitals in the study and companies that sponsor the study. Information will only be used and disclosed by Johns Hopkins as described in the consent form and in Notice of Privacy Practices; however, it cannot be guaranteed that people outside Johns Hopkins who receive the information will keep it confidential. The subject can cancel permission to use and disclose his/her information by contacting the Johns Hopkins Privacy Officer (instructions are included on the consent form). If permission is cancelled, no further information will be collected from that point, but information already collected in this study would not be affected. Subjects are informed during recruitment (“NA_00046970_Recruitment-

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TelephoneScreeningScript”) and consent (“NA_00046970_Consent Form”) that if researchers witness any abuse, neglect, or criminal activity, it must be reported to local authorities.

Data Protection Plan (to minimize risks)

1. Once signed, consent forms will be stored separately from all other project data in a locked filing cabinet in Dr. Granger's office. Only Dr. Granger will have access to these documents.
2. Questionnaires and biospecimens will be labeled with sequential bar-code numbers. Only Dr. Granger will have access to the codebook that links the information on the consent form to the bar-code ID.
3. Data transferred from the laboratories back to the JHU data core will be de-identified.
4. At JHU data will be stored in password protected computers, according to the NCS FISMA plan coordinated and implemented through the NCS JHU study site in the JHU SPH.
5. All staff have been required to complete data security training.

Financial

Though there is no direct cost to participate in the study, Johns Hopkins and the federal government do not have a program to pay the subject if he/she suffers adverse events from being in the study.

- If subject has health insurance: The costs for any treatment or hospital care received as the result of a study-related injury will be billed to subject’s health insurer. Any costs that are not paid for by the health insurer will be billed to the subject.
- If subject does not have health insurance: Subject will be billed for the costs of any treatment or hospital care received as the result of a study-related injury.
- Study-related injury (provided the costs are not the result of care required to treat an underlying disease or condition). Any costs that are not paid for by the study sponsor will be billed to the subject.

9. Benefits

There is no direct benefit to the participant from being in this study. This is a small pilot project that will inform a larger study. We will explore the feasibility of alternative approaches to collecting saliva samples and make recommendations for sampling methods to be used in the larger project. Participation helps the study team develop the simplest and most time efficient way to collect saliva samples from mothers and small children (ages 3 months through 3 years) with minimized discomfort.

10. Payment and Remuneration

Subjects will receive at total of \$25.00 for completing this study. Payment will be mailed to them when the samples are received at Johns Hopkins University. If subjects only complete the follow-up phone interview, they will receive partial payment of \$15.00.

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11. Costs

There is no cost associated with participating in this study, though samples will need to be transported to a location from which they can be mailed.