

**OMB SUPPORTING STATEMENT A FOR THE  
WOMEN'S HEALTH INITIATIVE OBSERVATIONAL STUDY**

**NHLBI/DPPS/WHIB**

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## **Attachments to Supporting Statement A**

Attachment 1: OS Data Collection Instrument List

Attachment 2: Next of Kin Questionnaire List

Attachment 3: Physician Questionnaire List

Attachment 4: Data Collection Background and Analysis Procedures

Attachment 5: NHLBI Advisory Council Minutes

Attachment 6: Certificate of Confidentiality

Attachment 7: IRB Approvals

## A. JUSTIFICATION

### A.1. Circumstances Making the Collection of Information Necessary

The Women's Health Initiative (WHI) comprises a group of research studies that will address critical issues about the most common causes of frailty, disability, and death among post-menopausal women aged 50 to 79 years. Authorization to conduct studies on women's health is contained in the reports of the Committee on Appropriations (House of Representatives - Report 102-121 and Senate - Report 102-104). The Public Health Service Act [42 USC 241(c)] further authorizes NIH to conduct such studies as the Women's Health Initiative.

This Initiative is comprised of two main investigational approaches:

- A large clinical trial (CT) to evaluate the clinical efficacy of promising, but unproven preventive approaches for specific diseases common among older women
- A companion observational study (OS) comprised of women ineligible or unwilling to participate in the CT, to evaluate risk factors for chronic diseases by following this large cohort of women and relating subsequent disease development to baseline assessments of historical, physical, and physiologic characteristics.

Recruitment for the Women's Health Initiative (WHI) began in 1993. When recruitment ended in 1998, more than 161,000 post-menopausal women between 50 and 70 years of age from 40 clinical centers across the U.S. had joined the WHI (68,132 in CT and 93,676 in OS; see attachment 4). [www.whi.org](http://www.whi.org).

<http://www.nhlbi.nih.gov/whi/>

The WHI was scheduled to close-out in 2005. Due to initial findings of the WHI and early stopping of the hormone trial interventions, it was determined that continued long-term follow-up for outcomes collection is necessary. Extended follow-up of the entire WHI cohort has contributed to the data investigators are already using to establish stable estimates of the

magnitude of risk factor impact on health in postmenopausal women. In 2010, a second contract extension will continue follow-up of consenting study subjects through 2015.

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) is planned between April and September, 2010. Currently approved procedures and forms will be used until October, 2010, when the WHI 2010 – 2015 will commence. All WHI participants will be 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. It is estimated that a total of nearly 100,000 women (85% of living participants, approximately 51,530 OS participants, and 42,550 CT participants) will enroll in the 2010-2015 extension. WHI 2010 - 2015 will focus on several important phenotypes: heart failure, atrial fibrillation, venous thromboembolism, coronary heart disease, peripheral arterial disease, and stroke. To achieve these objectives, the renewal will continue full outcomes ascertainment and adjudication in two important sub-cohorts: hormone trial participants and African American and Hispanic women. Self-reported outcomes data will be collected in the remaining cohort to serve as a platform for ancillary studies and a new generation of clinical trials. In 2011, a subsample of the oldest women in the cohort will be invited to a face-to-face visit, undergo physical measurements, and donate a blood specimen. The study structure will be streamlined into 4 regional field centers (RCs; selected from among the current 39 field centers) and a clinical coordinating center (CCC).

This OMB request is for a revision of the currently approved information collection of the Women's Health Initiative (WHI) Observational Study (OMB No: 0925-0414, Expiration date 05/31/2012) and for continued outcomes collection from proxies not included under NIH Clinical Exemption (CE-93-05-05) for the Women's Health Initiative Clinical Trial component. This revision of data collection involves extending the follow-up years to continue annual outcome ascertainment (using a new, combined annual medical history update form) and revisions to our annual aging-related outcome questions (activities of daily life, ADL.) Information collected from OS participants at less frequent intervals include a personal information update (to be collected once during this 3 year OMB submission period) and a repeat administration of the previously approved medication and supplement use questionnaire, to be collected in approximately 2013. (see Attachment 1 for data collection instruments; also page 16 for schedule of data collection.) In addition, beginning in 2011, a subsample of approximately 8000 of women aged 80 and older will be invited to participate in one face-to-face visit for physical measurements and blood collection. We estimated that approximately 45% (or 3600) will be OS participants. If WHI staff are unable to reach WHI participants for the annual contact, a small number of next of kin contacts are required. (See Attachment 2.) In circumstances where a participant has died and contact with next of kin is not successful, a very small number of health care providers will be contacted to obtain cause of death. (See Attachment 3.)

#### **A.2. Purpose and Use of the Information Collection**

As detailed in previous OMB submissions, the overall objective of the WHI is to provide new information on health and risk of disease among older post-menopausal women. The specific objectives of the OS are to provide reliable estimates of the extent to which known risk factors predict heart disease, cancers and fractures; identify new risk factors for these and other diseases in women; compare risk factors, presence of disease at the start of the study, and new occurrences of disease during the WHI in all study components; and create a future resource to identify

biological indicators of disease, especially substances and factors found in the blood. Continued follow-up of medical outcome occurrences will enhance achievement of the WHI original goals and increase the range of scientific issues that can be examined. A WHI reference list of current OS and CT findings is included in Attachment 4. Additional data analyses continue.

As outlined in the original WHI protocol, specific biomarkers will be assessed based on current and future hypotheses related to clinical endpoints. An overview and table regarding biomarker hypotheses (e.g., antioxidant vitamins, vitamin D receptor genes, and endogenous estrogen levels) and study endpoints are provided in Attachment 4. The WHI study/protocol allows for analysis and presentation of results in aggregate form only, thus all data including biological samples are void of personal identifiers.

### **A.3. Use of Information Technology and Burden Reduction**

The implementation of computer-assisted telephone interviewing for data collection forms was not considered appropriate or cost efficient for the WHI study due to the large number of subjects followed at 40 centers nationwide. The WHI forms are designed as self-administered questionnaires in a scannable mark-sense format to simplify completion and consequently reduce participant burden. The Clinical Coordinating Center (CCC) is responsible for mailing the forms to the participants along with a postage-paid addressed return envelope.

During the extended follow-up, the returned WHI participant forms collected by mail (Form 33, Medical History Update, Form 151, Activities of Daily Life, Form 153, Medications and Supplements Inventory, Form 154, Breast Cancer Prevention and Treatment Medications, and Form 155, Lifestyle Questionnaire) will be scanned and imaged at the CCC. Outcomes-related forms required for use in subsequent steps of outcomes documentation are transmitted electronically to the Regional Center (RC, previously referred to as field center). The WHI

Extension Study is currently funded through 2010. Plans for award of an additional extension period, the WHI 2010 – 2015 are underway.

If a participant does not respond to central mailings, WHI staff at the RC will contact the participant by phone for data collection. Forms collected by RC staff via telephone will be key entered by RC staff into a central database using data entry screens developed and provided by the CCC. Staff are trained and certified in data collection techniques that minimize entry errors.

The WHI uses high-powered, state-of-the-art computing and data management systems, which maximize data accuracy and simplify respondent burden. A central Oracle database is accessible by RC staff over the World Wide Web using personal computers preconfigured by the CCC. Each RC principal investigator is able to use this database for tracking and reporting. The CCC maintains a central repository of all WHI Extension Study data. The WHI database was created prior to the requirement for a Privacy Impact Assessment (PIA), but it has undergone an extensive review of the system security plan. The NHLBI Information Systems Security Officer certified the WHI system security plan in August 2005. The systems security plan will be reviewed and updated in 2010 at the award of the WHI 2010 – 2015 Extension.

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

The initial planning process for the WHI included scientists from 10 Institutes at the National Institutes of Health (NIH) as well as from other governmental agencies. These scientists evaluated the current research being funded or conducted by their Institutes to ensure that the WHI would be complementary to, but not overlapping with, planned or current government-supported studies at NIH or other agencies.



The successful recruitment of over 68,000 CT and about 93,700 OS women, aged 50-79, with a large proportion of minority participants, the long duration of follow-up and advanced technological assessments will permit scientific questions to be answered in the WHI that cannot be addressed by other large cohort studies. WHI data analyses to date have shown some intriguing results that will be explored in more detail with additional outcome data.

Extending the years of follow-up for outcome ascertainment of consenting WHI participants expands the range of scientific issues that can be evaluated in the CT and OS, and allows a reliable study of the longer term health benefits and risks of the CT interventions. The WHI will continue to be one of the largest studies ever to investigate the health of post-menopausal women and will provide the scientific and medical community and the public with this needed information.

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

A small number of physicians with medical responsibilities for participants in the CT and OS will be contacted for clarification of medical information (e.g., cause of death). Burden has been minimized due to implementation of study procedures that require pursuit of other data sources (e.g., hospital records, participant medical follow-up forms, and the National Death Index) prior to physician contact. The average total annual health care provider (or office staff) burden is estimated at less than one hour.

#### **A.6. Consequences of Collecting Information Less Frequently**

Established study procedures (see Attachment 4) for collecting medical history update information will be slightly modified during this OMB period, with the commencement of WHI2010 - 2015. The CCC will continue annual follow-up with a centralized mailing to obtain self-reported medical and aging-related outcomes. Since the previous OMB submission, the

Medical History Update and Activities of Daily Life forms have been updated. An additional form designed to capture specific aging-related outcomes (the Lifestyle Questionnaire) will be collected once during the WHI 2010 – 2015 period.

All eligible/consenting WHI participants will continue to be followed in the WHI 2010 - 2015 to collect data primarily on health outcomes using a modification of the procedures employed in OS follow-up over the last 10 years. As in previous years, medical history and personal information updates will be collected in an efficient and timely manner. The methods used to achieve the high response rates achieved in the OS mailings will continue in these follow-up years.

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

This study complies with all guidelines of 5 CFR 1320.5.

**A.8. Comments to the Federal Register Notice and Efforts to Consult with Outside Agency**

A 60-day Federal Register notice soliciting comments on the WHI Observational Study prior to submission to OMB was published in the Federal Register on January 20, 2010 (Volume 75, Number 12, pg 3237) and allowed 60-days for public comment. Two comments were received and appropriate responses were given.

The NHLB Advisory Council was approved the WHI 2010 - 2015 study in June 2009 (Attachment 5; WHI reference on page 4.) Questionnaires used in WHI from baseline to follow-up have been reviewed/modified and approved by Principal Investigators and outside consultants, and are now submitted for approval by OMB officials.

Recently, the WHI investigators, in consultation with non-WHI investigators with expertise in aging (Lisa Berkman, PhD, Harvard University; [lberkman@hsph.harvard.edu](mailto:lberkman@hsph.harvard.edu)

) and anxiety and stress (Naomi Simon, PhD, Harvard University; [nsimon@partners.org](mailto:nsimon@partners.org)), developed the Lifestyle Questionnaire to collect data on aging-related outcomes via a mailed form (see attachment 1.)

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

This information collection does not involve any payment or gift to respondents in the study.

**A.10. Assurance of Confidentiality Provided to Respondents**

The Privacy Act System of Records Notice which covers the WHI is entitled: Clinical, Basic and Population-based Research Studies of the National Institutes of Health (NIH), NHHS/NIH/OD: 09-25-0200 as published in the Federal Register, Vol. 67, No. 187/ Thursday, September 26, 2002/Notices pages 60776-60780. The authority for maintenance of this system for the WHI is 42 USC 241.

The WHI was issued an updated Certificate of Confidentiality in 2008, which extended the period of coverage and expands coverage to a sub-study of WHI Clinical Trial participants, the WHI Memory Study. (See Attachment 6.) WHI is in compliance with 45 CFR 46. The WHI is reviewed annually by the OHRP authorized IRBs at the contracted institutions. A current list of the IRB certification approval dates for the WHI Clinical Centers participating in the extended follow up is provided in Attachment 7.

Principal Investigators and their institutions at the WHI regional centers and the CCC are contractually obligated to comply with the Privacy Act of 1974, Public Law 93-579 as part of their contractual agreement with the NIH. Personnel at the clinical centers and at the CCC must undergo training and pass a written test before being certified to collect and handle data. All

regional center and CCC investigators and key personnel have received the NIH required training and education in the Protection of Human Subjects in Research.

#### **A.11. Justification for Sensitive Questions**

Potentially sensitive questions on baseline forms and justification for inclusion in this study were provided and approved in the initial OMB submission. The Assistant Secretary of Health, DHHS, issued a Confidentiality Certificate in 1994 for the WHI Clinical Trial and Observational Study, which was updated as described above in 2008. An overview of the information and justification for inclusion of potentially sensitive questions previously provided in the original submission is given below:

- Social Security Number - used for tracking purposes only; required for identifying and validating deaths from National Death Index searches. The initial Personal Information form that asked about Social Security Number contains the required language (e.g., legislation and authorization-concerning collection, use of the information and voluntary nature),
- Racial/ethnic group - necessary for subgroup analysis by ethnic group to evaluate differences in prevalence and incidence of certain disease entities,
- Total family income and finance questions - an important measure of socioeconomic status and predictor of disease development, medical care use, and longevity,
- Other medical issues - use of hormones to evaluate positive and negative associations with such diseases as cardiovascular disease, osteoporosis, and cancer; urine control/bladder function, an important outcome in an aging cohort which may be altered by various types of treatment (e.g., Hormone Therapy); health care utilization as an indicator of earlier disease identification and mortality,
- Alcohol consumption - required to evaluate the risk for disease (e.g., breast cancer) or to evaluate protection as in coronary heart disease.

- Thoughts and Feelings questions - aspects of mood, social support, and personal attitudes may be predictive of disease risk. Personal impact of disease on function and quality of life can be assessed along with life events that have been linked to chronic diseases and to mortality. Social support is related to morbidity, mortality, general functioning and health. As described in Section A.10 of this submission, steps have been taken to ensure confidentiality of data and to safeguard participants' paper and computerized files.

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

**Table A.12-1. Estimates of Annual Hour Burden**

Type of Respondent	Number of Respondents	Frequency of Response	Av. Time Per Response	Annual Hour Burden
OS Participants	42,550	1.12	.4155	19,801
Next of kin	941	1	.083	78
Physician/Office Staff	8	1	.085	.68
Totals	43,499			19,880

The number of OS respondents used in the calculation of response burden was based on an estimated attrition rate of less than one percent per year over the course of the study. The estimated number of OS respondents to be contacted for completion of annual medical history update forms, the activities of daily life form, the medication and supplement use forms, face-to-face visits, and personal contact information is presented in Table A.12-1.

The average annual burden of contacting next of kin to locate participants or to update medical information is estimated at 78 hours. In the case where cause of death cannot be confirmed through the usual sources or if the information is conflicting, additional information will be

sought from the participant’s health care provider. The average annual burden for contacting health care providers to assess participants’ cause of death is estimated at less than one hour.

As indicated on table A.12-1, the total annual hour burden for participants, next of kin, and physician/office staff is estimated at 19,880 hours (table calculations: number of respondents x frequency of response = total responses; total response x average time per response = annual hour burden). Although the CT has received clinical exemption, contact with the next-of-kin or physician for those participants is included in this burden submission.

The current expiration date for approved forms is May 31, 2012. The estimated average response time for form completion is shown in Table A.12-2 below.

**Table A. 12-2. Estimated average response time (minutes) for form completion**

Form # OS Participants	Response time
<b>Mailed Questionnaires:</b>	
20- Personal Information (update of pg. 1 only; 1 <sup>st</sup> year only)	3
33/33D- Medical History (Annual update; no outcomes to report)	5
33/33D- Medical History (Annual 12% subsample w/ 1 or more outcome)	17
151 –Activities of Daily Life	6
153 – Medications and Supplements (once this submission)	20
154* – Breast cancer treatment/prevention meds (once this submission)	5
155 – Lifestyle Questionnaire (once this submission)	25
<b>Face-to-Face Visit Data Collection:</b>	
80 – Physical Measurements	10
90 – Functional Status	10
100 – Blood Collection	10
<b>CT/OS Other Respondent Form:</b>	
9 – Participation Status	5
120- Initial Report of Death- for physician or next-of-kin	5

\*Study participants who report breast cancer diagnosis only

The estimated annualized cost burden to all respondents is \$397,617 (shown in Table A.12-3):

**Table A. 12-3. Annualized cost burden to respondents**

Type of Respondent	Number of Respondents	Frequency of Response	Hourly Wage *	Av. Time Per Response	Respondent Cost
OS Participants	42,550	1.12	\$20	0.4155	\$396,021

Next of Kin	941	1	\$20	0.083	\$1562
Physician or Office Staff	8	1	\$50	0.085	\$34
TOTAL					\$397,617

\*source for wage estimates: Bureau of Labor Statistics, [http://www.bls.gov/oes/2008/may/oes\\_nat.htm#b29-0000](http://www.bls.gov/oes/2008/may/oes_nat.htm#b29-0000)

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

There are no capital costs, operating costs or maintenance costs to report.

**A.14. Annualized Cost to the Federal Government**

For the OS study, the estimated average annual contract costs (including direct and indirect costs) in this 3 year submission for the 4 regional centers and the clinical coordinating center are as follows:

Regional Centers	\$1,200,370
Clinical Coordinating Center	<u>\$2,047,363</u>
Annual Contract Costs	\$3,247,733

NIH costs for staff time for project development, implementation and monitoring are estimated at \$16,000 annually. Printing costs are estimated at \$75,000 annually. The average annualized cost to the Federal Government for the OS study in this submission period is estimated at \$3,338,733.

**A.15. Explanation for Program Changes or Adjustments**

The total annual respondent hours requested in this submission is 19,880, compared to the current inventory of 23,607. This reduction in burden results from a program adjustment. It is primarily due to a reduction in the number of participants estimated to consent to continued follow-up in the WHI 2010 – 2015.

The WHI protocol will change somewhat in the fall of 2010. All WHI participants still in active follow-up will be invited to continue their participation in the WHI by mailed consent. Once continuing commitment to the study is confirmed, participants will complete annual data collection forms primarily by mail with follow-up for additional details, if needed, typically by phone. In addition, a one-time home visit sub-study is planned to collect standardized clinical measures and collect blood on 8000 women over 80 years of age. Full outcomes ascertainment and documentation will occur in two important sub-cohorts of women—those in the hormone trials, plus minority women with genome-wide scans--totaling ~24,000. We will continue to obtain self-reported clinical outcomes data in the ~76,000 participants who are not in the hormone trial or minority cohort. This will facilitate ancillary studies and consortium studies requiring large numbers of outcomes.



A summary of OS Participant data collection is included in the table below:

Form #	Name	Change since last submission?	When administered					
			Oct-2010		Oct-2011		Oct-2012	
			Sep-2011		Sep-2012		Sep-2013	
33/33 D	Medical History Update	Yes, combined w/ the former F33D	X		X		X	
20	Personal Information Update (1st page only)	No	X					
151	Activities of Daily Life	No	X				X	
153	Medication and Supplement Inventory	No					X	
154	Breast Cancer Prevention and Treatment Medications*	No					X	
155	Lifestyle Questionnaire	New			X			
<b>Face-to-Face Questionnaires (subsample; ~8000 women &gt; age 80)</b>								
80	Physical Measurements	Previously approved forms			X			
90	Functional Status				X			
100	Blood Collection				X			

\*Form 154 administered only to women who report a breast cancer diagnosis

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

WHI Investigators will present statistical results by publishing in scientific journals (e.g. New England Journal of Medicine, Journal of the American Medical Association, Circulation), by presenting at scientific meetings (e.g., American Heart Association, Council on Cardiovascular Epidemiology, American Public Health Association), and by compiling special reports and monographs available to the scientific community. WHI publication guidelines have been written to foster the analysis and publication of data. Analysis of the OS baseline data began once recruitment was done for all participants and a clean data set was available. The CCC has created a baseline dataset for OS and CT participants. A WHI Baseline Monograph comprised of separate chapters on baseline characteristics of each WHI component was published in 2003(*Ann Epidemiol* 2003; 13: S5-S17). Subsequent WHI publications have referred to specific and

pertinent baseline data presented in the monograph. Publications presenting baseline and preliminary data analysis findings are included in the reference list in Attachment 4. Additional analysis of the OS and CT data and subsequent publications of study results is underway.

The estimated project time schedule for OS activities completion after OMB approval is provided in Table A.16-1 below.

Table A.16-1. Project Time Schedule	
Collection of medical history updates	1-30 months
Documentation/Adjudication of outcomes	2-34 months
Analysis of outcomes data initiated	12 months
Submit supporting statement for continuance	30 months
Completion of outcomes collection	36 months

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

OMB expiration date is displayed on all participant data collection documents.

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

Collection of information encompassed by this OMB request complies with 5 CFR 1320.9.