Supporting Statement B

GuLF STUDY:

Gulf Long-Term Follow-Up Study

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This is being submitted as a Revision.
Yellow highlights indicate changes since the last submission in 2010.

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B. COLLECTIONS OF INFORMATION EMPLOYING STATISTICAL METHODS

B.1. Respondent Universe and Sampling Methods

The respondent universe and sampling methods for selecting and enrolling the cohort were described in our original submission and are not repeated here. Instead, this section focuses on methods for identifying and selecting participants for follow-up data collection from among those who enrolled in the cohort.

As part of the baseline enrollment effort, 32,762 participants completed the baseline telephone interview and were enrolled into the Full Cohort. All members of the Full Cohort agreed to provide annual updates to their contact information and to be followed over time for cancer and mortality outcomes through passive public health record surveillance. The Active Follow-up Sub-cohort consists of ~20,000 participants who completed the enrollment questionnaire and the home visit examination (~11,200) and a random sample of the remainder of the Full Cohort (~8,800). Members of the Active Follow-up Sub-cohort will be followed via biennial telephone interviews. We expect 16,000 (~80%) to complete the first follow-up telephone interview, and 15,000 (~75%) to complete the second follow-up telephone interview. We will target all participants for each follow-up interview, so participants who do not complete the first follow-up interview are not precluded from completing the second one. Participation rates may be lower if efforts to trace hard-to-reach participants are not as successful as we anticipate or rates could be higher if tracing and outreach efforts work better than expected.

A subgroup of ~4,600 members of the Active Follow-up Sub-cohort will be invited to complete a supplemental mental health questionnaire module at the time of the first follow-up telephone questionnaire, and again 6, 12, and 24 months later, to assess mental health trajectories among those affected by the oil spill and utilization of mental health services in the Gulf region. We anticipate that at least 2,000 participants will complete all four waves of mental health follow-up. The Biomedical Surveillance Sub-cohort (N~6,000) is a subset of the Active Follow-Up Sub-cohort that has been selected to receive a comprehensive clinical examination, based on completion of the baseline home exam, residence within reasonable driving distance of clinics in Mobile, Alabama and New Orleans, Louisiana,

and criteria related to potential for cleanup-related exposures, mental health distress, or baseline pulmonary function findings. We expect 4,000 participants to complete the examination (~67% participation rate).

Sample size considerations for the Full Cohort and Active Follow-up Sub-cohort were described in the first submission and are reviewed in the protocol included with this submission. Consistent with the overall aims of the GuLF STUDY, the comprehensive research-based clinical examination is designed to carry out more comprehensive clinical testing and mental health evaluations than could be completed during the baseline home visit. As demonstrated in Table 1, we are powered to detect relatively small differences in the prevalence of outcomes between exposed and unexposed participants when the frequency of the outcome is not rare among the unexposed. Similarly, as shown in Table 2, we also have power to detect small differences in continuous outcomes. Even if participation is as much as 25% lower than expected, our power calculations (not shown) indicate that the minimum detectable odds ratios (ORs) or mean differences will increase by less than 10-15%.

For subgroup analyses, power will be adequate (80%) to detect moderate odds ratios when the outcome is not rare among the unexposed and the prevalence of exposure is between 25 and 75%. For example, assuming an N of 700 for the exhaled breath condensate (EBC) analyses, when the proportion of the unexposed with the outcome is at least 10% and the prevalence of exposure is between 25 and 75% there will be adequate power to detect an OR between 1.6 and 2.1. When the prevalence of the outcome is lower among the unexposed and/or the proportion with the exposure is less than 10% or greater than 75%, larger ORs will be needed to attain adequate power.

Table 1. Minimum detectable odds ratios (OR) for a range of proportions of exposure and outcome frequencies, based on a two-sided test with alpha=5%, power=80%, and N=4,000

Frequency of outcome among unexposed	Proportion of cohort exposed to a given agent					
	5%	10%	25%	50%	75%	90%
	200	400	1,000	2,000	3,000	3,600
1%	3.72	2.88	2.26	2.12	2.39	3.34
5%	2.11	1.78	1.52	1.46	1.55	1.85
10%	1.79	1.55	1.37	1.32	1.38	1.59

Frequency of outcome among	Proportion of cohort exposed to a given agent					
	5%	10%	25%	50%	75%	90%
30% posed	1.53	1.37	1.24	1.21	1.25	1.37

Table 2. Minimum detectable mean differences for a range of proportions of exposure, based on a two-sided test with alpha=5%, standard deviation=1, power=80%, and N=4,000

Proportion of cohort exposed to a given agent	Mean Difference
5% or 95%	0.203
10% or 90%	0.148
25% or 75%	0.102
50%	0.089

The clinical examination is estimated to take approximately 4 hours to complete. Should the administration time of the clinical examination substantially exceed our estimates and/or prove unacceptable to participants during the run-in period or afterward, we will modify the administration of each examination to reduce burden. The two most time-consuming examination components are the neurobehavioral testing and pulmonary testing. If it is deemed necessary to substantially shorten the examination time, we may decide to assign participants to receive only the pulmonary testing (Exhaled Nitric Oxide, Exhaled Breath Condensate, and Pulmonary Function testing) or the neurobehavioral testing, but not both. A variation we might also consider is to include the much briefer assessment of pulmonary function that was performed during the home visit for those participants selected for the neurobehavioral testing arm. Should this modification be necessary, we will use a stratified random sampling method to assign individuals to either the "pulmonary" or the "neurobehavioral" group, with participants demonstrating poor pulmonary measures during their home visit being assigned to the "pulmonary" group. Those with "normal" pulmonary measures during their home visit will be randomly assigned to either the "pulmonary" group or the "neurobehavioral" group. Should we determine that this stratification is necessary either because other components of the exam are taking longer than anticipated

or if the length is unacceptable to participants, we estimate that it will shorten the clinical examination by approximately 45-50 minutes.

B.2. Procedures for the Collection of Information

Data collection for the biennial follow-up of the Active Follow-up Sub-cohort will be conducted using Computer Assisted Telephone Interviewing (CATI) software. Prior to the interview, participants will be mailed an invitational letter (Attachment 2) encouraging them to complete the follow-up questionnaire. The follow-up interview will take approximately 30 minutes (Attachment 3). The mental health questionnaire (Attachment 6) will be administered at the time of the first follow-up questionnaire, and again 6, 12, and 24 months later as part of the second follow-up telephone interview. The mental health questionnaire module takes approximately 15 minutes to administer.

We will request updated contact information from all participants annually, either as a stand-alone effort or as part of the follow-up telephone interviews. During stand-alone efforts, participants will receive emails and/or letters encouraging them to update their contact information using a secure section of the study website or by contacting the study hotline.

Routine surveillance of GuLF STUDY participants will be conducted during the follow-up years. Follow-up will include linkage with State Cancer Registries and state vital statistics, as well as linkage with the National Death Index (NDI). We will explore the feasibility of other passive monitoring for changes in health via linkage with other routinely collected surveillance data and electronic medical records that may become available.

The clinical examinations for the Biomedical Surveillance Sub-cohort will be performed in controlled clinical settings under the direction of health professionals from the University of South Alabama (USA) and Louisiana State University (LSU) Health Sciences Center. Eligible cohort members will receive a letter (Attachment 10) from the GuLF STUDY Principal Investigator and the director of the clinical site closest to their home inviting them to participate in the clinical examination. Coordinating center staff will contact eligible cohort members who do not respond to the letter within one week. Study center staff will schedule visits with contacted eligible cohort members who agree to participate.

Study staff will flag eligible cohort members who cannot be reached with existing primary and secondary contact information. The study coordinating center will send their names and other personally identifiable information (when available) to a commercial tracing service. All information exchanges will be encrypted using standard computer security and encryption protocols. If the commercial tracing service returns contact information, the coordinating center will attempt to contact the eligible cohort member. If contact is made and the eligible cohort member is willing to schedule the examination, the coordinating center will schedule the appointment at a date and time convenient for the cohort member. If updated contact information is not obtained, the coordinating center may deploy field staff to visit the eligible cohort member's last known address to obtain updated contact information and to schedule the visit. For eligible cohort members who cannot be reached by these methods, the coordinating center may also send emails and letters to their last known email or mailing address to encourage participation, and may telephone the alternate contacts provided by participants when they enrolled or last updated their contact information to confirm or update contact information.

A confirmation letter (Attachment 12) will be sent to the selected participant 4 to 5 days in advance of the scheduled visit along with preparatory materials, which include a one-page summary of key information in the consent form (Attachment 13), a list of answers to frequently asked questions (Attachment 14), pre-visit instructions (Attachment 15) and directions to the clinical site. The clinical site will serve as the first point of contact for selected participants for questions about the examination and for cancellations and rescheduling.

The clinical examinations and procedures are described below, but briefly these research examinations will include anthropometric measurements, biological sample collection, neurobehavioral evaluations, pulmonary function testing, and mental health questionnaires. Questionnaire data will be collect via Computer Assisted Personal Interviewing (CAPI) software. The examination is expected to take about 4 hours to complete. Participants will be compensated for their time and travel costs.

Data collected during the clinical examination will be recorded in the Clinic Exam Questionnaire (Attachment 27) and the Mental Health Questionnaire (Attachment 28) modules of the electronic data

collection system. At the end of the examination, participants will be provided a report (Attachments 17-22) of clinical findings.

Table 4. Clinical Visit Overview

Activity	Time	Notes
Visit Scheduling	N/A	• Initiation mailing • Scheduling calls • Pre-visit procedural eligibility assessment • Confirmation letter and visit preparation materials mailed
Arrival and Greeting	5 min.	• Greetings and introduction to study staff
Informed Consent	10 min.	• Review and obtain informed consent
Anthropometric Measures	10 min.	• Height, Weight, Waist and Hip Circumference
Physiological Measures	5 min.	• Resting Blood Pressure and Heart Rate
Biological Specimen Collection	15 min.	• Hair, Blood, Toenail Clippings*, Saliva, and Urine Collection • Finger stick for Hemoglobin A1c • Provide training and materials for serial saliva samples (for a subset)
Clinic Visit Questionnaire	15 min.	• Clinic Visit Questionnaire
Neurobehavioral Tests	50 min.	• Symbol-Digit • Finger Tapping • Simple Reaction Test • Continuous Performance • Trailmaking • Digit Span • Match to Sample • Progressive Ratio
Peripheral Nervous System Tests	25 min.	• Standing Balance • Standing Steadiness • Vibrotactile Threshold Testing • Visual Acuity • Visual Contrast Sensitivity • Handgrip Strength • Walking Speed • Long Distance Walk (400m)

Activity	Time	Notes
eNO and EBC	15 min.	• Exhaled Nitric Oxide • Exhaled Breath Condensate (for a subset)
Pulmonary Function Testing***	30 min.	• Pre/post-bronchodilator spirometry
Mental Health Assessment	40 min.	• Questionnaire administration and referral, if needed
Biological Specimen Processing	N/A	• Process, aliquot, label, and temporarily store specimens
Report of Findings	10 min.	• Handout provided with clinically relevant findings and recommendations for seeking additional care, if indicated • Referral provided, if needed
Check-Out and Remuneration	5 min.	• Remuneration
Clean-up and Specimen Shipping	N/A	• Samples packed and shipped in batches by clinical staff
Total time	**~ 4 hrs.**	

Study computers with whole-disk encryption will be issued to clinical sites, as required by the security plan in effect for the GuLF STUDY. A clinical data management program with CAPI modules and a scheduling system will be utilized to standardize data collection and centralize the storage of study data. The system will be accessible only to project team members at the coordinating center and clinical sites, via an encrypted, secure connection to GuLF STUDY central servers (VPN or Secure-Socket-Layer). Thus, no project data will be archived on remote computers for long-term storage. Study data recorded on the neurobehavioral and PFT computers will be uploaded weekly and stored in a secured, password-protected database at the study coordinating center. The system has user access rights designed to ensure site personnel have access only to participants assigned to their site, and cannot see data collected elsewhere. Any ancillary data collected using 3rd party software (e.g., pulmonary function data) will not, whenever possible, contain personally identifying information.

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

A key to achieving high response rates and long-term participation is not to simply contact participants when data are needed, but rather to maintain regular contact and to share information about study progress and findings. We plan to send the Full Cohort annual requests (via email and letter) to update their contact information through an application on the study website or by contacting the study hotline. Any mailings that have been "returned to sender" will undergo tracing to identify updated address information. Individuals lost to follow-up events (i.e., telephone interviews and clinical examinations) will be traced using traditional tracing services. Annual newsletters will provide the cohort with information on study progress and findings. We will also utilize social media and community partnerships to keep affected communities informed about study progress and to seek advice about retention plans.

Participants who are invited to complete the follow-up telephone questionnaires will receive an advance mailing encouraging them to complete their interview. Several days later, telephone interviewers will actively contact participants, invite them to complete the interview, and address any questions or concerns before seeking consent to continue with the interview. We will seek updated contact information for those we cannot reach through traditional tracing services, and we will also reach out to secondary contacts provided as part of the baseline interview. Mailings will be sent to participants who cannot be reached after these approaches are carried out.

For the clinical examination, eligible cohort members will receive a letter from the GuLF STUDY PI and the director of the clinical site closest to their home inviting them to participate in the clinical examination. The letter will be on GuLF STUDY letterhead and will contain the logos of both the GuLF STUDY and the clinical site closest to the subject's home. This letter will explain the purpose and components of the examination and how to contact the study center to schedule the examination. Coordinating center staff will contact eligible cohort members who do not respond to the letter within one week. Study center staff will schedule visits with contacted eligible cohort members who agree to participate.

Study staff will flag eligible cohort members who cannot be reached with existing primary and secondary contact information. The study coordinating center will send their names and other personally identifiable information (when available) to a commercial tracing service. If the commercial tracing service returns contact information, the coordinating center will attempt to contact the eligible cohort member. If contact is made and the eligible cohort member is willing to schedule the examination, the coordinating center will schedule the appointment at a date and time convenient for the cohort member. If updated contact information is not obtained, the coordinating center may deploy field staff to visit the eligible cohort member's last known address to obtain updated contact information and to schedule the visit. For eligible cohort members who cannot be reached by these methods, the coordinating center may also send emails and letters to their last known email or mailing address to encourage participation, and may also call alternate contacts provided by participants.

A confirmation letter will be sent to the selected participant 4 to 5 days in advance of the scheduled visit along with preparatory materials, which include pre-visit instructions, a list of answers to frequently asked questions, a one-page summary of key information in the consent form, and directions to the clinical site. The study center will serve as the first point of contact for selected participants for questions about the examination and for cancellations and rescheduling.

In order to promote the clinical examinations more generally, we will engage eligible cohort members and their local communities through our community advisory group (CAG), the study website, social media (e.g., Facebook, Twitter).

Should the administration time of the clinical examination substantially exceed our estimates and/or prove unacceptable to participants during the run-in period or afterward, we will modify the administration of each examination to reduce burden.

Based on response rates after the first few months of clinic operation and experience gained with recruiting participants living far from the clinic sites, we may modify the criteria for selecting supplemental participants (e.g., by expanding or contracting the distance requirement) for the clinical examination – with the goal of completing 4,000 examinations.

For reasons of logistics, cost, and procedure standardization, we will have only two main clinic sites, one in Mobile, AL and the other in New Orleans, LA. However, reluctance of cohort members to travel long distance to get to a clinic site may lower participation rates. We will provide reimbursement for travel expenses, lodging and meals, as needed, to accommodate participants who live further away from the two main clinic sites in Mobile, AL and New Orleans, LA.

Finally, participants will receive $10 for completing the mental health questionnaire (at each of four time periods) and $100 for each clinic visit, in addition to travel reimbursement (up to $75).

B.4. Test of Procedures or Methods to be Undertaken

We established and continue to solicit new contacts with several community organizations, representative worker organizations, advocacy groups, and state and local government representatives to identify the primary health issues of concern locally and to discuss study implementation issues across the five-state area.

All procedures and questionnaires underwent internal testing prior to implementation and are modeled on proven methods in previous studies. Finally, the information gleaned from each activity allows further refinement of all study materials and procedures. Forms were shortened and modified to streamline data collection, thus reducing the burden on participants.

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

Dr. Dale P. Sandler, Chief, Epidemiology Branch, NIEHS, the Principal Investigator on this study, developed the statistical approach for the study in conjunction with the study team listed below. Data will be collected and managed by SRA. The study team will analyze the data and consult with experts in biostatistical methods as needed. The analytical team and consultants are listed below.

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