Section 1
WHI Extension Study Protocol Outline

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Women's Health Initiative (WHI) Extension Study Protocol
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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 this additional follow-up is to describe the longer term effects of the original interventions, to document change in hormone use in participants from the hormone therapy trials, to expand the range of scientific questions that can be reliably addressed in the WHI, and to provide an infrastructure able to support additional investigations requiring some of the unique features of a very large longitudinal study of postmenopausal women. The Extension Study activities, funded through the National Heart Lung and Blood Institute (NHLBI), will be planned, conducted, and reported over the time period July 1, 2004 – March 31, 2011 at 39 Field Centers (FCs) and a Clinical Coordinating Center (CCC). The Extension Study will also provide an infrastructure to facilitate the use of data and specimens by WHI investigators throughout the Extension period, and by outside investigators under an NHLBI Broad Agency Announcement beginning in 2006.

2. Background

In 1993, recruitment began for the Women's Health Initiative (WHI), one of the largest studies on the health of postmenopausal women ever done. The WHI 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.

When recruitment ended in 1998, more than 161,000 women between 50 and 79 years of age had joined the WHI (68,132 in CT and 93,676 in OS) and were scheduled to complete follow-up in March 2005. Participants in the DM and CaD trials remained on intervention until the last clinic visits. The E+P intervention was terminated in July 2002 at the recommendation of the WHI Data and Safety Monitoring Board (DSMB), 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 (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 Women's Health Initiative, WHI participants, and major study findings to date are described elsewhere (The Women's Health Initiative Study Group, 1998; Anderson et al, 2003).

2.1 Considerations for Follow-up of WHI Participants

An additional 5 years of high quality clinical outcome ascertainment, through March 2010, will increase the range of scientific issues that can be examined in the CT and OS, and will allow a reliable study of the health benefits and risks of the CT interventions (average intervention periods of 5.6 to 8.5 years among CT components) over an average total follow-up period of 13 years (12 years in the CaD trial). The longer follow-up will provide important information on outcomes that might be affected by study treatments only many years after the initiation of intervention, and on outcomes that were too uncommon for clear results to emerge during the initial follow-up period.

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) in order to determine whether or not the same risk factors operate to the same degree across such subgroups.

2.2 Considerations for Additional Data Collection from HT Participants

An additional 5 year post-intervention follow-up for breast cancer was envisaged in the original HT trial protocol, based on a projected 10-year lag to full intervention effect. This extended follow-up remains important for the HT component, even though these interventions were stopped early. Data from the E+P trial suggested that an increase in breast cancer risk may be cumulative over six or more years of exposure and considerable interest remains regarding the duration of this adverse effect post-intervention. The E-alone trial results suggested some early reduction in breast cancer risk which was unanticipated and has lead to concern that any such early reduction may be transient and perhaps be followed by elevated risk. To help clarify the effects of HT interventions on breast cancer risk over an average 13-year follow-up period, the Extension Study will assess use of hormone therapy and alternative preparations through 2010 and obtain annual mammogram reports throughout 2005-2007 from women who enrolled in the HT trial.

3. Study Objectives

The primary objectives of the extended follow-up are:

Objective 1: To study the maintenance and long term effects of the original WHI interventions on the primary and subsidiary outcomes as originally defined.

Objective 2: To describe the effects of the original WHI interventions on rarer clinical events for which the original study was underpowered to address during the initial phase.

Objective 3: To describe the experience of women in the HT trials after cessation of study pills and to assess their use of HT or other preparations for menopausal symptoms and osteoporosis prevention and treatment.

Objective 4: To enhance the WHI resource and its utilization by collecting and analyzing clinical outcome data and selected additional exposure data over the time period 2005-2010.

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 Extension Study, participating women will continue to be associated with the same components and randomization assignments in which they were originally participating.

4.2 Study Population

Participants for the Extension Study are drawn from the population of WHI participants. In the original WHI, eligibility and exclusion criteria were as broad as possible in order 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].

For the WHI Extension Study, to minimize selection bias by encouraging a high response rate within the constraints of consent, the eligibility criteria for the Extension Study are:

Inclusion Criteria:
1. Previously enrolled in one or more components of the Women's Health Initiative.
2. Providing written informed consent for extended follow-up.

Exclusion Criterion: Deceased

4.3 Outcomes of Interest

The primary outcomes for the clinical trial remain as originally defined. To support the broader scientific objectives of the Extension Study, some that are uniquely feasible in a very large study of older women, information on additional health events will be ascertained when information about these diagnoses can be reliably obtained though self-report (or proxy report in the case of death or incapacity) within the available resources. Selected reports will be documented and adjudicated based on study priorities. The selected outcomes are presented by study component in *Table 1*.

Table 1
Outcomes by Study Component and Level of Information Required.

A—Adjudicated medical records; D—Documented for ICD9 coding; S—Self Report only

Outcome	CT	OS
CARDIOVASCULAR:		
Coronary heart disease	A	A
Angina	S	S
Coronary Artery Bypass Surgery (inpatient)	A	A
PTCA	A	A
Stroke	A	A
Transient ischemic attacks	S	S
Carotid artery revascularization (inpatient)	A	A
Congestive heart failure	S	S
Venous thromboembolic disease DVT PE (inpatient only)	A (HT only through 3/2007) S (all others)	S
Peripheral vascular disease	A	A
CANCER:		
Breast cancer	A	A
All other cancers except non-melanoma skin cancer	A	A
FRACTURES:		
Hip	A	A
Other fractures	S	S
OTHER AGE-RELATED DISEASES		
Diabetes mellitus requiring therapy	S	S
Hypertension requiring therapy	S	S
Hypercholesterolemia requiring therapy	S	S
Intestinal or colon polyps or adenomas	S	S
Macular degeneration	S	S
Osteoarthritis	S	S
Osteoporosis requiring therapy	S	S
Parkinson's disease	S	S
Systemic lupus erythematosus	S	S
SOCIAL/PSYCHOLOGICAL CONDITIONS		
Depression requiring therapy	S	S
Anxiety requiring therapy	S	S
OTHER		
Selected Hospitalizations for 2+ nights	D	D
Death from any cause	A	A

4.4 Sample Size and Duration

The original and projected sample sizes for each element of the partial factorial design are shown in *Figure 1*. It is anticipated that approximately 94% of those women who are alive and in contact with the study will consent to extended follow-up. Accounting for deaths and current loss to follow-up, the projected total sample size is 139,400, with 58,800 continuing CT participants (DM 42,300; HT 23,300; CaD 32,100) and 80,600 continuing OS participants. All participants will be followed annually, beginning in April 2005 and ending in March of 2010.

Figure 1
WHI CT Partial Factorial Design

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

			HRT (CaD)					
			Intact Uterus					**Not Randomized**
			Yes			No		
			E+P	Placebo		E-alone	Placebo	
			8506	8102		5310	5429	**40,785 (20,193)**
DM (CaD)	Intervention	19,541 (9645)	972 (596)	925 (577)		615 (371)	670 (430)	**16,359 (7671)**
	Control	29,294 (15,565)	1457 (917)	1304 (838)		1039 (639)	1068 (649)	**24,426 (12,522)**
	Not Randomized	19,297 (11,072)	6077 (3530)	5873 (3455)		3656 (2064)	3691 (2023)	
		68,132 (36,282)						

Power projections demonstrating the potential of longer-term follow-up to contribute to the identification of primary and secondary clinical outcome differences between randomization groups in the continuing components of the CT illustrating that the modest power for some comparisons may be significantly enhanced by longer term follow-up (see *Appendix B*).

Power calculations pertinent to the combined CT and OS as a cohort study with an anticipated size following re-consent of about 140,000 are also provided in *Appendix B.* Power calculations are also given for subcohorts of size 100,000 (white women alone, a 2-1 nested case-control study in entire cohort), 70,000 (OS alone using specialized exposure data), 30,000 (baseline age 70-79), 10,000 (Black/African American), and 5,000 (Hispanic/Latina).

4.5 Informed Consent

Consent Form template
The consent form templates (*Appendix A*) will constitute the basis for the development of each of the individual FC consent forms. FCs are strongly encouraged to use the template unchanged. Although FC are allowed to reword or add to the template, in line with local needs and Institutional Review Board (IRB) preferences, all key elements must be included. All changes must be clearly identified. The consent forms must include not only

the basic elements that must appear in all consent forms but also any items, such as possible adverse events, that are specific to the intervention being tested or procedure being conducted.

A checklist containing the key items necessary in the consent forms has been developed for use in reviewing the consent form proposed for each clinical site. The CCC will be responsible for reviewing each FC consent form in accordance with this checklist after approval by the local IRB. If an IRB-approved consent form is found by the group performing the review either not to contain all key points, or to misstate a point (e.g., underplay a potential adverse event), the responsible investigator will be informed. The investigator must then discuss all identified problems with the relevant IRB and revise the forms and processes to address all identified concerns. All revised consent forms must then be re-reviewed and approved by the study review group.

NHLBI program staff will monitor performance of this process. Notice of receipt of IRB approval and confirmation that all consent forms contain the necessary elements will be provided by the group responsible for review (e.g., a subcommittee of the investigators or data coordinating center staff) to the NHLBI.

No site will be allowed to begin enrolling participants until it has obtained final approval from its IRB and from the review group.

Administration of consent
The participant's full understanding of the study purpose and activities is important for ethical reasons and for adherence with study protocol. Prior to any Extension Study activities, material written in large print in English or Spanish that describes the study in general terms will be given. This information may be provided in-person or by mail contact, based on FC considerations and local IRB policies.

WHI participants will be given a copy of the Extension Study informed consent to read and sign. For mail contacts, a phone number will be provided for the participant to call and ask questions. At this time or shortly thereafter, participants will also be asked to provide a supplemental consent to permit use by "for profit" entities of previously collected biologic specimens. The decision to sign or decline the supplemental consent will not have any bearing on the participants' original WHI consent or the WHI Extension Study consent. All participants will be given a copy of each consent form she has signed for her records.

5. Study Plan

5.1 General

All eligible WHI participants will be invited to join the Extension Study, either at the final transition visit/contact (CT), or following the final transition mailing (OS). Once enrolled in the Extension Study, participants will complete annual data collection forms primarily by mail with follow-up for additional details typically by phone. Retention efforts will be employed throughout the extension period to maintain contact with participants and encourage continued participation.

5.2 Enrollment

For CT participants, the transition to the Extension Study occurs at the final ("close-out") WHI clinical center visit, scheduled to occur between October 2004 and March 2005. At this clinic visit, clinic staff provide CT participants an explanation of the Extension Study protocol and ask them to consider providing written informed consent. Participants will be asked to view the video providing standardized information about the possible uses of existing blood specimens and asked to consider providing consent for use of their specimens by private for-profit entities. Participants will also be asked to review and update their personal contact information.

Of particular concern is that the enrollment rates and the distribution of risk factors among those enrolled in the Extension Study do not differ in important ways between randomization groups. Full enrollment offers the best means of eliminating selection bias and as such, all women who may be contacted shall be invited to participate. Further, all efforts to recruit women from a particular CT component should be standardized to avoid differential accrual between randomization groups.

Enrollment of OS participants will be initiated following the centralized mailing of transition ("close-out") packets in April 2004 to spring 2005. OS participants will be given the same information about the Extension Study protocol and asked to consider providing written consent for extended follow-up and to update their personal contact information. These OS activities may be conducted by mail or in-person, per local field center human subjects' requirements. OS participants will be provided written information about the possible uses of existing specimens and asked to consider providing consent for possible use of their specimens by private for-profit entities.

Because completeness of follow-up is necessary to guard against selection bias, a target enrollment has been set at 95% of all WHI participants who are alive and not considered lost-to-follow-up. Because the response rate to OS mailings has been near this level based on three mailings and a follow-up phone call, this serves as a general guideline for the number of contact attempts that may be required to achieve this goal for FC using a mailing strategy.

5.3 Follow-up

All Extension Study participants will be followed annually to collect data primarily on health outcomes using a modification of the procedures employed in OS follow-up over the last 10 years. The CCC will initiate annual follow-up with a centralized mailing to obtain self-reported outcome events. To spread the work evenly throughout the year, approximately one-twelfth of the participants will receive the mailing each month, beginning in April 2005 for OS participants and October 2005 for CT participants, beginning one year after the final WHI (transition) contacts. The mailing for all extension participants will include an optical mark recognition *Form 133 – Medical History Update*, a postage-paid envelope, and a #2 pencil and will be sent bulk mail.

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 FC follow-up.

Participants will be asked to complete and return *Form 133* to the CCC for scanning. These data will be made available electronically to FCs for use in their subsequent outcomes documentation efforts. The CCC will send up to two additional mailings to non-respondents. FCs staff will attempt to contact those participants by phone who have not responded after the third mailing or who have requested phone follow-up. FC staff will be asked to briefly update personal contact information on each such contact. Women reporting study outcomes that require documentation will be contacted by FC staff to complete a *Form 133D – Medical History Update (Details)* to obtain additional detail on health event dates and providers, and ask the participant to complete a mailed release of information if needed and return it to the FC. FCs will use the release of information to obtain medical records for the designated events. Once complete, FCs will collect and assemble outcomes documentation into packets, remove confidential identifiers other than study ID, and forward to the CCC for review and distribution to physician adjudicators who will follow existing procedures for adjudicating cases.

DM-specific follow-up
As part of the WHI Extension Study goal of following up the low-fat dietary intervention effects, a 4.6% subsample of women who were in the WHI DM Trial (intervention and comparison) will be asked to complete one 24-hour recall. Half of the subsample will be asked to complete the recall toward the start of the WHI Extension Study (around 2006-2007) and half toward the end (around 2009-2010). About two weeks before the recall, women in the subsample will be mailed an approach letter with a serving size booklet. Verbal consent will be obtained during the telephone call before the dietary interview begins.

HT-specific follow-up: Follow-up packets mailed to HT participants will also include a *Form 160 – Hormone Use Update*. This form will also be returned to the CCC for scanning.

For the first two years of extension follow-up (through March 2007), FCs will collect annual mammography reports for HT participants. FCs will identify participants who are due for their annual mammogram through the Extension Study database and provide a reminder call or postcard to those participants. Once the FC staff collect the mammogram report, they will complete *Form 85 - Mammogram*. The WHI Extension Study will pay for mammograms obtained during these two additional years of follow-up if not covered by third parties.

5.4 Retention

Retention of study participants is an important focus after the participant is enrolled in the Extension Study. During the Extension, several retention activities used during WHI are continuing, including annual participant newsletters, updates of the participant's address provided by the US Post Office, regular review of contact information on all phone contacts, and collection of data from the participant's identified proxy.

Participant newsletter
All participants will receive a WHI newsletter annually. The purpose of the newsletter is to present WHI news and lay versions of results, to encourage retention of study participants, to promote participant identification with WHI, and to help keep addresses up-to-date. To help maintain contact, the newsletter is mailed by the CCC approximately 6 months before/after the annual data collection packet.

WHI DM Trial participants who were in the low-fat intervention Dietary Change arm will receive quarterly annual mailings (a continuation of the *WHIse Choices* newsletter) offering tips for maintaining the low-fat dietary pattern of the WHI DM Trial if they wish to do so. The mailings will include behaviorally and nutritionally based strategies and recipes. The writing style will follow the motivational interviewing principles of self-efficacy, empowerment, and exploration and resolution of ambiguity that began being implemented in the WHI DM intervention group in 1999. Because self-monitoring of food intake was found to be a strong correlate of adherence during the WHI DM Trial, the newsletters will invite women to continue self-monitoring. Each WHIse Choices newsletter will include a toll-free telephone number that women may call if they have questions or prefer not receiving the newsletters. Newsletters will be bulk-mailed from the Clinical Coordinating Center in Seattle, WA. Women who were in the WHI DM comparison group will not receive dietary mailings.

Maintaining current contact information
All CCC mailings to participants are imprinted with the CCC's return address and include a line requesting address corrections. The US Post Office notifies the CCC if the participant is deceased, if the packet is undeliverable to that address, or with information on a new address. For address corrections, CCC staff updates the participant's address in the database and mails a new packet to the participant, along with a Personal Information Sheet printed with information the participant previously provided. Participants are asked to review and update the sheet with any changes and to return it to the CCC with their form(s). If the current address is undeliverable or the participant is deceased, this information is noted in the database for use by FC staff. FCs 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, FC 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
Some follow-up contacts, because of a participant's illness, disability, or death, may need to be conducted by proxy. FC 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 participant forms packet to the proxy contacts previously identified by the participant.

5.5 Study Close-out

The final close-out data collection mailing will be similar to those sent during the previous years, with the exception that participants will be informed that this is the final mailing. A thank you letter will be included, as well as a summary of key publications.

6. Study Operations

6.1 Data Management

For data management and communication purposes, the CCC will provide each FC with a personal computer (PC), and a printer. The PC will be preconfigured with an Ethernet card, a read-write CD player, a thumb drive, and current versions of: Windows and Internet Explorer; Microsoft Office; Adobe Acrobat (for WHILMA reports); Citrix client; anti-virus software; anti-spyware software; Java Initiator for running Java applets under Internet Explorer. Five years, pre-paid, next day on-site maintenance (from vendor) will be provided. Each FC will be responsible for obtaining Internet access for this PC. No study data will be maintained on the PC.

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 FC staff over the World Wide Web. Each FC will be granted access to data only from participants from their FC and will be able to use this database for tracking and reporting.

All routine data will be collected and entered using standardized data collection forms. Participant forms mailed to the CCC (e.g., *Forms 133—Medical History Update* and *160—Hormone Use Update*) will be scanned and imaged at the CCC and the data and images will be provided in electronic format to the FCs for their use in subsequent steps of outcomes documentation. Forms used directly by FC staff (e.g., *Form 7—Participation Status, Form 111—Consent Status, Form 133D—Medical History Update (Details), Form 85—Mammogram*) will be key entered by FC staff into a central database using data entry screens developed and provided by the CCC. Adjudication forms will be completed by adjudicators and returned to the CCC for double 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 Study Oversight Committee (SOC) and its subcommittees and the NHLBI Project Office. The training and certification required for each study task is described in *Volume 2 - Procedures*. 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 FCs for resolution, and a systematic means of updating the central database based on their responses will be established. Standards for performance are defined in the FC request for proposals and documented in *Volume 2 - Procedures*, and will be monitored initial by the Performance Monitoring Committee (PMC). FCs 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

6.3 Outcomes Adjudication

For purposes of attaining high quality outcome data consistent with the previous study period, outcomes ascertainment, documentation, and adjudication will follow the procedures developed for the WHI (Curb et al, 2003) with modest streamlining to reduce the overall effort. Each documented case of cardiovascular disease or death will be assigned to an experienced WHI adjudicator for review and coding. For all cancers, the outcomes packet will be submitted to the CCC for coding of primary site. For primary cancers of the breast, colon, rectum, endometrium, and ovary, the cases will be submitted for coding of more detailed tumor characteristics by a qualified SEER coder. Hip fractures and strokes will be adjudicated by established central adjudicators at UCSF and NIH, respectively. A standardized training in WHI adjudication will be required whenever a new adjudicator is added. The specifics for each scheme of adjudication within the cardiovascular, cancer, and fracture outcomes are detailed in *Volume 2 - Procedures*.

7. Study Monitoring and Data Analysis

7.1 General

Progress in the Extension Study will be monitored in several ways: reports on participant enrollment, adherence to follow-up procedures, and accrual of key study outcomes. The CCC will provide regular reports to the SOC and the FCs, 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 Accrual

Accrual information by study component, age, racial/ethnic subgroup, and FC will be provided, as a fraction of women alive and in recent contact with WHI at the closeout/transition contact.

7.3 Adherence to Follow-up Procedures

A well-defined reporting system has been developed to document the completeness and timeliness of outcomes processing in the WHI. With the change in some aspects of implementation to a more centralized model, FC performance reports will reflect the timeliness and completeness of the process initiated at the time that the *Form 133—Medical History Update* form is entered into the Extension Study database and becomes available for FC processing. Timeliness and completeness of *Form 133D—Medical History Update (Details)*, 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.

Completeness of *Form 160—Hormone Use Update* and *Form 85—Mammogram* collection for HT participants will also be monitored.

7.4 Data Analysis

Analyses of longer term intervention effects will employ the 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. If V_i represents the conditional variance of O_i, then it follows 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).

To examine post-intervention effects, weighted and 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. Weights for post-intervention analyses will be defined to account for changing exposure to the interventions, lag-time and carry-over effects.

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. Methods to account for non-representative enrollment using 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, using data obtained in a reliability substudy. 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.
Simple graphical displays and standard statistical methods will be used to present biochemical, bone density, and nutritional results by treatment group, clinic, and time since randomization during the course of the CT. Similar displays will describe the frequency and severity of adverse effects.

Observational Study
The ability to estimate relative risks reliably for the outcomes of interest in the OS as a function of baseline characteristics (exposures, behaviors or biologic measurements), or as a function of changes in such characteristics between baseline and three years is dependent on the accurate 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 to be ascertained in the OS (e.g., nutrient intakes, blood cholesterol) are subject to noteworthy measurement error, a stratified 1% random subsample of the OS women had repeat baseline information and specimens obtained at between one and three months following their OS enrollment, and again at between one and three months following their three year clinic visit. This reliability subsample provides information of the reproducibility of the measurements taken (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 OS cohort, and the comprehensive set of measurements obtained allow a particularly thorough accommodation of confounding, by means of individual matching, stratification or regression modeling.

Relative risk regression methods (e.g., Cox, 1972) will also provide the primary data analytic tool for the OS. 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., Pepe et al, 1989; Espeland et al, 1989; Lin et al, 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 proceeds by selecting for each 'case' of a study outcome one or more 'control' women who have not developed the disease in question by the follow-up time at which the corresponding case was ascertained. Additional matching criteria in the OS will typically include baseline age, clinic, and date of enrollment, and depending on the analysis may also include racial/ethnic or socioeconomic group, or other factors. Nested case-control or case-cohort sampling provides the only practical approach to reducing the number of OS 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 analysis could be restricted to women with relatively low baseline blood cholesterol (e.g., lowest two quintiles) in order to avoid a complicated interpretation if the effect of interest happened to 'interact' with baseline cholesterol measurement. Furthermore the OS, by virtue of ascertaining a range on non-specific markers of debility or disease (e.g., serum albumin, hemoglobin; cancer biomarkers; baseline and follow-up disease prevalence by questionnaire and physical exam) may be able to examine whether the excess mortality associated with reduced blood cholesterol can be explained by the presence of recognized or latent disease. The careful accommodation of measurement error in predictor and confounding variables is particularly important in such risk-factor-change analyses.

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.

Clinical Trial and Observational Study
Separate analyses in both the CT and OS will be conducted according to self-reported baseline prevalence of the clinical outcome 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. 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.

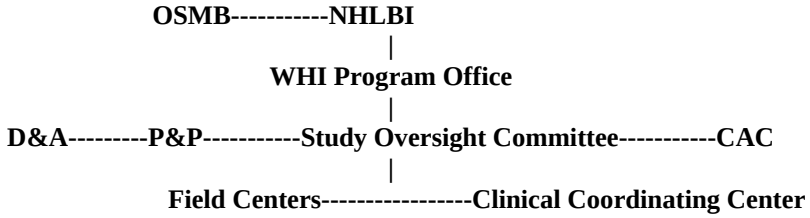
8. Ancillary Studies

Ancillary studies entail the collection of data or specimens from study participants of data, 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 FCs 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 Design and Analysis Committee, and following a favorable recommendation, approved by the NHLBI Project Office and the SOC. Upon their recommendation, ancillary studies will be submitted to the OSMB for notification or review according to existing NHLBI policies. 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 D&A and submitted to the CCC. External funding will typically be required. A separate policy document will be developed to govern ancillary study development and review based on that used for the original program.

9. Study Organization

The study organization includes the Program Office at the National Heart Lung and Blood Institute (NHLBI), 39 Field Centers (FCs), the Clinical Coordinating Center (CCC), and various WHI study committees. The WHI Committees draw their membership from within the participating investigators and staff from these institutions, and include a Study Oversight Committee (SOC), a Design and Analysis Committee (D&A), a Publications and Presentations Committee (P&P), and a Central Adjudication Committee (CAC). An external committee, the Observational Study Monitoring Board (OSMB), reports directly to the NHLBI. Aspects of the study organization are show in Figure 2.

Figure 2
Organization of the WHI Extension Study



9.1 Program Office

The study is being conducting out of the Office of the Director, NHLBI. NHLBI is the lead institute of a consortium of NIH institutes participating in the program. Within the NHLBI, the Director, WHI, is responsible for coordinating the program. 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 and other study materials in collaboration with other study units; provide training and other resources to FC staff for consent, enrollment, and outcomes collection processes; conduct centralized mailings and data collection for extended follow-up; coordinate outcomes 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 Field Centers (FC)

Field Centers will recruit and consent willing WHI participants into the Extension Study according to protocol inclusion and exclusion criteria; 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 FC investigators will participate in interim and final reports on all phases and activities of the program, lead and support scientific initiatives using the WHI resource and participate in study governance.

9.4 Study Oversight Committee (SOC)

The Study Oversight Committee will serve as the primary decision making body of the WHI Extension study. In addition to a Chair and Co-Chair, membership will include two representatives from the other three standing study committees, one representative from the NHLBI Project Office, and one from the CCC. The SOC will be the primary communication link for study investigators and will oversee and coordinate the activities of the other committees and working groups.

9.5 Design and Analysis Committee (D&A)

The Design and Analysis Committee will provide expertise on study design and analysis considerations and will review all WHI proposals for ancillary studies. As such, the D&A committee will ensure that proposals seeking access to specimens have adequate scientific merit, make efficient and appropriate use of the specimens, and are consistent with the scope of the 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, reviewing investigator-initiated manuscript proposals and abstracts, facilitating fairness in determination of authorship, reviewing and approving final manuscripts for publication, and tracking and reporting 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 Central Adjudication Committee (CAC)

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

9.8 Other Leadership and Committee Activities

The SOC 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 SOC. In addition, it is anticipated that the PMC and the Laboratory Working Group, implemented during the original WHI program, will continue to perform their respective functions of monitoring and promoting FC outcomes data collection processes and overseeing laboratory activities.

9.9 Observational Study Monitoring Board (OSMB)

As a continuation of the WHI Data and Safety Monitoring Board, the Observational Study Monitoring Board will review study activities and data to provide guidance as to the ethical conduct of the WHI. The OSMB will meet annually, either in person or by conference call.

10. Timetable

Protocol Development	07/04 – 09/04 (3 months)
OS participant enrollment and consent for Extension	09/04 – 12/05 (16 months)
CT participant enrollment and consent for Extension	10/04 – 12/05 (15 months)
Follow-up data collection	
OS participants	04/05 – 03/10 (60 months)
CT participants	10/05 – 03/10 (54 months)
WHI database closes	08/15/05
WHI Clinical Centers close, Field Centers open	09/15/05
Close-out Data	04/10 – 09/10 (6 months)
Data Analysis	04/10 – 03/11 (12 months)

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