OMB SUPPORTING STATEMENT B FOR THE

WOMEN'S HEALTH INITIATIVE OBSERVATIONAL STUDY

NHLBI/DPPS/WHIB

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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. An additional extension period through 2015 is planned.

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 8.)

The most recent data collection rates show that 98 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.

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). In brief, each clinical center is connected to the CCC forming a wide area network (WAN). The CCC is responsible for installing clinical center file servers and training clinical center staff on its use. Using the WAN, the CCC supports, maintains, and provides tape back-up for clinical center file servers. Data from all centers are consolidated into a central database at the CCC through computer linkage.

Each clinical center monitors the quality of data at its site. Data coordinators and other clinical 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 clinics on a regular basis and identifies apparent systematic performance biases among clinics and investigates possible causes. Reports on ascertainment and processing outcome data are critical tools for assessing clinical center performance.

Specific medical conditions (study outcomes) reported on medical history update forms are verified through pathology and medical record review. A trained clinical center outcome specialist requests medical records, monitors receipt of documents, and submits relevant documents to the central adjudicator to complete the outcome forms (see Attachments 13, 14). Participants are asked to sign a Medical Release Form (see Attachment 15) 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 16), 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 8).

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 16). 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. Tests of Procedures or Methods to be Undertaken

The baseline and screening forms for data collection (approved in the initial OMB submission) 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. Modifications were made to ensure the appropriateness for older women, minority women, non-native English speakers, and for those with limited literacy skills. Revisions to the forms included new items, clarifications, and skip patterns.

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/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), and Ross Prentice, Ph.D., and Garnet Anderson, PhD, both from the Fred Hutchinson Cancer Research Center at the Clinical Coordinating Center (206-667-4267).