GuLF Study:

Gulf Long-Term Follow-Up Study for Oil Spill Clean-Up Workers and Volunteers

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Table of Contents

List of Acronyms

ACD	Acid/Citrate/Dextrose
AE	Adverse event
AAPOR	American Association for Public Opinion Research
AIHA	American Industrial Hygiene Association
ASTHO	Association of State and Territorial Healthcare Officials
ATS	American Thoracic Society
ATSDR	Agency for Toxic Substances and Disease Registry
BFR	Brominated flame retardant
BISCO	Bayou Interfaith Shared Community Organizing
BP	British Petroleum
BPA	Bisphenol A
BPSOS	Boat People SOS
BRFSS	Behavioral Risk Factor Surveillance System
CAG	Community Advisory Group
CAI	Computer-Assisted Interview
CAPI	Computer-Assisted Personal Interview
CATI	Computer-Assisted Telephone Interview
CBC	Complete blood count
CDC	Centers for Disease Control and Prevention
CLSI	Clinical Laboratory Standard Institute
CNS	Central Nervous System
CPL	Central processing lab
CS	Clinical specialist
DMS	Data management system
DNA	Deoxyribonucleic acid
EPA	Environmental Protection Agency
EPL	Environmental Pathology Laboratories
ERS	European Respiratory Society
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in First Second
FMV	First morning void
FVC	Forced Vital Capacity
GCF	Gulf Coast Fund
GCP	Good Clinical Practices
GIS	Geographic Information System
GPS	Global Positioning System
HVA	Home Visit Agent
HVAC	Heating, ventilating, and air conditioning
IL-18	Interleukin-18 (IL-18)
IOM	Institutes of Medicine
IRB	Institutional Review Board
JEM	Job-exposure matrix

KIM-1	Kidney injury molecule-1
LFT	Liver function test
LN2	Liquid Nitrogen
MQVN CDC	Mary Queen of Vietnam Community Development Corporation
MVV	Maximum Voluntary Ventilation
NAGs	N-acetyl-beta-D-glucosaminidase
NDI	National Death Index
NGAL	Neutrophil gelatinase-associated lipocalin
NGO	Non-governmental organization
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NIOSH	National Institute of Occupational Safety and Health
NOAA	National Oceanic and Atmospheric Administration
NSDUH	National Survey on Drug Use and Health
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PAH	Polycyclic aromatic hydrocarbon
PEC	Petroleum Education Council
PFT	Pulmonary Function Testing
PTSD	Post traumatic stress syndrome
QEESI	Quick Environment Exposure Sensitivity Inventory
RBC	Red blood cells
RFP	Request for proposal
RNA	Ribonucleic Acid
VOC	Volatile organic compound
WBC	White blood cells

Protocol Summary

Full Title:	Gulf Long-Term Follow-Up Study for Oil Spill Clean-Up Workers and Volunteers
Short Title:	GuLF Study
Conducted by:	NIEHS and SRA (NIEHS Epidemiology Branch Clinical Research Contractor)
Principal Investigator:	Dale Sandler, Ph.D. Division of Intramural Research Epidemiology Branch National Institute of Environmental Health Sciences
Sample Size:	55,000
Study Population:	Workers and volunteers engaged or potentially engaged in oil spill clean-up operations in the Gulf of Mexico
Accrual Period:	1 or 2/2011 – 6 or 7/2012
Study Design:	Closed prospective cohort
Study Duration:	10 years initially, with the possibility of extending the follow-up period
Primary Objective:	To investigate potential short- and long-term health effects associated with oil spill clean-up activities/exposures surrounding the Deepwater Horizon disaster
Secondary Objectives:	To investigate biomarkers of potentially adverse biological effect in relation to oil spill clean-up activities/exposures
	To create a resource for additional collaborative research on focused hypotheses or subgroups
	To create a resource to better understand the short and long-term human health effects of oil and oil dispersants in the environment
Primary Endpoints:	Respiratory, genotoxic, hematologic, neurologic, immunologic, and mental health
Secondary Endpoints:	Cancer, reproductive, cardiovascular, hepatic, and renal effects

Précis

The Gulf Long-term Follow-up ("GuLF") Study will investigate potential short- and long-term health effects associated with the clean-up activities following the Deepwater Horizon disaster in the Gulf of Mexico on April 20, 2010. Crude oil, burning oil, and the dispersants used during clean-up efforts contain a range of known and suspected toxins. Over 100,000 persons have completed safety training in preparation for participation in clean-up activities related to the spill. While many of these individuals participated in active clean-up efforts, others did not. Exposures among persons involved in clean-up range from negligible to potentially significant, especially for workers involved in tasks associated with direct exposure to crude or burning oil, or to chemical dispersants. However, prediction of adverse health effects is not possible because the long-term human health consequences of oil spills are largely unknown due to the dearth of research in this area. The potential health effects associated with the levels of exposure experienced by clean-up workers are largely unstudied. Heat and stress experienced by these workers may also have adverse long-term health effects. In addition to the oil itself, the widespread economic and lifestyle disruption caused by the oil spill may contribute to mental health problems among this population.

The over-arching hypotheses of this study are:

1. Exposure to constituents of oil, dispersants, and oil-dispersant mixtures, and to spill-related stress by workers engaged in clean-up of the Deepwater Horizon oil spill are associated with adverse health effects, particularly **respiratory**, **neurological**, **hematologic**, and **psychological or mental health**.
2. There are exposure-response relationships between the above exposures and health effects.
3. Biomarkers of potentially adverse biologic effects are associated with the above exposures.

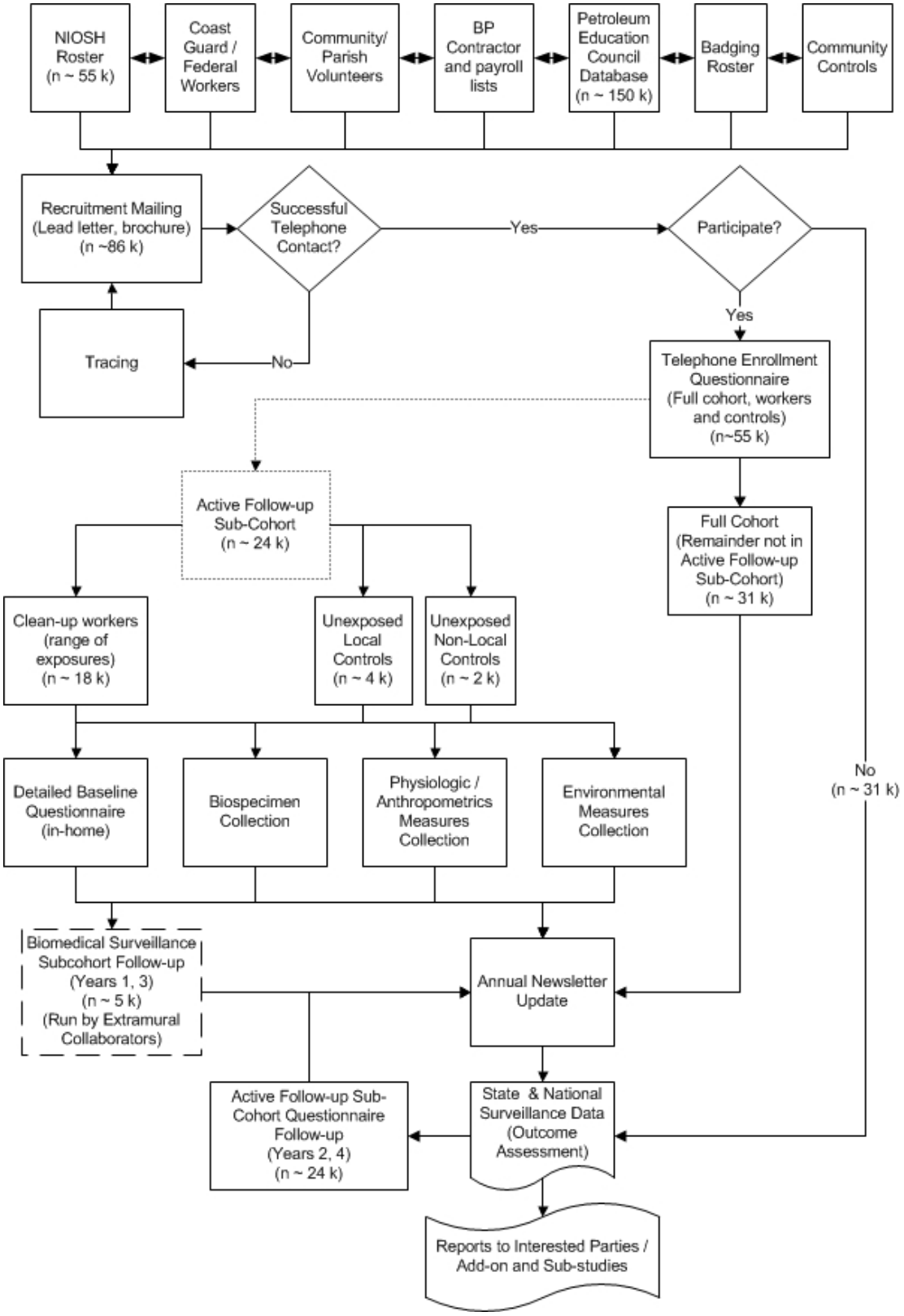
Based on what is known about individuals involved in clean-up efforts, the cohort will consist primarily of English-, Spanish-, or Vietnamese-speaking adults who performed oil-spill clean-up-related work ("exposed") and similar persons who did not engage in clean-up-related work ("unexposed" controls). Accommodations for enrolling participants speaking other languages will be developed through community collaborations as appropriate. Workers will be sampled from across job/potential exposure groups. A total of approximately 55,000 persons are expected to be enrolled into the cohort. A random sample of the full cohort, stratified by category of job/potential exposure (including N~6,000 with no oil-spill work to serve as controls) and oversampled for workers with higher potential exposures, will be enrolled into an *Active Follow-up Sub-cohort* (N~24,000). A random sample of the Active Follow-up Sub-cohort, also stratified by category of job/potential exposure and oversampled for workers with higher potential exposures, will be enrolled into a *Biomedical Surveillance Sub-cohort* (N~5,000). Participants will be interviewed about their clean-up-related tasks, demographic and socioeconomic factors, occupational and health histories, psychosocial factors, and physical and mental health. Members of the Active Follow-up Sub-cohort will also be asked to provide biological samples (blood, urine, hair, toenail clippings, and possibly saliva) and environmental samples (house dust) and will have basic clinical measurements (height, weight, waist and hip circumference, blood pressure, urinary glucose levels, FEV1 and FVC as a measure of pulmonary function) taken during home visits at baseline. The Biomedical Surveillance Sub-cohort will participate in a more comprehensive clinical assessment after the initial home visit,

including more comprehensive pulmonary function testing, neurological testing, and collection of additional biological and environmental samples. The specific tests to be performed and clinical protocols will be developed in collaboration with extramural investigators selected through a request for proposals (RFP). When developed, the protocol for this portion of the study will be submitted separately to the Institutional Review Board as a study amendment.

Exposures will be estimated using detailed job-exposure matrices developed from data from monitoring performed by different agencies and organizations during the crisis, as well as information on recommended or actual use of personal protection, information obtained by interview, and the available scientific literature. It should be noted that, in the absence of individual or group monitoring data for most workers, estimates of exposure, whether based on job activities or on more refined job-exposure matrices, will indicate the degree of *potential* exposure (i.e., exposure opportunity) rather than *known* exposure. We will investigate acute health effects via self-report from the enrollment interview among all cohort members and also via clinical measures and biological samples from Active Follow-up Sub-cohort members. All cohort members will be followed for development of a range of health outcomes through record linkage (cancer, mortality) and if feasible, through linkage with electronic medical records that may become available during the course of follow-up. Health outcomes among the Active Follow-up Sub-cohort will also be identified through self-report via periodic follow-up interviews. Additional outcome information will be obtained on the Biomedical Surveillance Sub-cohort from periodic follow-up clinical evaluations (e.g., spirometry, neurological testing) and analysis of follow-up biospecimens (e.g., immunologic parameters, liver function, renal function, DNA damage). Follow-up of the entire cohort is initially planned for 10 years, with extended follow-up possible depending upon scientific and public health needs and the availability of funds.

Recruitment of subjects should begin in January or February 2011, with the telephone interviews expected to be completed within 12-18 months and the baseline home visits within 18-24 months. For the home visits, we will initially target workers residing in the four most affected Gulf States (LA, MS, AL, and FL), although we may expand to other states if further information about the geographic distribution of workers and their potential exposures warrants additional follow-up in these states. We will work closely with a Community Advisory Board to develop community support for this study and appropriate communications and study materials.

Schematic of Study Design



Background Information and Scientific Rationale

There has been little research of the long-term health effects from oil spills despite the fact that between 1970 and 2009, there were 356 spills of more than 700 tons from oil tankers, with approximately 38 of these spills affecting coastal populations [International Tanker Owners Pollution Federation Limited (ITOPF) 2009, Aguilera, et al. 2010]. The Deepwater Horizon disaster, with its release of approximately 5 million barrels (~680,000 tons) of crude oil into the Gulf of Mexico, is far larger than any of these tanker spills. Given the magnitude of this spill and the scope of the potential exposures – at least 55,000 workers involved in clean-up efforts and countless residents of the affected areas – study of the human health effects of this spill is urgently needed to monitor Gulf clean-up workers and to understand the adverse consequences of oil spills in general.

Crude oil is a complex mixture containing a range of known and suspected toxins, including volatile organic compounds (VOCs), polycyclic aromatic hydrocarbons (PAHs), hydrogen sulfide, and heavy metals. VOCs, particularly benzene, have been linked to lymphohematopoietic malignancies [Savitz and Andrews 1997, Hayes, et al. 2001, Glass, et al. 2003, Steinmaus, et al. 2008, Baan, et al. 2009] and kidney dysfunction [Chang, et al. 2010]. They can also cause central nervous system (CNS) depression, respiratory irritation, and immune system alterations [Kirkeleit, et al. 2006, Gillis, et al. 2007, Lee, et al. 2007, Cho 2008]. Naphthalene, which causes olfactory neuroblastomas, nasal tumors, and lung tumors in rodents, is listed as possibly carcinogenic to humans (Group 2B) by IARC [IARC 2002]. Polycyclic aromatic hydrocarbons (PAHs) include known carcinogens and may alter reproductive and immune functions [Agency for Toxic Substances and Disease Registry (ATSDR) 1995]. Hydrogen sulfide can cause acute and chronic CNS effects such as headaches, poor attention span, poor memory, and poor motor function [Agency for Toxic Substances and Disease Registry (ATSDR) 2006]. Heavy metals found in crude oil, including arsenic, cadmium, chromium, manganese, copper, nickel, vanadium, and lead, have a range of adverse health effects, including neurotoxicity and carcinogenicity, renal and immunotoxicity [ATSDR 1999, 2004, 2005, 2007a, 2007b, 2008a, 2008b, 2009, Hazen, et al. 2010, Camilli, et al. 2010, Botello, et al. 1997].

Burning oil produces particulates, which have adverse cardiac and respiratory effects, and may generate dioxins because of incomplete combustion in the presence of chlorine in the sea water (Howard 2010).

The dispersants used to break up the oil contain a number of respiratory irritants, including 2-butoxyethanol, propylene glycol, and sulfonic acid salts. Heat and stress experienced by the clean-up workers may also have adverse health effects. In addition to exposures from the oil itself, the widespread economic disruption caused by the oil spill may also contribute to mental health problems in a population with potentially increased vulnerability due to prior exposures to trauma, financial strain and social stressors arising from other recent disasters [Galea, et al. 2008]. Such stressors may also adversely impact physical health.

The few studies that have evaluated the human health consequences of oil spills have primarily focused on acute physical effects and psychological sequelae. These studies have examined the *Exxon Valdez* (Alaska, 1989), *Braer* (Shetland Islands, UK, 1993), *Sea Empress* (Wales, UK, 1996), *Nakhodka* (Oki Islands, Japan, 1997), *Erika* (Brittany, France, 1999), *Prestige* (Galicia, Spain, 2002) and *Tasman Spirit* (Karachi, Pakistan, 2003) oil tanker spills. Most of these studies were cross-sectional. A number of the studies reported respiratory symptoms, including cough and shortness of breath

[Carrasco, et al. 2006, Janjua, et al. 2006, Meo, et al. 2009, Sim, et al. 2010]. In a follow-up study among clean-up workers of the *Prestige* oil spill, Zock et al [2007] observed that lower respiratory tract symptoms persisted 1 to 2 years after exposure had ended (although the excess risk decreased with increasing time from last exposure) and that the symptoms showed exposure-response patterns in relation to number of exposed days, exposed hours per day, and number of activities. Meo et al [2008, 2009] reported a reduction in forced vital capacity (FVC), forced expiratory volume in first second (FEV1), and forced expiratory flow and maximum voluntary ventilation (MVV), including exposure-response trends, in a small study of workers involved in the clean-up of the *Tasman Spirit* oil spill. Other commonly reported symptoms in these studies include itchy eyes, nausea/vomiting, dizziness, and headaches [Campbell, et al. 1993, Lyons, et al. 1999, Morita, et al. 1999, Carrasco, et al. 2006, Janjua, et al. 2006, Meo, et al. 2009, Sim, et al. 2010], and skin irritation/dermatitis [Campbell, et al. 1993, Janjua, et al. 2006, Sim, et al. 2010]. It is worth noting that, among Prestige oil spill clean-up workers, proper safety training was associated with greater use of protective equipment and a lower frequency of health problems [Carrasco, et al. 2006], which indicates that training can be effective in prevention.

In addition to health effects induced by chemical and physical exposures, physical and mental health may be adversely affected through pathways involving physiological and psychological responses to acute and chronic stressors related to the disaster. Adverse psychological consequences have frequently been linked to previous oil spills. Excess prevalence of generalized anxiety disorder, posttraumatic stress disorder (PTSD), and depressive symptoms were observed among communities affected by the *Exxon Valdez* oil spill approximately one year after the spill occurred [Palinkas, et al. 1993]. Similar patterns of higher anxiety and depression scores and worse mental health were observed among communities near the *Sea Empress* spill [Lyons, et al. 1999]. The *Braer* spill was associated with increased somatic symptoms, anxiety, and insomnia, but not personal dysfunction or severe depression [Campbell, et al. 1994]. Worse mental health scores were related to proximity to the *Prestige* spill [Sabucedo, et al. 2010].

In studying stress-related effects, it will be important to consider measures of mental health and biological response to evaluate both subjective and objective outcomes. In a community-based study of residents living near a petrochemical complex, perceived health was related to perceived risks due to chemical exposures, while inflammatory cytokine levels were related to objective proximity to the complex [Peek, et al. 2009]. In the same community, interviews after a petrochemical accident revealed significant decreases in perceived physical and mental health associated with multiple covariates, including lower education, distance and impact of the disaster [Peek, et al. 2008]. Susceptibility to the adverse effects of disasters may be increased by a variety of factors, including extent of exposure, female gender, middle age, ethnicity or minority status, pre-existing mental and physical health, economic and psychosocial resources [Norris, et al. 2002]. Consequently, the stress-related effects of the Deepwater Horizon Disaster may be amplified in a population still recovering from the impact of other recent disasters and in vulnerable subpopulations [King and Steinmann 2007, Galea, et al. 2008]. Research in the affected region also needs to take into account the unique history and potential vulnerability of migrants, ethnic or cultural minorities in the study population, e.g., Vietnamese [Palinkas, et al. 1992, Do, et al. 2009, Norris, et al. 2009].

Studies of genotoxicity and endocrine toxicity also point to potential adverse effects among oil spill clean-up workers. All but one of these studies were conducted among

clean-up workers involved in the *Prestige* incident. Findings include significantly higher DNA damage, as measured by the comet assay, but not cytogenetic damage, as measured by the micronucleus test, among exposed individuals compared to controls, which was related to duration of exposure [Laffon, et al. 2006, Perez-Cadahia, et al. 2006]. Clean-up workers were also found to have significantly elevated blood levels of aluminum, nickel, and lead, but decreased levels of zinc [Perez-Cadahia, et al. 2008]. In addition, exposed workers had significant decreases in blood prolactin and cortisol levels [Perez-Cadahia, et al. 2007]. A recently published study of the Prestige cohort [Rodriguez-Trigo, et al. 2010] found an increased risk of structural chromosomal alterations in circulating lymphocytes among exposed workers two years after the spill. These results are consistent with studies showing increased DNA damage in relation to low level exposure to benzene [Bagryantseva, et al. , Maffei, et al. 2005, Chen, et al. 2008, Fracasso, et al. 2010] and PAHs [Bagryantseva, et al. , Novotna, et al. 2007, Gamboa, et al. 2008]. On the other hand, a study of persons affected by the *Braer* spill [Cole, et al. 1997] found no evidence of genotoxicity through either DNA adducts in peripheral blood mononuclear cells or mutations at the *HPRT* locus in T lymphocytes.

Studies of upstream petrochemical workers, who are likely to have many exposures similar to that of oil spill clean-up workers, have reported excesses of leukemia, multiple myeloma, melanoma, and esophageal adenocarcinoma [Schnatter, et al. 1992, Kirkeleit, et al. 2008]. While such rare outcomes may take years to develop, immediate and lasting changes may be seen in intermediate biomarkers indicating toxic effects and potential for future disease risk. The immune system may represent a particularly sensitive and accessible system for determining physiological impact of oil spill exposures. For example, the hematotoxic and immunotoxic effects of benzene exposure have been well-described, occurring even at relatively low levels of exposure [Lan, et al. 2004]. These effects, indicated by downward shifts in leukocyte and red blood cell counts, may also be more apparent in susceptible subgroups defined by genetic variation in inflammatory, apoptotic, or metabolizing pathways [Lan, et al. 2005, Kim, et al. 2007, Lan, et al. 2009, Zhang, et al. 2010]. Benzene's toxicity to hematopoietic progenitor cells may also impart long-term effects on the immune system leading to premature immunosenescence. This idea is supported by the finding that higher personal benzene exposures in traffic officers were associated with significantly shorter leukocyte DNA telomere length [Hoxha, et al. 2009], a marker of immune aging that has been related to risk of multiple chronic disease outcomes and mortality. Other intermediate markers related to chronic disease risk include inflammatory cytokines, antibodies indicating reduced immunity to latent viral infections, or auto-antibodies, though limited information exists on these measures in past studies of oil spill or petrochemical workers.

1 Study Objectives

This research effort is designed to investigate potential short- and long-term health effects among workers engaged in clean-up activities surrounding the Deepwater Horizon oil spill. Given the very limited health effects research conducted to date on oil spill clean-up workers, the GuLF Study is designed not to study a few narrow *a priori* hypotheses, but rather to allow the investigation of a wide range of potential adverse health effects, including physical, psychological, and biological effects. The long-term goal of this study is not only to identify adverse health outcomes related to clean-up activities among the Deepwater Horizon responders, but also to assemble information

that can be used for prevention and intervention of adverse health outcomes in any future similar disasters.

The over-arching hypotheses of this study are:

1. Exposure to constituents of oil, dispersants, and oil-dispersant mixtures, and to spill-related stress by workers engaged in clean-up of the Deepwater Horizon oil spill are associated with adverse health effects, particularly **respiratory**, **neurological**, **hematologic**, and **psychological or mental health**.
2. There are exposure-response relationships between the above exposures and health effects.
3. Biomarkers of potentially adverse biologic effects are associated with the above exposures.

1.1 Primary Objective

The primary objective of the GuLF Study is to assess a wide range of potential short- and long-term human health effects associated with clean-up and disposal activities surrounding the Deepwater Horizon oil spill in the Gulf of Mexico. Health areas of interest include, but are not limited to, respiratory, cardiovascular, hematologic, dermatologic, neurologic, cancer, reproductive, mental health, substance abuse, immunologic, hepatic, and renal effects.

1.2 Secondary Objectives

A key aspect of assessing these health effects will be to investigate biomarkers of potentially adverse biological effect, including DNA damage, aberrant epigenetic profiles, and alterations in gene expression, some of which have been observed in previous studies of oil spill clean-up workers.

Additionally, secondary objectives of the study are to: 1) create a resource for additional collaborative research on specific scientific hypotheses or on subgroups of interest. We will work with external scientists to facilitate nested sub-studies within the existing cohort to examine outcomes and exposure subgroups of interest; and 2) create a resource to better understand the short and long-term human health effects of oil and oil dispersants in the environment.

1.3 Sub-study Objectives

At this time, one sub-study, the Biomedical Surveillance Sub-cohort, is planned as an integral part of the study proposal although the specific tests to be carried out and the implementation details are not yet designed. The detailed protocol (s) for this Sub-cohort will be developed in collaboration with extramural partners and will be separately peer-reviewed. Objectives of the Biomedical Surveillance Sub-cohort will include investigating immediate and ongoing physiological and clinical parameters in a group of highly exposed workers and a smaller number of unexposed workers. Establishing this exposure-enriched group that contains more detailed information on adverse outcomes and repeated biological measures will provide an important resource for longitudinal studies and enable nested comparisons with measures obtained on the larger cohort.

2 Study Design

2.1 Description of the Study Design

The GuLF Study has been designed to allow investigation of potential short- and long-term health effects associated with the oil spill clean-up work and to create a resource for collaborative research on specific scientific hypotheses or subgroups. It is an observational prospective cohort study that will create opportunities for both analyses of the full cohort as well as numerous nested analyses. The design will enable investigators to efficiently address specific hypotheses generated from previous studies of oil spill exposures and, importantly for an exposure that has not been studied in relation to long-term health outcomes, allow them more generally to identify new symptoms and conditions that may occur in excess among the exposed participants and determine the extent to which any physical and mental health conditions persist. The data and the biological and environmental samples that will be collected will allow examination of a wide range of health areas of interest, including respiratory, cardiovascular, hematologic, dermatologic, neurologic, cancer, reproductive, mental health, immunologic, hepatic, and renal. The study is planned to be at least 10 years in duration, although it is anticipated that the study may continue for 20 years or more, through record linkage, at a minimum. Prospective studies typically have a long-term design because some diseases of interest, such as cancer, generally have long latency periods, e.g., 15-20 years or more. Consequently, we will consider extending this study, based on what we learn during the initial study period, scientific and public health needs, and on the availability of funds.

2.1.1 Study Population

To capture a representative sample of the clean-up workers and controls, we will target individuals across the various categories of job/potential exposure from the Petroleum Education Council (PEC), National Institute of Occupational Safety and Health (NIOSH), or other worker/volunteer rosters, security badging and access lists, and other administrative lists maintained by BP contractors such as The Response Group (TRG) Swift, and Foresight Vantage (among others). These individuals are potential participants because they are believed to have engaged in clean-up work or participated in worker training modules in anticipation of such work. We will exclude individuals such as journalists who did not engage in clean-up activities but were required to undergo safety training to gain access to worker staging areas (and, therefore, may appear on the PEC list). These individuals will be determined from either the training lists (i.e., individuals who indicated that they intended to work for less than one week) or via screening questions during the enrollment telephone interview. We will use data from our planned mini-pilot (at the beginning of field work) to determine the feasibility of also *efficiently* identifying and excluding individuals such as caterers and administrative/office staff who engaged in clean-up *related* activities, but not clean-up activities *per se*; however, this issue is complex and requires data that will become available only after we go into the field. We define potentially *exposed* subjects as individuals who completed at least one day of oil-spill clean-up-related work, either paid or volunteer. We define *unexposed* subjects as eligible individuals who either 1) completed safety training in anticipation of performing clean-up work but did not do so or 2) engaged only in clean-up activities such as administration, oversight, and logistics that involved no exposure to spill-related oil, oil byproducts, or dispersants. Selection for the Active Follow-up Sub-cohort will cover all levels of potential exposure but will oversample workers with the

highest potential exposures to oil, oil byproducts and dispersants. We will conduct interviews in English, Spanish, and Vietnamese. Special accommodation will be made for those speaking other languages (e.g. Haitian Creole, Louisianan Creole, etc.), if feasible and warranted by the number of workers speaking these languages. PEC training was conducted in English, Spanish, and Vietnamese only so we do not anticipate a large number of those speaking other languages. However, should this change based on data from the PEC list or input from community groups, we will submit an amendment to the IRB with appropriate translated documents for approval.

2.1.2 Study Cohort and Sub-cohorts

After administering a screening enrollment questionnaire to each potential cohort member, we will use a two-stage sampling design to randomly sample individuals across categories of job/potential exposure for invitation to participate in the *Active Follow-up Sub-cohort* (N~24,000), which will be nested within the full cohort (N~55,000). We will also randomly sample individuals within the Active Follow-up Sub-cohort across categories of job/potential exposure for inclusion in the *Biomedical Surveillance Sub-cohort* ("tagging" N~6,250 with the expectation of obtaining agreement from N~5,000). This nested design represents an efficient and cost-effective way to include most of the clean-up workers in a prospective study and also to obtain comprehensive and detailed clinical and biologic information on a scientifically appropriate sample of the total group while maintaining statistical integrity through the use of the two-stage random sampling design. The study effort, participant commitment, and potential knowledge gain increases from passively followed members of the full cohort to members of the Active Follow-up Sub-cohort to members of the Biomedical Surveillance Sub-cohort. For each sub-cohort, we will oversample from job categories that had higher potential exposures and/or were smaller to ensure adequate representation of higher potential exposures and of all tasks performed.

Workers will primarily be identified from a combined list of workers who completed a voluntary NIOSH Roster form and additional workers identified through the PEC list and other lists that may become available of persons who may have been involved in clean-up activities (see Section 2.3.1 for a description of the lists of potential subjects.)

The *Active Follow-up Sub-cohort* will contain ~18,000 workers ("exposed") from across all job categories and ~6,000 controls ("unexposed"). While these groups are selected on the basis of their potential exposure to oil or dispersants used in clean-up, both groups will contain individuals who are "exposed" and not exposed to the stresses associated with having lost their source of income due to the oil spill or living with economic or social uncertainty due to their residential proximity to the spill. This sub-cohort will be largely restricted to persons residing in one of the four Gulf States primarily engaged in clean-up activities (LA, MS, AL, and FL), prioritizing workers closest to the spill area. Based on data on approximately 44,000 workers from the NIOSH roster, all but 8% of workers were from these four states. Eligibility may later be expanded to include other states based on information on the geographic distribution of workers that we will receive from the PEC list and other worker lists. We will recruit workers from other states only if it is determined, upon receipt of the potential subject lists that a large number of workers with potential high exposures came from a given state. For logistical reasons, we will not recruit controls from outside of the four most affected Gulf States. Federal workers (e.g. Coast Guard, Occupational Safety and Health Administration (OSHA), Fish and Wildlife Service (FWS), National Oceanic and Atmospheric Administration (NOAA), Environmental Protection Agency (EPA), and others) residing

outside of the four Gulf States and other workers who reside outside of the Gulf States are eligible to be included if they had potentially high exposures because of specific clean-up tasks performed. A Federal control group, within the larger sub-cohort control group, will be based on the large number of Federal responders whose participation in the clean-up was limited to roles such as administration, oversight, and logistics that provided no potential exposure to spill-related oil, oil byproducts, or dispersants. We will oversample certain categories of job/potential exposure of particular interest (e.g., those with potential direct exposure to fresh crude or burning oil or to chemical dispersants). Because there is a lack of centralized data concerning the distribution of categories of work/potential exposure and we are likely to determine this distribution only when the enrollment interviews are underway, we will periodically evaluate and revise as appropriate our sampling probabilities. These probabilities will take into account the distribution of jobs/potential exposures and statistical power. Participants in the Active Follow-up Sub-cohort will 1) be administered detailed interviews, 2) provide biological samples (blood, urine, hair, toe nail clippings, and possibly saliva) and environmental samples (house dust), and 3) have basic clinical measurements taken at enrollment, and 4) will be administered two follow-up interviews. In contrast, passively followed members of the full cohort will be administered only a brief telephone interview at enrollment. Disease and mortality during follow-up will be obtained via linkage with cancer registries and State vital statistics records.

The controls will preferentially be drawn from the PEC/NIOSH lists, which include some individuals who were trained in anticipation of being hired for clean-up work but were never hired. At some time during the peak work weeks, employers were advised that heat related health issues might be especially problematic for obese workers or those with high blood pressure. Although pre-employment screening may have been advised, it is uncertain whether or not it was systematically carried out, and if done, may have been contractor specific. Therefore, because some potential workers may have been turned away due to health concerns, potential controls will be asked why they did not participate in clean-up activities. Those indicating they did not qualify for medical reasons will be excluded as will those who completed training to facilitate receipt of a badge to enter the area, with no intention of performing any clean-up related tasks.

We estimate that there will be sufficient potential workers with minimal exposure for internal comparison to serve as controls. However, if it turns out that our estimates are incorrect and we need to consider other mechanisms to enroll a comparison group, we will consider other approaches such as direct media or asking participants to tell their friends and colleagues about the study and have their friends and colleagues contact the study directly.

Because some workers from the four Gulf States will come from areas away from the affected communities and because controls from the affected communities may have experienced some spill-related exposures, including stress and social disruption, we will establish two control groups. Persons from the lists described in Section 3.3.1 who are determined to have not engaged in clean-up activities and are eligible for this study will be placed in either a “local” control group or a “non-local” control group. The “local” control group will consist of controls residing within the affected communities. Their inclusions in analyses of the health effects of chemical exposures will account for the stress and other psychosocial factors experienced by clean-up workers residing in the affected communities. The “non-local” control group will consist of individuals residing within the affected states, but outside of the affected communities. These individuals will serve as a control group in evaluation of spill-related stress and other societal effects

that may affect both exposed clean-up workers and unexposed controls residing in the affected communities. Based on residence information from the 44,000 persons in the NIOSH roster, 77% of the workers were "local" (i.e. lived in a coastal county in one of the four states). Consequently, we will oversample "non-local" trainee controls to provide sufficient statistical power for analyses involving this group. A third control group will consist of the large number of Federal responders whose participation in the clean-up was limited to roles such as administration, oversight, and logistics that entailed no exposure to spill-related oil, oil byproducts, or dispersants.

Passively followed members of the full cohort will be those individuals who completed an enrollment interview but were not included in the Active Follow-up Sub-cohort because 1) they did not reside in one of the targeted Gulf States, 2) they were not randomly sampled for inclusion in the Active Follow-up Sub-cohort, or 3), they were unable or unwilling to participate in active follow-up but are willing to be tracked over time. Outcomes follow-up will be obtained via linkage with State cancer registries and vital statistics databases.

The *Biomedical Surveillance Sub-cohort* will be an intensively evaluated subgroup nested within the Active Follow-up Sub-cohort. It will be sampled from across the categories of job/potential exposure and from controls, with oversampling of workers with the highest potential exposures. Potential members of this sub-cohort will be identified during the enrollment interview, based on their reported clean-up activities. To achieve our target of ~5,000 members in this sub-cohort, we will identify ~6,250 potential members during the enrollment interview, assuming that ~80% will ultimately agree to participate in the further procedures required of the Biomedical Surveillance Sub-cohort (given that they already agreed to participate in the Active Follow-up Sub-cohort and will receive the benefit of more detailed health monitoring during the study) when they are re-contacted later by extramural collaborators. This sub-cohort will undergo the same baseline and follow-up procedures as the rest of the Active Follow-up Sub-cohort, but will additionally participate in multiple follow-up visits involving health assessments that include spirometry with bronchodilator challenge and neurological testing and collection of repeat biological and environmental samples. This sub-cohort will undergo more intensive biomonitoring than the rest of the Active Follow-up Sub-cohort, including having their complete blood counts (CBCs), white blood cell (WBC) differentials and more comprehensive urinalysis measured at baseline. [Note: These tests will be performed for all 6,250 identified as potentially eligible for the Biomedical Surveillance Sub-cohort as they must be performed on fresh samples. Similarly, lymphocytes will be extracted and cryopreserved for the larger sample of potential participants.]

Protocols for the additional clinical examinations will be developed and implemented in collaboration with local university partners identified through a request for proposals (RFP) and, therefore, will not be discussed further in this protocol. These will undergo separate scientific and Institutional Review Board (IRB) review. Consideration will be given to focusing on the more highly exposed Gulf States (e.g. Louisiana and Alabama) to facilitate comprehensive health examinations. We anticipate a standardized core protocol with room for unique investigator initiated options to address additional hypotheses.

2.1.3 Exposure Reconstruction

Although monitoring data will be available on some individuals for some exposures, most participants in the study cohorts will lack such measurements. Because it is critical to

have some indication of quantitative levels of exposure, it will be necessary to construct exposure indicators from the available individual and environmental monitoring data, characteristics of clean-up tasks, work locations, and times that these events occurred. Given the absence of individual or area/group monitoring data for most workers, it is important to note that estimates of exposure, whether dichotomous (exposed/unexposed) or semi-quantitative (e.g., none, low, medium, high), will reflect *potential* exposure rather than *known* exposure and references in this protocol to exposures, except where indicated otherwise, should be interpreted as such. We will validate the self-reported clean-up activities with security badge and payroll records to the extent possible using available data. Moreover, we will work with survey methodologists to ensure valid data collection. Investigators who are experts in industrial hygiene exposure assessment will assemble exposure data and construct job-exposure matrices for the exposures of interest using monitoring data from multiple sources. These monitoring data, including individual measurements for some workers, area measurements, and Health Hazard Evaluations, were collected during clean-up activities and monitoring by OSHA, NIOSH, NOAA, EPA, Fish and Wildlife Service, US Geologic Survey, the Coast Guard, and British Petroleum (BP). An interagency meeting was convened on August 19 in Washington, DC to discuss these issues and identify sources of data that could be used to reconstruct worker exposures across all tasks. An example of these environmental monitoring data is provided in Appendix U. This spreadsheet was first created by EPA as a way to identify data streams and later expanded to identify any sampling within the Deepwater Horizon Response that may be redundant or complementary. It will serve as a useful springboard from which to start cataloging the available environmental data and will aid in the exposure assessment process.

In addition, available chemical analysis data of oil from the well, the dispersants used, samples of weathered oil, and weather data from the period of the spill clean-up will be considered in relation to exposure opportunities. This information will be assembled for the exposure panel and may be used in exposure estimation and reconstruction. By linking this exposure information with self-reported activity data, exposures will be estimated for all included workers, including those from Federal agencies/institutions. We will also use environmental samples (house dust), if available and appropriate, and questionnaire data to identify relevant occupational and non-occupational exposures. Lastly, we will evaluate existing exposure measurements on beach clean-up workers and consider collection of additional biomonitoring data for this large subgroup if clean-up efforts are still underway at the time of cohort enrollment. A detailed protocol of exposure assessment procedures will be developed by the study investigators in close collaboration with the panel of experts described above.

We will work closely with academic and federal partners such as OSHA and NIOSH to convene a panel of experts to systematically work through these exposure assessment issues and develop a scientifically sound method for assigning exposures to the study participants. This expert panel will develop a Job-Exposure Matrix (JEM) based on the varied work tasks of cleanup workers and volunteers. Different dichotomous and ordinal ranking metrics may need to be developed for the different chemicals and exposure pathways that may be associated with different health effects. For example, a single metric will probably not capture important differences in PAH exposure from particle inhalation among oil burn workers versus dermal PAH exposure of absorbent boom operators. The exposure metrics will not only need to consider differential exposures based on job task, but will also need to consider the duration of exposures (e.g., hours per day, total days of work).

One of the challenges of this research is that most workers and controls will have exposures to many of the chemicals of interest that are unrelated to the oil spill. Most persons are exposed to benzene in ambient air (usually at very low levels) and to PAHs from inhalation, dietary ingestion, and house dust. Such exposures are particularly common among residents along the Gulf coast in Louisiana. There are also a number of consumer products that contain 2-butoxyethanol or propylene glycol, two dispersant ingredients of potential interest. Some workers and controls could have significant occupational (non-spill related) exposures to some of these chemicals. In most cases, these types of "background" exposures are likely to have similar distributions among the worker and control populations. However, the study will need to carefully consider and collect information to characterize these exposures. For example:

- Commercial boat operators who participated in cleanup activities could potentially receive higher long-term exposures to fuel oil and engine exhaust, with many of the same chemical constituents as found in the spilled oil, compared to a control group that did not include active boat operators.
- Workers may come from Gulf coast locations affected by point sources of petrochemical pollution not experienced by control living inland or in other states.
- Workers hired directly by BP or its long-term contractors may have had other oil industry jobs.
- Workers hired early on may include those with prior training in hazard remediation and may have been involved in cleanup from other smaller spills.

This potential confounding will be addressed through questionnaire data (occupational and other relevant activities/exposures), GIS mapping as appropriate, and analysis of biological and environmental samples. The expert panel will need to address these and other challenges that face this critical component of the study.

While we have already consulted individually with other researchers who have examined health effects associated with past oil spills, we are exploring the possibility of convening an exposure assessment workshop of all of these study investigators to explore lessons learned and to discuss findings to ensure that the GuLF Study is conducted to the state-of-the-science.

It is important to note that many scientifically rigorous epidemiologic studies have successfully used qualitative or semi-quantitative data derived from job-exposure matrices to investigate exposure-disease associations [Coble, et al., 2009, Allen, et al., 2006, Baris, et al., 2004, Kromhout, et al., 1995, Laakkonen, et al., 2008, Young, et al., 2004, Richardson, et al., 2008, Lee, et al., 2003, Elci, et al., 2003]. This representative sample of studies linked job titles and usual job activities to available monitoring data to create job-exposure matrices that were used to estimate exposures in the study population. Indeed, the epidemiologic investigations surrounding the *Prestige* oil spill response in Spain utilized self-reported exposure information to assess health outcomes that otherwise might have been missed [Suarez, et al. 2005, Carrasco, et al. 2006, Zock, et al., 2007], Such studies have yielded scientifically valuable information and demonstrate the important role that qualitative and semi-quantitative exposure data and/or job-exposure matrices can play in epidemiologic research.

Although the development and evaluation of job-exposure matrices for the present worker population would ideally have been done prior to beginning subject recruitment, this was not a feasible option for this study, as is typically the case for studies responding to disasters. A large amount of monitoring data has already been collected,

is currently being aggregated, and will be available to us. Our main concern to this point has been to design a scientifically rigorous study that we can get into the field as quickly as possible and 1) capture the self-reported activities, dates, times, locations, etc. of clean-up work that these workers engaged in before their memories fade and 2) enroll these workers into the study before they move, change phone numbers, or otherwise become lost to follow-up.

2.2 Eligibility Criteria

We anticipate screening as many as 90,000 individuals in order to recruit approximately 55,000 volunteers primarily from the four most affected Gulf States* (LA, MS, AL, and FL) into the cohort, which will include a randomly sampled Active Follow-up Sub-cohort of approximately 24,000 individuals nested within it. Eligibility criteria for the cohort include:

- 21 years of age or older
- Fall into one of two oil-related exposure categories:
    - *Potentially exposed* subjects must have completed at least one day of oil-spill clean-up-related work (other than safety training), either paid or volunteer.
    - *Unexposed* subjects will be individuals who were not directly involved in oil spill clean-up activities, but who worked near the oil spill or completed some oil spill worker training.

Invitation to enroll in the Active Follow-up Sub-cohort will be made based primarily on level of potential exposure as well as state of residence. Sampling probabilities will vary across categories of job/potential exposure, with probabilities of up to 100% for persons who report having engaged in oil clean-up related activities that are suspected of having high exposures (e.g. working at the source, skimming, incineration, booming (specifically retrieval of contaminated boom), wildlife clean-up, etc.). Available funding imposes an upper limit on the size of the Active Follow-up Sub-cohort, but the number of workers in different categories of job/potential exposure is currently unknown (and will likely remain unknown until interviewing commences). Consequently, sampling probabilities will be re-evaluated and adjusted periodically as study enrollment proceeds in order to realize the study objectives and achieve the target size of the Active Follow-up Sub-cohort.

Because of 1) the small proportion of non-Federal clean-up workers from outside of the four most affected Gulf States (< 8%, based on current data) and 2) the substantial logistical challenges of including these workers in the Active Follow-up Sub-cohort, we will include these individuals in the Active Follow-up Sub-cohort only if we determine that an appreciable number of them engaged in clean-up activities with high potential exposure. Otherwise, these individuals will be enrolled into the passive follow-up portion of the cohort. This strategy is the same as that employed for the Federal workers in this cohort.

2.2.1 Rationale for including only workers or those who were trained

Morbidity and mortality rates from the general population include individuals who are often too sick to work. Thus, those who are hired, or trained to be hired, are generally healthier than those who aren't trained because relatively healthy individuals are more

likely to gain employment and remain employed – a phenomenon known as the "healthy worker effect." The healthy worker effect is particularly relevant in the selection of unexposed controls. In order to obtain comparable controls for workers engaged in oil spill clean-up activities, we would need to find individuals who otherwise would have been able to work (i.e., were healthy enough to work), but weren't hired to do so, thus limiting their exposure. We plan to recruit from a master list that incorporates training and badging information (e.g., the NIOSH roster, PEC training lists, Coast Guard deployment logs, etc.) to identify workers who were trained to participate but may or may not have been engaged in clean-up activities ("exposed" and "unexposed," respectively). Since everyone in the spill area was required to have a badge, and completion of a basic training module was required to receive a badge, volunteers should have also completed one or more training modules before engaging in clean-up activities. Others who worked but were not trained through the PEC will also be eligible. This includes workers whose training was separately administered through Parish organizations and individuals who might not have completed required training modules for language or other reasons (e.g. crew on Vessels of Opportunity whose captains, only, received formal worker training).

While exposed and unexposed individuals will be recruited during the same enrollment period, if we aren't able to find suitable non-exposed individuals from this master list, we will seek matched controls in the community through references provided by the participants themselves, individuals from the BP claims databases, or other community selection techniques such as random digit dialing. This may involve more time than identification of controls from the clean-up training lists. We have planned for these activities to occur in the later months of recruitment so that we can focus on enrolling exposed workers first.

We will actively enroll any individual, 21 years or older who is on a worker or volunteer list describing any potential contact with oil and dispersants, regardless of their gender, racial and ethnic background, or pregnancy status. Approximately 19% of the 44,000 workers enumerated by NIOSH were women. Although we do not anticipate a large pregnant population, there may be individuals who were not aware that they were pregnant or who otherwise engaged in clean-up related activities despite knowing that they were pregnant and who may be recruited into the study.

2.2.2 Rationale for Exclusions

Participant selection and rationale for eligibility criteria have been described in detail in Section 3.2 - Eligibility Criteria. Enrollment is open to adults of all racial and ethnic background. Children will not be enrolled because they were not allowed to participate in clean-up activities. Study activities present minimal risk to pregnant women. Therefore, pregnant women will be allowed to enroll in the study, and women who become pregnant during the study will not be withdrawn.

Those who were deemed medically ineligible to participate in clean-up activities because of pre-existing conditions are excluded because they won't be representative of those individuals who were engaged in clean-up activities.

2.3 Recruitment

2.3.1 Recruitment Database

The cohort will be recruited over a 12-18 month period, starting in January or February 2011 with the baseline home visits completed within 18 months and will initially be followed annually for at least 10 years. (We anticipate that the cohort will be followed for up to 20 years to extract the maximum information from a study with a prospective design). Potential participants will be identified from the existing NIOSH Voluntary Worker Roster (N~55,000) which is being shared with the National Institute of Environmental Health Sciences (NIEHS) through a Data Transfer Agreement. The NIOSH roster is believed to contain a majority of the workers who engaged in clean-up activities, but is known to have left out workers who were on the job early, workers trained through special arrangements or certified as having been trained prior to the spill, and other potentially important worker groups. We have reached an agreement with BP for access to the larger Petroleum Education Council (PEC) list of individuals who completed one or more safety training modules (N≈110,000) and will seek similar agreement to obtain other known lists of individuals involved in clean-up activities (e.g., parish responder lists, BP contractor payroll, and lists of Federal workers and contractors deployed to, or otherwise engaged in, on-site clean-up activities in, the Gulf, including the Coast Guard, OSHA, NIOSH, NOAA, EPA, Fish and Wildlife Service, US Geologic Survey, National Guard, etc.). Because the NIOSH roster was developed in connection with worker training, it is expected that most, if not all, names from the roster will be included on the PEC list. Some, but not necessarily all, of those identified through Federal worker lists will also appear on the PEC list. Some workers trained through Parish organizations and crew members on Vessels of Opportunity are not expected to be found on the PEC list. Thus as many as 130,000 may be enumerated through all lists combined. The PEC list may include some duplicate names as a few workers were required to complete additional training modules at a later date as workplace hazards were identified. Some of these lists, such as those of employees of Federal agencies/institutions, will contain mostly, if not entirely, persons involved in clean-up operations; other lists, such as the PEC list, will include a substantial proportion of persons who did not participate in clean-up (but may have taken the safety training in anticipation of doing so) and can be identified only at the time of the telephone interview. We will work as quickly and efficiently as possible with collaborating partners and other federal agencies in obtaining access to these lists. Time is of the essence because we wish to interview clean-up workers and collect biologic and environmental samples during clean-up activities or as shortly thereafter as possible. This is necessary because biologic indicators of exposure dissipate with time and individual's recall of their activities also diminishes. In addition, it is important to enroll subjects into the study before they move, change phone numbers, or otherwise become lost to follow-up. Getting into the field as soon as possible is also essential to maintain the goodwill of the affected communities, which will profoundly affect the enthusiasm, support, and cooperation they show towards this study.

These databases will be merged into a master recruitment file to identify and remove duplicates. We expect a total of about 130,000 names from the PEC list and other worker lists combined, which we are assuming will be reduced to about 90,000 after eliminating duplicate names and, if possible, those who completed training only to obtain access to the spill site, with no intention of engaging in clean-up work (e.g. reporters, government visitors, etc.). Where possible, we will infer potential exposure through the

training the individuals obtained, their reported or anticipated activities (collected on the NIOSH roster), and/or location in which they reported for work. However, we may not be able to definitively confirm oil spill clean-up related activities until we interview the participant and ascertain the types of activities that they performed. Thus, initial exposure characterization will involve a two-stage process where a participant is flagged for potentially being exposed/non-exposed which may later be modified based on information from the telephone enrollment questionnaire will include a series of questions which will ascertain exposure. Exposure classification for enrollment purposes into the Active Follow-up Sub-cohort will be based on the participant's answers to these exposure questions. We will try to identify and prioritize enrollment of individuals with likely exposures so that we can better characterize their exposures, but given the limitation of not knowing a participant's true exposure status prior to their interview, we will most likely be enrolling exposed participants and unexposed controls at a comparable rate.

2.4 Community and Scientific Outreach

The goal of the community outreach efforts is to fully apprise the community of study activities, to ensure community collaboration and support in all aspects of the study including design, implementation, evaluation, translation, and to disseminate findings and results. Close and ongoing community engagement is expected to enhance the scientific validity of the study, make it more broadly relevant from a public health perspective, and expand its benefits to the affected communities.

2.4.1 Meetings with potentially affected groups

We have already established contacts and are continuing 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 four state area.

We have conducted a series of meetings with state and local health department representatives as well as with the NGOs that span the various advocacy and occupational groups representing the workers involved in clean-up throughout the Gulf. We met with groups in Mississippi and Alabama during the week of September 12, 2010; Florida the week of September 19, 2010; and Louisiana during the week of October 3, 2010. Other meetings are ongoing.

The groups we have contacted span cultural, religious, occupational, and state and local government sectors and are continuously updated as more information and contacts are made (current as of 10/22/2010). These groups serve as important links into the community and can act as an informal Community Advisory Board for study protocol issues and concerns for study investigators until a more formal Board can be established. The groups listed below the groups that we have identified and established contact with:

- Advocates for Environmental Human Rights
- Alabama State Health Department

- Alliance Institute
- Asian Americans for Change, Mississippi
- Bayou Grace Community Services
- Bayou Interfaith Shared Community Organizing (BISCO)
- Boat People SOS (BPSOS)
- Coastal Family Health Center
- Commercial Fisherman of America
- Deep South Center for Environmental Justice
- Gulf Coast Fund for Community Renewal and Ecological Health (GCF)
- Gulf Restoration Network
- Interfaith Disaster Network
- Isle de Jean Charles Band of the Biloxi Chitimacha
- Local chambers of commerce
- Louisiana Bayoukeeper
- Louisiana Bucket Brigade
- Louisiana Department of Health and Hospitals, Region 1
- Louisiana Department of Health and Hospitals, Region 3
- Louisiana Disaster Recovery Foundation, Oil Spill Recovery Policy & Advocacy Initiative
- Louisiana Justice Institute
- Louisiana Oystermen Association
- Louisiana Shrimp Association
- Mary Queen of Vietnam Community Development Corporation (MQVN CDC)
- Mississippi Center for Justice
- Mississippi Commission on Volunteer Service
- Mississippi Gulf Coast Community College
- Mobile BayKeeper
- Moving Forward Gulf Coast, Inc.
- Parish Presidents
- South Bay Communities Alliance, Inc.
- SeaGrant Programs in LA, MS and AL
- St. Bernard Project
- Steps Coalition
- The Village/El Pueblo
- Tri-Coastal Community Outreach
- Turkey Creek Community Initiatives
- United Commercial Fisherman Association of Louisiana
- United Houma Nation
- Vietnamese American Young Leaders Association of New Orleans
- Vietnamese Martyr's Church
- Zion Travelers Cooperative Center

The meetings conducted to date with state and local health department and community group representatives have already led to several improvements in questionnaire development and study design. For example, the questionnaire has been revised to:

- Better define labor categories;
- Better characterize definitions of exposure;
- Improve the ability with which the workers can recall key dates in their work history; and
- Include questions about the symptoms that are of the greatest concern to the workers so that prevalence rates can be reported to the community.

Additionally, these meetings have allowed us to expand the resources included in the health referral network and enabled us to better tailor messages to participants about the study's purpose and the importance of their participation. They have also provided us with a better understanding of the barriers in recruitment and enrollment and how to use community-based strategies to avoid these barriers.
As we further extend community outreach efforts, we will identify Community Outreach Coordinators to organize and implement outreach activities in each of the Gulf States who will:

- Help to build strong relationships with NGOs representing the worker and volunteer populations across the four Gulf Coast States.
- Augment an advertising campaign (as described in Section 3.4.3) with grass-roots promotional activities including local media placement (church bulletins, community newspapers, etc) and community presentations.
- Assist in recruitment of special populations as needed.

In addition to the continuing efforts with public health and community group representatives, we have been conducting outreach in the following ways:

Webinars. NIEHS hosted a 90-minute webinar with local researchers, community organizations and others interested in the GuLF Study on August 17, 2010 and a two-hour Webinar on September 15, 2010. The purpose of the webinars was to announce publicly the plans for the GuLF Study and obtain feedback on study design and implementation from interested stakeholders. Prior to the webinar, NIEHS distributed a draft GuLF Study Concept document and a Key Points document. Each webinar was well attended by over 100 participants and we have received multiple offers from community organizations to provide assistance for the study. Suggestions made during and after the webinar have been incorporated into the study design. Additional webinars are planned at future dates to be determined to continue information exchange and dialog.

Phone briefing. As a follow-up to the first webinar and next step in the community outreach efforts, we will invite key stakeholder groups, such as from the list above to a follow-up phone briefing. The purpose of the phone briefing is to meet individually with each stakeholder group to review the study aims and implementation, answer any question or concerns about the study, establish a dialog with stakeholders, and begin discussions on the primary health issues of concern for their constituents. Approximately 10-15 phone briefings will be conducted each lasting up to 30 minutes. At the end of the call, we will document any action items and discuss plans for future meetings in person.

In-person meetings. As a follow-up to the phone briefings, we will travel to the four Gulf States to meet in person with the community stakeholder groups. During the in-person sessions, we will request to meet both with organizational leadership in addition to their constituents. The purpose of these meetings is to further build strong community ties

and gather information to finalize the study design. Due to the short timeline to study launch we will immediately conduct informal discussions with leadership and listening sessions with their constituents. The topics of these discussions are expected to broadly include possible barriers to study implementation, resolutions to those barriers and the best methods to communicate with study participants and publicize the study.

HRSA and State Health Department meetings. Meetings were conducted with State and local Health Department representatives beginning the second week in September, 2010, including a combined meeting of leadership from Health Service Regions covering the Gulf States on September 9-10, 2010. These meetings were intended to inform state and local leadership about study plans and to obtain input into study design and implementation. A specific focus of these meetings was to develop strategies for community based health and mental health referrals for participants identified as needing follow-up medical care (e.g. for follow-up of elevated blood pressure, or glucosuria) or identified as having unmet mental health or social service needs. While the GuLF Study is not designed to provide medical care to its participants, we will work closely with local health officials to provide the appropriate referral information to participants identified as having unmet medical and/or mental health needs.

Dockside Chats. Study staff joined the Unified Command in several Dockside chats with workers during the week of August 22, 2010. These informal sessions provided insight into some of the health and community concerns of workers from the affected region.

2.4.2 Community Advisory Group

A Community Advisory Group will be created to provide continued advice on the study and outreach efforts. The group will consist of up to 15 members representing communities as well as organizations representing worker groups from all four states as well as various occupational groups and is expected to engage in the following activities:

- Facilitate dialogue between community members and the study team
- Identify effective communication strategies and vehicles tailored to the communities' needs
- Assist in the dissemination of study related information locally and regionally
- Host community neighborhood meetings
- Proactively identify issues of concern with study implementation and options for resolutions
- Retain participants in the study over time

A Community Advisory Group chair will be carefully selected from among its members and will work in close collaboration with the study investigators. The Community Advisory Group will meet regularly throughout the entire study duration. Meetings are expected to occur more frequently during study planning and initiation and then less frequently in the out years of the study.

2.4.3 Communicating the Study to the Community

Communication of the study activities to oil spill clean-up workers and affected communities is essential. Many of these efforts will involve communications through

community leaders directly to their constituents, some will involve targeted outreach by the study and NIEHS, and other efforts will involve media-based outreach. Typically, it takes multiple points of contact to build study credibility and motivate an individual to participate in a health study, particularly a longitudinal health study. Although we will be working from a known population of oil spill clean-up workers, media-based efforts will afford the study legitimacy in an environment fraught with competing Katrina-focused studies, distrust of the government, and scientific complexity. Additionally, media-based outreach in conjunction with more direct-to-worker outreach will allow for the ability to reach a larger number of individuals in a very short time frame. The Community Advisory Group will be crucial in designing this process and enhancing its effectiveness.

Brochure. A study brochure (Appendix G) will be developed in English, Spanish and Vietnamese. The purpose of the brochure is to introduce the study and provide contact information though the hotline and website. The brochure will be sent with the lead letter inviting study participants during enrollment but may also serve a variety of other purposes for community outreach.

Hotline. We will establish a toll free hotline for the study. During enrollment, the hotline will be used for workers to return a call to participate in the study. A call center representative will answer the hotline during call center hours of operation, i.e. from 9 AM to 9 PM, Monday through Saturday and from 12 noon to 6 PM on Sundays. It will roll to an answering machine after hours with all calls to potential participants returned the following day. Call center hours will be determined based on input from the community groups as to what would be acceptable.

Internet. We will maintain a website to provide information about the study. The website will be updated regularly with details on recruitment efforts, study findings, and links to other organizations and information resources. Additionally, we will seek to have each of our community partners have a link on their website to the study website. We will also explore the possibility of using Web 2.0 resources such as Facebook and Twitter if we can be assured that participant confidentiality can be maintained and there are sufficient numbers of individuals within our study population and community who would be using these sites.

Advertising. Additional forms of media-based advertising will be determined in collaboration with key stakeholder groups. Based on preliminary conversations with various community groups, we anticipate utilizing media-based advertising to both increase awareness and credibility of the study as well as motivate participation. Radio may provide a good medium for communicating the study to certain segments of the population while outdoor advertising may appeal better to other segments. Whenever feasible, we will capitalize on opportunities to collaborate with community partners on radio or TV show interviews, local newspaper articles, and other media as a form of generating awareness and credibility for the study. Media outlets that have been suggested by community members thus far include:

- Radio stations: Q93, 98.5, 102.9, 106.7 (New Orleans, LA)
- Newspapers: Sun Herald, Mobile Press Register
- Television: WLOX, WDSU, WGNO

As a first step in developing a media campaign, we will enlist the support of a public relations/communications firm with an understanding of the various communities along the Gulf Coast in the post-Katrina era and experience using print, electronic and broadcast media to recruit for public health studies. To develop culturally competent

materials, this firm will develop key messages for different segments of the worker and volunteer populations and a communications plan to disseminate these messages. Prototype materials will be submitted for IRB review once they are developed along with details regarding the implementation of the communications campaign when the plan is determined at a later date.

2.4.4 Scientific Outreach

The Webinars specifically targeted members of the scientific community, including researchers from local universities, NIEHS grantees, and researchers with past experience studying communities involved in other environmental disasters such as the World Trade Center cohort. The study concept was reviewed by the National Institutes of Health (NIH) Institutes and Centers Directors at a regularly scheduled meeting. An early draft of the protocol outline was reviewed at a meeting August 12, 2010 with NIOSH and CDC. The proposal was discussed August 19, 2010 at a meeting of multiple federal agencies involved in some aspect of the Oil Spill response. Suggestions received during those meetings have been incorporated into the current protocol draft. The proposed study builds on ideas generated during a scientific meeting hosted by the Institute of Medicine (IOM) on June 22, 2010. In addition to undergoing scientific peer-review prior to submission of the study for NIEHS IRB review, the study received additional review by an IOM panel at a meeting held in Tampa, FL on September 22, 2010. Additionally, presentations of the study design have been (and will continue to be) made to a number of Federal panels and committees (e.g., Association of State and Territorial Healthcare Officials (ASTHO) and National Association of County and City Health Officials (NACCHO)). *The IOM is expected to provide ongoing scientific oversight. Oversight will also be provided (see below) by a Scientific Advisory Board appointed by the Chair of the NIEHS Board of Scientific Counselors, operating as a subcommittee of that Board.*

2.5 Enrollment Procedures and Enrollment Questionnaire

Initial contact with participants will be through a mailing which includes: 1) a one-page lead letter (Appendix F); 2) a study brochure (Appendix G) that will briefly outline the study purpose, study benefits, study sponsorship, contractor name, what will be asked of the participant, compensation if they participate, confidentiality assurance, importance of their participation, and contact information (contact names, toll-free telephone number, and web site address) if they would like more information; and 3) a work history form (Appendix K). Both the lead letter and the study brochure will contain instructions together with the toll-free telephone number for opting out of being contacted about participating in the study. Every attempt will be made to have the lead letter have the same message in English and either Spanish or Vietnamese, using both the front and back of the page. The lead letter will introduce the enclosed four-color, tri-fold study brochure which will contain instructional graphics and more details of the study. The lead letter and brochure will both point to the website address for additional information.

The lead letter will also introduce the work history form. The work history form will serve as a memory aid and facilitate recall of the participants' clean-up related activities. It provides a mechanism for participants to organize their oil spill clean-up job history before the telephone interview, by jotting down dates and tasks performed for each job held during the time-period of oil-spill clean-up. Workers will be asked to keep the form where they can easily retrieve it for the telephone interview. The form will not be collected.

The telephone contact schedule will be coordinated with the lead letter mailing by parsing the sample into batches and working the mailing and then calling one a batch at a time. Mailing of letters to each batch of names will precede calling by at least two weeks to allow the letter and brochure to be delivered and the potential participant to opt out of the study. The letter envelopes will request USPS to forward mail and to provide us with an address update. Mail returned as undeliverable and with address update notifications will be flagged for tracing.

At least two weeks after the lead letter mailings, the associated telephone numbers will be released to telephone interviewers to commence screening and enrollment dialing and interviewing. Interviewers will discover unusable telephone numbers – fast busy, disconnected, no one by that name, etc. Telephone numbers with outcome codes indicating they are unusable will be flagged for tracing. The telephone number management system will apply calling algorithm rules to each telephone number based on the pattern of interim outcome codes assigned by the interviewers at each dialing (e.g., no more than two calls per day), varied times of day and weekend, weekend only, once-a-day only, wait for a cool down period (initial refusal), scheduled call-backs, soft appointments, etc. The telephone number management system will enforce these rules when delivering telephone numbers to the interviewers. Calls will be conducted from 9 AM to 9 PM (local), Monday through Saturday, and 12 PM to 6 PM (local) on Sunday, if acceptable to the community.

The interviewing staff will include a group of interviewers who are bilingual in English and either Spanish or Vietnamese. We will attempt to identify the primary language of each potential participant in advance of assigning calls to interviewers by considering surname and other information that may be available in the master recruitment dataset (e.g. variable indicating primary language in the NIOSH roster data). Potential participants will be assigned to an interviewer who is fluent in their primary language and English. In some cases, the call assignment process may fail to overcome language barriers between the interviewer and the participant, and the interviewer may be forced to abort the call. If the call is aborted, the interviewer will make notes about the call and attempt to classify the primary language of the potential participant so that the call can be reassigned to the appropriate interviewer.

The entire screening and enrollment telephone call will take approximately 30 minutes to complete. Should the respondent be selected for active follow-up and agree to participate, their contact information and scheduling information will be transmitted to one of 14 regionally distributed clinical field supervisors who will assign the respondent to the most geographically proximate Home Visit Agents (HVA) under their supervision.

Alternative strategies may be employed to enroll potential participants without phone numbers or who cannot be reached by telephone, especially those from populations of special interest such as Vietnamese fishermen involved in the Vessels of Opportunity Program. We will work with community partners to bring such workers to community centers where they may be interviewed by phone or in person or arrange for home visits to complete the enrollment questionnaire (please see section 2.8 for additional details).

2.6 Tracing

Tracing will be conducted if we are unable to contact the participant by telephone or reach them through the contact person they named on the NIOSH roster data. Participants who cannot be initially reached with roster information will be flagged and

submitted for tracing in monthly batches. Fortunately, we have cell phone numbers (at least for those listed on the NIOSH roster) which should significantly improve our ability to contact participants. However, we are aware that participants may follow regional practices found post Katrina and use “disposable” cell phones only for the time needed. We have projected the need to conduct tracing for as much as 15 percent of the sample and expect that we subsequently will be unsuccessful in tracing 5 percent of this group. Recruitment and tracing efforts will be carried about by different staff members so that the time required for tracing does not disrupt the recruitment process.

Rigorous locating operations will be instituted to reach study participants based on the contact information obtained through the automated batch tracing databases, such as Lexis Nexis Accurint, Telematch, Pension Benefit Information, National Change of Address, and Trans-union as well as InfoUSA and Experian.

2.7 Procedures for Enrolling Cohort Members

Participants will be randomly sampled across categories of job/potential exposure reported during the enrollment interview, with oversampling of categories with higher potential exposures, for invitation to participate in the Active Follow-up Sub-cohort. Additionally, controls will be randomly sampled for invitation to participate in the Active Follow-up Sub-cohort.

Persons who are not randomly selected for inclusion in the Active Follow-up Sub-cohort or who decline to participate in the Active Follow-up Sub-cohort will be enrolled as passively followed members of the full cohort. They will have given verbal consent for completing the telephone interview, providing annual updates on contact information, and having their health and vital status tracked via electronic data. They will include individuals across the range of exposures, including controls. Because this group will include persons not selected into the Active Follow-up Sub-cohort, it will likely be disproportionately weighted towards workers with lower potential exposures to oil-spill related chemicals.

2.7.1 Recruitment and Retention

Effective recruitment is critical to the success of this study yet the nature of the study population, protocol, and the long follow-up period present inherent challenges to recruiting and retention. A multi-faceted approach to participant recruitment and retention will take into account best practices in the participant recruitment literature as well as proven methods utilized in past studies conducted in similar populations.

Participation rates in health studies and surveys have been declining for the last several decades. This general trend serves as backdrop to several specific challenges inherent to this study.

One significant challenge in recruiting and retaining participants will be to address the unique circumstances faced by Gulf Coast families both prior and subsequent to the Deepwater Horizon Oil Spill. Many of the affected communities were already under economic stress because of Hurricane Katrina and the recent recession, which makes it difficult to engage them in research even under the best circumstances. Gulf Coast families are experiencing further environmental, financial, and health-related impacts since the disaster. Recruitment and retention strategies must take into account these

day-to-day circumstances and other obligations such as employment, childcare, etc. to mitigate known barriers to participation.

A related challenge will lie in gaining credibility and cooperation from a population that may be wary of research studies conducted by outsiders, particularly government-based studies. It will be important to demonstrate an understanding of the circumstances these individuals face. Recruitment strategies are needed that position the team to capitalize on community outreach efforts as well as efforts to brand the study as something other than "just another government study." As with all studies, potential participants may be reluctant or unable to spend the time or experience the inconvenience involved in study participation. Recruitment strategies are needed to overcome these sources of reluctance and present the study as beneficial.

After participants are enrolled in the study, maintaining their continued participation over the full follow-up period is critical. Participants will relocate, experience family disruptions such as divorce, death or illness, undergo economic changes, and realize logistical difficulties. Strategies are needed that motivate continued participation and alleviate logistical constraints.

For all of these reasons, this study will develop a comprehensive recruiting and retention plan designed to maximize participation for the entire duration of the study with assistance from the Scientific and Community Advisory Committees, while using study resources efficiently. Although monetary incentives may be necessary, an array of other strategies will be applied to cultivate a sense of loyalty, commitment, and appreciation among study participants and oil-spill communities to the study. We will work closely with state and local officials and local community groups to tailor an approach that will resonate with the local community and foster participation in the study.

2.7.2 Recruitment/Retention Strategies and Approach

Importance. Recruitment interviewers will be trained to convey an appropriate sense of the importance of the research among both exposed and unexposed individuals. This importance relates not only to the oil spill, but also, more generally, to all of the health, environmental, and psychological impacts (e.g., displacement, stress, exposures) associated with disasters, ultimately to support a better understanding of how to respond to such disasters. This will be reinforced throughout the study with communications from health officials and study investigators.

Direct Benefit. The main benefit is pride in having participated in an important public health research effort for their communities. Participants will receive some results from the medical testing. Recruitment approaches will be designed to minimize any potential gap in perceived study benefit between the exposed and unexposed.

Study Identification and Branding. The study will be presented publicly in a manner that appropriately conveys its importance both to participants and to other audiences.

The study website will include information for the public as well as a place for participants to learn more about the study, receive important study information, and allow for the opportunity to email study investigators to schedule visits and update contact information. Scientific publications and results will be posted on the website.

News items and press releases will announce and publicize the study while reflecting local interest group and health department participation. Participants will also receive annual newsletters to keep them informed about the progress of the study.

2.8 Recruitment of Special Populations

Based on data from the NIOSH roster and from reports from the field, we are currently planning to recruit Vietnamese, Spanish, and English speaking participants. Speakers of other languages may be targeted later through special accommodations such as facilitated interviews by a relative or community representative speaking one of these languages or through RFPs (and funded via subcontracts), as described below. Although they may represent a small fraction of the worker population, it may be important to include the Vietnamese and other unique ethnic subpopulations in the Gulf region who may have participated in oil spill clean-up. Based on initial feedback from the community, a multi-modal approach may be needed to ensure sufficient participation amongst these groups that may have had elevated exposure through the Vessels of Opportunity program and other clean-up related activities. Our planned multi-modal recruitment approach would consist of the standard recruitment package of a mailed recruitment letter and study brochure, but also additional community meetings to explain the purpose of the study, opportunities to enroll in-person and/or at a centralized recruitment facility, and other techniques to be developed in conjunction with input from community representatives and state and local health officials. These groups will be included in our pilot effort to provide adequate feedback to the rest of the study.

2.8.1 Special Issues in Recruiting Vietnamese Participants

To address issues around literacy, outreach, and access to the Vietnamese population specifically, we will identify and work with NGOs having connections to, and understanding of, this community. For example, in analysis of data from the NIOSH roster and anecdotal reports from persons in the field it appears that Vietnamese workers are substantially underrepresented on the NIOSH roster and may be similarly underrepresented on the PEC list relative to the general population. This may be due to language / literacy barriers that resulted in Vietnamese workers not receiving the worker training or completing the NIOSH roster. To help identify these workers and suitable controls, and to overcome language and cultural barriers to their participation in this study, we will work closely with community groups, enlisted via RFPs (and funded via subcontracts to the study contractor), that are integrated in the Vietnamese community/communities. These groups include Asian Americans for Change, Boat People SOS, Mary Queen of Vietnam Community Development Corporation, Vietnamese American Young Leaders Association of New Orleans, and Vietnamese Martyr's Church. Many of these community groups, along with Parish governments in Louisiana, have maintained separate lists of clean-up workers from their communities. We will meet with these community groups to explain the purpose of the study, the importance of participation of Vietnamese clean-up workers, the study methods, what will be expected of the participants, and how these groups can help us, and we will attempt to address their concerns.

For groups that agree to assist us in recruitment, we will work with their staff to develop strategies and resources that are both culturally and scientifically appropriate for promoting the study and identifying potential study participants. These groups will be asked not to recruit study participants *per se*, but rather to assist in developing interest and support for the study so that study staff can then approach potential participants in a methodologically rigorous manner. They may be asked to produce and provide to study investigators regularly updated lists of persons who they know or believe to have participated in oil spill clean-up activities, including names, telephone numbers,

addresses, and other appropriate contact information (especially for any persons without telephones). They will be requested to provide some basic demographic information and reason for refusal for any workers who indicate that they are unwilling or unable to participate in this study. They will also be asked to provide similar lists of Vietnamese controls who are comparable to the clean-up workers they identify, based on criteria that they will develop together with study investigators. However, it may prove necessary to carry out a parallel supervised process to enroll this group, allowing subcontractors to conduct in-person screening interviews rather than telephone interviews. In that case, we will work with community groups to implement enrollment and data collection directly but provide sufficient oversight to ensure protocol standardization.

To minimize bias in subject selection and data collection, we will attempt to conduct all telephone interviews and in-home visits by study staff in Vietnamese. We will work with community group staff to approach persons who do not have telephones or other individuals recommended by the community group staff who could serve as liaisons. For persons for whom telephone interviews are not appropriate or possible, interviews will be conducted in-person, either at the subject's home or at another suitable location. While we will make every effort to provide Vietnamese-speaking phlebotomists/interviewers, it may be necessary in some cases to provide a trained Vietnamese translator with English-speaking phlebotomists/interviewers. In order to ensure full enumeration of the potential cohort, participants and those who decline to participate will be asked to provide names and contact information of any other Vietnamese clean-up workers they may know. In order to facilitate engagement, commitment, and valid data collection within this community, we will take the necessary steps to maintain as much transparency as possible including inviting community stakeholder groups to the interviewer training sessions and inviting them to assist in developing the training materials to ensure cultural competency among the study staff. We will review these procedures on an ongoing basis and modify them as needed to achieve the dual goals of enumerating as fully as possible the workers and suitable controls in this community, and recruiting and interviewing them in a scientifically rigorous manner.

2.8.2 Special Issues in Recruiting Creole-Speaking Persons

Anecdotal reports indicate that Creole-speaking persons in the Gulf have also been involved in clean-up activities. These persons are likely to be substantially underrepresented on the NIOSH, PEC, and other worker training lists because most of these trainings have been conducted only in English, Spanish, and Vietnamese. We have no information on how many such workers there were nor on what types of clean-up activities did they engage in. To fill in these critical information gaps, we will issue RFPs to local community groups to help us enumerate these population(s) that may be under-represented in other worker lists. If we determine through these means that there are sufficient numbers of potentially exposed workers in this population, we will work with community stakeholder groups to promote the study and help recruit the workers and appropriate controls from this population in a similar manner to that described above for the Vietnamese.

2.8.3 Special Issues in Recruiting Women

Women will be recruited into the cohort by the same eligibility and selection criteria as men. However, some additional sex-specific questions, focusing on menopausal status, reproductive history, and pregnancy status, will be included in the enrollment

questionnaire. Potential sub-studies of women will be considered later, based on the number of women, their exposure profiles, and the numbers of outcomes of interest.

2.8.4 Special Issues in Persons with Reactive Airways Disease

We may consider focused sub-studies among persons identified with, or suspected to have, reactive airways disease at enrollment. The timing and nature of these sub-studies will depend on the number of such persons identified during enrollment and will be described in more detail at a later date.

2.8.5 Other Special Populations

Other subgroups may be identified for add-on studies of **focused** hypotheses related to **specific** exposures or health outcomes. These studies may be initiated by us or by extramural collaborators. Participants will be informed that such **add-on** studies may be possible and that separate informed consent to participate will be obtained.

2.9 Home Visit

Participants selected for the Active Follow-up Sub-cohort will be scheduled for an in-home visit by a field staff member (i.e., a home visit agent or HVA). We will ensure that Home Visit Assistants (HVAs) hired for this study have the necessary education, qualifications and experience to conduct the required home visit activities, or we will provide additional training as needed. We currently plan to hire qualified staff of Certified Medical Assistants (CMAs) who can do both phlebotomy and interviewing. During our initial contact with the participant, we will note their ethnic status and, if they are selected for participation in the Active Follow-up sub-cohort, do our best to match them with a field interviewer of the same ethnicity, though this may not always be possible. Whenever possible, the staff will be hired from within the local communities so they should be familiar with local norms.

Home visits will be scheduled seven days a week between the hours of 8 AM and 9 PM local time. Sunday visits will not be scheduled in communities for which this is considered socially unacceptable. We anticipate that the home visit will take 2-3 hours to complete. By going to participants' homes to complete data collection for the Active sub-cohort rather than requiring that they make their own arrangements for specimen collection or visit a central location, we minimize their burden for study participation while maximizing the likelihood that we will be able to collect the desired study data, biospecimens, and environmental samples.

During the home visit, the HVA will administer informed consent (Appendix D). Should the participant be unable to read, the HVA will read the informed consent verbatim to the participant in front of a witness to ensure the participant understands all aspects of the study. The HVA will return the signed consent document and completed questionnaires to the study office by overnight carrier. Present plans are for biospecimens and environmental samples to be sent by priority overnight carrier to the central processing laboratory (CPL) for additional processing and storage. Because commercial carriers do not operate on Sundays, we are investigating use of specialty couriers that can make these off-hour pick-ups and deliveries, but typically at a premium price. We are currently exploring options for batching Sunday collections or having samples delivered to a central site for shipping to minimize specialty courier costs.

2.9.1 Advance Study Packet

In advance of the home visits, we will assemble and mail to each participant a home visit kit containing the following materials needed to conduct the visit:

- Appointment cover letter (Appendix R);
- Home visit preparation instruction sheet (Appendix S and Appendix T);
- FAQs (Appendix H);
- Informed consent form for the participant to review in advance (Appendix D);
- Informed consent quick reference guide (Appendix E)
- Urine collection container and lid along with detailed instructions for collecting a first morning void (FMV);
- ID labels for participant -specific documents and specimens/samples.

The HVA will bring all other materials needed for the home visit.

2.9.2 In-Home Visit

At the beginning of the visit, the HVA will obtain informed consent prior to conducting any study procedures. Additional details concerning the informed consent procedure can be found in Section 10.2. After consent is obtained, the HVA will ask if the participant wants abnormal test results for clinical and laboratory assessments conducted at the time of baseline visit reported to their health care provider and obtain contact information for that provider. The HVA will collect physiologic and anthropometric measures; biological specimens (e.g., blood, hair, nail, and urine); environmental samples (e.g. house dust); and administer a baseline questionnaire. The HVA will also determine and record the latitude and longitude of the home using a handheld Global Positioning System (GPS) device; this information will be used in later Geographic Information System (GIS)-based studies to determine residential proximity to sites of potentially relevant environmental exposures, such as petroleum refineries and toxic waste dumps and incinerators. If a subject is interviewed away from the home, their residential address will be collected (along with nearest cross-street and landmarks) so that it can be more accurately geocoded using existing software geocoding tools; this will also be done for previous addresses as indicated in the subjects residential history. Table 1 provides an overview and approximate timeline of the home visit activities.

Table 1. Home Visit Overview

Activity	Estimated Time	Notes
Interview is assigned to HVA, and HVA calls participant to schedule in-home visit	N/A	Scheduled at least 3-5 days in advance. Provide toll free number and website to reschedule if necessary
Mail Home Visit Kit	N/A	Packet arrives 3-5 days in advance of scheduled home visit
First morning void urine collection*	N/A	Collected by the participant using urine collection kit provided

Activity	**Estimated Time**	**Notes**
Arrival, greeting and set-up	5 minutes	
Informed consent	15 minutes	Review and obtain informed consent
Anthropometric / Physiologic measures collection	20 minutes	Ht, Wt, BP, Waist and Hip Circumference, Spirometry
Biological specimen collection and labeling	20 minutes	Hair, Nail, Blood, Toenail Clippings
Questionnaire measures collection	60 minutes	
Environmental sample collection and labeling	10 minutes	Dust collection
Biological specimen processing and labeling	10 minutes†	
Urine dipstick analysis for glucosuria and writing of report	5 minutes	
Debriefing of blood pressure, pulmonary function, urinary glucose and BMI results report to the participant	10 minutes	
Clean-up and packing	10 minutes	
Departure	**Total time:** 2 hours, 45 minutes	
Post-visit processing		Shipping and data back-up

** If first morning void collection has not been obtained when the study staff arrive, the HVA will request that the participant provide a random or "spot" urine during the home visit instead.*
† Blood will be allowed to clot for at least 30 minutes while the baseline questionnaire is being administered to the study participant and will be centrifuged for 15 minutes following the questionnaire administration (and during the environmental sample collection) in order to minimize the biospecimen processing time and overall time spent in the home during this visit.

2.9.3 Baseline Questionnaire

The baseline questionnaire elicits information not included in the enrollment questionnaire, including more detailed information on residential and occupational history, personal and family medical history, alcohol and tobacco consumption, mental health and anxiety, and recent eating and drinking and use of medications.

Before designing the questionnaires, study investigators referred to questionnaires used by other data collection efforts occurring in the Gulf States, regionally, and nationally in order to facilitate regional and national comparisons and potential cross-study analyses. National studies such as the National Health and Nutrition Examination Survey (NHANES), Behavioral Risk Factor Surveillance System (BRFSS), and National Survey on Drug Use and Health (NSDUH) were used. We also referred to measures provided in the PhenX Toolkit in developing some sections of the questionnaire. We substituted sections from other questionnaires when we found something that appeared to work better or to better capture our study interests.

Detailed information on oil spill clean-up related activities in the enrollment telephone questionnaire completed by all participants; Questions collected at baseline during the home visit include: residential history; personal and family medical history; occupational history; reproductive history; history of military service; demographic and socioeconomic factors; alcohol consumption; mental health status; a neurocognitive screener; and other information, including hobbies, sleep patterns, tobacco use and environmental tobacco smoke exposure, and consumption of seafood from the Gulf of Mexico. Occupational histories will enable us to identify, and infer relevant exposures from, occupations such as employment in the petrochemical industry and commercial fishing. Separate questionnaire modules will be developed and administered to subgroups reporting prior employment in the petrochemical industry and prior experience in hazard remediation, including other oil spills or other substances such as lead or asbestos. Residential histories, together with Geographic Information Systems, will help us to infer potentially relevant environmental exposures from sites such as petroleum refineries and toxic waste dumps and incinerators. Additionally, hobbies and use and storage location of gasoline can be important indicators of non-occupational exposures. This exposure information will be incorporated into analyses of health outcomes related to the clean-up work. Information on history of military service will identify persons who may have pre-spill serum samples and medical data available through the Department of Defense Serum Repository and health care system and identify workers with potentially confounding military exposures. Although the interview asks for identifying information from the participant to facilitate follow-up and future linkage with external databases for GIS-based studies, the computer-assisted interview will be programmed to create a separate data file for identifying information in order to maintain a secure data system.

In developing our questions on environmental and occupational exposures, we first considered the chemicals that have been identified in the crude oil and also in the dispersants as identified by the National Toxicology Program (NTP). By linking to various national databases, we will be able to identify the potential toxicity of these agents. We also considered the frequency with which participants were engaged in oil-spill clean-up related activities and their past occupational and recreational exposures to these agents.

2.9.4 Anthropometric/Physiological Measures

The HVA will weigh (kg) participants and measure height (m), hip and waist circumference (cm), and take the participant's heart rate and blood pressure. Height (m) and weight (kg) will be measured using a metal tape measure and digital scale using standard methods from the NHANES IV national survey. All measurements will be taken three times. If a person is unable to stand, we will measure waist circumference and sitting height using the crown to rump method with a cloth tape measure, but we will not measure their weight. Instead, we will collect their self-reported weight). We will use a cloth tape measure to collect waist circumference. We will provide participants with a report of their anthropometric measures during the field visit. To reduce the amount of equipment needed and facilitate training and scheduling, we plan to perform pulmonary function testing during the home visit on members of the Active Follow-up Sub-cohort who live within the immediately affected areas, which represents approximately 75% of the members of this cohort.

2.9.4.1 Heart Rate and Blood Pressure Measurement

Three blood pressure and heart rate measurements will be collected by trained study staff. Heart rate will always be measured prior to respiratory testing. If a person's resting heart rate is > 120 beats/minute, they will be excluded from participating in the respiratory testing. Blood pressure will be measured three times using standard clinical oscillometric (not mercury-based) equipment and these results will be provided to the participant at the home visit along with information regarding what these blood pressure results mean using a form similar to that being used in the NIEHS Sister Study. Seated heart rate and blood pressure will be taken three times in rapid succession after a 5 minute rest period and the second and third readings will generally be used to calculate average values for analysis and reporting.

2.9.4.2 Pulmonary Function Testing

Pulmonary function testing (PFT) will consist of spirometry data collection. All PFT will be conducted using American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines [Pellegrino, et al. 2005].

The PFT will be performed using a portable, ultrasound transit-time based spirometer (EasyOn; NDD Medical Technologies, Chelmsford MA, USA, or a comparable model). A full Forced Vital Capacity maneuver will be used. We will obtain three ATS acceptable forced expiratory maneuvers out of a maximum of eight attempts. All spirometry examinations will be done with the person seated and wearing a disposable nose clip. We will use new individually packaged, disposable mouthpieces for each subject and a new spacer for each subject.

Combined with the symptom and medical history information, this objective measure of respiratory status will allow for an assessment of obstructive lung disease. By detecting these small changes in pulmonary function in the population as a whole, we will be able to make comparisons to other environmental exposures including air pollution and environmental tobacco smoke in order to assess the potential severity of their disease.

To the extent possible, we will ask participants to withhold their asthma inhalers on the day of the examination (a commonly used protocol). For those participants unwilling or unable to withhold medications, we will document this during the home visit. For all

participants, we will record the timing and dosage of all asthma medications over the preceding seven days.

To ensure quality results, we will conduct formal training and recertification on all field procedures. The HVA will be required to take a NIOSH-approved spirometry course, which is a well recognized training among medical professionals. In addition, all HVAs will complete the online exam and submit 10 practice tests administered by Hankinson Consulting, Inc (Athens, GA, USA). All spirometers will undergo standard quality checks before use in the field. To ensure high quality control and HVA feedback, we will use the reviewing software recently developed specifically for the EasyOn spirometer by Hankinson Consulting, Inc (Athens, GA). An expert in pulmonary function quality control will review all tracings on a weekly basis and override any software-provided readings if needed. The quality scores and other results will be electronically forwarded to field coordinators who will feed the quality information to the HVAs. If an unexpected number of unacceptable tracings occur, the HVA in question will be retrained.

Participants who answer yes to any of the following questions will not undergo spirometry during the visit:

- In the past three months, have you had any surgery to your chest or abdomen?
- In the past three months, have you had a heart attack or stroke?
- In the past three months, have you had a detached retina or have you had eye surgery?
- In the past three months, have you been hospitalized for any other heart problem?
- Are you pregnant?
- Are you currently taking medication for tuberculosis?

Additionally, if a participants resting heart rate is >120 beats/minute, they will be excluded from PFT.

Our exclusion questions include all of those used in BOLD [Buist, et al. 2007] and PLATINO [Menezes, et al. 2005], multinational studies that enrolled over 14,000 adults over age 40 years for pre and post bronchodilator spirometry with only trained technicians. No adverse events occurred in either the BOLD or PLATINO studies. These exclusions are considered very conservative and these questions are not generally asked before spirometry is done in clinical practice.

Figure 1. Example of EasyOn Spirometer and Disposable Mouthpiece

2.9.4.3 Glucosuria Testing

During the in-home visit, a small amount of the urine collected from each participant (described in section 2.9.5 below) will be transferred to a sterile cup. A commercially available dipstick will then be used by the trained study staff to measure the urinary glucose level. The result will be provided to the participant at the home visit, along with information regarding the meaning of the result, using the form in Appendix L.

2.9.5 Collection of Biological Samples

Biological specimens will be collected from participants in their homes by a trained HVA. The HVA will draw blood, retrieve urine specimens, and direct the participant to collect hair and nail samples. The following specimens will be collected:

- **Blood samples**: The HVA will collect 52.5 mL of venous blood into eight Vacutainer tubes:
  - *Lavender Top EDTA Tubes*: Three purple-topped tubes will be collected:
    - One 10 mL and one 6 mL tube will provide plasma, buffy coat, and red blood cells (RBCs) for future analyses.
    - One 2 mL tube will either be 1) analyzed for CBC with WBC differentials upon arrival in the central laboratory for persons tagged to be recruited for the Biomedical Surveillance Sub-cohort (N=6,250) or 2) processed for plasma, buffy coat, and RBCs for future analyses for the rest of the Active Follow-up Sub-cohort.
  - *Royal Blue Top EDTA Tube*: One 6 mL trace metals tube will frozen for future selected measurement of antimony, arsenic, cadmium, calcium, chromium, copper, iron, lead, magnesium, manganese, mercury, selenium, and/or zinc (i.e., all of the metals for which these trace metal tubes have been validated).
  - *Red Top Serum Tube*: Two 10 mL tubes with no additives will provide serum and clots, which will be frozen for future analyses.
  - *Yellow Top ACD-B Tube*: One 6 mL tube with Acid/Citrate/Dextrose Solution B tube will be collected from each participant for future analyses. How the specimen is processed will depend on whether the participant is a member of the Biomedical Surveillance Sub-cohort, as described below.
  - *PAXgene RNA Tube*: One 2.5 mL PAXgene blood RNA tube will provide stabilized whole blood for mRNA isolation for future analyses.
- **Urine**: Each participant will be asked to collect a first morning void (FMV) urine sample on the day of the scheduled visit in the collection container from the Home Visit Kit. If an FMV was not collected, the HVA will ask the participant to provide a "spot" urine. A small amount of the specimen will be transferred to a sterile cup during the home visit and used to measure glucose levels with a commercially available dipstick. Another portion will used for a more complete basic chemistry urinalysis (by dipstick) upon arrival in the central laboratory to measure protein, glucose, and several other parameters among persons tagged to be part of the Biomedical Surveillance Sub-cohort. The remainder of the urine sample will be processed in the Central Processing Laboratory for storage as described in Section 2.11 and as illustrated in Appendix C2.
- **Toenails**: The HVA will ask each participant to collect toenail clippings from each toe unless they have a medical or physical condition (e.g., diabetes) that would

prohibit collection. Toenail clippings will be stored as described in Section 2.11 for future analysis of metals. Participants will be advised in advance of the visit not to clip their toenails before the visit.

- **Hair**: Each participant will be ask to collect a small hair sample as close to their scalp as possible. Hair will be clipped to indicate which end is closest to the scalp and stored as described in Section 2.11 for future analysis of metals and cortisol.

Substantial volumes of biospecimens will be required for quality assurance and quality control (QA/QC), cross-sectional surveys, and assay validation over time, but will not directly contribute to addressing the specific aims of this study. To meet this need, we will collect an additional 40 mL urine and four additional tubes of blood, consisting of one 10 mL lavender top, one 6 mL royal blue top, one 10 mL red top, and one 6 mL yellow top (i.e., an additional 32 mL blood) from a 3% random sample of the Biomedical Surveillance Sub-cohort (N=150) and a ~0.7% random sample of the remaining Active Follow-up Sub-cohort (N=150). The extra urine needed (40 mL) will be taken from the sample already collected because participants collect urine in a larger cup and examiners typically pour out excess urine after filling the transport tubes. We will attempt to collect additional QA/QC samples from the group of 150 Biomedical Surveillance Sub-cohort participants at each subsequent visit in order to have serial samples that will be essential for certain assays.

In total, we will collect these additional QA/QC samples from 300 individuals. These samples will be processed and banked in the same manner as the main study samples. These specimens will be critical when serial samples or samples *known* to be from the source population are required. For these randomly selected individuals (n=300), an addendum to the consent document detailing this additional biospecimen collection will be administered and they will be remunerated with an extra $10 for these additional samples.

Saliva: All study participants who are unwilling or unable to provide a blood sample during the home visit will subsequently be mailed an Oragene OG-250 DNA Self-Collection kit, together with instructions for using and returning the kit, and a stamped, self-addressed padded envelope for returning the kit to the central processing lab (CPL). The CPL will store these samples as described in Section 2.11 and as illustrated in Appendix C.2.

2.9.6 Home Environment Sampling

The HVA will be trained to collect the following home environmental samples according to detailed sample collection protocols. These samples will provide valuable information about the home environment and enable researchers to better characterize and control for confounding based on residential exposures as opposed to exposure related to clean-up activities.

Household Dust: The HVA will collect a household dust sample using the alcohol wipe collection protocol from the Sister Study. This protocol calls for swiping areas in several rooms that are typically ignored in dusting, such as above door or window frames or the tops of bookshelves. In two Louisiana Parishes, the HVA will also collect a vacuum dust sample collected following the National Children's Study protocol. The HVA will bring a study-provided vacuum cleaner to collect the dust sample. A standardized area will be vacuumed, with dust collected into a special collection device inserted into the vacuum cleaner

hose. Collection of both wipe and vacuum samples will allow us to compare levels of specific exposures in dust and wipes and will serve as a pilot study for assessing the confounding impact of molds, dust mites, and other endotoxins and allergens on pulmonary function. The dust sample will be shipped to the CPL along with the biospecimens for further processing and storage as described in Section 2.11 and illustrated in Appendix C.Collecting household dust samples will enable a snapshot view of exposure to potential environmental confounders such as heavy metals, persistent organic pollutants, and (where vacuum samples are collected) endotoxins.

The Biomedical Surveillance Sub-cohort may afford further opportunity to validate the suitability of our proposed approach for rank-ordering exposure levels looking at potential confounders such as persistent organic pollutant levels using alcohol wipes and vacuum samples. We will explore the feasibility of other methods to assess household exposures, including a dipstick test of nitrates in water, and a semi-permeable membrane being developed at the EPA for the detection of volatile compounds.

2.9.7 In-Home Biospecimen Processing and Shipment

After blood collection, the HVA will allow the blood in the serum tubes to clot for 30 minutes before centrifuging the tubes in the participant's home and separating the serum and clot, which will be retained. At the same time, the HVA will centrifuge the 10 mL and 6 mL EDTA tubes, separating and retaining the plasma and the packed cells/buffy coat. The HVA will then package all of the biospecimens and environmental samples for shipment to the CPL. The ACD-B tube and the 2 mL lavender top EDTA tube will be shipped at ambient temperature. The remaining specimens and environmental samples will be shipped cool but not frozen, accompanied by a frozen cold pack. These materials will be shipped by priority overnight service to the central processing laboratory. All biological samples will be shipped according to local, state, and federal requirements governing shipment of biological specimens. In the event that specimens or samples are lost or damaged during shipment, the participant will be offered the opportunity to have specimens recollected, with a small compensation.

2.10 Reports to Participants, Health Care Referrals and Incident Reports

2.10.1 Overview

All HVA personnel will be CMAs with up-to-date CPR certifications. HVAs will receive additional training prior to beginning the study regarding the evaluation and testing procedures, form completion, handling of emergency situations, personal safety, signs of abusive behavior, and appropriate referral strategies for the locality. Prior to any home visits participants will receive information about the study including a brochure (see Appendix N) that lists healthcare providers in their area that can provide health care services, including any that can assist with free or reduced-cost services.

During each home visit, or participant encounter, the HVA will measure BMI, blood pressure, urinary glucose, and spirometry. With the exception of spirometry, which requires a specially trained reader to properly interpret the test results, the HVA will

inform participants of their test results at the time of evaluation, as well as any needed actions for identified abnormalities. The HVA will also observe participant behavior in case of any urgent physical or mental health behaviors requiring emergency intervention. Urgent observations or test findings (such as hypertensive crisis, acute mental or physical distress, abusive behavior, etc.) identified at the time of the home visit will be handled immediately as discussed below (Section 2.10.6.1, Follow-up of Urgent/Emergency Situations During In-person Encounter).

In addition to providing the participant with a written summary of test results and recommended actions (Appendix L and M), the HVA will perform the following actions:

1) Complete an Incident Report for any acute medical, mental health, or social problems (Appendix J, Baseline Questionnaire, Section N) and report the incident to their RM and the Coordinating Center to inform them of this action. The Project Manager will then immediately notify the NIEHS Principal Investigator of what transpired.
2) Enter the results of evaluations and their interpretations provided to participants, and actions taken about abnormal results into the CAPI system (Appendix J, Baseline Questionnaire, Section N).
3) Provide referrals for medical and mental health care, as needed, and document referrals (see sample referral handout in Appendix N).

Additionally, all participants will receive a follow-up letter and report within 1 month of the visit that reiterate the evaluation results (i.e. BMI, blood pressure, urinary glucose, and spirometry) and recommended actions (Section 2.10.6, Follow-up Reports and Information and Appendix P and Q). The participant's health care provider will also receive a copy of the report within one month of the encounter, if any significant abnormalities are detected and provided that the participant has indicated that they have a health care provider, consented to sharing this information with their provider, and have given their provider's name and contact information (Appendix O). For individuals in the Biomedical Surveillance Sub-cohort, CBC results and interpretations will be included in the report that accompanies the follow-up letter. Urgent findings identified by the laboratory will be phoned to individuals by the HVA or Call Center within one week of receipt from the laboratory (Section 2.10.6.3, Reporting of CBC Laboratory Tests).

2.10.2 Home Visits or Participant Evaluations at other Locations

2.10.2.1 Participant Mental and Physical Condition Observations

HVAs will be trained to remain neutral when asking questions about health conditions and to reply to responses with sensitivity. In most situations, empathetic and respectful listening and an understanding tone will help to calm the participant and allow him or her to proceed with the interview. However, we will train HVAs on several specific steps they can follow if a participant becomes distressed, such as:

- Reminding participants that their answers are confidential,
- Providing neutral feedback, such as "Thank you; I understand; We appreciate your participation in this important study,"
- Acknowledging a participant's hesitancy in answering a question, such as, "I understand that this may be difficult for you, so please take your time", and

- Reminding participants that it is okay to skip any question he or she does not feel comfortable answering.

Upon arrival for the home visit (or participant evaluation at another location), the HVA will quickly observe the participant's physical condition and mental health disposition. If the participant appears to be in physical or mental distress, the HVA will note their condition and ask the participant if they need immediate medical assistance or determine urgent care needs if the participant is unable to effectively communicate.

If a need for immediate care is identified, the HVA should call 911 or assist the participant in contacting emergency services, their healthcare provider, or other health care resources as appropriate. Information about the incident and disposition of the participant will be recorded in the Incident Reporting Form in the CAPI system (Appendix J, Baseline Questionnaire, Section N).

In circumstances when an HVA or interviewer identifies a participant who may be experiencing mental health issues—or more significantly, suicidal ideation, we will provide them with contact information for local, regional, state and national mental health resources that are available to help them deal with their issues. If the participant appears to be in imminent risk for self-injury (e.g., suicide), the HVA or interviewer will contact local emergency officials by calling 911 or other intervention hotlines as appropriate. As noted in the previous section, the HVA will immediately fill out an incident report in the CAPI system and also report the incident by phone, as described above.

If the HVA contacted 911 for an emergency situation, the HVA or Study Center representatives may immediately follow-up, or as soon as possible with respect to the situation, with the participant or their spouse to check on their current condition and determine future interest and ability to participate in the study. For non-urgent situations, the HVA will determine if the assessment should continue or be rescheduled to a better time.

2.10.2.2 Other Social Behavior Observations

During the encounter, the HVA will observe the household and be alert for unusual situations suggesting the existence of reportable (varies by state) social or abusive behaviors. If anyone in the home environment is in immediate danger, the HVA will end the visit, call 911, complete an incident report, and report the event by phone. Should a HVA witness signs that lead to suspicion of child, spouse or elder abuse while in the participant's home, the HVA will generate an incident report in the CAPI system at the conclusion of the visit and report the incident by phone, as discussed above. Such situations will not be discussed with the participant, except in instances where it appears that the study participant is the victim of abuse. In those cases, the HVA will discreetly ask if the participant would like to be put in touch with someone who might be of assistance.

2.10.2.3 Incident Report Form

An incident report form will be completed by the HVA for all acute medical, mental health, and social problems that are observed during encounters with participants

(Appendix J, Baseline Questionnaire, Section N). This report will be accessible in the CAPI system on the HVA's laptop, and it will include workflow features that prompt the HVA to take appropriate action based on evaluation findings, observed behaviors, or noted circumstances. The CAPI system will also be programmed with automated data checks that alert Coordinating Center staff to problems that require immediate attention and follow-up, such as telephone follow-up to a participant who required a 911 response for a hypertensive crisis. The principal investigator will be responsible for reporting to the IRB all acute medical, mental health, and social problems that are observed during encounters with participants that result in a call to 911 or social services as well as any adverse events that result from study interventions or protocol violations. Due to the unique nature of the study population which is under substantial stress due to job losses associated with the oil spill and major hurricanes and is medically underserved, it is expected that the majority of emergency contacts will be unrelated to the study per se, but due to the fact that we are screening for medical conditions among individuals without access to care and have an opportunity to observe individual and family behaviors because we will spend several hours in a participants' home. Such adverse events will be reported to the IRB within a month of occurrence allowing us to also provide information on the outcomes of the referrals. Adverse events resulting from the study protocol or any protocol violations will be reported to the IRB as soon the PI is made aware of the event.

2.10.3 Home Visit/Evaluation Measurements & Testing

Participant evaluations will include several measures and tests for which the results can be conveyed during the time of the HVA encounter providing potential health benefits for early recognition of disease, as well as enhanced opportunities for health education and utilization of health care resources. HVAs will be trained to provide participants with appropriate and standard feedback about their individual blood pressure and BMI measurements, and urine glucose results before departing the participant's home. HVAs will be trained to record all observations and in-home test results in the data management application as well as on participant **Test Result Forms** that provide the participant with a basic interpretation of the various measurements and test results. HVAs will also be trained to strictly follow scripts when conveying results to participants. The participant Test Result Forms will include scripts that provide recommended actions for participants to take depending on the measured values for each test. For each test result, we provide standard recommendations depending on the result value (see Test Results Forms in Appendix L).

As the HVA performs the various measurements and tests during the visit, the results will be recorded into the data management system and also transcribed onto pre-printed test result forms for each test. The HVA will provide these forms filled-in with the measured results to each participant and go over the results with the participants and any suggested follow-up actions. If any of these results are abnormal, the relevant test result form indicates what actions the participant should take and how soon. With the possible exception of extremely elevated blood pressure, most abnormal findings will lead to a recommendation to contact their health care provider or other community healthcare providers for additional evaluation within a specified time interval.

2.10.4 Follow-up Actions for Abnormal Findings

2.10.4.1 Medical Referral Guidelines

During the home visit or encounters at other locations, participants will receive handouts that provide results of their evaluations, interpretation of findings, recommended action based on findings, and health care referrals for any abnormal results (if needed). These results will be also summarized in a follow-up mailing to participants one month after the visit. The letter will thank participants for their participation in the study, introduce the summary report of findings and recommended actions, and remind them of study activities in the coming years. The handouts and summary report will provide information on BMI, blood pressure, urinary glucose, and pulmonary function test results. The CBC results for the Biomedical Surveillance Sub-cohort will also be included in the summary report, along with recommended actions. The CBC analysis will be done in a Clinical Laboratory Improvement Amendments (CLIA) certified laboratory (as will any future clinical tests that may be reported back to participants). The urine glucose screening test performed in-home has a CLIA waiver (FDA 2010).

During the consent process, participants will be asked if they would like the study to send abnormal evaluation findings to their health care provider and whether they would like a referral for health care, if they do not have a health care provider but need to see one based on evaluation findings.

If the participant asks that evaluation results be sent to their health care provider, the HVA will collect the name and contact information for the health care provider and record the information in the CAPI system. Within a month of the visit, the results of evaluations and advice regarding health care referrals will be shared with the participant's health care provider, if any abnormal evaluation findings were detected. Any evaluation finding that does not fall within the normal ranges will result in a letter to the health care provider. The health care provider will receive a cover letter that briefly describes the study and the reason the results are being sent, as well as a copy of the summary report that all participants will receive by mail. If the participant does not have a health care provider, the HVA will provide information about local health care resources, if warranted, based on abnormal evaluation findings. Participants who receive a referral will be instructed to present the health care provider with the results handouts at the time of the referral visit.

The advice that participants receive about medical referrals will be based on level of urgency of their findings. For example, the referral levels for hypertension are based upon recently published guidelines from the American Heart Association (AHA) for blood pressure. We tended to select the more conservative guidelines when there were several choices, given the fact that the community under study includes many without access to care and the fact that our study will be highly visible and we want to err on the side of caution. Nonetheless, levels of urgency can vary across practitioners and communities; setting levels too low may unnecessarily over-burden area medical care systems, while setting them too high may put participants at risk. The frequency of referral for care will be monitored as will the outcomes for referrals deemed urgent. If it is determined that we are making too many unnecessary referrals or that these guidelines are inconsistent with local practice, we will consider other less conservative standards. Any proposed changes would be brought back to the IRB for evaluation.

Participant referrals or follow-up instructions will be categorized into one of the five classifications below, based upon their test results or findings (see Table 2 below).

1. **Emergency:** The HVA is instructed to terminate the interview immediately and assist the participant or family members in contacting emergency medical services or their treating physician.

2. **Urgent**: The Urgent referral category is divided into two levels depending upon the urgency of the results or findings.

> Level 1: the participant is asked to follow-up with their health care provider in 72 hours.
>
> Level 2: the participant is asked follow-up with their health care provider in one week or two week intervals depending on the urgency of the results. HVA or Call Center staff will follow-up with all "Urgent" referral category participants by phone to assess their disposition.

3. **Check-Up:** The participant is asked to follow-up with their health care provider within one to two months.

4. **Routine Care**: The participant is advised to seek guidance from health care providers to learn about healthy lifestyle choices to help prevent disease.

5. **No Referral**: Results are within the normal range.

Alert Levels for Laboratory Results & Spirometry Interpretations:

CBC Abnormalities:

Alert levels for CBC abnormalities will trigger "Urgent" referrals. Within one week of Alert Level findings being reported by the laboratory, participants will be notified by phone and advised to follow-up with a health care provider in either 72 hours for Alert Level 1 findings or one-to-two weeks for Alert Level 2 findings (as indicated in Table 2). The chosen laboratory urgent referral action levels were based upon values used for the Jackson Heart Study of African-American males and females ages 35-84 living in the Jackson, Mississippi area and reference values used by our central diagnostic laboratory. The Alert Level 1referrals for total white blood cell count ($\leq 1.1 \times 10^3$ / µL), hemoglobin (≤ 6.1 g/dL) and hematocrit (≤18.1%) lead to a recommendation for participant follow-up in 72 hours. These thresholds are based upon the "panic levels" from our central diagnostic laboratory.

Spirometry Abnormalities:

Alert Level for post-exam spirometry interpretations will be reported to participants by phone within one week of receipt from the central laboratory. Participants will be advised to follow-up with a health care provider within one week (as indicated in Table 2). The spirometry alert level for an urgent referral utilizes the lower limits of normal (LLN) which is an index derived from population data based on race, age, sex, and height. The LLN is designed to be the 5th percentile for the index (FEV1, FVC, & Fev1/FVC) of interest (Roberts 2006). The use of FEV1 < 50% results in a "severe classification" regardless of obstructive or restrictive conditions and is consistent with ATS guidelines, assuming a valid and interpretable test (Pellegrino 2005). Given the nature of worker cohorts we do not expect to see very many participants in the severe category

Table 2. Medical Care Referral Guidelines

Evaluation	Findings	Referral	Comments
Blood Pressure	SBP ≥ 180 or DBP ≥ 110	Emergency*. Seek emergency care immediately. **Based on AHA 2010 guidelines*	HVA to contact 911 or help assist with referral as indicated. HVA / Call Center to follow up with participant by phone ASAP.
	SBP 160 to 179 or DBP 100 to 109	Check-up. See health care provider within one month.	Results provided to participant during encounter and mailed to participant within one month.
	SBP 140 to 159 or DBP 90 to 99	Check-up. See health care provider within two months.	Results provided to participant during encounter and mailed to participant within one month.
	SBP 120 to 139 or DBP 80 to 89	Routine. Those with slightly high BP advised to discuss need for any additional evaluations of lifestyle changes with HCP.	Results provided to participant during encounter and mailed to participant within one month.
	SBP < 120 AND DPB < 80	No Referral.	Results provided to participant during encounter and mailed to participant within one month.
Urine Glucose	Glucose > trace OR Trace glucose with specific symptoms* of diabetes. **frequent urination & thirst*	Urgent. See health care provider within one week.	Results provided to participant during encounter and mailed to participant within one month. HVA / Call Center to follow up with participant by phone within two weeks of encounter.
	Negative glucose with symptoms of diabetes OR Trace glucose with no symptoms* of diabetes	Of Potential Concern. See health care provider within one month	Results provided to participant during encounter and mailed to participant within one month.
	Glucose negative, no symptoms* of diabetes,	Normal. No Referral.	Results provided to participant during encounter and mailed to participant within one month.
BMI	Obese (≥ 30) Overweight (25 to 29.9) Normal (18.6 to 24.9) Underweight (< 18.5)	Routine. If overweight or underweight, discuss results and potential lifestyle changes with health care provider.	Results provided to participant during encounter and mailed to participant within one month.
Spirometry	ALERT LEVEL Either FEV_1, FVC, or FEV1/FVC below lower limits of normal AND FEV_1, < 50% predicted	Urgent Referral. See health care provider within one week. HVA / Call Center contacts participant by phone within one week of receiving spirometry evaluation	Participant advised to see HCP within one week of receiving phone call. Results mailed to participant within one month**.**

Evaluation	Findings	Referral	Comments
	Either FEV_1, FVC, or FEV1/FVC below lower limits of normal AND FEV_1, ≥ 50% predicted	Check-up. See health care provider within one month.	Results mailed to participant within one month.
	FEV_1, FVC, and FEV1/FVC all above lower limits of normal	No Referral.	Results mailed to participant within one month.
CBC **Total White Blood Cell Count**	ALERT LEVEL 1* All: ≤ 1.1×10^3	Urgent Referral. HVA / Call Center contacts participant by phone within one week of receiving results.	Participant advised to see HCP within 72 hours of receiving phone call for alert level 1. Letter with results mailed to participant within one month of receipt from lab.
	Results between alert level and normal reference range	Check-up. See health care provider within two months.	Letter with results mailed to participant within one month of receipt from lab.
	Within lab normal reference range	No Referral.	Letter with results mailed to participant within one month of receipt from lab.
CBC **Hemoglobin**	ALERT LEVEL 1* All: ≤ 6.1 ALERT LEVEL 2 Males: > 6.1 to 12 OR >20 Females: > 6.1 to 10 OR >17	Urgent Referral. HVA / Call Center contacts participant by phone within one week of receiving results.	Participant advised to see HCP within 72 hours of receiving phone call for alert level 1. Participant advised to see HCP within two weeks of receiving phone call for alert level 2. Letter with results mailed to participant within one month of receipt from lab.
	Results between alert level and normal reference range	Check-up. See health care provider within two months.	Letter with results mailed to participant within one month of receipt from lab.
	Within lab normal reference range	No Referral.	Letter with results mailed to participant within one month of receipt from lab.
CBC **Hematocrit**	ALERT LEVEL 1* All: ≤ 18.1 ALERT LEVEL 2 Males > 18.1 to 35 OR >53 Females > 18.1 to 30 OR >50	Urgent Referral. HVA / Call Center contacts participant by phone within one week of receiving results.	Participant advised to see HCP within 72 hours of receiving phone call for alert level 1. Participant advised to see HCP within two weeks of receiving phone call for alert level 2. Letter with results mailed to participant within one month of receipt from lab.

Evaluation	Findings	Referral	Comments
	Results between alert level and normal reference range	Check-up. See health care provider within two months.	Letter with results mailed to participant within one month of receipt from lab.
	Within lab normal reference range	No Referral.	Letter with results mailed to participant within one month of receipt from lab.
CBC **Platelets**	ALERT LEVEL <50 x 10^3 OR >500 x 10^3	Urgent Referral. HVA / Call Center contacts participant by phone within one week of receiving results.	Participant advised to see HCP within two weeks of receiving phone call. Letter with results mailed to participant within one month of receipt from lab.
	Results between alert level and normal reference range	Check-up. See health care provider within two months.	Letter with results mailed to participant within one month of receipt from lab.
	Within lab normal reference range	No Referral.	Letter with results mailed to participant within one month of receipt from lab.

** Alert Level 1 for total white blood cell count, hemoglobin, and hematocrit are based on central diagnostic laboratory reference values.*

Note: Other alert levels are based on a combination of central diagnostic laboratory reference values and alert values used for the Jackson Heart Study

If the participant has abnormal test results, the HVA will suggest appropriate follow-up with their healthcare provider. If the participant does not have a healthcare provider, they will receive referrals for medical and mental health care providers, as needed, including those providers that can assist with free or reduced-cost services (see Appendix N for example of Healthcare Provider Resource Information).

For example, Louisiana State Health officials in District 1 have indicated that they are willing and able to help individuals identify and access healthcare providers in their community, if needed, and a growing list of community clinics are available to see participants at little or no cost. Such referral information is being developed on an ongoing basis, in close coordination with state and local health departments, non-governmental organizations, and the local communities to help ensure appropriate medical and mental healthcare referrals. It is anticipated that such information will continue to evolve and require frequent updating. In order to ensure that this task is being explicitly addressed, Study Coordinators located in the Gulf States will work with health officials and communities in this matter.

Additionally, we are working with state and local public health officials to identify any additional public health information and resources related to weight control, hypertension, diabetes, and other conditions that the HVAs can provide to the study participants for educational and public health benefit.

2.10.5 Abnormal Findings Form

The HVA will document all evaluation findings in the CAPI system while they are conducting the visit. This CAPI module that collects evaluation findings will contain workflow features that prompt the HVA on how to proceed when abnormal findings are obtained. The HVA will review the actions and check the appropriate items on the checklist for cues as to subsequent steps to be taken depending on the findings or situation (Appendix J, Baseline Questionnaire, Section N). Once this information has been uploaded to the central database, selected responses will trigger further actions for the HVA and Coordinating Center staff, such as follow-up phone calls, follow-up letters, and assistance with referrals.

2.10.6 Follow-up Reports & Information

2.10.6.1 Follow-up of Urgent/Emergency Situations During In-person Encounter

If the HVA contacts 911 for an emergency situation, the HVA or Study Center representatives may immediately follow-up, or as soon as possible with respect to the situation, with the participant or their spouse to express our concern, check on their current condition and determine future interest and ability to participate in the study.

2.10.6.2 Follow-up Letters to Summarize Evaluation Findings and Encourage Recommended Actions

Within one month of the home visit, we will mail the participant a follow-up letter with a summary of their evaluation results (see Appendix P and Q). This letter will also contain information reiterating their results and recommended actions.

2.10.6.3 Reporting of CBC Laboratory Tests

For individuals in the Biomedical Surveillance Sub-cohort, CBC results and interpretations will be included in the report that accompanies the follow-up letter. Urgent findings identified by the laboratory will be phoned to individuals by the HVAs or Call Center within one week of receipt from the laboratory. HVAs or Call Center staff will also follow-up with participants within two weeks of sharing the results by phone to see if they need additional assistance scheduling an appointment with a health care provider. The date of all follow-up mailings will be recorded in the data system, any returned mailings will be noted, and those that cannot be reached by mail will be contacted by phone, if possible. Results of follow-up phone calls, including dates and times of calls, responses, advice, and referrals given to participants will also be entered into the data system.

2.10.6.4 Reporting of Spirometry Results to Participants

For participants that complete spirometry evaluations, interpretations of their results will be included in the report that accompanies the follow-up letter. Alert Findings identified during evaluation of their measurements will be phoned to individuals by the HVAs or Call Center within one week of receipt from trained pulmonary study reviewers. Urgent Referrals for participants to see their HCPs within one week will have HVAs or Call Center staff follow-up with participants within two weeks of sharing the results by phone to see if they need additional assistance scheduling an appointment with a health care provider. The date of all follow-up mailings will be recorded in the data system, any

returned mailings will be noted, and those that cannot be reached by mail will be contacted by phone, if possible. Results of follow-up phone calls, including dates and times of calls, responses, advice, and referrals given to participants will also be entered into the data system.

2.10.6.5 Results Reporting to Physicians

If any of the participants' evaluation findings are abnormal and the participant has a health care provider and consents to sharing evaluation findings, we will mail the health care provider a cover letter explaining the study and a copy of the summary of results and recommended actions that was sent to the participant. This report will be sent to the health care provider within one month of the home visit along with relevant contextual information such as normal value ranges (see Appendix O) so that the physician can provide the appropriate care to their patients.

2.11 Laboratory Biospecimen Processing and Storage

Once the biospecimens have arrived in the Central Processing Laboratory they will undergo additional processing to separate out the various components (serum, plasma, cell fractions) and aliquoting of samples into small volumes for cryostorage, before being transferred to the long-term storage facility.

2.11.1 Central Laboratory Processing

Active Follow-up Sub-cohort Sample Processing: The ACD tube will be cryopreserved with 10% DMSO and aliquotted into cryovials, which will be subjected to programmed cryopreservation and stored in LN2. The Trace Metal and PAXgene samples will be frozen in their original tubes at -20°C. The serum and plasma will be aliquotted into cryovials and stored in LN2. The RBCs/buffy coat (from the 10 mL and 6 mL EDTA tubes) will be aliquotted into cryovials and stored in LN2. The 2 mL EDTA tube will be aliquotted as whole blood into cryovials and stored at -80°C. The urine and saliva samples will be aliquotted and stored at -80°C. The blood clots will be aliquotted and stored at -80°C. The hair samples and dust wipes will be stored at -20°C. Toenail samples will be stored with desiccant, under controlled ambient temperature and humidity.

Biomedical Surveillance Sub-cohort Sample Processing: Samples from persons tagged as eligible for inclusion in this sub-cohort will be processed in the same manner as those of the rest of the Active Follow-up Sub-cohort except that, promptly upon receipt at the central processing laboratory, 1) A portion of the urine sample will undergo a more comprehensive dipstick urinalysis, 2) The 2 mL EDTA tube will be analyzed for CBC with WBC differential, and 3) The ACD-B tube will undergo discontinuous density gradient centrifugation to isolate the lymphocytes, which will be mixed with 10% DMSO, aliquotted, and subjected to programmed freezing and storage in LN2.

The CPL will prepare the accumulated samples for transport in bulk for archive storage at the NIEHS Repository. All samples will be transferred to the NIEHS Repository for storage in liquid nitrogen or -20°C/-80°C mechanical freezers, as appropriate for each sample, within one week of receipt.

2.11.2 Study Sample Long-Term Storage at the NIEHS Repository

Environmental Pathology Laboratories (EPL) is the contractor that operates the NIEHS Repository. EPL is located in Keystone Park, in close proximity to the NIEHS campus in the Research Triangle Park in North Carolina.

The EPL Repository is a state of the art storage facility which integrates structural, mechanical, electrical, HVAC, liquid nitrogen (LN2), and backup and monitoring systems to maintain ideal storage temperatures. These systems ensure specimen integrity and long-term preservation while supporting the safe and efficient storage of frozen specimens.

EPL's Repository houses a wide variety of biological and environmental samples and provides storage space for frozen, refrigerated, and room temperature specimens and associated data. The 17,000 square foot facility provides space for ultra-low temperature mechanical and liquid nitrogen freezers, data and specimen storage, and a processing laboratory. Nearly 10,500 square feet of space is dedicated to frozen storage, with a capacity of approximately 185 ultra-low temperature mechanical and liquid nitrogen freezers depending on the types of specimens to be stored. Additionally, the facility has three -20°C walk-in freezers totaling 675 square feet of space. Currently, EPL has over 3.5 million frozen specimens stored in archival storage.

EPL has over 25 years experience managing and operating archives and repository storage facilities for government and commercial clients. EPL provides qualified professional and technical personnel, materials, equipment and facilities for the receipt and long term, secure storage of samples, packaging of the samples for shipment, processing requests for samples and for aliquoting and labeling new samples, as well as distributing requested data and specimens.

Aliquots of a given type will be divided across liquid nitrogen and -20°C/-80°C mechanical freezers, as appropriate for each sample, to maximize integrity of the samples during long-term storage and to reduce risk of complete loss due to freezer failure.

2.11.3 Analyses (including future studies)

Subjects targeted for the Biomedical Surveillance Sub-cohort (exposed and unexposed participants) will have their CBC and WBC differentials measured in the 2 mL lavender top tube promptly upon receipt of the tube by the central processing laboratory. This will allow assessment of these measures among many, if not all, workers with the highest expected benzene exposure (e.g., from exposure to crude oil or burning oil). These sets of samples will be flagged prior to shipping and the lab will be separately notified of these samples. The 2 mL lavender top tubes from all other subjects will be processed in the same manner as the other lavender top tubes. Future analyses performed on incoming fresh blood specimens in the sub-cohort may also include flow-cytometry to determine changes to specific cell populations, such as CD4 or CD8, CD17, and regulatory T-cells.

Subjects targeted for the Biomedical Surveillance Sub-cohort also will have a portion of their urine samples used for a basic chemistry urinalysis (Multistix Pro 10LS reagent strips) to measure protein, creatinine, blood, leukocytes, nitrite, glucose, ketone, pH, and specific gravity immediately upon receipt of the urine samples at the central laboratory.

All other samples will be processed and banked for future analyses.

Future analyses, to be conducted among targeted subsets of the cohort, may include assessment of DNA damage via assays such as the alkaline comet assay and the micronucleus test on the cryopreserved lymphocytes [Chang, et al. 2006, Zijno, et al. 2007]; global hypomethylation and average telomere length in DNA from buffy coat; liver function tests (LFT) on serum; total immunoglobulins, autoantibodies, and inflammatory markers in the serum; antibodies indicating loss of latency of chronic infections such as Epstein-Barr virus and herpes viruses; gene expression related to exposure to benzene and other VOCs using the sample in the PAXgene tube; N-acetyl-beta-D-glucosaminidase (NAGs), beta-2 microglobulin, microalbuminuria, neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), liver-type fatty acid binding protein in the urine to assess kidney injury; polymorphisms in genes encoding metabolizing enzymes for benzene, other VOCs, and PAHs. The specific assays and markers listed here are intended only to give an indication of the *types* of test that we may want to perform later and that are being performed now in similar contexts. In order to take best advantage of rapidly emerging technologies, we will determine – and justify – the specific approaches to use around the time that we are ready to undertake such analyses. We have developed our biospecimen collection, processing, and storage protocols to allow as wide a range of analyses as can be anticipated, including those not yet developed.

Exposure markers measured in stored specimens may include arsenic, cadmium, chromium, copper, lead, manganese, mercury, and zinc, in the whole blood (royal blue top tubes, which have been validated for these metals), to be based on toxicological analyses by other agencies of the oil from this spill; more distant exposure to metals in the toe nail clippings; cortisol and more distant exposure to metals in the hair; cortisol and urinary catecholamines in urine specimens.

If any workers are still engaged in clean-up or terminated clean-up within 30 days of enrollment in the cohort, we may also examine more transient markers of exposure, including urinary levels of benzene, toluene, mandelic acid, trans-muconic acid, hippuric acid; and hemoglobin-PAH adducts.

2.12 Follow-Up of Cohorts

2.12.1 Telephone Questionnaires (Year 2 and 4)

Biennial follow-up of all Active Follow-up Sub-cohort participants will be conducted via telephone. In-person interviewing, self-reported mailed questionnaires, and web-based questionnaire options will be explored as needed to increase response rates. These individuals will be asked to provide updates information on risk factors and outcomes that they have experienced since their last study interview. Additional follow-up questions can be developed based on the results of the baseline assessment. We plan on developing and seeking the necessary approvals for this questionnaire closer to the time of administration.

2.12.2 Biomedical Surveillance Sub-cohort Follow-up (Year 1 and 3)

Participants selected for the Biomedical Surveillance Sub-cohort will undergo more extensive testing and follow-up. These exams will be administered through an external contract or contracts run in collaboration with extramural collaborators. Detailed neurobehavioral, neurocognitive, and peripheral neuropathy measures will be collected.

More thorough respiratory function testing, including bronchodilator challenge, will be performed. Additional tests and follow-up questionnaires and protocols will be determined with the extramural collaborators and necessary approvals will be obtained through the respective organizations.

2.12.3 Annual Morbidity and Mortality Outcomes (Year 2 and later)

Routine surveillance of GuLF study participants will be conducted beginning in Year 2. 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.

2.12.4 Follow-up in Years 6-10

Routine surveillance of all GuLF study participants, using the NDI, potentially available electronic medical records, and state cancer registries (among others), will be conducted to investigate any morbidity and mortality associated with clean-up related activities.

Telephone interviews may be administered to all Active Follow-up Sub-cohort participants in Years 6-7 and 9-10, using questionnaires similar to those used in Years 2 and 4 (see 2.12.1 above), but possibly including additional questions based on the results of follow-up to date.

2.13 Retention Strategies

The strategies outlined in this section are intended to maximize retention, and in some cases recruitment, efforts. These strategies will capitalize on the community outreach and engagement efforts as a core activity of the study design and implementation activities and build on the trust and rapport between the local members of the research team, the target communities and public health leadership across all four states.

A key to high response rates and long-term participation is not to simply contact participants when data are needed but rather to maintain contact in small ways and provide useful information including study results back to participants on a regular basis. We will provide regular feedback about study progress and group results as well as make sure we show our appreciation to the participants for their tremendous commitment to this study. We will also meet regularly as a study team to review progress made on retention efforts and obtain direct feedback to follow-up where necessary.

2.13.1 Annual Update of Contact Information

In order to minimize loss to follow-up, we will provide participants with contact information update forms that they can use to inform us of changes in their contact information. Update forms will be sent to participants once they have completed the interviews and home visit and will be included with all subsequent study mailings for use as needed. Thank you letters following the initial visit will include a GuLF Study magnet that reminds participants to “keep in touch” and includes pertinent contact information. The study website will also feature an “update contact information” button on the

homepage to securely register changes in contact information through an encrypted server.

In addition, efforts will be made to update contact information annually. Participants will be asked to complete a one-page update form annually, whether or not they have had any changes in their contact information. Any mailings that have been "returned to sender" will undergo tracing to identify updated address information. Individuals lost to follow-up will be traced using traditional methods such as internet and other phone-book searches, credit bureaus, and the Social Security Death Index.

2.13.2 Newsletters and Other Mailings

Similar to the study website, annual newsletters will provide information on study progress and findings. Additionally, we will send birthday cards or holiday cards every year to enrolled participants along with small incentives/tokens of appreciation such as pens, notepads, calendars, and magnets with the study logo on them to maintain contact and long-term study interest.

2.13.3 Study Website

We will maintain a website to provide information about the study. The website will be updated regularly with details on recruitment efforts, study findings, and links to other organizations and information resources. Additionally, we will seek to have each of our community partners have a link on their website to the study website. As feasible, the website may contain details on upcoming or ongoing health research studies of oil spill workers. In order to support retention efforts, study participants will also be able to provide study investigators updates to their contact information via a secured web form on the website.

2.13.4 Social Media

Segments of the oil clean-up worker population are active social media users partly due to long trips away from home. Social media such as Facebook can be used to reach these workers to build study credibility, provide more frequent updates, and prompt participation in the out years of the study. However, as we expect web access to be quite incomplete, this approach is not expected to be effective across the cohort. As part of our outreach and retention efforts, we will explore the use of Web 2.0 resources (e.g. Facebook, Twitter, etc.) to encourage awareness and credibility and facilitate follow-up. We will explore the possibility of establishing a presence on a site such as Facebook and maintain study updates as well as other information related to the spill. We envision that study participants can opt to be emailed when updates are provided to the social media site or may even chose to be a "friend" of the site. Additionally, we envision that we will be able to reach out to community organizations and invite them to be a "friend" of the site. Because the social media landscape will undoubtedly change during the study duration, we will continue to monitor for opportunities to utilize this technology for maintaining contact and encouraging retention in study activities. However, we must be assured that participant confidentiality will be maintained and that a significant proportion of participants are actively participating in these media to justify the feasibility of creating and maintaining these resources. We will seek IRB approval for all social media advertising activities. The addition of the use of social media must be reviewed and approved by the IRB in accordance with NIH policy prior to implementation

and we will consult with a computer specialist regarding security issues prior to opening any account.

2.13.5 Community Partnerships and Outreach

As described in Section 2.4 - Community Outreach, we will utilize linkages with the communities in all four states to augment recruitment efforts. Similarly, we will utilize community partnerships and relationships with other organizations to support retention efforts. First, we will continue to convene the Community Advisory Group (CAG) on at least a semi-annual basis throughout the life of the project. Subcommittees of the CAG may be created where necessary to address retention activities and other challenging situations regarding the cohort. We will rely on the leaders within each community to recommend retention strategies best utilized with their constituents. As we continue to develop relationships with communities, we will incorporate these strategies and revise the plans for study retention.

2.14 Remuneration

In addition to non-monetary incentives such as refrigerator magnets, chip clips, stationery, and pens, participants in the Active Follow-up Sub-cohort will receive remuneration for their time and effort in the form of pre-paid gift cards or phone cards. A monetary incentive will be offered to participants at the baseline home visit. Gift cards with a $50 value will be given to participants immediately upon completion. Participants will be asked to acknowledge their receipt of their gift card by completing a form (Appendix V), which will be returned by the HVA to the study office with other study materials. If the Participant also provided an additional Quality Control Sample for the study, they will be given an additional $10 gift card, receipt of which will also be acknowledged on this form. The amount of remuneration for each study event is summarized in the table below. A separate remuneration schedule will be developed for the more comprehensive activities of the Biomedical Surveillance Sub-cohort.

Additional incentives for recruitment and participation such as drawings for prizes such as sporting event tickets, and recruitment events featuring food bank distributions, community health fairs, or other community events will be explored based on feedback from the community and assessment during the run-in phase of the study. We will confer with the appropriate scientific, community, institutional and ethical advisory boards to determine the appropriateness of these additional incentives.

Table 3. Remuneration for Completion of Study Events

Study Event	Active Follow-up Sub-cohort	Passively followed members of full cohort
Baseline Home Visit	$50	N/A
Duplicate Biospecimen Collection at Baseline Home Visit*	$10*	
Total in first year	$50 or $60*	N/A

** Only for the n=300 randomly selected individuals participating in the QA/QC biospecimen collection.*

2.15 Study Timeline

The GuLF Study investigators will engage community and scientific leaders during the study design process for input and refinement. A timeline of study activities is presented in Table 4.

Table 4. Study timeline

	Q3 2010	Q4	Q1 2011	Q2	Q3	Q4	Q1 2012	Q2	Q3	Q4	Q1 2013	Q2	Q3	Q4	Q1 2014	Q2	Q3	Q4	Q1 2015	Q2	Q3	Q4
Study Design and Scientific Input	●	●																				
Community Outreach	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Study Start			●																			
Subject Recruitment			●	●	●	●	●	●	●													
Enrollment Questionnaires			●	●	●	●	●	●	●													
Home Visits			●	●	●	●	●	●	●													
Biomedical Surveillance Sub-Cohort Follow-up							●	●	●	●												
Newsletter Follow-up							●	●	●	●												
Year 2 Follow-up											●	●	●	●								
Newsletter Follow-up															●	●	●	●				
Year 4 Follow-up																			●	●	●	●

3 Evaluation of Benefits and Risks

3.1 Potential Benefits

All study participants may benefit from positive feelings associated with participating in a study of the health effects of the oil spill that may be of value to their community. In addition the knowledge gained from this study may have a significant impact on future public health responses to similar disasters. It is also possible that participants may benefit directly from public health responses that are based on early findings from this study.

Participants in the Active Follow-up Sub-cohort may benefit from receiving results of medical evaluations and health care referrals that they may not otherwise receive (see Section 3.10. - Reports to Participants and Health Care Referrals).

3.2 Potential Risks

The questionnaires and procedures in this observational study present minimal risks to study participants. The questionnaires are based on instruments that are widely used in epidemiological studies. Adverse events associated with study procedures are expected to be uncommon and limited to mild and transient discomforts. In order to minimize risks to participants, all study procedures will be conducted by qualified, experienced, and well-trained field staff.

The main risk in questionnaire administration involves questions about sensitive health topics or personal experiences that may be traumatic. Participants will be told that they can skip any questions that make them feel uncomfortable or end the interview at any time. Participants will also be warned of the possibility of loss of privacy should their de-identified data distributed through controlled access procedures (see section 11.2a) be linked back to them in ways that cannot be foreseen at present.

Pulmonary function testing is considered safe. The primary risk, which is exceedingly rare, is fainting in older participants with impaired lung function. We minimize the chance that this rare event will occur first through our very conservative exclusions for pulmonary function testing – any heart attack or hospitalization for other heart problem or stroke in the past 3 months. Pregnant women will not undergo pulmonary function testing until at least 3 months post-partum. To further minimize risk of fainting, pulmonary function testing is done in a seated position, and study staff will be trained to look for signs of dizziness or other problems and to stop the maneuver if necessary. The risk of infection is all but eliminated by using disposable mouthpieces (spirettes). These disposable mouthpieces have the additional protection of having a built-in bacterial filter. In the PLATINO [Menezes, et al. 2005] and BOLD [Buist, et al. 2007] studies, home visits were conducted on 14,000 adults over age 40 by trained technicians only, without physicians present, and no adverse events were associated with in-home spirometry.

There may be some minor discomfort associated with blood collection, including temporary pain, bruising, or swelling at the phlebotomy site. Fainting during blood collection is exceeding rare.

There is also a remote risk of accidental disclosure of study information. Measures that will be taken to guard against accidental disclosures include maintaining complete confidentiality of the questionnaires and laboratory samples, use of secure data systems, and staff training (see Section 10.3 – Participant Confidentiality). Participants will also be warned of the possibility of loss of privacy should their de-identified data distributed through controlled access procedures be linked back to them in ways that cannot be foreseen at present.

4 Adverse Event Reporting

Adverse events associated with this study procedures are expected to occur very infrequently. Most of the potential risks associated with study procedures (see Section 3.2) is limited to mild, transient discomforts of no clinical significance. Only clinically significant adverse events will be reported to the IRB. Examples of clinically significant adverse events include:

- fainting during spriometry or blood collection
- respiratory distress induced by spirometry that requires medical attention
- prolonged bleeding, hematoma formation, or infection associated with blood collection that requires medical attention

Field staff will be trained to detect and respond to clinically significant adverse events. They will also be expected to report clinically significant adverse events to the Coordinating Center immediately. Because some adverse event may not emerge until after the visit, participants will be instructed to call the study hotline if they experience a new or worsening health problem that could be due to a study procedure. The principal investigator will be responsible for reporting all clinically significant adverse events to the IRB within 72 hours of receiving notification that an event occurred.

A clinically significant adverse event will be reported as a serious adverse event if it is life threatening, causes persistent or significant disability, leads to death, or requires medical or surgical intervention to prevent one of these outcomes.

As described in Section 2.10.2, HVAs may encounter participants who report or display symptoms of acute, pre-existing medical or mental health conditions that are not related to participation in the study. HVAs may also observe unusual situations in the home that may suggest the existence of reportable social or abusive behaviors. In addition, the results of study procedures, such as blood pressure measurement, may indicate the need for immediate medical attention for previously undiagnosed or poorly controlled illnesses (see Section 2.10.4.1). Any pre-existing health problem or social situation that requires a call to 911 or social services will be reported to the IRB as an adverse event within one month of occurrence. The report will include information on the outcome of the actions taken in response to the event.

The investigator will report unanticipated problems to the IRB within 72 hours of identifying such an occurrence. Unanticipated problems are defined as any incident, experience, or outcome that meets **all** of the following criteria:

- unexpected in terms of nature, severity, or frequency given (a) the research procedures that are in protocol and informed consent and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research;

- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

5 Study Oversight

The Principal Investigator will monitor and evaluate the progress of the study, including periodic assessments of data quality and timeliness, participant recruitment, administration of informed consent, accrual and retention, participant risk versus benefit, performance of contractors and other factors that can affect study outcome. This monitoring will also consider factors external to the study when interpreting the data, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study.

The study team, all of whom will contribute to study oversight, has the experience necessary to provide this oversight. We list the investigators and their roles and responsibilities

- Dale Sandler, Ph.D. Principal Investigator NIEHS (Protocol development and overall oversight and responsibility for all parts of the study)
- Richard Kwok, Ph.D., Lead Associate Investigator, NIEHS (Protocol development and oversight over the day-to-day operations of the study, exposure assessment and coordination for all parts of the study)
- Lawrence Engel, Ph.D., Associate Investigator, Memorial Sloan-Kettering and NIEHS (Protocol and questionnaire development, and oversight over the neurologic and biologic areas of the study)
- Stephanie London, M.D., Dr.P.H., Associate Investigator, NIEHS (Oversight over the respiratory areas of the study)
- Aubrey Miller, M.D., M.P.H. Associate Investigator, NIEHS (Oversight over the medical and medical alert / referral areas of the study)
- Christine Parks, Ph.D., Associate Investigator, NIEHS (Oversight over the immunologic areas of the study)
- Aaron Blair, Ph.D., Consultant, NCI (Consultation on overall study implementation and design and exposure reconstruction)
- John Hankinson, Ph.D., Consultant, Hankinson Associates (Consultation on pulmonary function testing and interpretation)
- Mark Stenzel, Consultant, Exposure Assessment Applications, LLC. (Consultation on exposure assessment and industrial hygiene)
- Patricia A. Stewart, Ph.D., Consultant, Stewart Exposure Assessments, LLC. (Consultation on exposure assessment and industrial hygiene, development of exposure metrics for study participants)

SRA International (SRA), a provider of professional research services company, will provide support for this study through an existing contract with the NIEHS. SRA will

oversee the day-to-day activities of the study with oversight from the NIEHS investigators. SRA will be responsible for recruiting and enrolling participants, conducting home visits, managing study data, providing laboratory processing services, and completing follow-up telephone interviews. All SRA staff and any SRA subcontractor staff will have the proper education, experience, and training required for their role in the study. Staff members who interact with participants or have access to study data will be trained in human subjects research protections, the study protocol, and study procedures relevant to their role. They will also be required to sign confidentiality agreements. SRA's telephone interviewers are hired and payrolled through staffing agencies, consistent with standard industry practices, but are trained and managed directly by SRA. The responsibilities of SRA's key subcontractors and collaborators are described below.

- ClinForce, a medical research staffing agency, will identify, hire, and payroll home visit agents and regional field managers. SRA will be responsible for training, equipping, and managing the work of all field staff.
- Social and Scientific Systems, Inc. (SSS), a provider of professional research services, will provide central laboratory processing services through a subcontract with SRA.
- Experimental Pathology Laboratories (EPL) will provide biorepository services under an existing contract with the NIEHS.

A GuLF Study Scientific Advisory Board will be established as a subcommittee of the NIEHS Board of Scientific Counselors to provide additional oversight. This Board will include one or more members of the Board of Scientific Counselors, scientific experts, community representatives and Federal agency representatives. A separate Community Advisory Board, consisting of representatives of key study populations in the affected states, also will be established. Through funding made possible by a Gift to the NIH, the NIH has arranged to have the Institute of Medicine review the initial plans for the study and monitor study progress. The IOM held its first meeting focused on the GuLF Study on September 22, 2010. It is expected that the IOM will meet twice a year for several years, and then annually to review study progress and findings. An Interagency working group made up of representatives from each Federal Agency involved in some aspect of the oil spill response met on August 19, and is also expected to meet regularly to provide study oversight.

6 Statistical Analysis Methods

6.1 Treatment of Exposure Status and Health Outcomes

Estimates of quantitative levels for specific exposures will be developed to the extent possible by the industrial hygiene team. Exposure status (e.g. any contact with crude oil, dispersants, or relevant crude oil specific chemicals, e.g., benzene, heavy metals, etc.) will also be defined dichotomously as "exposed" or "unexposed" based on the definitions given above for the study population and an activity-based exposure reconstruction (Sections 3.1.1 and 3.1.3). Similarly, health outcomes will be examined quantitatively where appropriate (e.g., FEV1/FVC, CBC measures), and will also be defined as "present" or "not present" based on the existence of specific endpoints within each

disease area of interest (respiratory, cardiovascular, hematologic, dermatologic, neurologic, cancer, reproductive, mental health, immunologic, renal, liver).

We expect that very few workers engaged in clean-up *related* tasks, but not in clean-up *per se,* such as those providing only administrative, logistical, or personnel support, will be enrolled in the cohort because of the initial screening. However, any such workers found to be enrolled in the cohort will be placed in an "unexposed worker" category and excluded from most analyses because their exposure profile will be fundamentally different from that of the other clean-up workers and they are likely to differ in important, potentially unmeasured, respects (e.g., physical activity, socioeconomic status, health care access or quality) from the other clean-up workers. We will revisit this approach after examining results from the mini-pilot to determine whether this should be incorporated into the full study.

6.2 Statistical Methods to Address Study Objectives

The objectives of this study are to evaluate and characterize relationships between exposures to oil, oil byproducts and/or chemical dispersants, and stress associated with the disaster and short- and long-term health effects. General analysis methods to address these objectives are as follows:

- **Descriptive analyses** will be conducted as a precursor to other investigations. Rates and proportions will be estimated and bivariate relationships will be explored using cross tabulations. 95% confidence intervals (CIs) will be estimated where appropriate.
- **Acute- and Short-term Outcomes:** Acute- and short-term health effects that may have been incurred during or immediately following exposure will primarily be assessed during baseline data collection and in the immediate follow-up time-period. Relationships between exposures and these outcomes will be investigated at the most basic level by fitting regression models: logistic regression models for dichotomous outcomes to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for each exposure and least squares regression for continuous outcomes to estimate betas and standard errors (SEs) for each exposure. Relevant demographic variables (e.g., sex, age, race, socioeconomic status indicators) and other exposures will be included in the regression models as covariates and effect modifiers. More refined analyses will incorporate specific characterizations of exposure, such as type of work performed, location, nature, and duration of exposure, protective equipment used, and ultimately a quantitative index of exposures developed by a panel of industrial hygienists and other exposure experts to reflect the risk factors of interest. Outcomes that will be evaluated include respiratory symptoms, nausea, headaches, dermatitis, depressive symptoms, anxiety, FEV1/FVC, CBC components, WBC differentials, DNA damage, etc.
- **Long-term Outcomes:** Long-term health effects that may be incurred in the years following the exposure will be assessed at regular intervals through follow-up by interview or linkage with disease/mortality registries. Relationships between exposures and dichotomous health outcomes will be investigated by fitting binomial repeated measures models to each outcome, using standard statistical software

such as SAS Proc GENMOD and Proc MIXED. Exposure effects will be assessed via ORs for each observation period. Non-dichotomous outcome measures will be investigated using generalized linear models; appropriate transformations will be used to satisfy model assumptions. Relevant demographic variables (e.g., sex, age, race, SES indicators) and other exposures (including ongoing, repeated environmental variables where available) will be included in the repeated measures models as covariates. These outcomes will include cancer, neurological (neurocognitive, neurobehavioral, neurophysiological) deficits, cardiovascular injury, reproductive effects, persistence of early effects, among others.

Various refinements to these basic methods as well as these additional analyses will also be pursued:

- **Confounding and Effect Modification:** Potential confounders and effect modifiers will be introduced into the models to determine the extent to which they might influence any effect. A potential confounder will be retained in the model if its inclusion changes the estimated effect of an exposure or the length of its 95% confidence interval by 10% or more. Stratified analyses will also be used, as appropriate. Information on many of these factors will be obtained by interview, but others may come from analysis of biologic specimens. . In addition, we will perform sensitivity analyses to assess the impact of unmeasured confounders, classification errors (for both exposures and outcomes), and selection bias on estimates of exposure-disease association. This will be done in part using probabilistic methods to quantify the likely effects of misclassification of dichotomous measures [Fox, et al. 2005, Chu, et al. 2006] and polytomous measures [Arah, et al. 2008].

- **Repeated measures**: Repeated measurements on individual components of long-term health outcomes (examples: reported numbers of days experiencing asthma symptoms, FEV1/FVC) will be investigated for association with exposure through repeated measures mixed-effect models, while introducing appropriate effect modifiers. In particular, pulmonary function measures provide objective data that complement less objective self-reported symptom data, but are typically quite variable. Results from other studies suggest that, at a given time point, we can expect to detect differences in FEV1 as low as 5% between subgroups of about 250 participants per group with 80% power. Analyses to compare larger subgroups, compare groups across multiple time points, detect changes over time, or investigate the FEV1/FVC ratio all involve more stable measures or comparisons and so will exhibit greater statistical power.
- Non-reversing binary prospective outcomes, such as incident diagnoses, will also be modeled using Cox proportional hazards models.

6.3 Interim and Safety Analyses

Adverse events associated with study procedures such as blood draws and pulmonary function testing are expected to be uncommon and limited to mild and transient

discomforts. Such events will be monitored through interim reports. Interim reports will also be used to monitor parameters that characterize the conduct of the study, such as pace of recruitment, completeness of scheduled activities, time lags associated with data entry and laboratory testing, as well as QC reports for issues such as inter-observer variability and inter- and intra-laboratory variability. Study statisticians will develop these and other reports. No early stopping rules are in place for this study since there is no treatment and no anticipated risk to participants. Analyses of short-term health outcomes will be conducted after completion of baseline visits. Other interim analyses may be conducted in a blinded fashion so as not to influence investigators or study staff with respect to the conduct or completion of the study.

6.4 Laboratory QA/QC Analyses

Laboratory QA/QC data will be reviewed for evidence of excessive variability and for trends indicating shifts in process control. Data from blind QC samples submitted to laboratories will be analyzed and within-pair coefficients of variation (CV) for internal (within laboratory) consistency samples will be calculated. Inter-laboratory reliability will be investigated by analysis of results of laboratory same-sample analyses. The duplicate blood and urine samples collected from randomly selected individuals in the study (mentioned in Section 2.9.5) will provide specimens for these QA/QC efforts. These individual and pooled samples will be used for quality control purposes such as assessing long-term storage effects and assay batch variability.

6.5 Sample Size Considerations and Power

6.5.1 Estimated sizes of worker (exposed) and non-worker (unexposed) groups

Based on currently available information, we anticipate that when we merge the PEC list, the NIOSH list, the lists of workers from Federal agencies that may be included in this study (e.g., Coast Guard, Fish and Wildlife Service, US Geologic Survey), and other worker lists, and then remove duplicates, persons who provided no contact information, and persons who indicated that they intended to work on clean-up for less than one week (< 0.2% of the early NIOSH roster, but possibly a larger number; likely to be persons with no intention of engaging in clean-up work), the merged list will contain approximately 90,000 names. Based on early NIOSH information, approximately 92% of these persons will be from one of the four most affected Gulf States. Restriction of the workers, for logistical reasons, to persons from the four Gulf States and to those workers from outside of those states who experienced certain high exposures such as to benzene, burning oil, and dispersants will produce a list of approximately 86,000 persons. It is expected that after loss to follow-up, non-response, and refusal, about 55,000 eligible persons (a 60-65% participation rate) will complete the enrollment questionnaire. These 55,000 persons will comprise the full cohort. Among this group, we estimate that about 43,000 (80%) will have engaged in clean-up activities while the remaining 12,000 (~20%) did not. These 12,000 unexposed persons will include up to several thousand Federal responders who engaged only in response activities such as administrative, oversight, or logistical support that did not involve any contact with spill-related oil, oil byproducts, or dispersants.

There are sufficient eligible persons to recruit 18,000 workers and 6,000 controls into the Active Follow-up Sub-cohort, assuming a 70% participation rate among persons who have already enrolled in the full cohort by participating in the telephone interview. The size of the Active Follow-up Sub-cohort has been capped at 24,000 in light of available funding and statistical power considerations; the base population is large enough that this target is achievable even with a modestly lower participation rate. Based on current information, we estimate that about 26% of the eligible controls are from outside the immediately affected communities. By oversampling these non-local controls, we expect to recruit approximately 2,000 non-local controls and 4,000 local controls, with both groups including Federal controls as described above.

The expected participation rates provided above are reasonable, given anecdotal reports from collaborating federal agencies, media reports, and feedback from community groups and focus groups of clean-up workers that indicate widespread concern about potential health effects from the oil spill among clean-up workers and members of the affected communities. Furthermore, it is possible that the eventual cumulative total of workers will be greater than is currently estimated. We will know the real total only after we have obtained worker lists from other agencies and local communities engaged in clean-up and crossed the lists to identify unique additional workers who did not complete PEC training. *In any case, power calculations indicate that even if actual participation rates turn out to be as much as 20% lower than those indicated above, this study will still be sufficiently powered to achieve its specified aims, with an increase in minimum detectable ORs or differences of less than 10-15%.*

The rest of the full cohort (N~31,000) will comprise individuals to be passively followed who either were not randomly sampled to be part of the Active Follow-up Sub-cohort or who refused to be part of the Active Follow-up Sub-cohort (but participated in the enrollment telephone interview). This represents about 25,000 workers and about 6,000 controls.

Thus, the total size of the full cohort is anticipated to be approximately 55,000 persons (43,000 workers and 12,000 controls), consisting of 24,000 members of the Active Follow-up Sub-cohort (18,000 workers and 6,000 controls [4,000 local and 2,000 non-local, including Federal]) and 31,000 passively followed members of the full cohort (25,000 workers and 6,000 controls).

Based on other prospective observational studies, we anticipate 90% follow-up and participation in telephone interviews after enrollment for the Active Follow-up Sub-cohort. Thus, completed follow-up interviews are expected for approximately 18,000 workers and 5,400 controls in Years 2 and 4.

6.5.2 Sample Power

This study is designed not around a few narrow *a priori* hypotheses, but rather to allow the investigation of a wide range of potential adverse health effects. The study size and the number of individuals who experienced a given exposure – and the consequent statistical power – have largely been determined by the number of individuals involved in the clean-up operations and their distribution by task/exposure. While this study will have limited power to examine certain rarer exposures or outcomes in the near future, this is the largest study to date of oil spill clean-up workers and it is important that we address, to the extent feasible, the wide range of public health concerns. It is a prospective study and as time passes, if the exposure continues to exert an impact on some health outcomes, power will increase.

Table 3 presents minimum detectable odds ratios across a range of proportions of exposure among the workers and of health outcome among the controls. Estimates are shown separately for analyses of the full cohort and of the Active Follow-up Sub-cohort, including all controls or including only the non-local controls. Estimates are also shown for analyses of the Biomedical Surveillance Sub-cohort. All estimates are based on a two-sided test with α=5% and power=80%. As the table shows, this study has excellent power to detect small risks, except when exposure or outcome is rare. For example, in an analysis of the full cohort, if 10% of the workers received a given exposure (e.g., high exposure to VOCs) and the incidence or prevalence of disease is 1%, this study would have sufficient power to detect an OR of at least 1.56 when using all 12,000 controls and 1.86 when using only the 2,500 non-local controls. In an analysis restricted to the Active Follow-up Sub-cohort, with proportion of exposure of 10% and disease incidence/prevalence of 10%, the minimum detectable OR would be only 1.27-1.32 when using the full control group (N=6,000) or the non-local control group (N=2,000). The Biomedical Surveillance Sub-cohort, with 4,500 workers and 500 controls, provides adequate statistical power to detect odds ratios of at least 1.58 when 25% of workers received a given exposure and the incidence or prevalence of disease is 10%. For perspective, estimated relative risks of lower respiratory tract symptoms observed among clean-up workers in previous oil spills ranged from 1.5 to 3.6 [Janjua, et al. 2006, Zock, et al. 2007, Meo, et al. 2009, Sim, et al. 2010]. Thus GuLF Study is sufficiently powered to observe such relative risks for these outcomes.

Table 3. Minimum detectable odds ratios for a range of proportions of exposure among the workers and for all controls vs. non-local controls, based on a two-sided test with α=5% and power=80%

Size of control group (i.e., all vs. non-local)	**Proportion (N) of workers exposed to a given agent**					
	5%	**10%**	**25%**	**50%**	**75%**	**100%**
Full cohort: 43,000 workers, 12,000 controls:						
	N=2,150	N=4,300	N=10,750	N=21,500	N=32,250	N=43,000
Proportion of controls with outcome=1%						
12,000[a]	1.74	1.56	1.41	1.35	1.33	1.32
2,500[b]	2.02	1.86	1.76	1.72	1.71	1.70
Proportion of controls with outcome=10%						
12,000[a]	1.23	1.17	1.13	1.11	1.10	1.10
2,500[b]	1.30	1.25	1.22	1.21	1.21	1.21
Proportion of controls with outcome=30%						
12,000[a]	1.15	1.11	1.08	1.07	1.07	1.07
2,500[b]	1.19	1.16	1.14	1.14	1.14	1.13
Active Follow-up Sub-cohort: 18,000 workers, 6,000 controls:						

	N=1,000	N=2,000	N=5,000	N=10,000	N=15,000	N=18,000
Proportion of controls with outcome=1%						
6,000[a]	2.20	1.88	1.63	1.53	1.49	1.47
2,000[b]	2.38	2.12	1.93	1.86	1.83	1.82
Proportion of controls with outcome=10%						
6,000[a]	1.36	1.27	1.19	1.16	1.15	1.15
2,000[b]	1.40	1.32	1.27	1.25	1.24	1.24
Proportion of controls with outcome=30%						
6,000[a]	1.24	1.18	1.13	1.11	1.10	1.09
2,000[b]	1.26	1.21	1.17	1.16	1.16	1.15

Biomedical Surveillance Sub-cohort: 4,500 workers, 500 controls:

	N=250	N=500	N=1,250	N=2,500	N=3,750	N=5,000
Proportion of controls with outcome=1%						
500[a]	4.48	3.78	3.28	3.09	3.02	2.99
Proportion of controls with outcome=10%						
500[a]	1.89	1.71	1.58	1.54	1.52	1.51
Proportion of controls with outcome=30%						
500[a]	1.58	1.46	1.37	1.34	1.33	1.33

[a] All controls in cohort/sub-cohort
[b] Non-local controls in cohort/sub-cohort

Minimum detectable differences for continuous outcomes are presented in Table 4. Differences are expressed in standard deviations (SDs) and are based on a two-sided test with α=5% and power=80%. Results are shown separately for analyses of the full cohort and of the Active Follow-up Sub-cohort including all controls or including only the non-local controls. In addition, estimates are shown for analyses of the Biomedical Surveillance Sub-cohort. This table demonstrates that the present study has sufficient power to detect small differences in continuous outcomes. For example, in an analysis of the full cohort that examines an exposure of 10% prevalence, we will be able to detect minimum differences of less than 0.050-0.071 SD. A similar analysis in the Active Follow-up Sub-cohort will be able to detect minimum differences of less than 0.09 SD (0.075 when using all 6,000 controls and 0.089 when using the 2,000 non-local controls). Such an analysis in the Biomedical Surveillance Sub-cohort will have sufficient power to detect a minimum difference of 0.177 SD. For perspective, in a study of volunteers involved in the Prestige oil spill clean-up and unexposed controls [Laffon, et al. 2006], results of the comet assay in peripheral blood leukocytes showed differences between the two groups of approximately 4.3 SD in comet tail length. A study of health effects related to the Tasman Spirit oil spill found a difference of about 0.6 SD in symptom scores between coastal residents affected by the spill and persons living away from the

site of the spill [Janjua, et al. 2006]. The present study is very well powered to detect such effects.

Table 4. Minimum detectable differences, in standard deviations, for continuous outcomes for a range of proportions of exposure among the workers and for all controls vs. non-local controls, based on a two-sided test with α=5% and power=80%

Size of control group (full vs. non-local)	**Proportion of workers exposed to a given agent**					
	5%	**10%**	**25%**	**50%**	**75%**	**100%**
Full cohort: 43,000 workers, 12,000 controls:						
	N=2,150	N=4,300	N=10,750	N=21,500	N=32,250	N=43,000
12,000[a]	0.066	0.050	0.037	0.032	0.030	0.029
2,500[b]	0.082	0.071	0.062	0.059	0.058	0.058
Active Follow-up Sub-cohort: 18,000 workers, 6,000 controls:						
	N=1,000	N=2,000	N=5,000	N=10,000	N=15,000	N=18,000
6,000[a]	0.101	0.075	0.055	0.046	0.043	0.041
2,000[b]	0.109	0.089	0.074	0.069	0.067	0.066
Biomedical Surveillance Sub-cohort: 4,500 workers, 500 controls:						
	N=250	N=500	N=1,250	N=2,500	N=3,750	N=5,000
500[a]	0.217	0.177	0.148	0.137	0.133	0.131

[a] All controls in cohort/sub-cohort
[b] Non-local controls in cohort/sub-cohort

Finally, power calculations indicate that even if participation rates turn out to be as much as 20% lower than expected, the minimum detectable ORs or differences will increase by less than 10-15%.

7 Analysis Plan

7.1 Primary Endpoints

Given the very limited health effects research conducted to date on oil spill clean-up workers, the GuLF Study is designed not around a particular *a priori* hypothesis, but rather to allow investigation of a wide range of potential adverse health effects, including physical, psychological, and biological effects. These include both short-term and long-term effects focused on, but not limited to, the following areas: respiratory, cardiovascular, hematologic, dermatologic, neurologic, cancer, reproductive, mental health, immunologic, hepatic, and renal. A priori outcomes of greatest interest based on previous studies are respiratory effects, neurological dysfunction, and genotoxic and hematologic effects.

Questionnaire-based exposure information will be examined in relation to outcomes in both prospective and cross-sectional analyses in the full cohort or sub-cohorts. Because many biological and environmental assays are expensive and samples are limited, we also plan to carry out nested case-control or case-cohort studies within the cohort.

Many of the primary exposure measures will be from job-exposure matrices (JEMs), which will be developed by the investigators using time-specific task and exposure data from a range of sources. These will be semi-quantitative (e.g., 5-point scale). They will be treated in statistical analyses as ordinal values or, depending on distribution or scientific considerations, collapsed into fewer categories (e.g., high vs. low).

Endpoints will be identified through several means. First, we will use the self-reported health information provided in the enrollment interview(s) to define case groups or to assign quantitative or semi-quantitative health categories for a given outcome or constellation of outcomes, as appropriate. Self-reported health histories from this interview will be used to identify outcomes with an onset or increase in severity after the subject began clean-up work (i.e., not a pre-existing condition). Some self-reported health information may be validated in sub-studies through subsequent information provided, with participant permission, by the subject's doctor, the subject's medical record, and/or the subject him/herself. Second, we will have clinic information such as the FEV1/FVC results collected at enrollment from all subjects who live within the immediately affected areas and the urinary glucose results obtained at enrollment from all subjects.

We will examine results of a Complete Blood Count (CBC) with white blood cell differentials among members of the Biomedical Surveillance Sub-cohort. Endpoints will include total WBCs, individual WBC components, red cell measures, and platelets. White blood cell and platelet counts have been found to be significantly reduced among workers with low exposure to benzene, with reduced hemoglobin concentration among workers with higher exposure to benzene [Lan, et al. 2004]. To explore potential effects of metals, particulates, and stress, we will examine measures of the acute phase response (C-reactive protein), inflammatory cytokines, as well as anti-nuclear and thyroid antibodies. We will also examine results of the urinalysis (for protein, creatinine, blood, leukocytes, nitrite, glucose, ketone, pH, and specific gravity) among members of the Biomedical Surveillance Sub-cohort.

In subsets of the Active Follow-up Sub-cohort or the Biomedical Surveillance Sub-cohort defined by higher or lower stress exposure and in vulnerable sub-populations, we will also examine antibodies to latent viral infections as indicators of sub-clinical depressed immunity. Antibodies to latent infections have been studied frequently in relation to the physiological impact of stress, and may vary according to socioeconomic factors [Aiello, et al. 2009, Dowd and Aiello 2009]. We will also examine stress-associated immunosenescence as indicated by average leukocyte telomere length and stress biomarkers [Epel, et al. 2004, Parks, et al. 2009], which along with viral antibodies may be related to a variety of chronic disease outcomes. Such tests may be performed using baseline samples or, for the Biomedical Surveillance Sub-cohort, samples collected at subsequent visits may be utilized.

For a subset of subjects representing high and low exposures to agents known or suspected to be nephrotoxic, including volatile organic compounds and heavy metals, and also unexposed subjects, we will examine urinary markers of kidney injury, including N-acetyl-beta-D-glucosaminidase (NAGs), beta-2 microglobulin, microalbuminuria,

neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), and liver-type fatty acid binding protein.

We will similarly conduct liver function tests using sera from a subset of subjects having either high or low exposures to agents known or suspected to alter liver function, including volatile organic compounds, PAHs, and heavy metals, and also unexposed subjects.

For a subset of subjects representing high and low exposures to agents known or suspected to be genotoxic, including volatile organic compounds, heavy metals, PAHs, and hydrogen sulfide, and also unexposed subjects, we will examine results of DNA damage assays, The specific assays will be determined, based on the current state of the art around the time that we are ready to undertake these analyses, as described above in section 3.11.3. They may include the comet assay and the micronucleus test. Comet assay measures will include the tail moment, defined as the product of the percentage of DNA in the comet tail and the tail length, and the tail intensity, defined as the percentage of DNA in the tail. Micronucleus test measures will consist of the frequency of micronuclei and the frequency of binucleated micronucleated cells.

During follow-up of the cohort, we will identify incident outcomes or changing severity of those outcomes via self-reported health status in follow-up interviews, via linkage with cancer and vital status registries, and via testing of follow-up biospecimens. Our analyses will consider onset or changes in severity relative to both enrollment health status and health history, as appropriate. For some subjects, such as Coast Guard members, we may be able to obtain additional information from electronic medical records.

Continuous outcome measures such as FEV1/FVC will be treated as continuous and/or categorized according to appropriate cutpoints in statistical analyses. They will be log-transformed as needed.

Initial analyses will be largely descriptive, including examination of distributions of jobs, exposures, demographic and lifestyle factors, health history, and recent health outcomes at enrollment. We will quantify and examine patterns of missing data and outliers. We will perform data cleaning as appropriate. To the extent possible, we will explore potential bias in subject selection and reporting.

We will next conduct cross-sectional analyses, consisting primarily of comparisons of prevalence or extent of a given outcome by clean-up task or estimated exposure to a given factor (from the JEM). These will be performed using least squares regression for continuous outcomes or logistic regression for dichotomous outcomes, adjusted for confounders as appropriate. We will explore possible modifiers of effect such as race, sex, baseline health characteristics, lifestyle factors, and access to health care by also conducting stratified analyses by these factors, as appropriate and as numbers permit.

When follow-up data become available, we will also be able to perform prospective analyses linking clean-up activities/exposures to incident outcomes using Cox proportional hazards regression. We will use logistic regression for nested case-control analyses. Extent of change of outcomes will be assessed using least squares regression. Confounding and effect modification will be addressed as described above.

Clinical protocols for a number of outcomes, including respiratory and neurologic effects, will be developed and carried out in collaboration with local university partners identified through a request for proposals (RFP). Therefore, analysis of these outcomes will be addressed in a later protocol.

8 Training, Quality Control, and Quality Assurance

8.1 Staff Recruitment and Enrollment Process

8.1.1 Telephone Interviewers

Locating and screening tasks will be conducted by approximately 50 trained telephone interviewers working part time over different shifts. Interview staff will be given training on good practices in interviewing—locating, gaining cooperation, overcoming barriers to participation and correctly coding outcomes, and American Association for Public Opinion Research (AAPOR) code of ethics which includes training on confidentiality and non-disclosure, and other training in human subjects research. Trainees also receive interactive cultural competence training. Administrative aspects of the computer-assisted telephone interviewing (CATI) system and time record keeping are practiced.

The training program will be tailored to meet the specific needs of this study, including a discussion of successful approaches for conducting interviews with people facing the continuing life disruptions following Hurricanes Rita/Katrina and now the BP oil spill. Interviewers will learn the best methods for refusal avoidance and conversion techniques, and will receive extensive hands-on training with the Computer-Assisted Interviewing (CAI) questionnaire. They will also learn the most effective ways to explain the importance of participating in the study, and how to best answer questions about the study's purpose and process. Interviewers will be trained to make respondents aware of other sources of information about the study, such as the study website. Training will include sensitivity exercises designed to ensure that interviewers show unconditional positive regard for participants. Interviewers will be trained to use positive rather than patronizing language, use structured probes, check for respondent fatigue, and offer encouragement without leading the respondent to respond in a specific way. The training will focus on the three general challenges in interviews—communication, stamina, and cognitive challenges—and specific recommendations for overcoming these challenges.

Each training topic will be reinforced with group discussion and interaction, trainer demonstrations, and classroom practice and discussion. Role-playing and practice will be used.

Confidentiality safeguards will be maintained throughout the data collection period. All study personnel will be trained in their responsibilities under HIPAA to protect the confidentiality and privacy of each participant's personal health information. The training will also describe the civil and criminal penalties if an interviewer violates a participant's right to privacy. All interviewing staff will be required to sign a Confidentiality Agreement and an Affidavit of Nondisclosure as part of their training on protecting the privacy and rights of respondents. Training will also include identification of social and mental health issues in need of intervention and appropriate protocols for seeking outside support or making community referrals.

Individual Telephone Interviewer performance will be monitored by Telephone Supervisors using Computer Assisted Telephone Interviewing (CATI) and telephony technology that permits silent monitoring of voice together with key-stroke by key-stroke monitoring within the CATI instrument. The supervisors will systematically select interviewers for monitoring and will formally evaluate performance providing praise or corrective feedback, as appropriate. Evaluations are maintained in individual

interviewer performance files and are regularly reviewed by the call center manager for purposes of performance recognition, performance improvement coaching or dismissal.

The call center manager will frequently review recruitment and enrollment statistics in the study database to ensure that participants are being enrolled consistent with the distribution of the various study populations of interest in the selected sampling frame. Weekly reports will summarize recruitment statistics which also will be discussed at weekly project meetings. If it appears that too many or not enough of given subgroups are being enrolled, study staff, investigators will meet SRA's statistical and programming staff to consider adjusting the calling cue to rebalance the recruitment calls as appropriate. SRA's Director of Survey Activities will closely monitor day-to-day call center activities to ensure that call center staff is closely adhering to recruitment and enrollment quality and productivity goals.

8.1.2 Home Visit Personnel

Home visits will be conducted by as many as 60-80 home visit agents (HVA) and 8-12 Regional Managers (RM). In this study, it will be important to retain HVAs with particular aptitude, skill, and sensitivity in working with persons having experienced natural disaster, life disruption, and probable dislocation.

Training for home visit data collection will start with a Regional Manager training sessions that precede the HVA training. This RM training will focus on data collection procedures, management of HVAs, the importance of data quality and cost containment, and reporting. Following the RM training, training sessions will be held for the HVAs. The field data collection trainings will be conducted both in person and over the internet. The training sessions will consist of large-group exercises, demonstrations, round-robin and dyad mock interviews, and question-and-answer sessions. HVAs will be trained and tested on their mastery of the ethics and protection of human subjects in research, establishing rapport, setting visit dates, obtaining informed consent, and administering questionnaires. They will also be trained in the clinical portion of the study protocol and tested specifically on the clinical protocol components to include setup, preparation and shipping of biological samples. The training will also include practice session. The HVA will practice the complete baseline protocol under the close supervision of the field supervisors and trainers.

Periodically, RMs will accompany the HVA for follow-up assessment of performance. Deviations from protocol evidenced in the receipt of data or specimens will be reported to project management staff at SRA and the RM will follow-up with corrective training or dismissal of the HVA as appropriate. The investigators and the NIEHS IRB will be informed of all deviations.

Field activities will be closely monitored by SRA's Director of Laboratory Services and the Home Visit Coordinator who will monitor field operations and the Storage Coordinator, who will monitor activities of the central processing laboratory, the testing laboratory and archiving of specimens at the NIEHS Repository, managed by Experimental Pathology Laboratories.

The Home Visit Coordinator will monitor home visit activities to ensure that these are proceeding according to schedule. The Home Visit Coordinator will interact with the RMs on a frequent/near daily basis to ensure that HVAs are receiving home visit assignments and that they are receiving the necessary home visit supplies to complete the visits in a timely manner. The Storage Coordinator will also ensure that HVAs are

processing and shipping the collected study specimens immediately upon completion of the visits and closely monitor arrival of collected study specimens at the CPL and will ensure that these are being processed according to the study protocol. The Storage Coordinator will also ensure that processed samples are being routinely transferred to the NIEHS Repository under appropriate transport conditions. The Storage Coordinator will also work closely with the Repository Staff to ensure that study samples are entered into storage and that final storage locations (e.g., freezer, shelf/rack/box/column/row) are sent to SRA for import into the study database.

8.1.3 Monitoring of Recruitment and Field Activities

Recruitment, retention and field operations are a challenge in most studies. SRA will generate routine reports for the investigators that summarize recruitment, enrollment, and retention rates, as well as outcomes of operation processes. Frequent reviews of study status reports will allow the investigators and SRA to identify problems early and make adjustment to keep enrollment and study operations on track. Examples of the types of reports that SRA will generate include:

- Call center reports that monitor telephone questionnaire outcomes, such as call rescheduling (soft refusal) rates, duration of interviews, and points of break-off for incomplete interviews.
- Enrollment reports that present contact and participation rates for the telephone enrollment questionnaire both overall and for different demographic subgroups.
- Home visit reports that monitor outcomes of field activities, such time required to schedule appointments, no-show and reschedule rates, missed procedure rates, and duration of visits.

8.1.4 Personal Safety

During our training sessions for HVAs, we will emphasize the importance of safety during in-home visits and awareness of local laws and regulations. For example, we will instruct the HVAs to stay on main thoroughfares and well-lighted routes as much as possible when traveling and give them the option of terminating a visit if there are safety concerns. The police and sheriff's departments will be informed of the project's presence in their county/parish. Each HVA will be issued a cell phone that they can use to make emergency calls during travel to or from subjects' homes as well as during the visit. SRA is also making provisions for HVAs to request an escort for home visits in neighborhoods where there may be safety concerns or for home visits during evening hours or to remote locations.

Regional managers will—if not already familiar with their assigned area of operation—consult with local law enforcement officials to determine what, if any, "trouble spots" may exist in their area. When participants who live in these areas are scheduled for home visits, the Regional Managers will share this information with the HVAs so that escorting arrangements can be made and extra travel precautions can be made as necessary. In addition, we will work with local health departments and other community groups to find alternate locations in which to conduct interviews if safety is a major concern.

After training, each HVA will have a fundamental and operational knowledge of the following principles:

- Come prepared for the neighborhood, based on the informal information gathered from the scheduling call, a preview of the neighborhood, and information from your supervisor,
- Always be aware of your environment
- Leave the house and reschedule if you think it is necessary for your safety,
- When concerned about an area or participant, keep your supervisor aware of when you are to arrive and when you expect to leave,
- Call your supervisor when you do leave.
- Emergency telephone numbers are programmed for speed dial into each HVA's cell phone

8.1.5 Mandatory Reporting Requirements

In addition to personal safety training, the HVAs will be trained to detect signs of turmoil and abuse in the homes. Should a HVA witness signs of child, spouse or elder abuse while in the participant's home, the HVA will immediately generate an incident report and transmit this to their Regional Manager and to the Coordinating Center. The Coordinating Center will immediately contact the NIEHS Project Officer and after appropriate consultation will report the situation to local authorities in accordance with applicable laws.

8.1.6 Identifying and Dealing with Mental Health Issues

It is possible that HVAs (and telephone interviewers) may encounter situations in which a participant may be emotionally upset by recalling aspects of the oil spill that affected them personally. We will train HVAs on how to identify and deal objectively with subjects who may be anxious, stressed, or depressed because of their circumstances. HVAs will be trained to remain neutral and focused and to present all survey questions in a consistent manner so that response bias is not introduced. In most situations, empathetic and respectful listening and an understanding tone will help to calm the participant and allow him or her to proceed with the interview. However, we will train HVAs on several specific steps they can follow if a participant becomes distressed, such as:

- Reminding participants that their answers are confidential,
- Providing positive, neutral feedback, such as "Thank you; I understand; We appreciate your participation in this important study," etc.
- Acknowledging a participant's hesitancy in answering a question, such as, "I understand that this may be difficult for you, so please take your time", and
- Reminding participants that it is okay to skip any question he or she does not feel comfortable answering.

In circumstances when an HVA or interviewer identifies a participant that may be experiencing mental health issues—or more significantly suicidal ideation—we will provide them with contact information for local, regional, state and national mental health resources that are available to help them deal with their issues. If the participant appears to be at significant imminent risk for self-injury (e.g., suicide), the HVA or interviewer will contact local emergency officials by calling 911 or other intervention hotlines as appropriate. As in the previous section, the HVA will immediately fill out an incident report and telephone their RM and Coordinating Center to inform them of this

action. The Project Manager will then immediately notify the NIEHS Project Officer of what transpired.

8.1.7 Reporting Individual Results to the Participants

HVAs will be trained to provide participants with appropriate and standard feedback about their individual blood pressure and BMI measurements, preliminary pulmonary function test observations, and urine glucose results before departing the participant's home. HVAs will be trained to record all observations and in-home test results in the data management application as well as on participant Test Result Forms that provide the participant with a basic interpretation of the various measurements and test results. HVAs will also be trained to strictly follow scripts when conveying results to participants. The participant Test Result Forms will include scripts that provide recommended actions for participants to take depending on the measured values for each test. For each test result, we provide standard recommendations depending on the result value (see also section 2.11 and the Test Results Forms in Appendix X). **"Normal" results** or expected test values will be relayed as such and the participant will be told that no additional actions are necessary. If test results or measures are **slightly or moderately elevated or abnormal**, the HVA will instruct the participant that he or she should consult with their healthcare provider at an interval defined by the test in question to discuss the significance of these results. If test results or measures are **markedly elevated or abnormal**, the HVA will instruct the participant to seek medical evaluation as soon as possible. HVAs will be trained not to offer any medical advice or to discuss study results in more detail or to engage in general discussions with the participant about any health-related issues.

HVAs will ask the participant if they would like information on healthcare facilities in their local area that can provide medical treatment or care. If they receive an affirmative response, the HVA will use the GuLF Study Resource Guide to provide a list of local providers. If the participant declines, the HVA will re-emphasize to the participant that there are local providers available and that they can contact the study helpline at any point to receive information about resources that are available to them.

The HVA will note in the CAPI system which resource contacts were provided to the participant as well as what follow-up recommendations were given. When these data are uploaded to the network, the system will auto-generate reports of participants who should receive follow-up calls to assess whether the participant contacted their healthcare provider or one of the healthcare/mental health resources provided by the HVA (or interviewer).

Once specimens from participants who are members of the Biomedical Surveillance Sub-cohort have been transported to and processed by the Central Processing Laboratory, additional test results such as the complete blood count with white blood cell differential and a complete urinalysis will be entered into the study database. Additionally, pulmonologist interpretations of the pulmonary function test results will also be captured in the study database. The data management system will then generate a test result letter and an enclosure with a complete summary of all test findings along with their interpretations and recommendations for follow-up that will be sent to the participant.

8.2 Data Quality Control

8.2.1 Data Collection Quality Control

At the core of our data collection efforts, we will use a commercially available survey platform. The platform has the following features:

A flexible interface for loading complex sample data initiates and drives study recruitment activities.

A Computer-Assisted Telephone Interview (CATI) component that guides project personnel through the interview process to determine eligibility. This component provides complex branching and algorithm support to collect data, make eligibility determinations, schedule future contact and direct the management of the new recruit's case to regional field supervisors. The CATI system allows data managers to monitor the recruitment process and all call center operations and success metrics. All CATI data are updated and managed in the central data management system. A notification system text-messages all receiving field representatives and managers when new cases are assigned to them.

A CAPI component running on field laptop computers to administer study questionnaires and capture clinical evaluations. The CAPI component guides field personnel through a questionnaire that has complex and conditional branching as well as rostering. The CAPI system provides real-time data validation, ensuring data are valid when captured and the immediate correction of data after an error is detected.

A central management tool ensures that all CAPI and CATI data are collected into a single repository and manages the aggregation of laptop interview data. Field representatives connect to the communications portal (described below) using secure internet technology, and automatically upload collected interview data and download preparatory data for forthcoming interviews. CATI user data are managed via the same software tool that reads and writes data directly to the database.

8.2.2 Data Storage

All study data are housed in a single SQL Server data repository stored in the secure data center. This single database ensures that all system users are accessing the same database; allows for greater control via role-based access privileges; provides a robust architecture to support backup, security, and disaster recovery; and provides the flexibility needed to change the data input mechanisms that could change during a potentially very long study.

8.2.3 Data Management & Communications

The communications portal provides a single access point for all study data, reports, status updates and communications. The communications portal provides the ability to record, track, and analyze information associated with all types of case management activities such as scheduling, field interviews, tracking, and data acquisition. Project field personnel and other authorized project personnel connect to the communications portal over the Internet, go through an authorization process to establish an SSL connection, and have access to a variety of functions that support their work. These functions include the ability to:

- Upload and download interview data
- Update interview schedules; view upcoming workloads for self or field staff (for supervisors)
- View data completeness reports including status of lab data
- Receive updates from project management including updated modules, with training provided
- Transmit laboratory data, receive validations
- Report and track errors or technical support needs and follow them to closure
- Receive warnings about overdue lab data transfers
- Update participant profile information if within user rights
- Keep track of project personnel; review training completeness reports and training records
- Monitor call center performance

Field representatives or managers connect to the Data Management System (DMS) using laptops with real-time, whole-disk encryption. Data will be transferred from the laptop to the DMS over the Internet or using smart phone tethering technology to gain Internet access. The DMS is integrated with email, enabling key events to trigger emails accessible via smart phones, ensuring that our distributed workforce is as current with information as possible. Regular data transmissions are required of all field personnel and phone email messaging prompt field staff to establish a data upload session if overdue.

The communication portal is key to the success of this project as it provides the most timely, accurate information and delivers it to project staff in real-time. For example, it is crucial that supervisors monitor recruitment and enrollment trends, and compare these results against various call center operations to improve overall recruitment success rates. Furthermore, enrollment success measures are compared based on time of day, call center operators, source of telephone number, and ordinal number of call attempts in order to identify trends that suggest necessary modifications.

8.3 Laboratory Procedures

8.3.1 Laboratory Data Quality Control

The study laboratories that will be selected to analyze the study specimens will be evaluated in part based upon their existing performance measures to assure the quality of their testing results. This includes (1) internal and external quality control and proficiency testing programs, (2) testing methodologies *vis à vis* industry standards such as those published by the Clinical Laboratory Standard Institute (CLSI) and the American Industrial Hygiene Association (AIHA), (3) assay standardization to ensure the desired analytical range and sensitivity/specificity, and (4) methodology validation and analytical instrument performance using CLSI standard GP-31A and others, and pre- and post-analytical processes such as specimen receipt and accessioning, sample

aliquoting and batching, treatment of out-of-range results, reporting, and electronic data transfer.

A continuing performance review on both external and internal quality control programs will be conducted prior to commencing study data collection. Once home visits have begun and biospecimens and environmental specimens are submitted for analyses, test reproducibility and accuracy will be monitored as follows:

- *Assay Variability/Reproducibility:* Intra-assay (measurement) variability will be assessed through replicate assays conducted on the same day and in the same run. Inter-assay variability will be assessed through replicate assays conducted on different days in different runs.
- *Testing Accuracy:* Assessing the accuracy of test results presumes that there are available "gold standards" for each analyte of interest. While it is possible to quantitatively determine the amount of some analytes present (generally chemical compounds such as cotinine, lead, BFRs, and phthalates), definitively quantifying biological analytes such as IgE allergens, endotoxins, mold, and fungi, or volatile analytes such as formaldehyde and VOCs is more problematic and assay dependent. Biospecimen controls, environmental controls, and split specimens will be implemented for this purpose.

Laboratory testing quality will also be monitored by requiring submission of regular QC results as well as periodic proficiency testing program results. Modifications to testing procedures or sample processing/ extraction procedures will be avoided or minimized to the extent possible.

8.3.2 Quality Control Specimen Collection

To preserve valuable study subject materials, we will collect biospecimens and environmental samples from up to 200 randomly selected anonymous donors to use for quality control. These will be used to create samples that can be inserted blindly for quality control when laboratories process or analyze GuLF Study samples, to assess drift over time in laboratory analyses, and to provide a sample source for assay development and testing. These samples will be in addition to the quality control samples that will be collected from a random subset of cohort members and that are essential for analyses requiring serial samples or known representativeness of the study cohort. The volunteers providing these samples will be selected to be roughly similar to the clean-up worker population. Each person will provide blood, urine, saliva, hair and nail clippings, and household dust samples. Blood will be stored as serum, plasma, and blood clots in cryovials in vapor phase liquid nitrogen. Urine will be stored in cryovials in vapor phase liquid nitrogen. Dust wipes and hair samples will be stored at -20°C. Toenail samples will be stored with desiccant under controlled ambient temperature and humidity. We will collect these samples from anonymous donors under a separate protocol.

8.4 Run-in Period

Study personnel, procedures and forms will need to be tested in order to determine whether planned data collection efforts will yield valid and reliable results in the most time and cost efficient manner. We plan to conduct a 4-5 week run-in period of the study

in one geographic location within the study area. We aim to recruit N~1000 participants during the run-in period and schedule as many in-home visits as possible during this time. This will establish a vanguard group of participants to allow us to test the questionnaires and, as the participants move through the phases of the study, the protocols to ensure that the GuLF Study data collection efforts will work as planned. We will evaluate the data from the field as it becomes available and any necessary alterations in the study protocol that will need to be made can be identified and adjudicated accordingly based on the results of this vanguard group. The IRB will be notified of any necessary changes to the protocol.

9 Human Subjects Protections

9.1 Institutional Review Board

The investigator will submit the protocol, informed consent form, questionnaires, proposed recruitment materials, and other materials for participants to the NIEHS IRB for review and approval. Subjects will not be enrolled until the submission has been approved in writing by the IRB chair. Once the protocol is approved, the principal investigator will be responsible for obtaining IRB approval during annual Continuing Review for the duration of the study.

The principal investigator will submit and obtain approval from the IRB for all amendments to the protocol, informed consent form, and other study documentation referenced above. Amendments will not be implemented without prior IRB approval, except where necessary to eliminate immediate hazards to participants. The principal investigator will report adverse events, protocol deviations, inadvertent loss or disclosure of data, and loss of samples in accordance with IRB policies.

9.2 Informed Consent Process

Informed consent is an ongoing, interactive process that is initiated when the discussion regarding study participation begins and continues throughout the study. The consent process will begin with a lead letter and study brochure that provides an overview of the study and what it means to participate. During the telephone enrollment call, recruiters will explain the reason for the call, reference the lead letter and brochure that were sent by mail in advance of the call, introduce the study, and seek verbal consent for the initial screening and enrollment process. Participants will be informed that they will receive an annual Newsletter for the duration of the study and be asked to provide periodic contact information updates. The elements of passive follow-up via linkage with Cancer Registries, Vital Statistics and other data sources will be described and verbal consent will be obtained. They will also be informed about data sharing policies and that they may be contacted for potential participation in related studies but that they would have an opportunity to consent or not consent at that time.

Those who are eligible for participation in the Active Follow-up Sub-cohort will receive additional information about the study and will be invited to schedule a home visit. Field staff will obtain written informed consent from participants prior to conducting any study activities during the home visit. In order to ensure that participants make an informed decision about enrollment, field staff will review the study's purpose, procedures, risks, and benefits, as well as the rights of research participants. Explicit consent will be sought for sharing individual-level data with qualified researchers committing to maintain

participant confidentiality and comply with their consent provisions, similar to NIH policies for data sharing in genome-wide association studies (http://grants.nih.gov/grants/gwas/).

Field staff will allow the participant ample time to review the consent, ask questions, and obtain clarifications regarding the study prior to agreeing to enrollment. After voluntarily agreeing to take part in the study, participants will be asked to sign and date a current IRB-approved informed consent form. Field staff will return the signed consent to SRA for storage in the central study file. A copy of the consent form will be provided to the subject along with a summary of the key points in the consent document and a study FAQ document – a series of answers to questions participants may have about aspects of the study.

The consent form will contain contact information (i.e., toll-free phone number) for study staff that will be available to answer questions that may arise after the visit. Questions about study participation will also be addressed at the time of follow-up interviews.

Passively followed participants will receive an enrollment packet after the enrollment call is completed. The packet will contain information that describes the study and provides contact information for study staff, including the toll-free study phone number and address for the study website. They will receive a description of what they agreed to during the telephone call and will be provided with information on how to withdraw from the study if they have changed their mind about long-term passive participation.

All participants will receive an annual newsletter that contains updates about study progress and findings (see Section 3.L.ii – Newsletters).

9.3 Participant Confidentiality

All study personnel will be required to complete on-line training in the protection of human research subjects. The investigators and study staff will strictly maintain participant confidentiality. This confidentiality will be extended to cover questionnaire data, clinical assessments, biological samples, and environmental samples.

All study-related information will be stored securely. All study datasets, laboratory specimens, and administrative forms will be identified by a coded number in order to maintain participant confidentiality. All records that contain names or other personal identifiers will be stored separately from study records identified by code number. All databases will be secured behind firewalls with password-protected access systems. Worksheets, lists, logbooks, appointment books, and any other documents that link participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access.

A Federal Certificate of Confidentiality will be obtained for this study. The Certificate will help protect against disclosures of study-related information by Federal, State or local civil, criminal, administrative, legislative, or other proceedings, although it will not guarantee that data cannot be released. Participants will be informed about the certificate during the informed consent process.

9.4 Study Discontinuation

Participants may voluntarily withdraw from the study for any reason at any time. Participants will be informed that unless explicit written instructions are received,

investigators will continue to use data and samples collected up to the point of withdrawal although no new information will be collected from them. Study staff will effectively destroy all known remaining biologic and environmental samples by anonymizing the samples using a newly assigned ID number and report what was done to both the subject and to the IRB. This decision will not affect the subject's participation in this protocol or any other protocols at NIH. Anonymizing the samples will effectively terminate any association the samples have with the study participant, fulfilling their request, while simultaneously providing samples that can be used for laboratory QA/QC procedures. However, should the subject specifically request it, we will physically destroy all remaining samples.

Study staff will seek feedback from the participant to determine reasons for discontinuation and to identify any barriers that can be addressed to keep the participant in the study. The reasons for all discontinuations will be recorded in the data collection system and routinely monitored by the investigators. Common barriers to ongoing participation may be addressed by changes in retention strategies or study design.

10 Data Handling and Record Keeping

10.1 Data Capture Methods

The core of the data capture system will rely on an industry standard field data collection system, using standard technologies. The system platform must allow for:

- A flexible interface for loading complex sample data initiates and drives study recruitment activities.
- A Computer-Assisted Telephone Interview (CATI) component that guides project personnel through the interview process to determine eligibility. This component provides complex branching and algorithm support to collect data, make eligibility determinations, schedule future contact and direct the management of the new recruit's case to regional field supervisors. The CATI system allows data managers to monitor the recruitment process and all call center operations and success metrics. All CATI data are updated and managed in the central data management system. A notification system alerts all receiving field representatives and managers when new cases are assigned to them.
- A Computer-Assisted Personal Interview (CAPI) component running on field laptop computers to administer study questionnaires and capture clinical evaluations. The CAPI component guides field personnel through a questionnaire that has complex and conditional branching as well as rostering. The CAPI system provides real-time data validation, ensuring data are valid when captured and the immediate correction of data after an error is detected. SRA will prepare all CAPI systems, ship them to kickoff training, train personnel to use the system, and support the laptop PCs and CAPI applications via a toll-free and email helpdesk function.
- A central management tool that ensures that all CAPI and CATI data are collected into a single repository. The centralized data management and aggregation tool will manage the matriculation of data from field interview data platforms to the

centralized data repository. Field representatives will connect to the communications portal (described below) using internet SSL technology, and automatically upload collected interview data and download preparatory data for forthcoming interviews.

10.2 Data Management Responsibilities

The captured data will be stored in a comprehensive data management system (DMS) that centralizes study information into an integrated solution. From the time that participants become part of the potential sample to the time they are complete, all project data are managed and tracked in the DMS. Project personnel will have an appropriate "view" into the data using role-based access control. The DMS will support the full scope of study data management activities, including management of study sampling; collection of field and laboratory data; management of participant activities (case management); reporting of all data collection efforts and status; and preparation of analysis datasets.

The heart of the DMS will be the database server. The database server will be configured for 24/7 operation, and provide the capability of offsite backups.

The DMS also includes a communications portal which provides a single access point for all study data, reports, status updates and communications. The communications portal serves as the gateway between users and the data repository. The portal enables the ability to record, track, and analyze information associated with all types of case management activities such as scheduling, field interviews, tracking, and data acquisition. Project field personnel and other authorized project personnel connect to the communications portal over the Internet, go through an authorization process to establish an SSL connection, and have access to a variety of functions that support their work. These functions include the ability to:

- Upload and download interview data
- Update interview schedules; view upcoming workloads for self or field staff (for supervisors)
- View data completeness reports including status of lab data and abstracted medical records
- Receive updates from project management including updated modules, with training provided
- Transmit laboratory data, receive validations
- Report and track errors or technical support needs and follow them to closure
- Receive warnings about overdue lab data transfers
- Update participant profile information if within user rights
- Track project personnel; review training completeness reports and training records
- Monitor call center performance

Field representatives or managers connect to the DMS using laptops over the Internet or using smart phone tethering technology to gain Internet access. The DMS is integrated

with email, enabling key events to trigger emails accessible via smart phones, ensuring that our distributed workforce is as current with information as possible. Regular data transmissions are required of all field personnel, and field staff are prompted to establish a data upload session if overdue.

The communication portal is key to the success of this project as it provides the most timely, accurate information and delivers it to project staff in real-time. For example, it is crucial that supervisors monitor recruitment and enrollment trends, and compare these results against various call center operations to improve overall recruitment success rates. Furthermore, enrollment success measures are compared based on time of day, call center operators, source of telephone number, and ordinal number of call attempts in order to identify trends that suggest necessary modifications.

10.3 Data Access and Sharing

Given the public health importance of research on the health effects of the Deepwater Horizon disaster and its aftermath, results from the GuLF Study will be made available for research use by any interested and qualified investigator or organization, within the limits of providing appropriate protection of research participants and compliance with their informed consent. Policies for data access will build on NIH established policies for controlled access to individual-level data in genome-wide association studies, as described at http://grants.nih.gov/grants/gwas/ and open-access data sharing policies developed for other NIH sponsored longitudinal studies. Researchers interested in obtaining controlled-access GuLF data will agree to keep the data secure, use the data only for the approved research purposes, and not to attempt to identify individual study participants. In recognition of the rights and intellectual contributions of the GuLF investigators to publish data within a reasonable timeframe, outside researchers will also agree to observe a twelve month moratorium on submitting abstracts and publications using the data. Data and documentation will be made publicly available soon after collection along with information on all data that have been or will be collected. Typically (e.g. as currently practiced on dbGaP, protocols, descriptions of data and files, and counts of responses are available online. Summary descriptive tables may also be posted. In order to prevent accidental disclosure of individual participant data, de-identified datasets are separately provided to qualified requesters; individual level data are not posted online. Access to the data will be granted by an NIH Data Access Committee which will ensure that these conditions are met initially and monitor subsequent compliance during the study.

10.3.1 Access to Biospecimens and Use of Cohort for Add-on Studies

Additionally, other investigators (both at NIH and outside) may wish to study the stored biologic and/or environmental samples or propose add-on studies that generate new data and/or involve direct participant contact. In that case, NIEHS IRB approval must be sought prior to any sharing of samples. Any clinical information shared about the sample would similarly require prior NIEHS IRB approval. Procedures and guidelines for proposing new assays or add-on studies will be established and posted. An independent committee will be established to review proposals for scientific merit, feasibility, and impact on the study cohort.

10.4 Study Records Retention

All study records will be retained indefinitely. Study records that will be retained include IRB approvals and correspondence, signed informed consent forms, tracking logs, contact information update forms, and other study documentation that may be developed during the course of the study. To protect against accidental or premature destruction of these documents, the records will be maintained in a secure, locked storage areas that are only accessible to study staff.

All study data will be housed in a single data repository. This single database ensures that all system users are accessing the same database; allows for greater control via role-based access privileges; provides a robust architecture to support backup, security, and disaster recovery; and provides the flexibility needed to change the data input mechanisms that could change during a potentially long study.

Any loss or unanticipated destruction of samples or data (for example, due to freezer malfunction) that meets the NIH Intramural Protocol Violation definition or results in a violation that compromises the scientific integrity of the data collected for the study; will be reported to the NIEHS IRB.

At the completion of the protocol (termination), samples and data will either be destroyed, or after IRB approval, transferred to another existing protocol where they will be maintained in a repository as applicable.

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