Section 1
Women's Health Initiative (WHI) Extension Study Protocol
September 16, 2011

1. Summary of WHI Extension Study

The Women's Health Initiative (WHI) Extension Study will follow all consenting participants from each of the original WHI study components (randomized clinical trials of a dietary modification, hormone therapy, and calcium and vitamin D supplementation as well as the observational study) for health outcomes. 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. The Extension Study activities, funded through the National Heart Lung and Blood Institute (NHLBI), originally planned for 2005-2010, will be extended, continuing through March 31, 2015 and potentially beyond, as funding permits. Under the 2010 renewal, some streamlining of the program is incorporated with operations consolidated primarily into a small number of Regional Centers (RCs) and their Outcomes Collection Satellites (OCS) and the Clinical Coordinating Center (CCC). The WHI Extension Study will continue to provide an infrastructure to facilitate the use of data and specimens by WHI investigators throughout the Extension period, by outside investigators through collaboration, or through an independent process under an NHLBI Broad Agency Announcement.

2. Background

The WHI was one of the largest studies on the health of postmenopausal women done to date, Between 1993 and 1998, more than 161,000 women between 50 and 79 years of age joined the WHI which consisted of an Observational Study (OS) involving 93,676 women and a partial factorial Clinical Trial (CT) consisting of three components: a Dietary Modification Trial (DM) with 48,835 participants; a Hormone Replacement Trial (HT) with 27,347 participants, which included an Estrogen plus Progestin (E+P) arm (16,608 participants) and an Estrogen-alone (E-alone) arm (10,739 participants); and a Calcium and Vitamin D Supplement Trial (CaD) with 36,282 participants.

The original protocol indicated that study close-out was to occur between October 2004 and March 2005. Participants in the DM and CaD trials remained on intervention until their last clinic visits during this interval. The E+P intervention was terminated in July 2002 at the recommendation of the WHI Data and Safety Monitoring Board, following the findings that risks outweighed the benefits for combined hormone use (The Writing Group for the Women's Health Initiative, 2002). The E-alone intervention was stopped in March 2004 at the direction of the NHLBI based on an increased risk of stroke and the unlikelihood of being able to establish either CHD benefit or an adverse effect on breast cancer (The Women's Health Initiative Steering Committee, 2004). Participants in both hormone trials continued to be followed, including annual mammography, through the scheduled close-out visits. Participants in the OS were followed annually by mail until the final cycle of mailings that began in spring of 2004. Details on the design of the WHI, WHI participants, and major study findings for the DM and CaD are described elsewhere (The Women's Health Initiative Study Group, 1998; Anderson et al, 2003, Prentice et al, 2006a, Beresford et al, 2006, Jackson et al, 2006, Wactawski-Wende et al, 2006; Howard et al, 2006).

Beginning in October 2004, participants were consented for the WHI Extension Study (ES). Overall, 82% of CT participants (52,176) and 73% of OS participants (63,230) agreed to further follow-up (115,406 total). The ES follow-up entailed an annual mailing to obtain self-reported outcomes, hormone use among HT trial participants, and quality of life. Other data collection included a one-time collection of historical diagnoses of Parkinson's disease and diabetes (ES Year 1), and medication and supplement use during (ES Year 5). Throughout the initial extension period, participants previously randomized to the intervention arm of the DM trial received a quarterly newsletter to promote maintenance of the dietary behaviors taught by the intervention. To assess dietary intake during this period, random samples of DM participants completed a 24-hour dietary recall in ES Years 1 and 5.

2.1 Considerations for Follow-up of WHI Participants

Continuing high quality clinical outcome ascertainment will increase the range of scientific issues that can be examined. In particular additional follow-up will allow the WHI to address questions related to rarer health conditions and those primarily found in women of advanced age. 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; identify new risk factors; explore risk factors of uncertain status or factors which have yet to be identified; help elucidate the mechanisms underlying the excess risk of mortality at low levels of weight, cholesterol, and blood pressure; and to examine subgroups of women (for example by race, age, SES) to determine whether or not the same risk factors operate to the same degree across such subgroups. Most CVD events and deaths occur in older women, women over the age of eighty. This is the most rapidly growing demographic in the US, and WHI has one of the largest cohorts of older women, with over 30% of the 115,000 enrolled in the Extension study having reaching their ninth decade by 2009.

As envisioned, continued follow-up will also provide the basic infrastructure on which additional, high quality investigations can be supported in a cost-efficient manner. Maintaining contact with these long-standing participants and obtaining information on their health status through an efficient nationwide mechanism will create opportunities to explore related topics (e.g., biological mechanisms of disease, predictors of healthy aging) in more depth or to evaluate emerging interventions that may prevent morbidity and mortality in this increasingly important age-group at lower cost.

Additional follow-up will also allow a reliable study of the longer term health benefits and risks of the CT interventions including those that may be affected by study treatments only many years after the initiation of intervention (e.g., mortality), particularly for the hormone therapy trials.

2.2 Considerations for Additional Data Collection from HT Participants

In the first report from post-intervention follow-up for the E+P trial, no statistically significant increased cardiovascular risks were observed in the women assigned to CEE plus MPA as compared to women assigned to placebo, although point estimates suggested the possibility of some continuing adverse effects for stroke and venous thrombolembolic disease (Heiss et al, 2008). The protective effect of E+P on fractures had also diminished (Heiss et al, 2008). Evidence of some dilution of E+P effects on breast cancer incidence was observed (Chlebowski et al, 2009) but a greater risk of fatal and nonfatal malignancies occurred after the intervention in the CEE plus MPA group and the global risk index remained significantly elevated in women randomly assigned to the combined hormone group (Heiss et al, 2008). While these reports on the early post-intervention period found few statistically significant effects, longer follow-up is needed to track the trajectory of these effects and determine whether there is persistent harm for stroke, VT, breast cancer and other cancer incidence and mortality as well as to examine any longer term effects of this 5-year intervention on women in their eighth and ninth decade.

Post-intervention follow-up of the E-alone trial through 2009 found no associations with risk of CHD, deep vein thrombosis, stroke, hip fracture, or colorectal cancer, but a nominally statistically significant decreased risk of breast cancer was observed over the mean 10.7 years of follow-up and median 5.9 years of CEE use (LaCroix et al, 2011). These findings reinforce the outcome-specific differences in hormone therapy effects.

Post intervention findings from the DM and CaD trials have not yet been published but will be developed on the complete database from the 2005-2010 Extension study..

2.3 Considerations for Additional Data Collection from Minority Women

In 2007, NHLBI initiated the SNP Health Association Resource (SHARe) program to create a widely shared resource of genome-wide SNP typing and multiple phenotypes for gene discovery. Beginning in 2008, WHI participated in this program, contributing specimens and data from approximately 9,000 African Americans and 4,000 Hispanic participants to this unique database for the discovery of gene associations with common discrete clinical phenotypes. Because of the large numbers of racial/ethnic minority women participating, WHI will complement substantially the heart failure research in ARIC and Framingham, and the GWAS efforts in other

NHLBI cohorts. Continued follow-up of these participants and collection of high quality clinical outcomes data will increase the value of this resource and support the overall mission of SHARe.

3. Study Objectives

The primary objectives of the continuing WHI Extension Study are:

Objective 1: To study factors leading to an increased risk of CVD in older women of diverse race and ethnicity, including CHD, stroke, heart failure, atrial fibrillation, PAD, and VTE, and conversely to examine the factors that determine absence of CVD as part of successful aging.

Objective 2: To study the longer-term effects of estrogen plus progestin and estrogen alone on cardiovascular disease, cancer and fracture incidence and mortality.

Objective 3: To serve as a platform, at low incremental cost, for a new generation of prevention trials of lifestyle interventions or supplements affecting the overall health of older women.

Objective 4: To serve as a platform, at low incremental cost, for studies of the health of post-menopausal women as they age.

To achieve these objectives full outcomes ascertainment and documentation will occur annually in two important sub-cohorts of women—those in the hormone trials, plus African-American and Hispanic women—a target of 24,000 of whom 8,000 will be over age 80, and 10,000 will be racial/ethnic minorities. In addition, self-reported outcomes for the full range of health conditions will be collected annually from the entire cohort to support the same high quality documentation of their outcomes as funding permits.

4. Study Design

4.1 Overview

The original WHI design was composed of two primary study components, a partial factorial randomized clinical trial and an observational study. Women participating in the CT accepted randomization into the DM or HT trials (or both). After one year of CT participation, they were offered randomization into the CaD trial. Women not eligible or interested in the CT were offered enrollment into the OS. For the continuation of the WHI Extension Study, participating women will continued to be associated with the same study component(s) to which they were originally enrolled.

4.2 Study Population

In the original WHI, eligibility and exclusion criteria were as broad as possible to increase the generalizability of the results to the population of postmenopausal women. The original study inclusion criteria were identical for all components and consisted of:

- Age 50-79 years at initial screening
- Postmenopausal
- Expected to live in the same geographic area for 3 years
- Willing to provide written informed consent

Exclusion criteria were specific to each of the components and were related to safety, adherence and retention issues, and competing risks [see WHI protocol Section 4.4 for details].

The WHI Extension Study will include all participants from the WHI who provide written informed consent indicating their willingness to be followed in the future.

4.3 Outcomes of Interest

To support the broader scientific objectives of the WHI Extension Study, some that are uniquely feasible in a very large study of older women, information on a broad range of health events and conditions will be

ascertained through both active and passive follow-up mechanisms. With the increased emphasis on heart disease and aging, several new study outcomes are now included. In most cases, outcomes will be ascertained initially though self-report (or proxy report in the case of death or incapacity). Selected self-reported outcomes will be documented and adjudicated based on study priorities and funding as described in *Table 1*.

Medical Records Cohort (MRC): Full outcomes ascertainment and documentation will be conducted in two important sub-cohorts of women: those in the hormone trials plus all African American and Hispanic participants.

Self-Report Cohort (SRC): The remaining WHI Extension Study participants will be followed with outcomes ascertainment limited to self (or proxy) report or passive follow-up sources of information unless or until funding is obtained to collect their medical records.

Table 1
Outcomes by Study Component and Level of Information Required.
A—Adjudicated medical records; S—Self/Proxy Report/Passive follow-up only;
L—Limited documents reviewed for capture of other events/ ICD9 coding;

Outcome	Medical Records Cohort (MRC)	Self-Report Cohort (SRC)
CARDIOVASCULAR:		
Coronary heart disease	A	S
Angina	S	S
Coronary Artery Bypass Surgery	A	S
PTCA	A	S
Heart valve problem/repair[1]	A	S
Aortic aneurysm[1]	A	S
Stroke	A	S
Transient ischemic attacks	S	S
Carotid artery disease	A	S
Heart Failure[2]	A	S
Atrial Fibrillation[1]	A	S
Venous thromboembolic disease 3	A	S
Peripheral vascular disease	A	S
CANCER:		
All sites except non-melanoma skin cancer	A	A
FRACTURES:		
Hip	A	S
Other fractures	S	S
OTHER AGE-RELATED DISEASES		
Chronic obstructive pulmonary disease (COPD)1	S	S
Diabetes mellitus requiring therapy (insulin, pills, diet)	S	S
Hypertension requiring therapy	S	S
Intestinal or colon polyps or adenomas	S	S
Macular degeneration	S	S
Osteoarthritis or arthritis associated with aging	S	S
Parkinson's disease	S	S
Systemic lupus erythematosus	S	S
SOCIAL/PSYCHOLOGICAL CONDITIONS		
Moderate/severe memory problems (dementia/Alzheimer's)	S	S
OTHER		
Selected Hospitalizations for 2+ nights	L	S
Falls	S	S
Hysterectomy	S	S
Death from any cause	A	S

[1] - Outcome added for 2010-2015 Extension
[2] - Previously by self-report only
[3] - Originally in HT only

4.4 Sample Size

The original sample sizes for each study component and each arm of the partial factorial design are shown in *Figure 1*. In 2004-2005, all living WHI participants who permitted study contact were invited to participate in the WHI 2005-2010 ES. Over 115,000 participants consented (77% of eligible participants, 71% of original enrollees), resulting in the distribution by study component shown in Figure 1(lower panel). For the continuation of the Extension Study, all living participants under active surveillance in 2010 will be invited to participate in ongoing follow-up. It is anticipated that approximately 80% of these will consent to continuing follow-up.

Figure 1
Original and Extension Study Enrollment by Study Component

	CT	OS	Total
Original WHI enrollment	68,132	93,676	161,808
2005-2010 Extension Study enrollment	52,176	63,230	115,406

WHI CT Partial Factorial Design

Number of women enrolled in the original trial WHI components
(Numbers in parentheses represent enrollment in the CaD trial)

			HT (CaD)					
			Intact Uterus					Not Randomized
			Yes			No		
			E+P	Placebo		E-alone	Placebo	
			8,506	8,102		5,310	5,429	40,785 (20,193)
DM (CaD)	Intervention	19,541 (9,645)	972 (596)	925 (577)		615 (371)	670 (430)	16,359 (7,671)
	Control	29,294 (15,565)	1,457 (917)	1,304 (838)		1,039 (639)	1,068 (649)	24,426 (12,522)
	Not Randomized	19,297 (11,072)	6,077 (3,530)	5,873 (3,455)		3,656 (2,064)	3,691 (2,023)	
Total		68,132 (36,282)						

Number of women consenting to the 2005-2010 Extension Study by original WHI trial components
(Numbers in parentheses represent original CaD trial enrollment)

			HT (CaD)					
			Intact Uterus					Not Randomized
			Yes			No		
			E+P	Placebo		E-alone	Placebo	
			6,545	6,243		3,778	3,867	31,743 (16,946)
DM (CaD)	Intervention	14,769 (7,920)	741 (493)	712 (466)		448 (286)	499 (337)	12,369 (6,338)
	Control	23,089 (13,090)	1,140 (756)	1,028 (714)		753 (494)	794 (518)	19,374 (10,608)
	Not Randomized	14,318 (8,852)	4,664 (2,887)	4,503 (2,817)		2,577 (1,598)	2,574 (1,550)	
Total		52,176 (29,862)						

Power calculations pertinent to the combined CT and OS as a cohort study for a range of sample sizes that may represent either the entire cohort or key component specific or racial/ethnic subgroups are included in Appendix B.

5. Study Plan

5.1 General

All WHI CT/OS participants still in active follow-up will be invited to continue their participation in the WHI-ES 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 in-person visit is planned to collect standardized clinical measures, limited functional status information and blood on 8000 women over 78 years of age. A closely associated ancillary study will collect more in-depth measures of physical activity in conjunction with the in-person visit. Retention efforts will be employed throughout the WHI-ES to maintain contact with participants and encourage continued participation.

5.2 Re-consent

All WHI Extension Study Participants who have not declined further contact are eligible to continue in the WHI-ES. The re-consent process will occur between April and March, 2011. In April 2010, the CCC will send the annual study newsletter to participants. This newsletter will introduce the continuation of the program, the planned re-organization and what it means for them, and will let them know to expect the consent mailing within a few weeks.

In May through June 2010, the CCC will send a consent packet to each woman who is eligible for mailed contact. The consent packet will contain a personalized letter asking her to consider continuing in the study, two copies of the informed consent document, a Personal Information Update, and a self-addressed, postage-prepaid envelope. All consent materials will be provided in large print in English or Spanish. A copy of the consent is included in Appendix A. Participants will be asked to return one copy of the consent form and the Personal Information Update to the CCC in the enclosed pre-addressed envelope. Women who have not responded to this mailing within 4 weeks will be sent a second consent mailing. A toll-free number will be provided for women to call if they have questions.

Women who do not respond to either consent mailing will be contacted by telephone by staff from the WHI Field Center that is currently responsible for their follow-up. Typically, at least 3 attempts to contact will be required for each participant by September 30, 2010. Once contacted, Field Center staff will insure that the participant has received the mailing, explain the nature and purpose of the continuing activities and answer any questions she may have. If the participant no longer has the consent documents, Field Center staff will arrange for the CCC to mail another packet.

Women who are currently followed only by phone will be contacted first by the responsible WHI Field Center to ascertain interest and willingness to continue. If the woman indicates continuing interest, the Field Center will arrange for the CCC to send a consent mailing to her.

5.3 Follow-up

Continuing Extension Study participants will be followed annually, primarily by mailed questionnaires from the CCC, to collect data primarily on self-reported health events and related conditions, using a modification of the procedures employed previously. To spread the work evenly throughout the year, approximately one-twelfth of the participants will receive the mailing each month, beginning in August 2010 for participants who consent by July 2010**.** The contents of the mailing will vary by year, as indicated in Table 2 but will always include *Form 33 - Medical History Update* and a postage-paid envelope.

Follow-up packets returned by the US Postal Service to the CCC with a change of address notification will be sent a personal contact information update form and follow-up packet by first class mail. Participants with undeliverable packets will be flagged in the Extension Study database for RC follow-up.

Participants will be asked to complete and return their forms to the CCC for scanning. Non-respondents will receive one additional mailing from the CCC. Once a sufficient interval after the last mailing has passed with no response, Regional Center (RC) or Outcomes Collection Satellite (OCS) staff will attempt to contact those participants by telephone to collect this information. In addition, RC/OCS staff will also telephone participants who have requested telephone follow-up. RC/OCS staff will be asked to review personal contact information on each such contact.

Because of the nature of the medications inventory forms, participants will be given an option of completing these by phone. As previously implemented in the 2009 cycle, a toll-free number will be provided with the mailed questionnaire.

Table 2: Data Collection Schedule[§]

Form #	Data collection	2010-2011	2011-2012	2012-2013	2013-2014	2014-2015
-	Re-consent and Personal Information Update	X				
33	Medical History Update	X	X	X	X	X
151	Activities of Daily Life (ADL)	X		X	X	X
155	Lifestyle Questionnaire (includes ADL)		X			
153	Medication and Supplement Inventory			MRC		
	In-person visit Consent		IPV			
100	Blood Collection and Processing		IPV			
80	Physical Measurements		IPV			
90	Functional Status		IPV			

X = all Extension participants; MRC = Medical Records Cohort; IPV = In-person visit participants
[§]Copies of forms can be found in Appendix C

Medical Records Cohort Specific Outcomes Collection Activities:

Data from the scanned Form 33 will be made available electronically to Regional Centers for use in their subsequent outcomes documentation efforts. RC/OCS staff will review Form 33 from Medical Records Cohort members for completeness and for potential health events requiring retrieval of medical records. RC/OCS staff will telephone the participant, as needed, to clarify or complete responses on these questionnaires. If the participant has signed the Release of Information located on the back of Form 33, RC/OCS staff will use this form to obtain medical records for the designated events for participants in the Medical Records Cohort. If needed, RC/OCS staff will obtain an institution-specific release of information from the participant. RC/OCS staff will collect outcomes documentation and then assemble them into packets. They will label each document with the participant's study ID, electronically scan the entire outcomes packet, and forward the scanned documents to the CCC for review. The CCC will remove all confidential identifiers and forward the chart for subsequent adjudication according to existing procedures for adjudicating cases.

Self-Report Cohort Specific Outcomes Collection Activities: Data from the scanned Form 33 will be stored at the CCC for use as self-reported events. If funding becomes available, documentation and adjudication as described for the Medical Records Cohort may be implemented for selected outcomes or selected participants.

Passive Follow-up: At regular intervals, the CCC will obtain information on vital and health status for the entire cohort, as applicable, through accessing national databases such as the National Death Index (NDI), and the Center for Medicare and Medicaid Services (CMS), cancer registries, and large health maintenance organizations such as Kaiser Permanente. This information will be linked to the existing database for use in

studies to examine additional health outcomes, health care utilization and aspects of quality of care, and comparative effectiveness.

5.4 In-person Visit

A target sample size of 8,000 women aged 72 or more will participate in the in-person visit (WHI Long Life Study), scheduled to begin in late 2011. To complete data collection on 8,000 women, an eligible population of approximately 10,000 women will be selected for inclusion as follows: All WHI Memory Study (WHIMS) participants and non-WHIMS MRC participants who will (1) be at least age 72 by 12/1/2011 and (2) have baseline biomarker data (glucose, insulin, CRP, creatinine, triglycerides, total cholesterol, LDL, and HDL) available. Participants will be excluded if they reside in an institution (e.g., skilled nursing facility).

The data and blood collected in this study will establish a new baseline from which numerous studies on aging and health/disease can be conducted. A brief clinical assessment will be conducted on all participants, including an assessment of functional status. The primary aims of the blood collection are to (1) establish a repository of new baseline biospecimen on this cohort, (2) replenish the WHI biospecimen resource for members of this cohort with a new source of good quality extracted DNA and RNA, plasma, serum, and RBCs for future standard clinical laboratory assays as well as cytokines, proteomics, metabolomics, and other assays that have yet to be imagined, and (3) obtain CBC data (e.g., hemoglobin, white blood cell count) and CVD biomarker data (glucose, insulin, creatinine, CRP, total cholesterol, HDL, LDL, and triglycerides).

A closely related ancillary study, Objective Physical Activity and Cardiovascular Health in Women Aged 80 and Older (OPACH80, PI Andrea LaCroix), is likely to be funded. The goals of this study are similar to the in-person visit in that the objective is to increase understanding of the health of aging women – specifically the association of physical activity with cardiovascular events and total mortality. OPACH80 was designed to collect most of its data as part of the in-person visit. This protocol treats OPACH80 as part of the In-person Visit. The eligible population for OPACH80 will be identical to the In-person Visit with one exception: OPACH80 will exclude women who are non-ambulatory.

Consent: Over a 12 month period, the CCC will send an In-person Visit consent mailing to the selected women. The initial consent mailing will be preceded by an Advance Postcard designed to pique the interest of eligible women. The consent packet will include a letter explaining the nature and purpose of the study, two copies of a consent form and a self-addressed, postage pre-paid envelope. The women will be given a toll-free number to call with questions and asked to sign the consent and return the signature page from one copy of it to the CCC in the envelope provided. One week after the initial consent mailing, all women will receive a thank you/reminder post card. Women who have not responded within three weeks of the initial mailing will be sent a second consent packet. Finally, women who have not responded within 6 weeks of the initial consent mailing will be called by interviewers from FHCRC-based staff - (Collaborative Data Services (CDS) or CCC staff) for telephone consent. Typically, the CDS staff will make at least 3 attempts to contact non-responders to obtain telephone consent. A similar consent process was successfully implemented for the WHI Extension II consent. However, for the in-person visit telephone consent will be confirmed at the outset of the in-person visit and documented by the woman's signature on a consent form.

Scheduling: Once the CCC has received documentation of consent for a woman (signed copy of the consent form or telephone consent form signed by the interviewer who obtained telephone consent), the CCC will notify the organization subcontracted for the data collection (Examination Management Services, Inc. – EMSI), providing them with the participant's name, address, telephone number and study ID. The EMSI staff will contact the participant to arrange a mutually agreeable date, time and location for an in-person data collection visit. The visit may occur in the participant's own home or, if she prefers, her physician's office or a facility operated by EMSI.

Training/Certification: In concert with EMSI's project coordinator, the CCC will develop, test (alpha and beta), revise if needed, and implement a centralized Web-based training program for all EMSI examiners (also referred to in this protocol as research assistants - RAs) who might be assigned to WHI participants. The Web-based training program will culminate in a test, with feedback provided for every incorrect answer and ≥ 90% correct answers required for certification. If initial testing results in <90% correct answers, repeating the training course a week later will be required. If more than one month has passed between a RA's certification

and assignment to a WHI case, re-certification will be required. If less than one month has passed between an RA's certification and assignment to a WHI case, review of the training course will be highly encouraged.

Data Collection: In addition to the project-specific training, EMSI will ensure that each RA scheduled to collect data from a WHI participant is trained/certified on protection of human subjects in research, trained/certified in phlebotomy, passed a felony record search and drug screen, completed a customer service training program, and completed/passed a HIPAA training program. The EMSI Scheduling staff will have a separate training/certification program developed by the CCC – as will the FHCRC-based staff who will conduct the telephone consent calls.

The in-person visit will require about 70 minutes and include:

- Physical measurements: height, weight, blood pressure, pulse, waist circumference
- Blood draw (~ 31ml)
- Physical function measurements: balance, gait speed, chair stand, grip strength
- OPACH80 adds the following to the in-person visit (among ambulatory participants):
    - Delivery of a self-explanatory survey packet
        - physical activity questionnaire
        - a monthly falls/injuries reporting system (via postcard)
    - Delivery of a self-explanatory physical activity monitor packet and brief instruction on use of the monitor by participants for seven days following the in-person appointment

Blood Processing: Immediately after the in-person visit, the RA will travel to an appropriate location to prepare the blood vials within two hours of draw for overnight shipment to the central lab (FHCRC Specimen Processing Lab). Upon receipt of each in-person visit shipment, the central lab will open the package and assess the contents for completeness and adequacy of packaging, deliver the CBC vial to the testing lab (Seattle Cancer Care Alliance Hematology Lab), and process the remaining blood vials according to the manual of operations. Blood samples will be frozen and stored for future DNA and RNA extraction (within ~ one month). All other aliquots will be frozen and shipped to the WHI Biorepository. One of the serum aliquots for each participant will be sent from the Biorepository to the University of Minnesota Fairview Lab for biomarker testing (lipids, glucose, insulin, creatinine, and CRP) within approximately 6-12 months of the draw date.

Data Processing: Immediately following the shipment of blood to the central lab, EMSI will fax the completed study forms to EMSI's central office, where they will be stored only as an electronic image. Original hard copy forms will be held securely at the branch office until it receives official notification from WHI that the project is completed, at which time the hard copy forms will be shredded. Daily, EMSI's central office will submit electronic copies of collected data forms to the WHI CCC via FTP. Data will be reviewed and key-entered by WHI CCC staff.

Post-visit Letter: Within about two weeks of the in-person visit, the CCC will send participants a thank you letter. The letter will include the participant's CBC results and advice for discussing the results with their doctor if necessary. (If the CBC results require urgent action, a CCC staff member will call the participant in advance of the letter.) If the participant returns the physical activity monitor as instructed, the letter will also include a $25 gift card as small token of our appreciation. (The mailing and the gift card will be paid for with OPACH80 funds, should funding be awarded.) As the biomarker assays (lipids, glucose, insulin, creatinine, CRP) will not be completed until ~6-12 months after the blood draw, those results would not be considered clinically relevant – and will not be provided to the participant.

Post- In-person Visit OPACH Calibration Study: Following the in-person visits, OPACH80 will conduct an accelerometer (physical activity monitor) calibration study among 200 participants. The calibration study data will be collected at two WHI clinic sites (Stanford U. and U. of Alabama, Birmingham). Women will be eligible to participate in a clinic visit if they meet the following criteria: (1) residence near either the Stanford or Birmingham clinic, (2) originally recruited into the WHI at either Stanford or Birmingham, (3) wore the physical activity monitor for seven days, (4) able to walk without a walker, (5) lack major mobility disability as determined by a score of ≥ 4 on the Short Physical Performance Battery (SPPB), (6) able to walk at least 400 meters (self-reported), (7) no history of clinically significant CHD (MI or angina), emphysema, asthma, or other condition causing chest pain or shortness of breath during walking, and (8) willing to participate and to provide informed consent. The initial eligibility list will be prepared by the CCC based on WHI database information and the SPPB performed at the in-person visit. The Stanford and Birmingham clinic staff will collect remaining

exclusion criteria data during a brief (~10 minute) phone interview. Final decisions on eligibility will be made by the CCC.

Calibration Study Consent: The in-person visit consent form will mention the possibility of a future invitation for a clinic visit. Once selected as eligible for the clinic visit, women will be called by staff at the CCC or her WHI Regional Center, invited to join the clinic phase of the study, and introduced to the clinic visit activities. If interested and willing, a clinic appointment will be set. At the clinic visit, the participant will have time to read the in-person visit consent form and ask questions to the clinic staff. If the participant signs the consent, the clinic visit assessments will continue. Calibration study participants will receive a $25 gift card for participating.

The calibration study clinic visit will take 30 - 90 minutes and include:

- Body height and weight using a calibrated balance-beam scale and a standiometer.
- CHAMPS physical activity questionnaire and WHI Physical Activity Questionnaire (PAQ), which will provide contemporaneous measures of physical activity level and walking performance.
- Rating of perceived exercise capacity using a scale developed by Wisen [Wisen et al, 2002] that explained 66% of the variance in aerobic capacity in women age 20 to 80.
- 400 meter walk, using the protocol of the LIFE-P study that involves walking 10 laps around an indoor course. The test is stopped if participants cannot complete the walk in 15 minutes. Participants may use a cane during the walk, but cannot use a walker or other assistive device.
- Accelerometer and step counts during the 400 meter walk, measured using the Actigraph GT3X during the walk with the step counter function turned on.
- Accelerometer counts/min and oxygen consumption during standardized tasks.

Quality Control: The CCC will monitor the quality, quantity, and timeliness of all in-person visit operations, including the calibration study. The CCC project coordinator will meet via conference call at least monthly with the EMSI project coordinator to review reports (training, scheduling, and visit completion), discuss concerns and successes, and make adjustments as required. Adherence to the in-person visit protocol will be monitored by the CCC via direct site visit observations, review of completed forms, reports from the central lab, and EMSI routine performance reviews.

5.5 Retention

Retention is an important focus after participants are enrolled in the Extension Study. Several retention mechanisms used during WHI will continue, including an update of contact and proxy information at the time of reconsent, annual participant newsletters, updates of the participant's address provided by the US Post Office, and review of contact information on all phone contacts.

Participant newsletter

The CCC will send all participants an annual WHI newsletter. The newsletter will present WHI news and lay versions of results, and will support retention through promotion of participant identification with WHI and address maintenance. To help maintain contact, the newsletter will be mailed by the CCC approximately 6 months before/after the annual data collection packet.

Maintaining current contact information

All CCC mailings to participants will be imprinted with the CCC's return address and include a line requesting address corrections. The US Post Office will notify the CCC if the participant is deceased, if the packet is undeliverable to that address, or with information on a new address. For address corrections, CCC staff will update the participant's address in the database and mail a new packet to the participant, along with a Personal Information Update. Participants will be asked to review and update their contact information and to return it to the CCC. If the current address is undeliverable or the participant is deceased, this information will be noted in the database for use by RC/OCS staff. RC/OCS will use those methods developed in WHI to trace participants with undeliverable addresses to obtain new contact information. No additional mailings will be sent to a participant until the undeliverable address is corrected.

At each telephone contact with participants, RC/OCS staff will review and update the participant's address, phone number(s) and other contact information in the Extension Study database.

Data collection by proxy
Because of a participant's illness, disability, or death, follow-up contacts may need to be conducted by proxy. RC/OCS staff will be responsible for assessing the need to use a proxy respondent and noting this in the Extension Study database. Based on these database flags, the CCC will send the participant forms packet to the proxy contacts previously identified by the participant.

6. Study Operations

6.1 Data Management

For usual data management and communication purposes, each Regional Center and Outcomes Collection Satellites will provide their own personal computers with Windows 7, Internet Explorer 8, and office applications, and reliable and continuous access to the Internet. A small network printer and scan guns are also recommended at each site.

The CCC will provide each Regional Center and their Outcomes Collection Satellites a complete scanning system for electronically scanning outcomes documentation. This system will include a PC, scanning software and a scanner which will be shipped first to the CCC for configuration and then to the RCs. This system will need to reside on the parent institution network with reliable and continuous access to the Internet.

The CCC will maintain a central repository of all WHI and Extension Study data. For the Extension Study, a central Oracle database will be made accessible by RC/OCS staff over the World Wide Web. Each RC/OCS will be granted access to confidential data only from participants for whom they are responsible for tracking and reporting.

All routine data will be collected and entered using standardized data collection forms. Optical scan formatted forms (e.g., *Form 33/—Medical History Update, Form 151—Activities of Daily Living, Form 155—Lifestyle Questionnaire*) returned to the CCC will be scanned and imaged at the CCC and the data and images will be provided in electronic format to the RC/OCS as needed for their use in subsequent steps of outcomes documentation. Form 153 will be data entered at the CCC. Forms used directly by staff (e.g., *Form 7—Participation Status),* will be key entered by staff into a central database using data entry screens developed and provided by the CCC.

For putative heart failure events, the CCC will provide electronic copies of the assembled medical records to the central record abstraction site. Trained medical records abstractors will review these records and complete the data collection tool with on-entry editing, using ongoing training, re-certification and quality control protocols. Once medical record abstraction is complete, electronically generated summaries of abstracted medical record information, together with scanned portions of the pertinent medical record will be provided to the CCC for distribution to event adjudicators.

Adjudication forms will be completed by adjudicators and returned to the CCC for key-entry.

6.2 Quality Assurance

The quality of study-wide operations, data, and products will be assured by clear and complete documentation, central and local training and certification, routine reports, and task specific quality assurance measures (e.g., chart audits, duplicate data entry) as deemed appropriate by the CCC, the Steering Committee (SC) and its subcommittees and the NHLBI Project Office. The training and certification required for each study task is described in Extension Study Manual. In addition the CCC will perform cross-sectional and longitudinal edits of the central database. Data queries resulting from these edits, and from reporting and analysis activities, will be submitted to the RC/OCS for resolution, and a systematic means of updating the central database based on their responses will be established. Standards for performance will be proposed by the Performance Monitoring Committee (PMC), approved by the Steering Committee, documented in Extension Study Manual, and monitored by the PMC. Regional Centers or Outcomes Collection Satellites determined to be operating below acceptable performance levels will be required to submit plans for remedial

action to the PMC for approval and will be subject to more frequent monitoring and other actions determined by the PMC and/or the NHLBI to be needed to assure adequate data collection.

6.3 Outcomes Adjudication

For purposes of attaining high quality outcome data consistent with the previous study period, outcomes ascertainment, documentation, and adjudication will generally follow the procedures developed for the WHI (Curb, et al, 2003) and modified for the 2005-2010 Extension Study with modifications to include the newley added endpoints . Each documented case of cardiovascular disease, stroke, hip fractures or death in the Medical Records Cohort will be assigned to an experienced WHI adjudicator for review and coding. Outcomes packet for all cancers will be submitted to the CCC for coding of detailed tumor characteristics by a qualified SEER coder. A standardized training in WHI adjudication will be required whenever a new adjudicator is added.

Heart failure cases from the MRC will be forwarded to the Heart Failure coding center at University of North Carolina, Chapel Hill, for abstraction. The specifics for each scheme of adjudication within the cardiovascular, stroke, cancer, and fracture outcomes are detailed in the Extension Study Manual. If additional funding becomes available to document outcomes in the Self-reported Outcomes Cohort, the same adjudication procedures will be used.

7. Study Monitoring and Data Analysis

7.1 General

Progress in the Extension Study will be monitored in several ways: reports on consent, response to annual mailings and phone follow-up contacts, completeness and timeliness of data collection, and accrual of key study outcomes. The CCC will provide regular reports to the Steering Committee and the RC/OCS, as well as to the Observational Study Monitoring Board (OSMB) and the NHLBI. Reports on event rates by randomization group in the CT will be provided annually to the OSMB. These reports will provide the basis for considerations of remedial actions or protocol changes and for considerations of directed publications and notifications to participants.

7.2 Re-consent

The proportion of participants reconsenting will be tabulated by original study component, age, racial/ethnic subgroup, and responsible field center, as a fraction of eligible participants as defined at the time of the initial consent mailings in May 2010 and as a fraction of the originally randomized or enrolled participants.

7.3 Adherence to Follow-up Procedures

Completeness of data collection will be routinely reported by follow-up year and data collection form. Submission of Form 33 will serve as the primary indicator of participant retention and adherence to follow-up.

A well-defined reporting system has been developed to document the completeness and timeliness of outcomes processing in the WHI. RC/OCS performance reports will reflect the timeliness and completeness of the process initiated at the time that the *Form 33—Medical History Update* form is entered into the Extension Study database and becomes available for RC/OCS processing. Timeliness and completeness of outcomes packet formation and submission to the CCC will be the primary areas of review. Timeliness of cancer coding and adjudication of other outcomes will also be monitored. The PMC will review outcomes performance reports prepared by the CCC and the overall timeliness of outcomes processing and monitoring.

7.4 Analyses of the WHI cohort

The original purpose of the WHI Observational Study was to establish a resource in which risk factors for the major causes of death and disability in postmenopausal women could be examined. With the termination and unblinding of the Clinical Trial interventions, the entire cohort of WHI participants can be used for this same purpose, expanding the sample size available for many studies. These joint analyses are facilitated by the fact

that these study populations were recruited and followed in parallel by the same investigators and institutions using primarily the same data collection protocols and instruments. .

The ability to estimate relative risks reliably for the outcomes of interest in the WHI as a function of baseline characteristics (exposures, behaviors or biologic measurements), or as a function of changes in such characteristics between baseline and one or three years is dependent on the accurate measurement of the characteristics (and outcomes) under study, and the accurate ascertainment and proper accommodation of all pertinent confounding factors. Even measurement error that is nondifferential in the sense that it is unrelated to disease risk given the 'true' characteristic values, can severely attenuate or otherwise distort relative risk estimates. Since many of the characteristics ascertained (e.g., blood analytes, 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 (Langer et al, 2003), and can be used, under classical measurement error assumptions, to correct relative risk estimates for non-differential error in predictor and confounding variables. The 1% reliability sample was stratified on age, racial/ethnic group, and socioeconomic group. The size of the WHI study population, and the comprehensive set of measurements obtained allow a particularly thorough accommodation of confounding, by means of individual matching, stratification or regression modeling. Since, the measurement properties of some exposures of interest (e.g., self-reported nutrient consumption; self-reported physical activity patterns) involve more measurement error properties that are more complex that those acknowledged by the classical measurement model, including important systematic biases, WHI investigators have carried out nutrition and physical activity biomarker studies in subsets of WHI cohorts. These biomarker sub-studies have potential to yield calibrated exposures throughout WHI cohorts for some nutrients and for activity-related energy expenditure. Results using this calibration approach have begun to be published (Neuhouser et al, 2008; Prentice et al, 2009) and several other applications are underway. The WHI is in a unique position to lead a new cycle of more reliable association studies in the important diet, physical activity, and energy balance areas of epidemiology, during upcoming years.

Relative risk regression methods (e.g., Cox, 1972) will continue to provide the primary data analytic tool for the observational analyses. These methods, which can be thought of as an extension of classical person-year methods that avoids the assumption of constant disease risk for a study subject across the follow-up period, allow flexible modeling of the risks associated with the characteristics under study, as well as flexible accommodation of potential confounding factors, by means of stratification, matching, or regression modeling. Though less well developed they can also accommodate the types of reliability sample alluded to above (e.g., Prentice, 1982;, Pepe et al, 1989; Espeland et al, 1989; Liu and Liang, 1992), in order to produce 'deattenuated' relative risk estimates. Finally, relative risk regression methods are also readily adapted to accommodate nested case-control (Liddell et al, 1977; Prentice and Breslow, 1978) and case-cohort (Prentice, 1986) sampling schemes.

Nested case-control sampling typically 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 may include baseline age, clinic, and date of enrollment and study arm(s), and depending on the analysis may also include racial/ethnic or socioeconomic group, history of study disease, or other factors. Nested case-control or case-cohort sampling provides the principal practical approach to reducing the number of women whose blood specimens need be analyzed and processed, if the measurements of interest cannot be assumed to be stable over time. For example, certain of the antioxidant concentrations to be measured in blood specimens are known to substantially degrade over the course of a few months or years of storage, in which case the follow-up-time-matched aspect of the nested case-control approach is essential to valid relative risk estimation. For measurements that are stable over time, however, case-cohort sampling could provide an alternative that has some decided advantages. 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.

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 an 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 of 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.

Appendix 3 of 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, many of which can be applied to subgroups of the larger WHI cohort.

7.5 Analyses of the Clinical Trials

Further analyses of intervention effects on the defined primary and secondary endpoints of each trial using post-intervention data will include both cumulative effects examining the entire interval since randomization and analyses limited to the post-intervention period. The primary analysis strategies will be informed by those of the original protocol, under the intention-to-treat framework and will employ either the unweighted or weighted (2-sided) log rank statistic as originally described (The Women's Health Initiative Study Group, 1998). Such a statistic can be written

$$T = \Sigma\, w_i\, (O_i - E_i)$$

where w_i is the value of the weight function evaluated at the i^{th} largest time from randomization to clinical outcome event among women in both groups, O_i is one or zero depending on whether the outcome occurred in a woman in the treated group or not, and E_i is the conditional expected value of O_i, under the null hypothesis of no treatment effect. If V_i represents the conditional variance of O_i, then it follows from the uncorrelatedness of the elements of this summation that the variance (σ^2) of T is estimated by $\sigma^2 = \Sigma\, w_i^2 V_i$ and the test for differences between groups is then made by referring T^2/σ^2 to the 95th percentile of a chi-square distribution on one degree of freedom.

The weighting was intended to enhance test power under the expectation that intervention versus control disease incidence ratios increase in absolute value approximately linearly as a function of time since randomization. The weights w_i were chosen to equal time from randomization up to a disease-specific maximum (three years for cardiovascular disease and fracture occurrence, 10 years for cancer occurrence and total mortality) and to be constant thereafter. Because this assumption was supported in some instances in the hormone trials and not in others, both weighted and unweighted statistics will be used, with unweighted statistics as the default test statistics unless a prior evidence had suggested otherwise (e.g., for effects on cancer incidence). In analyses of post-intervention effects, unweighted time to event analyses will be conducted, typically using date of the close-out visit (or date of official notification of study closure for the HT trials) as the "time zero" for these analyses.

Analyses of intervention effects will typically be stratified on baseline age (50-54, 55-59, 60-69, 70-79), and self-reported prevalent disease (if applicable) for that outcome, and the categories of the other interventions. The primary HT comparisons will be examined separately based on baseline WHI hysterectomy status.

To assess potential selection bias among Extension Study participants relative to the initial trial cohort, comparisons of demographics, health history, adherence to intervention and key outcome event rates will be made between Extension Study enrollees and non-enrollees using data from the initial WHI database. If an assumption of no selection bias is supported, women who did not consent to the Extension Study will be censored at their last follow-up contact during the original WHI study, except for total mortality analyses where vital status information will be obtained from the NDI. Methods to account for non-representative enrollment using inverse sampling probability weighted tests may be employed if there is evidence of noteworthy selection in Extension Study enrollment.

All analyses of clinical trial results will be reported as two-sided tests with acknowledgement of multiple testing issues, either by appropriate adjustment of p-values and confidence intervals or by an acknowledgement of the number of tests performed.

More detailed explanatory analyses will include tests for group differences with concomitant adjustment for covariates, as well as explanatory analyses that examine the extent to which an intervention benefit can be explained by changes in intermediate variables and outcomes (e.g., nutritional and biochemical measurements). These analyses will be conducted using relative risk regression methods, with appropriate account of measurement error in the intermediate variable measurements as necessary, using data obtained in the aforementioned reliability sub-study. Nested case-control and case-cohort sampling procedures (see next subsection) will be used in most such analyses since stored materials used to determine immediate variable values will not be routinely analyzed for the entire CT cohort.

7.6 Joint Analyses of Intervention Effects in the Clinical Trial and Observational Study

The parallel nature of the CT and OS components and the OS assessment of exposures related to the interventions under test in the CT support an important opportunity to examine discrepancies between the results of these two study designs, ascertain potential reasons for these differences, and in some circumstances, use these combined analyses to refine and extend the results of the CT, as has been used in several publications already (e.g., Prentice et al, 2005, 2006b, 2008a, 2008b, 2009). In such studies, separate analyses in both the CT and OS will be conducted according to self-reported baseline prevalence of the intervention being analyzed. In fact, whenever applicable, relative risk analyses based on randomized CT comparisons will be accompanied by corresponding OS relative risk analyses. The comparability of these analyses is enhanced by the common aspects of baseline data collection procedures and outcome determination procedures in the CT and OS. Estimated relative risk functions from the two sources will take suitable account of prior "exposure" histories and of measurement error in exposure assessment. Under circumstances in which careful analyses of this type lead to substantial agreement between CT and OS results, analyses will be conducted to extrapolate the relative risk results beyond those examined in the CT, using the OS (e.g., to longer durations of treatment or to important cohort subsets). For many observational analyses, joint analyses of the CT/OS cohorts with stratification on cohort will also be a useful strategy for examining possible explanations for differences between relative risks in the CT and OS.

7.7 Statistical Considerations for High Dimensional Data

The analysis of high-dimensional data, especially as generated by genetic and proteomic (nested case-control) studies, requires particular care. Typically laboratory assays used to generate these types of data have high run-to-run variability, and appropriate use of normalization techniques is critical. This is true both for “gene-chips” used for genome-wide association studies, large scale genome-wide studies used to study smaller number of variants, and sequencing and proteomic technologies, although the actual type of normalization differs between different technologies.

Several of these technologies use “labeling approaches”, where two samples are assayed simultaneously and the resulting data are compared between the two samples. For such assays it is critical that either the labeling is randomized, or that it is balanced between cases and controls. For some technologies the amount of missing data can be substantial and assuming the design is balanced is not sufficient in the analysis. Instead, labeling should be properly accounted for in the analysis.

Genetic data has by design a substantial amount of built-in quality control that can be exploited in the analysis. Genetic examples include Hardy-Weinberg equilibrium, especially for control subjects of a single race/ethnicity, and comparisons of minor allele frequencies between the study subjects and publicly available databases, such as HapMap. For many technologies the amount of missing data over the all measurements, e.g., genes, is a good indicator of the reliability of the non-missing measurements on the same subject, and minimum completion quality standards are critical to data quality.

Most proteomic ‘discovery’ data generated in WHI derive from mass spectrometry-based technologies. Valuable standardization can be achieved by isotopic labeling (e.g., with heavy or light acrylamide, which binds to cysteine residues in proteins/peptides) of the samples to be compared (e.g., cases of a given disease

versus corresponding matched controls),thereby focusing on relative rather than absolute protein abundance estimation.Since the number of differences (out of a few hundred proteins quantified)is typically expected to be small in such comparative studies, which may involve the use of pooled plasma or serum for reasons of throughput, useful normalization can be achieved by shifting the log-concentration ratios in a given experiment to have a median of zero. Additional important quality control can be achieved by imposing stringent standards for peptide and protein identification, and by allowing for any differential labeling effects through random assignment of labels to case and control specimens , and through formally allowing for label effects in regression analyses.

For high-dimensional technologies typically many tests are carried out simultaneously. It is critical that in these situations there is appropriate control for multiple comparisons. Such a control can be done using a Bonferroni correction, by computing appropriate False Discovery Rates (FDR), or sometimes using permutation tests. An additional approach may be to tests groups of genes or proteins in the form of pathway analysis. WHI-related statisticians are actively engaged in the development of efficient methods for gene/protein set analytic methods that are suited to application in genomic and proteomic studies.

Replication of these results in independent datasets is one of the most important methods for assuring validity of these findings. These studies may be conducted with WHI, where feasible, or often may involve collaboration with other studies. WHI data may also be used to validate the results arising from other such studies.

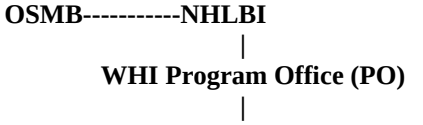
8. Ancillary Studies

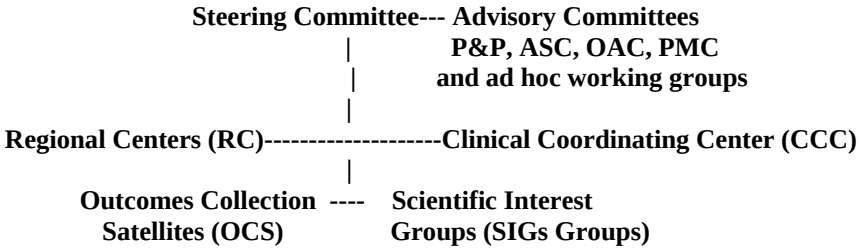
Ancillary studies entail the collection of data or specimens from study participants, or the conduct of additional analyses of existing materials or samples, that are outside the specific scientific objectives of a parent study. Such studies may involve all or as few as one of the WHI Regional Centers, Outcome Collection Satellites, former WHI Field Centers, or the CCC. Ancillary studies must not interfere with the basic objectives of the Extension Study. Proposed ancillary studies will have a separate protocol which will be reviewed in regard to impact on ongoing elements of the program, and for scientific merit, initially by the Ancillary Study Committee (ASC), and following a favorable recommendation, approved by the Steering Committee (SC) and the NHLBI Project Office. All such efforts must undergo separate review by the institutional review boards of the institutions participating operationally in the study and separate informed consent may be required. If separate consents are required, the consent forms must be approved by the ASC and submitted to the CCC. Approved ancillary studies requiring separate informed consents will be submitted to the OSMB for notification or review according to existing NHLBI policies. External funding will typically be required.

9. Study Organization

The study organization includes the Program Office at the National Heart Lung and Blood Institute (NHLBI), a small number of Regional Centers (RCs) and their associated Outcomes Collection Satellites (OCS), and the Clinical Coordinating Center (CCC). To promote continued involvement of a broad range of investigators, WHI Committees will draw their membership and leadership from the former WHI Field Centers as well as participating investigators and staff within continuing institutions. A streamlined governing structure will include a Steering Committee (SC), an Ancillary Study Committee (ASC), a Publications and Presentations Committee (P&P), an Outcomes Adjudication Committee (OAC), and a Performance Monitoring Committee (PMC). An external committee, the Observational Study Monitoring Board (OSMB), reports directly to the NHLBI. Aspects of the study organization are shown in *Figure 2*. Details of the governance plan will be documented separately.

Figure 2
Organization of the WHI Extension Study





9.1 Program Office

The WHI Extension Study is being conducted out of the WHI Branch in the Division of Cardiovascular Sciences, NHLBI. The NHLBI Project Office oversees technical aspects of the program, and the Contracts Office oversees fiscal aspects.

9.2 Clinical Coordinating Center (CCC)

The Clinical Coordinating Center will develop an initial and final Protocol; develop a procedures manual, data collection forms and other study materials in collaboration with other study units; reconsent participants into the Extension Study; provide training and other resources to Regional Center staff for outcomes collection processes; conduct centralized mailings and data collection for extended follow-up; document outcomes for participants assigned to be followed by the CCC, coordinate medical records abstraction, outcomes adjudication and coding; redevelop and deploy modified information technologies consistent with the ongoing study needs; provide regular reports on study progress; provide statistical support for the analyses of study results; lead and support scientific initiatives using the WHI resource; participate in study governance.

9.3 Regional Centers (RC)

Because the outcomes documentation process will now be limited to participants in the Medical Record Cohort, reducing the overall effort, the operations of the 40 former Field Center operations will be consolidated into a small number of Regional Centers and the Coordinating Center. The Regional Centers will be responsible for documenting outcomes and for advancing science--including mentoring new investigators. To facilitate efficient collection of outcomes documentation, Regional Centers may contract with former Field Centers to conduct data collection for a defined subset of participants. For purposes of data collection these Outcomes Collection Satellites will assume the responsibilities of the Regional Center for the participants assigned to them.

Regional Centers and Outcomes Collection Satellites will ascertain clinical outcomes; accumulate and maintain participant files in a secure fashion; use the CCC-developed study database to enter and manage all participant data collected locally; and perform study procedures according to protocol. In addition Regional Center investigators will participate in reporting on all phases and activities of the program, lead and support scientific initiatives using the WHI resource and participate in study governance.

9.4 Steering Committee (SC)

The Steering Committee serves as the primary decision making body and communication link for study investigators. The SC oversees and coordinates the activities of the other committees and working groups, replacing the former Executive Committee. Membership will be composed of four Regional Center PIs, four other regional representatives, four chairs of other standing committees, one representative from the NHLBI Project Office, and two from the CCC.

9.5 Ancillary Study Committee (ASC)

The Ancillary Study Committee will advise on policies and procedures with respect to ancillary study activities and will review all WHI proposals for ancillary studies, and will provide expertise on study design and analysis, as needed. The ASC will ensure that proposals seeking access to specimens have adequate scientific merit, make efficient and appropriate use of biospecimens, and are consistent with the mission of WHI.

9.6 Publications and Presentations Committee (P&P)

The Publications and Presentations Committee advises on policies and procedures related to publications and presentations from the main study and ancillary studies, encouraging the development of manuscripts and presentations, review investigator-initiated manuscript proposals and abstracts, facilitate fairness in determination of authorship, review and approve final manuscripts for publication, and track and report on the progress of manuscript development. The P&P will also advise on what data if any, can be released to non-WHI investigators prior to their publication.

9.7 Outcomes Adjudication Committee (OAC)

The Central Adjudication Committee will oversee adjudication of clinical outcomes, advise on outcomes associated data collection and clinical outcome coding, advise on new findings in the literature, and provide input to the Performance Monitoring Committee.

9.8 Performance Monitoring Committee (PMC)

The Performance Monitoring Committee will be responsible for monitoring study performance in outcomes collection processes including timeliness and completeness of Form33 follow-up and timeliness of outcomes documentation.

9.9 Other Leadership and Committee Activities

The Steering Committee will establish working groups or task forces to address specific needs as they arise. Membership will be drawn from the Extension Study investigators, supplemented by outside researchers as needed to supply relevant expertise. These groups will exist on a time limited basis for the performance of the charge established by the SC.

9.10 Scientific Interest Groups (SIGs)

The purpose of WHI Scientific Interest Groups is to optimize the use of the WHI resource by stimulating scientific exchange and encouraging collaboration. These groups may be formed around different types of foci, including disease entities, scientific disciplines, exposures or interventions. Formation of a Scientific Interest Group for a new topic area requires approval of the Steering Committee. Participation in Scientific Interest Groups is voluntary and is not required for proposing or conducting manuscripts or ancillary studies related to those topics.

9.11 Observational Study Monitoring Board (OSMB)

As a continuation from the previous Extension Study, the Observational Study Monitoring Board will review study activities and data to provide guidance as to the ethical conduct of the WHI. The OSMB meets annually, either in person or by conference call and reports to the NHLBI.

10. Timetable

Protocol Development	11/09 – 12/09 (2 months)
Participant enrollment and consent for Extension	5/10 – 3/11 (11 months)
Follow-up data collection	Annual
In-person Visit	2011-2013
Close-out	Dependent on future funding
Data Analysis	Ongoing

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Section 1
WHI Extension Study Protocol Outline

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