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: Legislative Authority

Attachment 2: OS Participant Questionnaires

Attachment 3: OS Participant Questionnaire Instructions

Attachment 4: Next of Kin Questionnaires

Attachment 5: Next of Kin Questionnaire Instructions

Attachment 6: Physician Questionnaires

Attachment 7: Physician Questionnaire Instructions

Attachment 8: Data Collection Background and Analysis Procedures

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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. (See Attachment 1.)

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).

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 will

contribute to the data investigators are already using to establish stable estimates of the magnitude of risk factor impact on health in postmenopausal women.

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.

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 05/30/2009) 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 outcome ascertainment using annual medical history update forms and aging-related outcome questions (activities of daily life, ADL.) Information collected from OS participants at less frequent intervals include personal information and proxy information updates (collected once during this 3 year OMB submission period) and two new forms collecting information on medication and supplement use (proposed to collect this information once in FY 2009 and once again toward the end of the proposed Extension period, in about 2014.) These new medications and supplement use forms replace information previously collected in this cohort by in-person visits between 1996 - 2001, and represent a paper data collection instrument derived from previously approved data collection procedures coupled with expert advice. (See Attachments 2, 3.) If WHI staff are unable to reach WHI participants for the annual contact, a small number of next of kin contacts are required. (See Attachments 4, 5.) 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 Attachments 6, 7.)

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 in the whole cohort 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 8. Additional data analyses are underway.

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 8. 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 (Form 33, Medical History Update, Form 151, Activities of Daily Life, Form 153, Medications and Supplements Inventory, and Form 154, Breast Cancer Prevention and Treatment Medications – see attachments 2, 3) 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 Field Center, FC (previously referred to as clinical center or site). Although this supporting statement covers three years of continued follow-up, the extension study period is currently funded through 2010. An additional extension period through 2015 is planned.

Forms collected by FC staff via telephone will be key entered by FC 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 FC staff over the World Wide Web using personal computers preconfigured by the CCC. Each FC principal investigator is granted access to data only from participants from their center and 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.

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

The initial planning process for the WHI included scientists from l0 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 could 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 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. As WHI participants age, the annual death rate is slightly increasing, so burden in this category has increased slightly since the previous submission. However, the

average total annual health care provider (or office staff) burden is still estimated at less than one hour.

A.6. Consequences of Collecting Information Less Frequently

Established study procedures (see Attachment 8) for collecting medical history update information will continue during this OMB period. The CCC will continue annual follow-up with a centralized mailing to obtain self-reported medical and ADL outcomes. Since the previous OMB submission, the Medical History Update and Activities of Daily Life forms are unchanged. The one-time only addendum which was developed to correct an omission in previous medical history update forms (Form 134) and was presented in our last OMB submission has been completed , and therefore is not included in the burden this submission.

The proposed new forms collecting medications and supplements use by participants will replace information previously collected during in-person clinic visits conducted among WHI OS participants between 1996 and 2001. Without updated medications and supplement data, the WHI is unable to continue to support pharmacoepidemiology studies.

Once the close out activities for OS and CT participants completed in 2005, the Extension study began. All eligible/consenting WHI participants are followed 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 December 30, 2008 (Volume 73, Number 250, pp. 79889-79890). One comment was received and appropriate response was made.

The NHLB Advisory Council was approved the WHI Extension study in May 2003 (Attachment 9; WHI reference on page 8.)

Questionnaires used in WHI from baseline to follow-up have been reviewed/modified and approved by Principal Investigators and outside consultants, and subsequently approved by OMB officials.

Recently, the WHI investigators, in consultation with non-WHI investigators with expertise in epidemiology (Annette Fitzpatrick, University of Washington) and pharmacy (Shelley Gray, University of Washington), developed forms to collect updated medications and supplements exposure data via mailed forms (see attachment 2.)

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. (See Attachment 10.) The authority for maintenance of this system for the WHI is 42 USC 241.

The WHI was issued an updated Certificate of Confidentiality this year, which extends the period of coverage and expands coverage to a sub-study of WHI Clinical Trial participants, the WHI Memory Study. (See Attachment 11.) 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 12.

Principal Investigators and their institutions at the WHI clinical 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 field 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. <u>Justification for Sensitive Questions</u>

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., HRT); 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. <u>Estimates of Hour Burden Including Annualized Hourly Costs</u>

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

Type of Respondent	Number of Respondents	Frequency of Response	Av. Hrs. Per Response	Annual Hour Burden
*OS Participants	63,230	1.1	.338	23,509
Next of kin	1163	1	.083	97
Physician/Office Staff	9	1	.085	.77
Totals	64,402			23,607

* Add 6,323 to number of respondents due to calculations in system for the "Frequency of Response" being 1.1.

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, and personal and proxy 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 97 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 23,607 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, 2009. 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 #	Response time
20- Personal Information (update of pg. 1 only; 1st year only)	3
33- Medical History (Annual update)	5
33D-Medical History Update-Detailed (Annual 10% subsample)	10
151 –Activities of Daily Life	6
152 – Health Follow-up by Proxy (update of previous information; 1st yr only)	3
153 – Medications and Supplements (once this submission)	20
154 – Breast cancer treatment/prevention meds (once this submission)	5
CT/OS Other Respondent Form:	
24 – Locating Hard to Reach Participants	5
120- Initial Report of Death- for physician or next-of-kin	5

The estimated annualized cost burden to all respondents is $377,744 (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	63,230	1.1	$16	0.338	$376,143
Next of Kin	1163	1	$16	0.083	$1,544
Physician or Office Staff	9	1	$50	0.085	$38
TOTAL					$377,725

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 submission for the 39 clinical centers and the CCC are as follows:

Field Centers $1,429,549

Clinical Coordinating Center $2,543,635

Annual Contract Costs $3,973,184

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 in this submission period is estimated at $4,064,184. The total estimated cost to the Federal Government for the Observational Study portion of this 15.5-year project is $145,320,955.

A.15. Explanation for Program Changes or Adjustments

The total annual respondent hours requested in this submission is 23,607, compared to the current inventory of 18,319. This slight increase in burden results from a program adjustment. It is primarily due to:

- An increase in the estimated percentage of participants who will need to complete Form 33D (Medical History Update – Detail) due to a potential self-reported medical outcome of interest on Form 33 (Medical History Update.)
- The reinstatement of medication and supplement usage data collection originally collected between 1996 and 2001.

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

Form #	Name	Change since last submission?	When administered		
			2009	2010	2011
33	Medical History Update	No	X	X	X
33D	Medical History Update Detailed	No	X	X	X
20	Personal Information Update (1st page only)	No	X		
151	Activities of Daily Living	No	X	X	X
152	Proxy Update	Yes, adapted from Form 9	X		
153	Medication and Supplement Inventory	New	X		
154	Breast Cancer Prevention and Treatment Medications	New	X		

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 8. 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 information collection documents.

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

Collection of information encompassed by this OMB request complies with 5 CFR 1320.5.