Supporting Statement A for

Women's Health Initiative Observational Study

NHLBI/DCVS/PPSP/EB

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Check off which applies:

- New Revision
- X Revision with Change
- Reinstatement without Change
- Extension
- Emergency

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ATTACHMENTS

A. Justification

The Women's Health Initiative (WHI) is a long-term national health study that has focused on strategies for preventing heart disease, breast and colorectal cancer, and osteoporotic fractures in postmenopausal women. These chronic diseases are the major causes of death, disability, and frailty in older women of all races and socioeconomic backgrounds.

This multi-million dollar, 15-year project, sponsored by the National Institutes of Health (NIH), National Heart, Lung, and Blood Institute (NHLBI), involves 161,808 women aged 50-79, and is one of the most definitive, far-reaching clinical trials of post-menopausal women's health ever undertaken in the U.S. The WHI Clinical Trial and Observational Study focused on many of the inequities in women's health research and will continue to provide practical information to women and their physicians about hormone therapy, dietary patterns, calcium/vitamin D supplementation, and their effects on the prevention of heart disease, cancer and osteoporotic fractures.

The WHI had two major parts: a randomized Clinical Trial and an Observational Study. The randomized controlled Clinical Trial (CT) enrolled 68,132 postmenopausal women between the ages of 50-79 into trials testing three prevention strategies. If eligible, women could choose to enroll in one, two, or all three of the trial components.

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). **www.whi.org**

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 was 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.

Recruitment into the first 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 the second WHI Extension Study began in March 2010 and 93,558 participants enrolled (52,063 OS; 41,495 CT.) The purpose of extended follow-up is to expand the range of scientific questions that can be reliably addressed in the WHI, to provide an infrastructure able to support additional investigations requiring some of the unique features of a very large longitudinal study of aging in postmenopausal women, and to describe the longer term effects of the original interventions, particularly for hormone therapy. Under the 2010 renewal, streamlining of the program was incorporated with operations consolidated primarily into four Regional Centers and their Outcomes Collection Satellites and the Clinical Coordinating Center.

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 07/31/2016) 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). If WHI staff are unable to reach WHI participants for the annual contact, a small number of next of kin contacts are required. 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.

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 to inform development of approaches to disease prevention. 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 over the last five years enhances achievement of the WHI original goals and increases the range of scientific issues that can be examined. A WHI reference list of current OS and CT findings is included in Attachment 1. 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 1. 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.

The WHI Extension Study is currently funded through April 2021. The objectives of the WHI Extension study continue to be:

- Expand knowledge about the determinants of cardiovascular disease in older women (and conversely determinants of successful aging with absence of cardiovascular disease);
- Expand the study as a scientific resource for the research community;
- Mentor young investigators;
- Facilitate a new generation of large simple prevention trials.

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 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, and Form 151, Activities of Daily Life) 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.)

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 re-certified the WHI system security plan in November 2012, which will be updated within 60 days of new contract award anticipated in April 2016.

WHI Investigators have considered the potential to move to electronic data capture, but the following factors have argued against the transition:

1) Introducing a new electronic data capture system to WHI participants will not replace need for paper forms. WHI participants are currently between 66 and 101 years of age and as a group, they are less able and willing to embrace new technologies. More than 70% of our participants report using the computer for email or internet access, but their uptake of and facility with these technologies are highly variable across age and SES

2) WHI mailings have been highly successful. WHI has achieved and maintained a remarkably high retention rate; more than 93% respond annually, the vast majority of which is based on our bulk mail effort. WHI participants have responded very positively to mailings.

3) In addition, families will often respond to physical mailings that reach a participant who has become incapacitated or died. Email or other electronic communications may never be visible to the loved ones of a participant so these forms of communication would not trigger them to respond to us.

4) Electronic services also do not provide automated notices of address or vital status corrections as supported by the US Postal Service, nor would they easily facilitate the collection of the medical release forms that are incorporated in the annual mailings.

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 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 approximately 1.24 hours.

A.6 Consequences of Collecting the Information Less Frequently

Established study procedures **(see Attachment 1)** for collecting medical history update and activities of daily living information will be continued during this OMB period. The CCC will continue annual centralized mailings to obtain self-reported medical and aging-related outcomes.

All eligible/consenting WHI participants will continue to be followed in the WHI 2015 - 2020 to collect data primarily on health outcomes using 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.8.1 Comments in Response to the Federal Register Notice

A 60-day Federal Register notice soliciting comments on the WHI Observational Study prior to submission to OMB was published in the Federal Register Vol. 81 on April 4, 2016, Pages: 19207-19208, Document Number:2016-07487 and allowed 60-days for public comment. No comments were received.

A.8.2 Efforts to Consult Outside Agency

The NHLB Advisory Council was approved the WHI 2015 - 2020 study at the October 2013 meeting **(Attachment 2)** Questionnaires used in WHI from baseline to follow-up have been reviewed/modified and approved by Principal Investigators, and are now submitted for approval by OMB officials.

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A.9 Explanation of Any Payment of 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.

Personally Identifiable Information is collected in this study. 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 3.) 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 4).**

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.12.1 Estimated Annualized Burden Hours

Total annual burden is reduced since the previous submission due to completion of data collection of form 156 (Supplemental Questionnaire.) Respondents fall into three general categories: WHI study participants (citizens who consented to volunteer their time to respond to surveys about their health), WHI participants next of kin (when the participant is unable to provide the requested information for some reason), and WHI study participants health care providers (contacted only when the participant and her next of kin are unable to provide the requested information.) Burden is estimated by multiplying the estimated number of respondents by the estimated time needed to complete the form.

Table A.12.1 Estimated Annualized Burden Hour

Form Name	Type of Respondent	Number of Respondents	Number of Responses per Respondent	Average Burden Per Response (in hours)	Total Annual Burden Hours

Medical History Update	Participants	40203	1	7/60	4690
Activities of Daily Life	Participants	40203	1	6/60	4020
Personal Information Update	Participants	40203	1	3/60	2010
Initial Notification of Death	Next of Kin	900	1	5/60	75
Initial Notification of Death	Physician/ Office Staff	15	1	5/60	1
TOTAL		41,118	121,524		10,796

A.12-2 ANNUALIZED COST TO RESPONDENTS

Cost was estimated by multiplying the number of respondents from the general population (WHI study participants and their next of kin) by the time needed to respond, using the mean hourly wage estimated by the Bureau of Labor Statistics. For health care providers, the same methodology was used, except the Physicians/Office Staff salary estimated by averaging mean salaries for RN, NP, and MD (internist).

A.12-2 Annualized Cost to the Respondents

Type of Respondent	Number of Respondents	Average Burden Per Response (in hours)	Hourly Wage Rate*	Respondent Cost

OS Participants and Next of Kin	41103	25/60	$23	$17126.25
Physicians/ Office Staff	15	5/60	$57	$71.25

May 2014 National Wage Estimates, BLS – mean hourly wage
Physicians/Office Staff estimated by averaging RN, NP, MD
http://www.bls.gov/oes/current/oes_nat.htm#00-0000

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, 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 75 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 approximately 1 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 10,796 (table calculations: number of respondents x frequency of response = total responses; total response x average time per response = annual hour burden). Although the WHI 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 July 31, 2016. 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
Mailed Questionnaires:	
20- Personal Information (subset of OS who report changes)	3
33- Medical History Update	7
151 –Activities of Daily Life	6
CT/OS Other Respondent Form:	
120- Initial Report of Death- for physician or next-of-kin	5

A.13 Estimate of Other Total Annual Cost Burden to Respondents or Record Keepers

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

A.14. Annualized Cost to the Federal Government

The Women's Health Initiative is largely being conducted by contractors. At the same time, there are NHLBI staff time for study oversight. The total annualized cost to the U.S. Government for information collection on the WHI Observational Study Participants is $3,313,170 per year.

TABLE A.14-1 ANNUALIZED COSTS TO THE GOVERNMENT FOR INFORMATION COLLECTION, THOUSANDS OF DOLLARS

Staff	Grade/Step	Salary	% of Effort	Fringe (if applicable)	Total Cost to Gov't
Federal Oversight					
Contracting Officer	14-5	133,264	10		13,326
Contracting Officer's Representative	12-5	82,359	10		8,236
Contractor Cost					
Salary					1,247,128
Materials, Supplies, and Equipment					5,974
Travel					11,508
Consultants					140,552
Other Direct Costs					129,450
Subcontracts					690,334
Indirects					1,088,223

Total					3,313,170

A.15 Explanation for Program Changes or Adjustments

The total annual respondent hours requested in this submission is 10,796, compared to the current inventory of 14022. This reduction is primarily due to the completion of data collection for Form 156 (Supplemental Questionnaire) that was included in the last three-year OMB submission, but is not included in this submission.

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

For collections of information whose results will be published, outline plans for tabulation and publication. Address any complex analytical techniques that will be used. Provide the time schedule for the entire project, including beginning and ending dates of the collection of information, completion of report, publication dates, and other actions.

A.16 - 1 Project Time Schedule

Activity	Time Schedule
Collection of medical history updates	1 - 2 months after OMB approval
Documentation/Adjudication of health outcomes	3 - 8 months after OMB approval
Analyses	12 - 18 months after OMB approval
Publication	18 months after OMB approval

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: None