

Supporting Statement B for

WOMEN'S HEALTH INITIATIVE OBSERVATIONAL STUDY

NHLBI/DCVS/PPSP/EB

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Federal Government Employee Address:

Name: Shari Eason Ludlam, MPH

Address: 6701 Rockledge Drive, Rm 10194, Bethesda, MD 20892

Telephone: 301-435-6667

Fax: 301-480-1455

Email: ludlams@mail.nih.gov

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B. Collection of Information Employing Statistical Methods

This information collection does involve statistical methods.

B.1 Respondent Universe and Sampling Methods

By study design, the respondent universe for the Observational Study (OS) is integrated with that of the Clinical Trial (CT). Women who initially expressed interest in the CT but found to be ineligible or unwilling to participate were asked to join the OS. Each of the 40 clinical centers were contracted to recruit a specific number of eligible OS women, between 1110 and 3885, based on the demography of their designated catchment area. Minority women were to be represented in the overall sample in at least the proportion found in the general population of women aged 50-79 (17% according to the 1990 census). The WHI had a target of 20% minority representation in the study. The recruitment phase of the WHI was completed in December 1998. Over 68,000 women enrolled in CT (18.3% minority). Enrollment into the OS reached 93,676 (16.5% minority).

Recruitment into the WHI Extension Study occurred between October 2004 and March 2005. Of those women eligible for Extension Study enrollment, 63,230 (72.9%) WHI Observational Study participants, and 52,176 (82.4%) Clinical Trial participants consented to follow-up through 2010.

Recruitment into a second WHI Extension Study (commonly called WHI 2010 – 2015) was completed between April and September, 2010. All WHI participants were invited to provide informed consent for continued follow-up of clinical outcomes, return of study questionnaires, and willingness to be approached for future ancillary studies including clinical trials. 93,558 participants enrolled.

Extended years of follow-up to continue the ascertainment of medical history update information from OS participants will increase the range of scientific issues that can be examined in the WHI study. The original WHI protocol provides power calculations for OS analyses as a function of disease rate, exposure frequency, relative risk, follow-up duration and importantly as a function of subsample sizes corresponding to racial/ethnic, age, and other important OS subgroups (**see Attachment 1**).

The most recent data collection rates show that 97 percent of the OS women who were sent annual self-administered questionnaires completed and returned the forms. To achieve this response rate, non-responders received up to two additional mailings and a reminder telephone call. Based on this experience, it is expected that the response rates for form collection in the extended follow-up years will result in similar response rates.

B.2 Procedures for the Collection of Information

A variety of important clinical and public health issues will be assessed in the OS. The most important objective is the testing of new hypotheses with regard to risk of cancer, cardiovascular disease, fractures and other major illnesses affecting post-menopausal women. This will be accomplished by relating information obtained on baseline characteristics to subsequent illness events and mortality as identified through follow-up mechanisms. In addition, the collection of biological specimens at baseline for storage and later analysis will allow etiologic hypotheses involving biomarkers to be evaluated in nested case-control or case-cohort. Forty clinical centers were initially awarded NIH contracts to serve as WHI screening centers for CT and OS participants. Due to performance issues at one of the clinical centers, extended years of outcome ascertainment for WHI participants from this clinical center continues under the direction of experienced CCC staff. In addition to recruitment, screening, data collection, and follow-up/clinic activities (now completed), WHI centers were responsible for timely outcomes ascertainment and data processing. For the WHI 2010 – 2015, the study structure was streamlined into 4 regional field centers (RCs) and a clinical coordinating center (CCC) and that configuration continues in the current follow-up period.

The Fred Hutchinson Cancer Research Center awarded the original contract to serve as the WHI Clinical Coordinating Center (CCC) and continues to have a significant role in the WHI extension phase of the study. The CCC has designed a computerized data management system specifically for the WHI study (see section A.3). The central Oracle database is accessible by RC staff over the World Wide Web using personal computers preconfigured by the CCC. The CCC supports, maintains, and provides tape back-up for the entire system. Data from all centers are consolidated into a central database at the CCC through computer linkage.

Each regional center monitors the quality of data at its site. Data coordinators and other regional center staff members carry out quality control procedures according to the established guidelines in the manual. Various reports can be generated to review and identify data quality.

The CCC reviews composite data from regional centers on a regular basis and identifies apparent systematic performance biases among sites and investigates possible causes. Reports on ascertainment and processing outcome data are critical tools for assessing regional center performance.

Specific medical conditions (study outcomes) reported on medical history update forms are verified through pathology and medical record review. A trained regional center outcome specialist requests medical records, monitors receipt of documents, and submits relevant documents to the central adjudicator to complete the outcome forms (**see Attachment 2**). Participants are asked to sign a Medical Release Form to release medical records for this review. Deaths are ascertained through the annual follow-up process and through the National Death Index, if participants cannot be located.

Relative risk regression methods will provide the primary data analytic tool for the OS. These methods are also readily adapted to accommodate nested case-control and case-cohort sampling schemes. Nested case-control sampling proceeds by selecting for each 'case' of a study outcome one or more 'control' women who have not developed the disease in question by the follow-up time at which the corresponding case was ascertained. Additional matching criteria in the OS will typically include baseline age, clinic, and date of enrollment, and depending on the analysis may also include racial/ethnic or socioeconomic group, or other factors. Case-cohort sampling involves the selection of a random, or a stratified random sample of the cohort to serve as a comparison (control) group for the cases of all the outcomes under study.

The ability to estimate relative risks reliability for the outcomes of interest in the OS as a function of baseline characteristics (exposures, behaviors or biologic measurements), or as a function of changes in such characteristics between baseline and three years is dependent on the accurate measurements of the characteristics and outcomes under study and the accurate ascertainment and proper accommodation of all pertinent confounding factors. Since many of the characteristics ascertained in the OS (e.g., nutrient intakes, blood cholesterol) are subject to noteworthy measurement error, a stratified 1% random subsample of the OS women had repeat baseline information and specimens obtained at between one and three months following their OS enrollment, and again at between one and three months following their three year clinic visit. This reliability subsample provides information of the reproducibility of the measurements taken, and can be used to correct relative risk estimates. The 1% sample was stratified on age, racial/ethnic group, and socioeconomic group.

Analyses that relate change in risk factors to disease risk have particular potential for gaining insight into disease mechanisms. For example, the OS provides a valuable forum for addressing the issue of whether or not the association between low blood cholesterol (e.g., <160 mg/dl) and excess non-cardiovascular mortality derives primarily from persons who have experienced major reductions in blood cholesterol over the preceding three years. In fact, the OS is large enough that such analysis could be restricted to women with relatively low baseline blood cholesterol (e.g., lowest two

quintiles) in order to avoid a complicated interpretation if the effect of interest happened to 'interact' with baseline cholesterol measurement. Furthermore the OS, by virtue of ascertaining a range on non-specific markers of debility or disease (e.g., serum albumin, hemoglobin; cancer biomarkers; baseline and follow-up disease prevalence by questionnaire and physical exam) may be able to examine whether the excess mortality associated with reduced blood cholesterol can be explained by the presence of recognized or latent disease. The careful accommodation of measurement error in predictor and confounding variables is particularly important in such risk-factor-change analyses.

A well-defined reporting system has been developed to document the completeness and timeliness of outcomes processing in the WHI. Performance reports reflect the timeliness and completeness of the process initiated at the time that the Medical History Update form is entered into the Extension Study database and becomes available for field center processing. Timeliness and completeness of Medical History Updates, outcomes packet formation, and submission to the CCC will be the primary areas of review.

Maintaining retention of study participants is an important focus in WHI. During the extended years of follow-up, several retention activities used in the main study continue, including annual participant newsletters (see **Attachment 3**), updates of the participant's address provided by the US Post Office, regular review of contact information on all phone contacts, and collection of data from the participant's identified proxy, when necessary.

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

Methods to maximize response rate are critical to ensure that complete follow-up of health outcomes and mortality is attained in the OS study. The OS study is not a probability sample but is comprised of a cohort of women who initially expressed an interest in participating in the CT but were found ineligible or unwilling to take part in that component. These women have volunteered to participate in this long-term follow-up study. The analysis is dependent on achieving the expected number of outcomes in this cohort. Detailed outcomes ascertainment procedures have been developed for the WHI (see **Attachment 1**).

Contact with enrolled OS participants is maintained annually for the duration of the current WHI follow-up period. OS participants are mailed a self-administered Medical History Update questionnaire to complete along with a postage prepaid return envelope. For participants who do not respond to the initial mailing, up to 2 additional mailings and several telephone contacts are initiated. Some follow-up contacts, because of a

participant's illness, disability, or difficulty in finding the participant, may need to be conducted by proxy (next of kin) during the extended follow-up years as previously done according to the guidelines in the WHI operational manual.

All participants will continue to receive a WHI newsletter annually (see attachment 3). The purpose of the newsletter is to present WHI news and lay versions of results, to encourage retention of study participants, to promote participant identification with WHI, and to help keep addresses up-to-date. To maintain current contact information, mailings to participants are imprinted with the CCC's return address and include a line requesting address corrections. The US Post Office notifies the CCC if the participant is deceased, if the packet is undeliverable to that address, or with information on a new address.

B.4 Test of Procedures or Methods to be Undertaken

The baseline and screening forms for data collection (approved in the initial OMB submission in the mid 1990s) were developed and reviewed by the CCC, NIH project scientists, investigators at the WHI clinical centers, and outside consulting scientists. These forms were based on those previously developed and used successfully in other studies, with the exception of Modifications made to ensure the appropriateness for older women, minority women, non-native English speakers, and for those with limited literacy skills. Revisions necessary to ensure appropriateness to the WHI population included new items, clarifications, and skip patterns. These modifications do not refer to revisions made since the forms were last reviewed by OMB in 2013.

The initial years of the WHI focused primarily on recruitment and screening activities, and administration of baseline forms, and thus offered the opportunity to evaluate the data collection instruments and data management procedures. WHI investigators on the OS Committee and other WHI advisory committees were chiefly involved in the development, review and pre-testing of these forms. Input from scientists at various agencies within the National Institutes of Health (e.g., National Cancer Institute, National Institute of Aging) and other organizations (e.g., the National Center of Health Statistics) were also obtained.

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

Numerous scientists were consulted on the initial development of the WHI study design, analysis plans and data collection forms. The CCC in concert with the investigators from the WHI field centers and the NIH, NHLBI Project Office will analyze the data. The CCC is responsible for providing analytic support. Statistical expertise is provided to

WHI by Nancy Geller, Ph.D., the National Heart, Lung and Blood Institute (301-435-0434),