SISOMB2016 ATTACHMENT 6:
NIEHS IRB CR

National Institutes of Health
Intramural Clinical Protocol Continuing Review Application

I. Protocol Information

Protocol number: 02-E-N271

Z Number

Principal Investigator Name: Dale P Sandler, Ph.D.

PI Contact Information:

Branch/Institute: EB / NIEHS

Office:

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Protocol Title: The Sister Study: Environmental and Genetic Risk Factors for Breast Cancer

Precis: We will study environmental and genetic risk factors for breast cancer in a cohort of
50,000 sisters of women who have had breast cancer. In the United States, there were approximately 192,000 new cases of breast cancer in 2001, with more than 200,000 cases expected in 2002. Breast cancer accounts for over 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. By focusing on a genetically susceptible group, more precise estimates of the contribution of environmental and other nongenetic factors to disease risk may be possible.
The cohort will be followed actively for the development of breast cancer and other diseases. We expect, on average, 300 new cases of breast cancer to be diagnosed each year in a cohort of 50,000 sisters aged 35â¿74 years. Thus, after five years of followâ¿up, we will have sufficient power, with about 1,500 new breast cancer cases, to address many key hypotheses regarding geneâ¿environment interactions. Baseline questionnaires, banked blood, urine, and toenail samples, as well as banked environmental samples will provide a rich resource for testing current and future hypotheses regarding breast cancer risk. Followâ¿up questionnaires will update exposure and medical histories as well as provide an opportunity to collect new data and environmental samples to evaluate emerging hypotheses. Nested caseâ¿control or caseâ¿cohort analyses will be carried out among sisters who develop cancer and a sample of those who do not, to assess specific geneâ¿environment interactions. Once assembled, the cohort also will provide the structure for assessing geneâ¿environment interactions in risk for other diseases and will provide opportunities for addon studies.
Because sisters of women with breast cancer have about twice the risk of developing breast cancer themselves and because they may share many relevant genes and exposures, the Sister Study will have greater efficiency than a similar size general population cohort. An advantage of the prospective design over populationâ¿based casecontrol studies is the collection of blood samples and risk factor information prior to the diagnosis of disease. Another advantage to the proposed design is that sisters of women with breast cancer are likely to be highly motivated to participate over time. While sampling may be prone to selfâ¿selection, the sampling for those who develop breast cancer will be identical to that for those who do not. Finally, we plan to collect detailed information on environmental and occupational exposures as well as environmental samples such as household dust and plan to enroll only those women who are willing to provide the biological and environmental samples. Most of the existing cohort studies have only limited information on environmental exposures, focusing largely on lifestyle factors and diet, and many include biological samples for only a portion of the cohort.
A nationwide publicity campaign coupled with an outreach program that takes advantage of the large networks of breast cancer advocates will be used to recruit a cohort of sisters that is ethnically, geographically, and socioâ¿economically diverse. Focus groups and preliminary study contacts suggest a high level of interest in the study among these advocacy groups and women with family histories of breast cancer. Ongoing pilot work has demonstrated the feasibility of recruiting sufficient numbers of women for the study.

Accrual/Recruitment Status:

- ☐ No Recruitment Planned
- ☐ Not Yet Recruiting
- ☐ Recruiting
  - ☐ Enrolling by Invitation
- ☐ Suspended
- ☒ No Longer Recruiting, subject follow-up only
- ☐ Open for Data Analysis

☐ If Expanded Access Study Update Status:

- ☐ Available: expanded access is currently available for this treatment.
- ☐ No longer available: expanded access was available for this treatment previously but is not currently available and will not be available in the future.
- ☐ Temporarily not available: expanded access is not currently available for this treatment, but is expected to be available in the future.
- ☐ Approved for marketing: this treatment has been approved for sale to the public.

Anticipated Date that the protocol will complete data Analysis: 09/30/2018

Primary Completion Date:

II. Study Population

Are you currently recruiting?

- ☐ Patients
- ☐ Healthy Volunteers
- ☐ Other Volunteers
- ☐ NIH Employees
- ☐ Non-English Speaking
- ☒ N/A

Does this research involve vulnerable or other special populations?

- ☐ Children
- ☐ Children who are wards of the state
- ☐ Prisoners
- ☐ Pregnant Women, Fetuses, or Neonates
- ☐ Adults who are or may be unable to consent
- ☒ N/A

III. Enrollment Information

Summary of Protocol Enrollment:

NIH/CC	Other Domestic Sites	Foreign Sites	Total	
60000	0	0	60000	Accrual Ceiling
0	0	0	0	New Subject Since Last CR
51118	0	0	51118	Aggregate Total Accrued

If the protocol is open to accrual but there has been no subject accrual, or accrual was lower than expected during this past year, provide an explanation below:

The majority of participants in this study were recruited at baseline. Intermittently over the course of the study, we may perfom an additional small recruitment of persons to provide biological specimens that can serve as controls in assays. No active recruitment is underway or are their plans to do so in the coming CR period.

Has analysis by Sex/Gender, Racial, and/or Ethnic Subgroups for Phase III clinical trials been conducted and have significant differences been found?

☐ Yes
a. Have analyses been reported? ☐ Yes ☐ No
b. Have significant differences been ☐ Yes ☐ No
☐ No
☒ N/A

If yes, please describe any differences

IV. Ionizing Radiation Use

☒ None
☐ Ionizing radiation exposure – medically indicated
☐ Ionizing radiation exposure – research indicated
☐ Research usage HAS NOT changed
☐ Research usage HAS changed
☐ Both

Radiation Safety Approval Radiation Safety

V. Investigational New Drug/Device/Biologic/Tobacco Product ☐ Yes ☒ No

This protocol is/is not subject to US Food and Drug Administration regulations or under an Investigational New Drug (IND) Application, Investigational New Biologic (BB IND) Application, Investigational Device Exemption (IDE) or Investigational Tobacco Product

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Commercially approved products used to test the research hypothesis

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Does the protocol involve a drug/device/product that may lead you or the NIH to receive payment or royalties ☐ Yes ☒ No

VI. Will the protocol involve any Tech Transfer Agreements?

☒ Yes
☐ CDA – Confidential Disclosure Agreement
☐ CTA – Clinical Trials Agreement
☐ CRADA – Cooperative Research and Development Agreement
☒ MTA – Material Transfer Agreement/Human Material Transfer Agreement
☐ MOU – Memorandum of Understanding
☐ Other,
☐ No

VII. Conflict of Interest

Has the Personal Financial Holdings Form (PFH) form been completed and submitted to the Deputy Ethics Counselor? ☒ Yes ☐ No

Date submitted to 10/12/2015 Date cleared by

VIII. Progress Information

Description of protocol progress/findings from this During the past CR period, Annual Health Updates and Detailed follow-ups were performed for 51,062 Sister and Two Sister participants. Also during this period, the Sisters Changing Lives second home visit and specimen collection was completed for 2,436 participants. As of September 8, 2015, a total of 2,891 incident breast cancer have

been identified. During the last CR period, we have undertaken a mammographic density collaboration with colleages at Columbia University. With respect to findings, we produced a number of publications this year and well as contributed to 5 consortia projects.

Have any amendments been approved since the last continuing review?

☐ No ☒ Yes

Three amendments have been made since the last continuing review:
LLL: Addition of the current English and Spanish newsletter
MMM: Ammendment to conduct a mammography pilot
NNN: Addtion of Dr. Melissa Troester as an associate investigator on this protocol

Have any unanticipated problems (UPs) occurred since the Initial Review (IR) or last CR?

☐ No ☒ Yes

Summary of unanticipated problems (UPs), reportable adverse events and deviations/violations as defined in the protocol since the last CR and in aggregate since the start of study.

Ther has been a Protocol violation and problem report since the last CR:
1. Protocol Violation H: A participant recruited into the Anonymous Sample Collection had blood drawn on 12/4/2014 and
was subsequently found to be ineligible. She was brought in for the pre-menopausal subgroup, but after blood draw was found to have had a partial hysterectomy and had been menopausal for a short time. The collected blood was destroyed.
2. Problem: We reported two protocol deviations in the protocol detailed in Appendix 4 Addendum. This problem involved Anonymous Sample Collection at the NIEHS CRU and involved administrative errors in payment and
the revised consent; neither posed additional participant risk: (1) Participant 2691727 completed six of the seven visits, but was submitted for the $100 additional compensation on 4/30/2015 for completing all seven visits. (2) Participant 2691727 missed visit 5 during which other participants were administered a revised consent regarding payment protocol, and subsequently completed the remaining two visits under the
original consent. This round of the anonymous sample collection has been completed and is now closed.
In addition, we had two occurrence of mis-directed mail that we are aware of during the last CR.

Have any subjects withdrawn from the study? ☐ No ☒ Yes

There have been no withdrawals during the course of the last continuing review period. We have had 2 withdrawals over the course of this study of approximately 51,000 women. One particpant withdrew because she was concerned about the safety of her personal information and wanted it deleted. Another participant withdrew due to an early morning follow-up phone call while she was on vacation in Hawaii. Her preferred call time was bracketed around Eastern Standard Time due to her primary residence.

Is this study monitored by a DSMB/SMC? ☒ No ☐ Yes

If yes, date of the last DSMB/SMC review

Has any information appeared in the literature, or evolved from this or similar research (published/unpublished), that might affect the IRB's evaluation of the risk/benefit analysis of human subjects involved in this protocol? ☒ No ☐ Yes

Risk/benefit	There is a small risk of breach of confidentiality; however, the study has a "Certificate of Confidentiality" to prevent compelled disclosure. Participants do not receive direct benefit from participating; however, they help increase knowledge about the causes, and perhaps future means of prevention, of breast cancer and other diseases.
Updated list of publications for this protocol for this reporting	See Attachment with List of Publications
Updated list of publications for this protocol for this reporting	The Sister Study is prospectively examining environmental and familial risk factors for breast cancer and other diseases in approximately 50,000 sisters of women diagnosed with breast cancer. Such sisters have about twice the risk of developing breast cancer as other women. Participants have been highly motivated, and response rates and compliance are high. Studying these sisters will enhance our ability to assess the interplay of genes and environment in breast cancer risk and to identify potentially preventable risk factors. The prospective design allows us to assess exposures before disease onset and avoid biases common to retrospective studies. Collection of baseline data, measurements, and specimens is complete. Cohort members will be followed for at least 10 years. Enrollment of parents of young onset breast cancer cases, including saliva collection for family-based analyses of the role of genetic factors in breast cancer risk, may continue later in the follow-up perio

IX. Signatures

Dale P Sandler	Dale P Sandler, Ph.D.	e-Signed on 9/10/15 3:55 PM
Principal Investigator Signature*	Print Name	Date
Dale P Sandler	Dale P Sandler, Ph.D.	e-Signed on 9/10/15 3:55 PM
Accountable Investigator Signature	Print Name	Date
Dale P Sandler	Dale P Sandler, Ph.D.	e-Signed on 9/10/15 3:55 PM
Branch Chief/CC Department Head Signature**	Print Name	Date

X. Approvals

David B Resnik	David B Resnik, J.D., Ph.D.	e-Signed on 10/9/15 12:14 PM
IRB Chair Signature	Print Name	Date
Stavros Garantziotis	Stavros Garantziotis, M.D.	e-Signed on 9/11/15 11:09 PM
Clinical Director Signature	Print Name	Date

XI. Concurrence

Tonica Johnson	CR	10/26/15
OPS Protocol Specialist Signature	Print Name	Date

* [X] Signature signifies that investigators on this protocol have been informed that the collection and use of personally identifiable information at the NIH are maintained in a system of record governed under provisions of the Privacy Act of 1974. The information provided is mandatory for employees of the NIH to perform their assigned duties as related to the administration and reporting of intramural research protocols and used solely for those purposes. Questions may be addressed to the Protrak System Owner.

** [X] I have reviewed this research project and considered the NIH Policy for Inclusion of Women and Minorities in Clinical Research. Taking into account the overall impact that the project could have on the research field involved, I feel the current plans adequately includes both sex/gender, minorities, children, and special populations, as appropriate. The current enrollment is in line with the planned enrollment report for inclusion of individuals on the basis of their sex/gender, race, and ethnicity and is appropriate and of scientific and technical merit.

DATE: October 9, 2015

TO: Dale P Sandler, Ph.D.
Principal Investigator, NIEHS

FROM: Resnik David, J.D., Ph.D.
Chair, NIEHS IRB
NIEHS Office of Human Research Compliance (OHRC)

SUBJECT: IRB Review of Protocol# 02-E-N271, The Sister Study: Environmental and Genetic Risk Factors for Breast Cancer
Final Approval

Your Continuing Review 12/10/2015 was approved at the October 01, 2015 IRB meeting. All stipulations, if any, have been met.

Your IRB approved Continuing Review 12/10/2015 application will be forwarded to the Office of Protocol Services for final processing. You will receive notification when the Office of Protocol Services completes the processing of this application.

The protocol expiration date is September 30, 2016.

IMPORTANT INFORMATION ABOUT YOUR PROTOCOL:

Please use the final approved version of the protocol and consent as a guide for documents submitted for the next review.

ANY change in research activity MUST receive IRB review and approval prior to implementation. Request for review of changes should be submitted as an amendment.

Adverse or unexpected/unanticipated events or new information that may alter the risk or benefit determination or subjects willingness to continue in the study must be reported in accordance with NIH policy. Additional reporting (for example, to the sponsor or FDA) may also be required.

As Principal Investigator you are responsible for informing the Associate Investigators of the status of this project.

Please contact the NIEHS Office of Human Research Compliance (OHRC) if you have any questions and/or concerns.