Supporting Statement A

The Sister Study PHASE 2:

Environmental and Genetic Risk Factors for Breast Cancer

(NIH/NIEHS)

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TABLE OF CONTENTS

LIST OF ATTACHMENTS

ATTACHMENT 1A: ANNUAL UPDATE FORMS

ATTACHMENT 1B ANNUAL UPDATE FORMS

ATTACHMENT 2A: FOLLOW-UP II (TRIENNIAL) FORMS

ATTACHMENT 2B: FOLLOW-UP II (TRIENNIAL) FORMS

ATTACHMENT 2C: FOLLOW-UP SCRIPTS BIENNIAL /TRIENNIAL

ATTACHMENT 3: CONSULTATION AND REVIEW RECORD

ATTACHMENT 4: STAFF CONFIDENTIALITY AGREEMENT

ATTACHMENT 5: CERTIFICATE OF CONFIDENTIALITY

ATTACHMENT 6: NIEHS IRB INITIAL REVIEW

ATTACHMENT 7: COPERNICUS GROUP IRB INITIAL REVIEW

ATTACHMENT 8: NIEHS IRB CONTINUING REVIEW (CURRENT)

ATTACHMENT 9: COPERNICUS GROUP IRB CONTINUING REVIEW (CURRENT)

ATTACHMENT 10: INFORMED CONSENT

ATTACHMENT 11: MEASURING STRESS IN THE SISTER STUDY

ATTACHMENT 12: WEB SCREENSHOTS

Summary

The Sister Study is a prospective cohort study of the environmental and genetic risk factors for breast cancer and other diseases among 50,000 sisters of women who have had breast cancer. The long-term design allows us to also study the impact of environmental and genetic factors on survival and outcomes following a breast cancer diagnosis.

In the United States, more than 200,000 new cases of breast cancer are diagnosed each year. Breast cancer accounts for ~30% of all new cancer cases among women and ~15% of cancer deaths. The etiology of breast cancer is complex, with both genetic and environmental factors playing a role. Currently established breast cancer risk factors account for less than half the variation in breast cancer risk across the United States, and known breast cancer genes are found in fewer than 10% of breast cancer patients. Although the concordance rate for monozygotic twins is less than 20% (underscoring the importance of environmental contributors), sisters of women with breast cancer have, on average, a 2-fold increase in risk for breast cancer themselves. By focusing on a genetically susceptible group, more precise estimates of the contribution of environmental and other non-genetic factors to disease risk may be possible and the power to study gene by environment interactions will be greatly enhanced.

Between August 2003 and August 2009, we enrolled just over 50,000 at-risk volunteers into a prospective cohort study known as the Sister Study. Sister Study participants were recruited from across the United States and Puerto Rico. They were between ages 35 and 74 at enrollment and had at least one full or half sister who was diagnosed with breast cancer. Participants were recruited through a variety of means including the media, breast cancer advocacy groups, medical practitioners, community partners, and Sister Study participants themselves. Recruitment strategies were designed to enroll a cohort of sisters that is ethnically, geographically, and socioeconomically diverse. At enrollment, participants provided complete histories of personal and family health, reproductive health, diet, and environmental and lifestyle exposures. They completed a home exam in which height, weight, waist circumference, and blood pressure were measured by an examiner who also collected a blood sample. Whole blood, serum,

plasma, blood clots, blood spots, and cryopreserved lymphocytes were stored for future use. Participants also provided a first morning urine sample, toenail clippings, and household dust wipe samples.

Now in Phase 2 of the Sister Study, the enrolled high-risk cohort is being followed actively for ten or more years for the development of breast cancer and other diseases. We anticipated, on average, 300 new cases of breast cancer to be diagnosed each year; thus after five years of follow-up, we will have sufficient power, with a minimum of 1,500 new breast cancer cases, to address hypotheses regarding gene-environment interactions that require large numbers of cases, although for some hypotheses and for studies of gene-environment or gene-gene interactions, larger samples will be required. Thus far 1,634 incident cases of breast cancer have been reported by participants. Baseline data, banked blood, urine, and toenail samples, as well as banked environmental samples will provide a rich resource for testing current and future hypotheses regarding risks for breast cancer and a wide range of other medical conditions.

Sister Study participants are contacted annually to track changes in their medical history. Every two to three years, participants are asked to provide more comprehensive health and exposure updates and to provide additional information on other factors that may affect disease risk/survival such as stress phenotype or diet. Over time, participants may be asked to provide additional biological or environmental samples and will be invited to participate in more focused clinical studies of specific outcomes.

During the course of the ten-year follow-up, some participants are reported as deceased or permanently incapacitated due to physical or cognitive impairments. These women are likely to have experienced significant, unreported health changes prior to death and prior or subsequent to incapacitation. When a death or incapacitating event is reported, the Sister Study will attempt to retrieve this missing health information, in the form of an Annual Update, in a timely manner through participants' next-of-kin or proxy.

[Conducted under Clinical Exemption CE 2009-09-004] Participants who develop breast cancer are asked to provide information about their diagnosis and treatment and asked to sign medical release forms allowing us to request medical records, additional details about diagnosis and treatment, and tumor tissue

and/or diagnostic H&E slides from their health care providers. Pathology reports (only) are sought from participants reporting other incident cancer (except non-melanoma skin cancer). Additional records may be sought to support specific future clinical studies. Similarly, additional information to allow disease confirmation or validation of self-reported diagnoses will be sought from participants who report other diseases of interest such as asthma, uterine fibroids, diabetes, thyroid disease, osteoporosis, rheumatoid arthritis and other autoimmune diseases, and neurodegenerative diseases.

Nested case-control or case-cohort studies will be carried out among sisters who develop cancer or other clinical outcomes of interest and a sample of those who do not, to assess specific gene-environment interactions or other hypotheses. Patients who develop breast cancer during the follow-up period for the Sister Study will continue to be followed to study the role of environment and genes in survival following breast cancer diagnosis. Add-on studies may collect serial biological samples from informative subgroups to evaluate preclinical biomarkers and assess changes in biomarkers over time.

The Sister Study completed PHASE 1 enrollment in August 2009, concluding contact with the public at large, and discontinued the data collection using Sister Study enrollment questionnaires and materials previously approved by OMB. Follow-Up I (biennial) was completed in 2012.

This application is to request renewed approval for PHASE 2 long-term follow-up of the enrolled cohort. Annual Update forms (ATTACHMENT 1) used yearly are submitted here for continued approval. Previous follow-up forms have been modified and are submitted here for approval for use in Follow-Up II (triennial; ATTACHMENT 2).

A. Justification

A.1. Circumstances Making the Collection of Information Necessary

The National Institute of Environmental Health Sciences (NIEHS) is responsible for conducting research on chemical, physical, and biological factors in the environment that affect human health. The **Sister Study**, with its focus on potential environmental causes of breast cancer, is supported by the mandate of NIEHS as defined by US Code Title 42, Chapter 6A, Subchapter III, Part A, Section 281, as amended by

the Health Research Extension Act of 1985, which is "the conduct and support of research, training, health information dissemination, and other programs with respect to factors in the environment that affect human health, directly or indirectly."

Breast cancer is the most common cancer among women in developed countries. In the United States, more than 200,000 new cases of invasive breast cancer are anticipated in 2012. Many of the best-understood risk factors are endogenous or are related to lifestyle choices that are not easily modified. Family history of breast cancer is one of the most well established risk factors for the disease with an approximate 2-fold increase in risk in first-degree relatives. No known genetic or environmental breast cancer risk factor or combination of risk factors has high enough relative risks to account for the observed association with family history.

The etiology of breast cancer is complex, with genetic and environmental factors likely playing a combined role. Identifying gene-environment or gene-gene interactions will be important in understanding breast cancer etiology and identifying prevention strategies. A number of genes already have been identified as candidates for study. Large-scale studies are needed to confirm reported gene-environment interactions and to test new biologically based hypotheses as both technology and our understanding of mechanisms improve over time. The Sister Study offers a unique opportunity to gather important epidemiological data that will make a difference in understanding the multi-factorial etiology of breast cancer.

There is suggestive evidence, including studies of disease patterns in migrants, to support a role of the environment in breast cancer risk, although specific environmental factors have not been clearly elucidated. With the exception of earlier studies of organochlorine pesticides, recent provocative studies of other endocrine disrupting chemicals, and earlier studies of irradiated populations, little work has been done in the area of non-lifestyle environmental factors. In part, this may be due to the difficulty of retrospectively measuring most environmental exposures. Few studies have examined occupational exposures among women, although there is evidence that some may play a role in breast cancer etiology. The National Toxicology Program has identified at least 35 mammary carcinogens, many of which have

not been evaluated in human studies. Agents on this list include pesticides and fumigants, chemicals used in manufacturing rubber, vinyl, polyurethane foams, benzene-based dyes, and some pharmaceuticals, as well as solvents.

The Sister Study is designed to investigate the independent and joint effects of genetic susceptibility and environmental, biological and lifestyle factors on the risk of breast cancer and other diseases in a cohort of sisters of women with breast cancer. In addition, we will have the opportunity to efficiently assess risks for other diseases with similar risk factor profiles or which are otherwise important causes of morbidity in women, such as cardiovascular disease, autoimmune disease, osteoporosis, and diabetes.

By focusing on sisters, the study has several unique advantages. Not only are the sisters of women with breast cancer at greater risk for breast cancer themselves (about a two-fold risk based on other studies and borne out in preliminary analysis of incidence in the Sister Study), they will have a higher prevalence of any genes that prove to be related to breast cancer risk and they should have a higher frequency of some risk factors due to behaviors and experiences they share with their sisters who have already developed breast cancer. The study is especially well suited to address hypotheses related to shared childhood and prenatal exposures, in addition to factors later in life. Our study will have greater statistical power than a similarly sized general population cohort (see **Sections B**). Furthermore, based on current experience, sisters of women with breast cancer are highly motivated to participate in breast cancer research. Participation and retention rates are higher than in other studies and the quality of data is high. These features will enhance both validity and statistical power to detect associations. The study is large enough to investigate many gene-environment interactions after five years of follow-up. Less common genes and rare exposures can be studied with continued follow-up of the cohort.

The prospective design offers several advantages over the retrospective case-control studies that have been most widely used to assess gene-environment interactions. The most often cited advantage of the case-control design is efficiency; in order to accrue the same number of cases in a population-based cohort, a substantially larger number of women must be studied. However, in retrospective studies, exposures must be ascertained after the occurrence of disease. Although certain exposures can be studied

retrospectively using questionnaires or, occasionally, using occupational or medical records, numerous potential biases can limit the ability to make causal inferences. In the Sister Study, we ascertain exposures and collected biological and environmental samples prior to the onset of disease. By banking samples for later analysis, we minimize the costs of measuring exposure, since only new cases and a sub-sample of non-cases will be analyzed.

We enrolled a cohort of just over 50,000 high-risk women (ages 35 to 74) who are the cancer-free sisters of women who have had breast cancer. This cohort is being followed annually for at least ten years. Comprehensive baseline questionnaire data, fasting blood, first morning urine, household dust and toenail samples were collected. Study questionnaires were designed to collect information on known, suspected, and speculative risk factors in order to maximize the chance of detecting environmental risk factors of concern to women. In order to address new hypotheses, it was necessary to also collect comprehensive data on what is currently known, to be able to account for these factors in other analyses. In contrast to previous cohort studies where environmental exposures are either ignored or addressed superficially, we aimed to collect sufficient data so that environmental risks can be conclusively identified, or in the event that risks are not confirmed, we can say that we have thoroughly investigated the possibility. Brief annual updates record changes in contact information, residence location and health. Follow-Up questionnaires address new hypotheses that arise and collect details on changes in health and exposures. Our study will assess hypotheses that derive from the scientific literature, but we also collect data on poorly studied exposures of concern to women. The incident cases that develop over time will be followed for the duration of the study, allowing us to also study the role of lifestyle, environmental exposures, and genes in prognosis and survival among women with cancer.

The Sister Study is an NIEHS intramural study designed to allow for trans-NIH and extramural collaboration. The study was developed in response to the heightened concern expressed by numerous women's and environmental groups about the possibility of increased breast cancer risk due to environmental causes, and the perceived lack of serious attention that had been paid to such concerns. In addition to consulting with scientific colleagues both within the government and at universities, we

solicited the input of groups such as the National Breast Cancer Coalition and other advocacy and interest groups and consumers as we planned the Sister Study and assessed its feasibility. Our Steering Committee and Scientific Advisory Boardare diverse groups of professionals in the various areas of this complex effort. They include experts in epidemiology, long-term cohort retention, breast cancer, biological specimen management, laboratory science, as well as representatives from various organizations focused on minorities, breast cancer support, and women.

A.2. Purpose and Use of the Information Collection

Information collected in this study will be used to further scientific understanding of the effects of environmental exposures by studying women with enhanced susceptibility to breast cancer and to address questions of concern to all women at risk for breast cancer. Epidemiologists and biostatisticians at NIEHS and their collaborators at other institutions will be responsible for testing the hypotheses of interest and disseminating results through the scientific literature. Results will be published in medical and epidemiologic journals as well as basic science journals when appropriate. Results will be presented at scientific meetings and at meetings of breast cancer advocates and other interested groups. Data will be used to assess current hypotheses regarding risk factors for breast cancer, to generate new hypotheses for subsequent analyses in the Sister Study, and specifically to identify preventable risk factors or combinations of risk factors. In addition to scientists and clinicians who will use this information in developing prevention strategies and to advise their patients, results will be reported to the women who participate in the study and to other women through the media, our website, and other Sister Study publications and newsletters. Results of the study may figure in future risk assessments and evaluations of the carcinogenicity of specific environmental agents and could be used in the development of exposure guidelines or standards, should important environmental risks be uncovered. Thus the results will be of use to Public Health officials, other scientists, physicians, elected and appointed officials, and women and their families.

The type and amount of information we collected at baseline *before* women develop breast cancer, and at subsequent yearly or Follow-Up intervals, fulfill many scientific and clinical needs. For breast

cancer, many of the exposures of interest, including endogenous hormone levels, micronutrients, and even some environmental exposures, are measured most accurately in biological samples collected before the onset of disease or treatment and their associated symptoms and biological and lifestyle changes. The cohort design allows us to collect data on exposures, including biological exposure measures, diet and lifestyle, *before* the onset of disease.

Brief self-administered forms are used annually **(ATTACHMENT 1)** to update changes in contact information and health status. Follow-Up II (triennial) forms **(ATTACHMENT 2)** record changes in health, lifestyle, occupational and environmental exposures and address new hypotheses. As technology for self-collected environmental samples improves, women may be asked to provide such samples (for example, using in-home water test kits) as part of the follow-up.

Women who develop breast cancer or other conditions of interest during the course of follow-up are asked to allow us to obtain medical records and tissue samples from their health care providers. [Conducted under Clinical Exemption CE 2009-09-004]

We completed full enrollment activities (data and sample collection) for the cohort, having enrolled 50,884 women whose sisters had breast cancer. Since the last review, participants have completed annual and biennial updates according to schedule. Average response rates for Update activities remain >90%. In addition, several reports have been published, describing factors under investigation:

In Press

Weinberg CR. Invited Commentary: Thoughts on assessing evidence for gene by environment interaction. *International Journal of Epidemiology*. 2012.*;* in press.

Parks, CG, D'Aloisio AA, DeRoo LA. Huber K. Rider L, Miller F, Sandler DP. Childhood socioeconomic factors and perinatal characteristics influence development of rheumatoid arthritis (RA) in adulthood. Ann Rheum Dis 2012; in press.

Fei C, DeRoo LA, Sandler DP, Weinberg CR. Fertility drugs and young-onset breast cancer: Results from the Two Sister Study. J Natl Cancer Inst 2012; in press.

Published

D'Aloisio AA, Baird DD, DeRoo LA, Sandler DP. Early-life exposures and early onset uterine leiomyomata in black women in the Sister Study. *Environmental Health Perspectives*. 2012 Mar;120(3):406-12. Epub 2011 Nov 2.

Fortier I, Doiron D, Little J, Ferretti V, L'Heureux F, Stolk RP, Knoppers BM, Hudson TJ, Burton PR; International Harmonization Initiative [plus 139 collaborators including DeRoo LA and Sandler DP]. Is rigorous retrospective harmonization possible? Application of the DataSHaPER approach across 53 large studies. *International Journal of Epidemiology*. 2011 Oct;40(5):1314-28.

Kim S, DeRoo LA, Sandler DP. Eating patterns and nutritional characteristics associated with sleep duration. *Public Health Nutrition.* 2011 May;14(5):889-95.
Kim S, Sandler DP, Carswell G, DeRoo LA, Parks CG, Cawthon R, Weinberg CR, Taylor JA. Telomere length in peripheral blood and breast cancer risk in a prospective case-cohort analysis: results from the Sister Study. *Cancer Causes & Control*. 2011 Jul;22(7):1061-6. Epub 2011 Jun 5.
Kim S, Sandler DP, Carswell G, Weinberg CR, Taylor JA. Reliability and short-term intra-individual variability of telomere length measurement using monochrome multiplexing quantitative PCR. *PLoS ONE*. 2011;6(9):e25774. Epub 2011 Sep 30.
Lin CJ, DeRoo LA, Jacobs SR, Sandler DP. Accuracy and reliability of self-reported weight and height in the Sister Study. *Public Health Nutrition.* 2011 Dec 9:1-11. Epub ahead of print.
Parks CG, DeRoo LA, Miller DB, McCanlies EC, Cawthon RM, Sandler DP. Employment and work schedule are related to telomere length in women. *Occupational and Environmental Medicine.* 2011 Aug;68(8):582-9. Epub 2011 May 2.
Shi M, Chiu GY, Hancock DB, London SJ, Zaykin D, Weinberg CR. Using imputed genotypes for relative risk estimation in case-parent studies. *American Journal of Epidemiology*. 2011 Mar 1;173(5):553-9. Epub 2011 Feb 4.
Shi M, Umbach DM, Weinberg CR. Family-based gene-by-environment interaction studies: revelations and remedies. *Epidemiology.* 2011 May;22(3):400-7.
Shi M, Weinberg CR. How much are we missing in SNP-by-SNP analyses of GWAS? *Epidemiology.* 2011 Nov;22(6):845-7.
Spector D, DeRoo LA, Sandler DP. Lifestyle behaviors in black and white women with a family history of breast cancer. *Preventive Medicine*. 2011 May 1;52(5):394-7. Epub 2011 Mar 17.
Weinberg CR, Shi M, Umbach DM. A sibling-augmented case-only design for assessing multiplicative gene-environment interaction. *American Journal of Epidemiology.* 2011 Nov 15;174(10):1183-9. Epub 2011 Oct 20.
D'Aloisio AA, Baird DD, DeRoo LA, Sandler DP. Association of intrauterine and early-life exposures with diagnosis of uterine leiomyomata by 35 years of age in the Sister Study. *Environmental Health Perspectives.* 2010 Mar;118(3):375-81.
Shi M, Umbach DM, Weinberg CR. Testing haplotype-environment interaction using case-parent triads. *Human Heredity.* 2010;70(1):23-33. Epub 2010 Apr 23.
Steiner A, D'Aloisio A, DeRoo LA, Sandler DP, Baird DD. Association of intrauterine and early life exposures with age at menopause in the Sister Study. *American Journal of Epidemiology.* 2010 Jul 15;172(2):140-8. Epub 2010 Jun 9.

A.3. Use of Information Technology and Burden Reduction

Web-based completion of annual updates and Follow-Up forms is available. Web-based instruments and Computer Assisted Telephone Interviews are integrated with the data system, so that data collected through multiple means can be seamlessly combined.

Computer Assisted Telephone Interview, or CATI, is a special data collection approach designed to reduce the burden to respondents and improve quality control. The Sister Study offers both web-based and CATI to complete Follow-Up forms. These technologies allows several advantages over the traditional pencil and paper method. First, less paper is required. Second, there is no "mail wait" to get the information from participants. Also, the telephone interview requires little reading for the participant, an important factor when a segment of the population has low educational level or poor eyesight. Last, data

extraction is more efficient with the CATI system as compared to the keyed entry method because skip patterns are automated and response inconsistencies can be queried at the time of the interview.

At enrollment during Phase 1 (*now completed*) name, address, SSN, date of birth, and medical information were collected. Personal identifiers are stored encrypted and separately from all other data. Now in Phase 2, PII are used to address Update and Follow-Up materials. A Privacy Impact Assessment was completed for the Sister Study information management system.

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

The information we collect is not available from other sources. There is little consensus in the scientific community on how the environment impacts breast cancer. While some studies have addressed environmental factors like diet, pesticides, and electromagnetic fields, no conclusive evidence exists because of limits in sample size and/or study design. Although there are cohort studies, such as Harvard's Nurses Health Study, that do address risk factors for breast cancer, none of these cohorts has collected substantial information on environmental and occupational exposures, and none includes biological and environmental samples for all of the participants. All of the existing cohorts focus on diet and other lifestyle factors. Large-scale prospective studies such as the Sister Study are needed to validate some of the already reported gene-environment interactions and to test new biologically-based hypotheses as both the technology and our understanding of synergistic mechanisms improve over time.

As noted above, there are important advantages to the Sister Study design. First, these sisters are at increased risk of breast cancer, likely due to shared genetic and environmental factors. Their family history increases the expected number of new cancers, the frequency of relevant gene polymorphisms, and the frequency of relevant exposures, making the study efficient compared to unenriched cohort designs. Second, because the study is prospective, blood samples and risk factor information were collected prior to diagnosis. A third advantage is that sisters are highly motivated, which should improve data quality and completeness and reduce loss to follow-up.

We are unaware of any duplication of this project with any other project now underway at other organizations. Several prospective cohort studies--for example, The Nurses' Health Study, Canadian

National Breast Screening Study, New York University Women's Health Study, Iowa Women's Health Study—have investigated breast cancer in women, but none have focused primarily on the gene-environment link, especially in terms of the broader external environment.

A.5. Impact on Small Businesses or Other Small Entities

None.

A.6. Consequences of Collecting the Information Less Frequently

Annual updates take ~10 minutes, and Follow-Up self-administered questionnaires are 75 minutes or less. Annual contact cannot be done less frequently because the analysis relies on exposure and health-status changes over time, and ascertaining cases close to the time of diagnosis is important. A participant's recall diminishes greatly with time, and death may occur. Annual contact is necessary to preserve reliability and completeness and will facilitate maintenance of the cohort and tracing of those few who are lost to follow-up.

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

There are no special circumstances relating to the guidelines of 5 CFR 1320.5 and the project fully complies.

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

A 60-Day Federal Register Notice was published on 15 August 2012. There was 1 public comment.

Early discussions were held with special interest groups to gain information on to what extent women who are at higher risk of developing breast cancer were willing to participate in a new longitudinal study requiring a long-term commitment and intense initial data collection. These meetings involved advocacy groups including cancer-free sisters, breast cancer survivors, Latina women, African-American women, lesbian women, and other minorites. Support for this study was overwhelmingly enthusiastic and the majority of comments were favorable. These discussions gave us specific and valuable feedback that was incorporated into our study protocol.

Efforts to consult both within and outside NIEHS at the time the Study was first developed are summarized in **ATTACHMENT 3**. Also listed in **ATTACHMENT 3** are the current members of the Sister

Study Scientific Advisory Board. Numerous researchers both within the NIH and in the extramural community were consulted during the planning of this study. Among the scores of scientists who were consulted during the early planning for the Study were, from the Division of Cancer Etiology and Genetics at the NCI: Drs. Patricia Hartge, Sholom Wacholder, Shelia Zahm, Aaron Blair, Jeffrey Streuwing, Louise Brinton, Rashmi Sinha, and Patricia Stewart; from the CDC: Drs. Thomas Sinks, Michelle Marcus, Heidi Blank, and Elizabeth Whelan (NIOSH); and from the National Institute of Aging, Dr. Tamara Harris. Other outside consultants include Drs. Pamela Horn Ross (Northern California Cancer Center -dietary phytoestrogens), Gladys Block (NCI - food frequency questionnaire), Julia Brody (Silent Spring Institute – exposure assessment) and Patricia Moorman (Duke University - medications and hormone replacement).

Our study was and continues to be formally reviewed within the NIEHS intramural community, NIEHS advisory boards, and externally by federal and academic experts. Many continue to serve on the Sister Study Scientific Advisory. The archived data and samples facilitate collaborations both within the NIH and in the extramural community.

Advisory to the study investigators in regular monthly meetings are the Sister Study Steering Committee, composed of NIEHS research staff Honglei Chen PhD (919-541-3782), Lisa DeRoo PhD (919-541-0799), Jane Hoppin ScD (919-541-7622), Stephanie London MD DrPH (919-541-5772), , and Jack Taylor MD PhD (919-541-4631), together with SSS senior staff — Sandra Deming Halverson and Deborah Bittner.

A.9. Explanation of Any Payment or Gift to Respondents

During PHASE 1, participants received a prepaid 120-minute phone card valued at less than $5 as an incentive to complete the interviews and specimen collection at enrollment. While the <$5 value was not equivalent to the value of the effort required of participants, it helped to convey our appreciation of that effort.

Other tokens such as newsletters, reusable grocery bags, magnets and bookmarks with the study logo are provided periodically to enhance participation and retention. Increasing response rates and retention

improve the quality of the scientific data we are collecting by minimizing response bias. Monetary and other incentives have been shown to significantly increase response rates and reduce the overall costs of follow-up.

A.10. Assurance of Confidentiality Provided to Respondents

Procedures to protect the confidentiality of the study population and the data collected include the following:

- The data constitute a system of records under the Privacy Act System (#09-25-0134). Federal Register Notice of System of Records of December 29, 1993**.**
- Each participant was assigned a study ID number. The ID alone is used to identify biological samples and all data forms. Only the ID number is entered into the database and used in the analysis of data. Subjects' names and addresses are stored separately.
- Any information linking subject's ID number to subject's name are kept in locked physical files or password-protected, restricted access electronic files at the North Carolina office of Social and Scientific Systems, Inc. (SSS), the NIEHS Epidemiology Branch Support Services Contractor.
- Employees of SSS undergo background checks, ethics training and sign a Pledge of Confidentiality **(ATTACHMENT 4)**.
- Only Sister Study research personnel have access to study data.
- Study results will be published in summary form only — no individual results will be published or shared.
- Shared samples and data will be provided without identifiers and study ID numbers will be scrambled to prevent accidental identification of participants.
- A **Certificate of Confidentiality** has been secured for this study **(ATTACHMENT 5)**.
- The proposal was initially reviewed by the NIEHS Institutional Review Board on 3/14/2002 (**ATTACHMENT 6**) and Copernicus Group IRB on 12/12/2006 **(ATTACHMENT 7).** Also attached is documentation from the most recent Continuing Reviews **(5/3/2012; ATTACHMENTS 8 & 9)**.
- Informed consent forms **(*completed in PHASE 1*; ATTACHMENT 10)** spelled out the steps taken to protect privacy. Similar information was provided verbally at the time of enrollment, again prior to the CATI interview, and on the website.

The biological and environmental samples collected will be stored indefinitely in a secure building for future testing and may be disposed of at any time at the Investigator's discretion. Specimens are

labeled with ID number only. These and related issues were explained in the Informed Consent documents. Specimens shared with outside researchers will be assigned a new identification number; the code linking the new and the old identification number will be known only to the NIEHS contractor responsible for the Sister Study field work. This new identification number will not be linked to any identifying information. Identifying information, such as name, social security number, or address will not be shared with other researchers. Samples will only be shared for scientifically valid studies that meet approved scientific and ethical standards. Samples and data that are shared can be used only for the specific research described in an approved research proposal and may not be used for other purposes without approval from the Sister Study investigators.

Participants may elect to leave the study at any time. As explained in the Informed Consent documents, no new data will be collected from patients who elect to drop out, but the data already provided will continue to be used in some analyses unless a written request to destroy data and specimens is received. Screening data on women who are found to be ineligible were not retained by the Sister Study.

A.11. Justification for Sensitive Questions

Breast cancer is a complex disease likely caused by many factors. Part 3 of Follow-Up I (biennial), which focused on psychological stress and related measures, has been modified for Follow-Up II (triennial). The questions addressing sensitive and personal issues such as personal experience with violence, physical and psychological abuse, and discrimination, and stress related to the sister's breast cancer diagnosis are not repeated in Follow-Up II. In order to carry out a comprehensive analysis of stress, some questions that are repeated from Follow-Up I focus on social support, personality traits and depression. The justification for each of these scales and their source and derivation is fully described in **ATTACHMENT 11**. As described in **ATTACHMENT 11**, stress may play an important direct or indirect role in risk for breast cancer and other health outcomes. It is likely however, that the relationship is complex and a comprehensive approach, including assessing acute and chronic stress at different time periods and accounting for factors that modify response to stress, is required. In addition to compelling scientific

evidence, we learned through our early focus groups that many women believe that stress plays a role in risk for breast cancer and other diseases, and we have been urged, by the various constituencies that have endorsed the Sister Study, to study this topic of high interest to women.

Information is collected directly from participants. Participation is voluntary, and respondents can withdraw from the study at any time. Participants may refuse to answer specific individual questions, including those they find to be too sensitive or personal. All information is kept confidential to the extent provided by law. At no time will any individualized genetic results be given out. We have a Certificate of Confidentiality in place for this study. Participant informed consent forms are attached in **ATTACHMENT 10.**

A.12. Estimates of Hour Burden Including Annualized Hourly Costs

For the remainder of the study, women will be contacted once each year to update contact information and health status (5-10 minutes per response); and asked to complete short (60-75 minutes, total) updates every two-to-three years. Contact of next-of-kin/proxies for deceased or incapacitated participants is included in the burden budget for Annual Update. The annual reporting burden is as follows: *Estimated Number of Respondents:* 50,884 study participants or next-of-kin/proxies. *Estimated Number of Responses per Respondent:* See annualized table below:

Estimated Annualized Burden Hours				
Activity	**Estimated Number of Respondents**	**Estimated Responses per Respondent**	**Average Burden Hours per Response**	**Estimated Total Burden Hours Requested**
Annual Updates	33,923	1	10/60	5,654
Follow-Up II (triennial)	16,961	1	1.25	21,202
TOTAL				**26,856**

Average Burden Hours Per Response:42 minutes; and *Estimated Total Annual Burden Hours Requested:* 26,856. The estimated total annualized cost to respondents $537,120 (assuming $20 hourly wage X 26,856). There are no capital, operating, or maintenance costs.

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

There is no other total annual cost burden to respondents or recordkeepers.

A.14. Annualized Cost to the Federal Government

The estimated cost of contracting out information collection is $95,159,703 over 14 years (beginning in 2004). Federal Salary Support is $282,193 per year. Cost of archiving samples is about $350,000 per year, including purchase of freezers. Over the next 3 years, the annualized cost to the Federal Government is expected to be $5,682,612 per year, totaling $17,047,835 over 3 years.

Expediture Category	Annual Cost	3-year Cost
Federal Salary	$282,193	$846,578
Direct:		
Labor	$1,214,284	$3,642,853
Benefits	$471,087	$1,413,261
Equipment/Supplies	$36,846	$110,537
Consultant Fees	$4,206	$12,619
Travel	$10,287	$30,861
Subcontracts	$877,143	$2,631,430
Operations Direct	$1,297,706	$3,893,117
TOTAL Direct	$3,911,559	$11,734,678
Indirect:		
Overhead	$578,703	$1,736,108
G&A	$481,524	$1,444,572
Subcontract Admin	$21,929	$65,786
Fixed Fees	$231,704	$695,113
TOTAL Indirect	$1,313,860	$3,941,580
Other Fees	$175,000	$525,000
TOTAL ALL	$5,682,612	$17,047,835

A.15. Explanation for Program Changes or Adjustments

Changes in burden and annualized cost merely reflect the anticipated progress and the next scheduled phases of the longitudinal study. Total burden request changes from 72,218 hours over 3 years (for 2009 revision) to 26,856 per year for the next 3 years. This **does not** however represent a change in Protocol — merely normal **as-planned** progression of follow-up.

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

The primary goal of the study is to identify environmental and familial risk factors for breast cancer and other diseases by studying a cohort of sisters of women who have had breast cancer. The Sister Study is not designed around one particular *a priori* hypothesis, but is designed to allow us to address a number of hypotheses regarding gene-environment interactions and risk for breast cancer. Current hypotheses regarding environment-gene interactions will be addressed in the early years of the study. The reports generated from this study will include the following risk factors that may be influenced by the action of genes with known polymorphisms:

A.16-1

Factor	Genetic Marker of Interest
Cigarette smoke	CYP1A2, NAT2, GSTM1, CYP1A1, DNA repair polymorphisms, CYP2A6, CYP2C9
Exogenous hormones	CYP17, CYP1A2, CYP1A1, estrogen receptor polymorphisms
Hormonal risk factors	CYP17, aromatase, hormone receptor polymorphisms
Oxidative stress	Genes involved in oxidative stress
Melatonin	Polymorphism screening
Nutritional and dietary factors	Vitamin D metabolism and receptor polymorphisms, CYP1A2, NAT2
Grilled meat consumption	GSTM1
Alcohol	ADH, ALDH, CYP2E1
Sunlight exposure	Vitamin D metabolism and polymorphisms
Calcium, calcium channel blockers	Vitamin D metabolism receptor, estrogen metabolism and receptor polymorphisms

Clearly, as enough cases accrue, scientific understanding of biologic mechanisms and genes will advance considerably. A prospective study such as the Sister Study is designed to respond to new hypotheses as they emerge.

A.16 - 2

Project Time Schedule

Activity	Time Schedule
Began vanguard phase of enrollment	August 2003
Began nationwide enrollment	October 2004
Completed PHASE 1 Enrollment questionnaires and	August 2009

collect specimens on 50,000 women	
Annual Update (self-administered questionnaire)	June 2005
Follow-Up I (biennial questionnaire)	Began March 2008
Analyses	Began mid-2007
Publication	Began 2007

A.17. Reason(s) Display of OMB Expiration Date is Inappropriate

We request continued approval to display the OMB control number without the expiration date on printed forms. This request is based on the precedent (see OMB No. 0935-0104: Medical Expenditure Panel Survey: Survey About Your Diabetes Care) that this is a longitudinal study scheduled to last for 14 or more years, and for which individual follow-up activities span across a number of years, thus across OMB expiration dates. Annual update forms,as well as two entire parts of the 3-part Follow-Up questionnaire, will be used throughout the length of the study. Therefore, the cost of multiple printing cycles, merely to change OMB date, rather than taking advantage of cost savings realized with larger batch printing of approved materials (hundreds of thousands of pages) that undergo little or no contextual change is inordinately costly to the government. Nonetheless, these items would continue to be included in each 3-year revision package sent to OMB for continuation of approval.

A.18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to certification for this submission.