This supplement contains the following items:

1a. Original protocol
1b. Final protocol
1c. Summary of changes:
   i. Changes through 2000\(^1\)
   ii. Changes due to stopping CEE+MPA HT trial in 2002\(^2\)
   iii. Changes between analysis plans\(^3\)
2. Final protocol to the extension study (2005-2010)
3. Final protocol to extension study (2010-2015)

\(^1\) There were no substantive changes in 2001.
\(^2\) There were no substantive changes after 2002.
\(^3\) The original statistical analysis plan and final statistical analysis plan are contained in section 7.4 of the original protocol and section 7.4 of the final protocol, respectively. Summary of changes between the analyses plan are noted in this document.
PROTOCOL FOR CLINICAL TRIAL AND OBSERVATIONAL STUDY COMPONENTS

June 28, 1993

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Supported by:
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APPENDICES
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1. SUMMARY

1.1. SUMMARY OF CLINICAL TRIAL

The Clinical Trial (CT) will evaluate the benefits and risks of hormone replacement therapy (HRT), dietary modification (DM), and supplementation with calcium/vitamin D (CaD) on the overall health of postmenopausal women. Health will be assessed on the basis of quality of life measurements, cause-specific morbidity and mortality, and total mortality.

A total of approximately 63,000 women aged 50-79 from about 45 centers will be randomized in a partial 3 x 2 x 2 factorial design and followed for an average of nine years. Women who are eligible and willing to participate in either the hormone replacement or dietary modification components or both may enter the trial, but participants will be encouraged to enter both components. Women in the hormone replacement component only will be randomized into placebo or estrogen arms if post-hysterectomy, and otherwise to placebo, estrogen or estrogen plus progestin arms. Women in the dietary modification component only will be randomized into one of two arms (dietary modification or no dietary modification), and women in both components will be randomized for both. One year after entry, all eligible trial participants will in addition be invited to be randomized into a further two arms (calcium/vitamin D supplementation or placebo).

It is hypothesized that estrogen replacement therapy (ERT) will reduce the risk of coronary disease and of osteoporosis-related fractures. Because progestin and estrogen (PERT) are commonly used together in order to diminish the risk of endometrial cancer, a PERT arm will be included for women with a uterus in order to assess whether the hypothesized beneficial effects on preventing coronary heart disease and fractures will be retained. The incidence of endometrial cancer and breast cancer will be monitored during and after the trial. The estimated sample size requirement for the primary outcome of coronary heart disease is 25,000.

Dietary modification in the form of a low fat eating pattern is hypothesized to reduce the risk of breast cancer, colorectal cancer, and coronary heart disease. The estimated sample size requirement for each of the primary outcomes of breast cancer and colorectal cancer is 48,000. The low fat eating pattern will include reduced intake of total fat and saturated fat, and increased intake of complex carbohydrate and fiber-containing foods.

Calcium/vitamin D supplementation is hypothesized to reduce osteoporosis-related fractures and colorectal cancer. It is estimated that 45,000 women will participate in this part of the trial.

1.2. SUMMARY OF OBSERVATIONAL STUDY

The Observational Study (OS) will consist of CT screenees who have participated in at least one visit but are either not eligible or not willing to participate in the trial, and who agree to participate in the OS. It is anticipated that about 100,000 women will be enrolled into the OS, and they will be followed for an average of nine years.

The OS will complement the CT. Data collected at baseline will be related to subsequent clinical events in order to examine the associations of known and putative new risk factors (and protective factors) with disease. Changes in characteristics over the first three years will similarly be related to subsequent clinical events. Serum, plasma, red cell, and buffy coat specimens will be collected and stored for subsequent analysis in cases and controls. The goals of these studies will be to (1) improve risk prediction of coronary heart disease, breast cancer, colorectal cancer, fractures, and total mortality in postmenopausal women, (2) create a resource of data and biologic samples which can be used to unearth new risk factors and/or
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biomarkers for disease, and (3) examine the impact of changes in individual characteristics on disease and total mortality.

2. BACKGROUND

2.1. GENERAL CONSIDERATIONS

The CT/OS is designed to address some of the major causes of morbidity and mortality in postmenopausal women: namely, coronary heart disease, breast and colorectal cancer, and osteoporotic fractures. Cardiovascular disease (CVD) is the most common cause of mortality in older U.S. women, accounting for 29-48% of all deaths in the age range 50-79. Coronary heart disease (CHD) by itself accounts for 13-22% of all deaths in this age range. Both absolute rates and proportional mortalities from these causes increase steeply with age. Among the cancers, breast cancer is the second most common cause of death. It accounts for 4-11% of deaths, and although rates increase with age the proportional mortality from breast cancer is higher at younger ages. Colorectal cancer is the third most common cause of death among the cancers (after breast and lung), and the second most common incident cancer. Rates increase with age and the proportional mortality is steady at about 4%. Death from complications of hip fractures approximate those for breast cancer and colorectal cancer. In addition, fractures account for much morbidity; the annual incidence of fractures increases from 0.5% of women aged 55-64 to 2.3% of women aged 75-84.

Clinical Trial

The goals of the treatments to be tested are to reduce both the morbidity and the mortality associated with the above diseases. Reductions in morbidity from these common diseases should translate into substantial improvements in the quality of life of postmenopausal women and to major societal benefits if the successful treatments are widely adopted by U.S. women. The treatments will also be studied in relation to a range of other diseases and age-related events.

Multiple outcomes will be studied in order to gauge the effect of the proposed interventions, and of the risk factors, on overall health. These include coronary heart disease, other cardiovascular diseases, breast and colorectal cancer, other cancers, and osteoporotic fractures. To assess overall benefit and risk for each of the treatments, overall morbidity and mortality, cause-specific morbidity and mortality, and measures of quality of life will be considered. Unresolved issues relating to possible adverse effects such as an increase in breast cancer or endometrial cancer on HRT, and an increase of renal calculi on CaD, will be examined.

Each of the treatments is expected to influence a number of outcomes. Thus, hormone replacement therapy may benefit both coronary heart disease and fractures; low fat dietary pattern may benefit breast and colorectal cancers and also coronary heart disease; and calcium and vitamin D supplementation may benefit fractures and also colorectal cancers. The trial has adequate statistical power for each of these outcomes (see Appendix III). In general, the trial does not have statistical power to test subgroup hypotheses; nevertheless, trends in certain subgroups will be of interest. Some of the treatments may have synergistic effects in the subgroups receiving a combination of treatments (e.g., HRT and low fat dietary pattern on coronary heart disease and low fat dietary pattern and calcium on colorectal cancer), while others may cancel out each other's effects (e.g., HRT and low fat dietary pattern on breast cancer). Negative interactions may exist, so that the effect of a combination of treatments may be little different from each treatment on its own (e.g., the combination of CaD and HRT may have no greater effect on fractures than either treatment alone). Other subgroup hypotheses are that benefit (or risk) may relate to some baseline characteristic (e.g., the protective effect of HRT on coronary disease may be greater in
women with existing CHD, while the risk of breast cancer may be exaggerated in women with a family history of breast cancer).

Observational Study

The OS will be used to improve risk estimates for cardiovascular disease, cancer, and bone fracture in women, so that high-risk women requiring possible treatment may be more precisely identified. Currently, risk factors in women are poorly quantified, or are unknown. The general approach to be used in the OS will be to use nested case-control or case-cohort analyses of the OS cohort in a variety of applications: to examine the associations of known or putative risk factors (including biomarkers) to disease status at baseline and during follow-up; to find new risk markers using the stored biologic samples and data as a resource; and to examine the association of change in known or putative risk factors on disease outcome.

The OS will provide information on the relationship of personal characteristics such as lipid levels, blood pressure, smoking habits, hormonal status, and dietary habits to future clinical events. The OS will also be used to identify new risk factors. Some of these can be hypothesized a priori, while others may arise later and can then be tested provided appropriate information and/or biological samples have been gathered and stored at baseline. Biomarkers of disease in the form of protein polymorphisms and DNA markers are increasingly being identified. The OS will also be used to examine the impact of involuntary change (i.e., change not induced by treatment) in risk factors on disease outcomes. For example, there is great interest currently in the phenomenon of excess mortality from a variety of causes in persons with low levels of blood cholesterol, albumin, and body weight. The OS will provide an opportunity to test the hypothesis that low levels of blood cholesterol are associated with mortality through the presence of underlying debility or disease which caused both a decline in previously higher levels, and subsequent mortality.

2.2. HORMONE REPLACEMENT THERAPY

2.2.1. Hormone Replacement Therapy and Coronary Heart Disease

The magnitude of the problem

The incidence of CHD increases substantially in the decades following the menopause. Both the rates and the proportion of all deaths from CHD increase with age. In 1988 the CHD mortality rates/100,000 (and percentage of all deaths) for U.S. women of ages 50-59, 60-69, and 70-79 respectively were 76 (13%), 260 (19%), and 718 (22%). Coronary heart disease (CHD) is the leading specific cause of death for women and accounts for the deaths of about 250,000 women each year (National Center for Health Statistics, 1990). CHD in women generally occurs 10-12 years later in life than in men, but because rates approach those of men in the older ages, and there are more older women than older men, overall about half of all coronary deaths occur in women. Almost all these deaths occur in postmenopausal women.

The potential role of hormone replacement therapy

The decrease in the circulating levels of estrogens following the menopause is thought to contribute to the increased rates of CHD (Barrett-Connor and Bush, 1991; Korenman, 1990; Godsland et al., 1987). In premenopausal women estrogens may retard the development of atherosclerosis and protect against CHD through their favorable effects on lipoprotein metabolism (and possibly on nonlipid factors such as fibrinogen, blood pressure, insulin levels, body fat distribution, and direct effects on the arterial wall). Reduction in estrogen levels may account in part for the observation that LDL-cholesterol levels increase during the transition into the menopause, and continue to increase for some 10-15 years thereafter. There is also a modest decrease in HDL-cholesterol levels during the menopause (Matthews et al., 1989). The effects of exogenous estrogens are pronounced: estrogen replacement therapy (ERT) decreases LDL-cholesterol levels by about 15% and increases HDL-cholesterol levels by a similar amount (Miller et al., 1991; Rijpkema et al., 1990; Walsh et al., 1991).
Some 32 studies have examined the relationship between exogenous estrogen use and CHD. A significantly reduced risk of CHD for women taking ERT has been reported in 11 of 15 published cohort studies and in each of three published cross-sectional angiographic studies (summarized in reviews by Bush et al., 1987; Stampfer et al., 1991; Grady et al., 1992). An additional 13 case-control studies reported less consistent results, and the single small clinical trial yielded promising but inconclusive results (Nachtigall et al., 1979). Various meta-analyses of the pooled studies have indicated highly significant average risk reductions for CHD of 35% to 45% (Bush et al., 1987; Stampfer et al., 1991; Grady et al., 1992), while risk reduction for the combined internally controlled prospective (n=12) and cross-sectional angiographic (n=3) studies was even higher at 50% (Stampfer et al., 1991). In some studies, risk reductions were observed for non-fatal as well as fatal CHD and other CVD, and for all-cause mortality.

At least three studies have reported that the risk reductions appear to be even more substantial in women with existing vascular disease (Bush et al., 1987; Sullivan et al., 1990; Henderson et al., 1991). The data on stroke are less consistent than that for CHD; combined fatal and nonfatal strokes appear not to be reduced, though the studies that provided separate data for fatal stroke consistently showed a decrease in ERT users (Grady et al., 1992). The benefits of HRT appear to increase with prolonged use and current use compared to previous use, though the data are scanty. It is not known whether obese women, who tend to have higher levels of endogenous estrogen, will have the same (hypothesized) benefits from HRT as do lean women.

It is also not clear whether the apparent benefits of ERT from these observational data are largely due to a process of self-selection by which healthier individuals are prescribed ERT, or by other selection biases in the inclusion of subjects or reporting of study results. Such biases may not only exaggerate the apparent benefit, but may also underestimate the magnitude of adverse effects. Studies that have attempted to control for confounders have generally concluded that hormone replacement exerts an independent effect (Stampfer et al., 1991; Henderson et al., 1991; Bush et al., 1987); however it is almost impossible to control adequately for these (and other, possibly unrecognized) sources of bias in observational studies. Therefore, although the observational studies provide a basis for developing a hypothesis that hormone replacement therapy may reduce the risk of CHD, such a hypothesis can only be tested reliably by a large, well designed randomized trial.

2.2.2. Hormone Replacement Therapy and Fractures

The magnitude of the problem

While fractures are not a major overall cause of death, those women who are hospitalized for hip fracture have a mortality rate as high as 30% from complications such as thromboembolism, fat embolism, pneumonia, and surgical deaths. Fractures are common at older ages and are a major cause of morbidity and loss of mobility (Black et al., 1992 a,b). A woman aged 50 has been estimated to have a 15% chance of being hospitalized for hip fracture during her remaining lifetime (Black et al., 1992 a, b). Annual fracture rates increase markedly with age, being negligible at ages below 55, but rising to 0.5%, 1%, and 2.3% in the age groups of 55-64, 65-74, and 75-84, respectively (Melton et al., 1987). For hip fractures the corresponding rates are 0.1%, 0.3%, and 1.2%. At any age the rates in women are about twice as high as those in men (Melton, 1990). Vertebral fractures are more common than hip fractures but are not usually associated with increased mortality. Other fractures which are associated with osteoporosis include fractures of the pelvis, distal forearm, and proximal humerus.

The potential role of hormone replacement therapy

In the main, fractures result from the interplay between bone mass and trauma (Grisso et al., 1991; Melton, 1990). Severe trauma may cause fractures irrespective of bone mass, while even daily activities may result in fracture when bone mass has been severely depleted. Bone mineral density is a particularly good predictor of fractures of the hip, spine, and radius (Black et al., 1992 a, b). Bone loss with aging occurs because the rate of bone formation does not keep pace with the rate of bone resorption. Postmenopausal
women lose about a third of their cortical bone and one-half of their trabecular bone. Risk factors relating to bone loss include female sex, increasing age, Caucasian race, oophorectomy, chronic use of oral corticosteroids, early menopause, prolonged immobility, and insufficient dietary calcium. Protective factors include estrogen replacement therapy, obesity, and physical activity (Melton, 1990).

Estrogen status is a particularly important determinant of bone mass. Women have an accelerated bone loss at a rate of about 3% per annum immediately following the menopause which is thought to be related to decreases in estrogen levels. Thereafter, bone loss with aging continues at a slower rate of about 1% per annum (Bilezekian et al., 1992; Steiger et al., 1992). Estrogens can prevent both these losses through preventing bone resorption but may be unable to actually increase bone mass (Bilezekian et al., 1992; Prince et al., 1991). Progestins may also aid the maintenance of bone mass. The major effect of estrogens on bone mass is in the years immediately following the menopause, while the peak rate of fractures occurs some decades later. Nevertheless, at any age estrogens may have the potential to prevent further loss of bone, suggesting that even at advanced ages women receiving estrogens may benefit compared to those who do not. Observational studies indicate that women taking estrogens do have greater bone mass and a lower fracture rate (Johnston et al., 1991). However, the effectiveness of estrogens in preventing fractures has not been adequately tested in a clinical trial, due to the large numbers of women needed to obtain a definitive result.

2.2.3. Potential Adverse Effects of Hormone Replacement Therapy

The use of estrogen increases the risk of endometrial cancer, and may increase the risk of breast cancer and of thromboembolism (Barrett-Connor, 1989; Colditz et al., 1990; Willett, 1989; Goldman et al., 1991; Whitehead et al., 1990).

Analyses of pooled observational data have yielded conflicting results in regard to the risk of breast cancer. Sources of bias exist in the observational data, and it is difficult to predict what their effect is on the findings. For example, closer monitoring of patients on HRT may result in more cancers being identified than in the control group, leading to an overestimate of the risk. On the other hand, doctors may be reluctant to prescribe HRT to high-risk women, which may lead to an underestimate of the risk. Meta-analyses indicate that the overall risk of breast cancer from estrogen appears to be increased by a nonsignificant 7% among users of estrogen replacement (Dupont et al., 1991). Risk appears to be related to duration of estrogen use (increasing by 20% after 10 years, and 30% after 15 years), timing (higher in premenopausal women), dose (higher at doses of conjugated equine estrogens above 1.25 mg/day), type of estrogen (higher for estradiol than conjugated equine estrogens), and family history of breast cancer (risk twice as high in women with a family history) (Steinberg et al., 1991). Importantly, there is no convincing evidence that conjugated equine estrogens at a dose of 0.625 mg/day is associated with significantly increased risk.

The relative risk for endometrial cancer incidence appears to be increased 4-to 10-fold over six years of treatment, and may persist for some years following cessation of treatment (Whitehead et al., 1990). However, the risk of death from endometrial cancer apparently is not increased. This may be because the endometrial cancers are identified early in these women who are generally under close surveillance, or because the type of endometrial cancer induced by estrogen therapy is relatively non-invasive.

Since CHD accounts for a far larger proportion of all deaths in postmenopausal women than cancers of the breast or endometrium combined, a reduction of 50% in CHD will far outweigh even substantial increases in the cancer deaths (Goldman et al., 1991). For example, at age 70-79 CHD accounted for 22% of all deaths in 1988, while cancer of the breast accounted for 4% and cancer of the endometrium for 1% (National Center on Health Statistics, 1990). ERT has also been reported to increase the risk of
thromboembolic events. However, thromboembolism accounted for only a small proportion of deaths (1%) in postmenopausal women.

The addition of a progestin may reduce or eliminate the risk of endometrial cancer (Whitehead et al., 1990), while the effect of progestins on breast cancer risk is uncertain. In practice, physicians are increasingly adding progestins to ERT in women who have an intact uterus. Progestins tend to reverse the increase in HDL-cholesterol engendered by estrogens, but appear not to influence LDL-cholesterol (Kushwaha et al., 1991; Miller et al., 1991; Rijpkema et al., 1990). It is not known whether the addition of a progestin will counteract the potential benefit of ERT on vascular disease. Progestins do increase the incidence of physical side-effects such as breast tenderness, bloating, edema, withdrawal bleeding, and abdominal cramping, and they also increase the incidence of psychological side effects such as anxiety, irritability, and depression. The side effects are dose-related, and are less frequent on smaller doses.

2.2.4. The Need for a Controlled Trial of Hormone Replacement Therapy

The proposed Clinical Trial has enormous public health importance, because the diseases to be studied (cardiovascular diseases and fractures) are common, and potential risk reductions obtainable are large. Even if the reductions in CVD mortality and fractures are more modest than those suggested by the observational studies, such reductions could still have a major public health impact, provided that they are not offset by substantial increases in deaths from breast cancer, endometrial cancer, or thromboembolic events.

Currently, a large proportion of physicians do not prescribe postmenopausal hormone replacement therapy beyond the few years after the menopause, either because they are not convinced that such therapy is effective, or because they are concerned about adverse effects. The unfavorable experience of men with preexisting coronary disease who were prescribed large doses of estrogens in the Coronary Drug Project (CDP) have raised doubts about the advisability of using estrogens in patients with CHD, even though the doses currently in use are much smaller than those used in the CDP and the effects in women may be quite different from those in men (Canner et al., 1986; Byar et al., 1988).

When they do prescribe estrogens to postmenopausal women for the purpose of reducing cardiovascular disease risk, physicians are unsure as to whether the estrogens should be accompanied by a progestin. Though progestins are commonly prescribed together with estrogens in women with a uterus (to protect against endometrial cancer), the epidemiologic data suggesting benefit in regard to CVD is confined to experience with ERT. Progestin-estrogen replacement therapy (PERT) partly reverses the metabolic effects of ERT, and thus may not have the same magnitude of effect on CVD as ERT. Because of these uncertainties, it is likely that large numbers of women who may benefit from hormone replacement therapy are not receiving it.

These doubts are unlikely to be resolved by further observational studies, because observational studies cannot adequately control for confounding due to differences in the characteristics of women who are treated with hormone replacement therapy compared to those who are not. The similarity of the risk reductions for CVD, CHD, and for all-cause mortality suggests that some or all of the apparent benefit associated with estrogen use may be due to confounding. Some of the possible confounding influences arise from the self-selection of women who go onto hormones, selection bias by physicians as to whom they prescribe hormones to, and socioeconomic biases. A clinical trial, in which selection bias is eliminated by random allocation to treatment and control groups, is needed to evaluate the true benefit of estrogen, and of estrogen plus progestin. Such a trial will provide critical guidance as to the indications for hormone replacement therapy for conditions other than the relief of postmenopausal symptoms, and the choice of agents (estrogen or estrogen plus progestin). In order to provide this guidance, the trial should test both ERT and PERT.
The Clinical Trial will be able to assess the benefits and risks of hormone replacement therapy, and thereby provide information on the global impact on women's health. The CT will evaluate the benefits and risks of hormone replacement therapy on CHD, cancers of the breast and endometrium, fracture rates (in particular, hip fractures), quality of life, and total mortality. In addition, information on the possible mechanisms (such as plasma lipids, clotting factors, blood pressure, plasma insulin, body fat distribution) through which estrogens mediate their putative protective effect on CHD will be obtained and analyzed during the trial.

2.3. DIETARY MODIFICATION

2.3.1. Dietary Modification and Breast Cancer

The magnitude of the problem

Among U.S. women, breast cancer is the cancer with the greatest incidence and the one with the second greatest mortality after lung cancer (National Cancer Institute, 1989). In 1991, approximately 175,000 cases of breast cancer were diagnosed and about 44,500 deaths occurred. In 1988 the national mortality rates in the age groups 50-59, 60-69, and 70-79 were 64, 96, and 124 per 100,000 (National Center on Health Statistics, 1990). Breast cancer incidence rates have increased about 1% per year since the early 1970's, whereas mortality rates have remained fairly stable over the past 50 years.

The potential role of diet

International breast cancer incidence rates among postmenopausal women show highly significant positive regression on corresponding per capita dietary fat supply (e.g., Armstrong et al., 1975; Prentice et al., 1990a). In fact, such analysis suggest that a 50% reduction from U.S. fat consumption levels could lead to a two and a half fold reduction (estimated relative risk of 0.39) in postmenopausal breast cancer incidence (Prentice et al., 1990a). Saturated fat, and particularly polyunsaturated fat, supply correlate with breast cancer incidence in these analyses.

Women migrating from low fat consumption to high fat consumption areas tend to adopt the higher breast cancer rates of their new country (e.g., Kolonel et al., 1991; McMichael et al., 1988; Margetts et al., 1991). In fact the three fold higher breast cancer incidence among Japanese women in Hawaii, as compared to Japanese women in Japan (Tominaga et al., 1985) appears to be quite consistent with the international regression analysis noted above upon acknowledging per capita fat supply differences between the two countries (Prentice et al., 1990a).

There is an extensive literature relating fat consumption in rodents to mammary tumor incidence (e.g., Carroll et al., 1975). Though these data have been variably interpreted, a recent meta-analysis (Freedman et al., 1990) indicates that dietary fat has a specific positive association with mammary tumor incidence, beyond the association that can be attributed to fat as a source of calories.

Analytic epidemiologic studies have tended to yield equivocal results concerning dietary fat and other dietary factors in relation to postmenopausal breast cancer risk (e.g., Greenwald, 1988; Prentice et al., 1988; Hulk, 1989). In large part, this may be due to a limited range of intakes of fat and other nutrients within populations studied, and to the known major random error that attends individual estimates of nutrient intakes based on available dietary assessment techniques.

These factors combine to reduce study power and to elevate the importance of minor confounding biases (e.g., Goodwin and Boyd, 1987; Prentice et al., 1989; Byar et al., 1989). Nevertheless, a meta-analysis of the raw data from 12 case-control studies, including several thousand cases and controls, yielded a highly significant positive association between estimated fat consumption and postmenopausal breast cancer risk (Howe et al., 1990). Moreover, the estimated risk relationship appears to be quite consistent with the
strong international regression analysis noted above. On the other hand, the three existing sizable cohort studies of dietary fat and breast cancer appear to yield conflicting results. The studies of Howe et al., (1991) and Kushi et al., (1992) report non-significant positive associations that appear to be consistent with the international analyses, while that of Willett et al., (1992) is not suggestive of any positive association between fat consumption and breast cancer risk.

Some of the studies alluded to above have suggested that vegetable intake, or related dietary intakes may be associated with reduced breast cancer risk (e.g. Howe et al., 1990). However, results concerning these associations have often been inconsistent or equivocal in individual analytic epidemiologic studies, quite possibly for the reasons mentioned above.

Feasibility studies of a low-fat eating pattern among healthy women in the age range 45-69 (e.g., Insull et al., 1990; Henderson et al., 1990; Gorbach et al., 1990) show that women randomly assigned to dietary intervention are able to reduce the fat content of their diet to about 20% of calories and to retain the dietary change for two years or more. Change in plasma hormone concentrations were also studied in a subset of women assigned to dietary intervention. These women were found to experience a significant, average 17%, reduction in plasma estradiol concentration (Prentice et al., 1990 b), thereby adding strength to the low-fat eating pattern and breast cancer prevention hypothesis.

2.3.2. Dietary Modification and Colorectal Cancer

The magnitude of the problem

Colorectal cancer is the third leading cause of cancer deaths in U.S. women and the incidence is third only to that of breast and lung cancer (National Cancer Institute, 1989). About 78,500 new cases were diagnosed in 1991 and approximately 31,000 deaths from colorectal cancer occurred. In 1988 national mortality rates for colorectal cancer in the age groups 50-59, 60-69, and 70-79 respectively were 21, 53, and 109 per 100,000 (National Center on Health Statistics, 1990).

The potential role of diet

Epidemiologic and animal studies conducted over the last few decades have established a fairly strong link between dietary factors and colorectal cancer (National Research Council, 1989). Various dietary constituents have been implicated, including fat, excess calories, and reduced dietary fiber. International correlation studies show an approximately linear relationship between total dietary fat availability and colorectal cancer risk (Carroll and Khor, 1975). In fact, such analyses suggest that a 50% reduction from U.S. fat consumption levels could lead to a three-fold reduction in colorectal cancer risk (Prentice et al., 1990 a). Studies in migrants from areas with diets low in animal fat and protein to areas with a more typical "Western" diet with high fat intakes show an increase in incidence of colorectal cancer among the migrants when compared to incidence in the country of origin (e.g. migration from Japan to Hawaii, Kolonel et al., 1981; and from Italy to Australia, McMichael and Giles, 1988). A National Cancer Institute sponsored clinical trial is currently assessing the ability of a low fat, high fiber diet to prevent the recurrence of colonic polyps, which are considered to be precursor lesions for colon cancer.

A rather large number of case-control studies have examined the relationship between estimates of dietary fat consumption, and colorectal cancer risk (e.g. Graham et al., 1988; Jain et al., 1980; Kune et al., 1987; Lyon et al., 1987; Potter et al., 1986; Slattery et al., 1988; Loe et al., 1989; Tuyne et al., 1987, Whitemore et al., 1990). The studies have tended to yield mixed and equivocal results (Kolonel et al., 1987), though collectively they seem to be fairly consistent with projections based on the strong international correlational results (Prentice et al., 1990a). Prospective study results have likewise given mixed results with a study of men of Japanese ancestry (Stemerman et al., 1984) not suggestive of a relationship
between saturated fat and colon cancer, while a recent study in U.S. nurses reported a significant positive association (Willett et al., 1990).

Several international correlation and case-control studies have shown inverse relationships between the intake of high fiber foods and colon cancer risk (National Research Council, 1989; Greenwald et al., 1987). High intake of fruits and vegetables has been fairly consistently related to lower risk of colon cancer, whereas the consumption of cereal grain products has been either unrelated or negatively associated with risk of colon cancer. Analytic epidemiological studies that have had a reasonable capability to assess dietary fiber have tended to suggest a protective effect for fiber consumption (e.g. Trock et al., 1990), while considerable recent interest focuses on the potential of various sources of fiber (e.g. wheat bran versus oat bran) to reduce colorectal cancer risk.

2.3.3. Dietary Modification and Coronary Heart Disease

The magnitude of the problem

See section on Hormone Replacement Therapy.

The potential role of diet in coronary heart disease

The etiology of coronary heart disease has been linked through international studies to the consumption of high fat diets. Saturated fat intake as a percent of calories correlated strongly ($r = 0.84$) with CHD mortality rates in the Seven Countries Study (Keys, 1980). A lifelong low fat diet may in fact exert beneficial effects on CHD rates beyond its influence on blood cholesterol. The slope of the line relating dietary percent calories from saturated fat is nearly two and one-half times greater than that which would be expected if saturated fat operated only by raising serum cholesterol. Migrant studies (e.g., Japanese migrants to Hawaii) suggest an important effect of saturated fat consumption on CHD rates (Robertson et al., 1977). As in the case of cancer, and probably for the same methodologic reasons, it has been difficult to demonstrate a consistent effect of saturated fat on CHD in analytic studies of individuals within populations.

Dietary factors other than saturated fat may influence CHD rates either via reducing blood cholesterol (e.g., food fiber), through decreasing levels of oxidized LDL (by increasing the intake of antioxidants such as selenium, vitamin E, ascorbic acid, and beta-carotene), through effects on the platelet function (fish oils), or through indirect or unknown mechanisms.

Role of serum cholesterol in CHD in women

Serum total cholesterol levels generally increase from young adulthood through middle age in both men and women, with levels for men generally higher. However, above age 65, cholesterol and LDL values are considerably higher in women than in men. Increasing levels of serum cholesterol correlate with an increasing incidence of CHD among women up to the age of 65 years. Beyond this age, the association is less robust, but fewer studies are available. There is some evidence that serum triglyceride levels may be predictive of CHD in postmenopausal women. Increasing high-density lipoprotein (HDL) cholesterol levels appears to be protective in women of any age (Manolio et al., 1992).

Cholesterol lowering and CHD

The major prospective primary and secondary prevention clinical trials that demonstrate a reduction of CHD events by lowering of plasma cholesterol levels by diet and/or drugs have been conducted in middle-aged men (Lipid Research Clinics, 1984; Frick et al., 1987). Studies in men and women have shown that restriction of dietary fat and cholesterol can lower plasma total and LDL-cholesterol, though the results appear to be somewhat less consistent in women (Ernst et al., 1980; Kris-Etherton et al., 1988). No studies have been conducted in postmenopausal women to determine the long-term effect of a low fat diet on lipid
levels. Furthermore, there have been no large randomized trials in women to study the effects of lowering lipids on CHD incidence. Women's Health Trial feasibility studies (Insull et al., 1990; Henderson et al., 1990) demonstrate a modest but highly significant reduction in plasma cholesterol concentration among women assigned to dietary modification.

2.3.4. The Need for a Controlled Trial of a Low Fat Eating Pattern

Many types of evidence bear upon the hypotheses of interest in the proposed dietary intervention trial, namely that dietary intakes of fat, grains, fruits and vegetables are related to the incidence of breast and colorectal cancers. Considerable differences of opinion continue to exist among scientists on the "diet-cancer" hypothesis, in large part due to numerous limitations and inconsistencies in the available data.

Animal experiments are important for demonstrating plausible biological mechanisms and for confirming or explaining the results of epidemiological studies, but their results cannot on their own be extrapolated to humans. If a marker for disease exists, then clinical metabolic studies may be performed to test the effect of dietary modifications on the marker. No such marker currently exists for breast or colorectal cancer.

Studies correlating international data on incidence of disease with food disappearance data and migrant studies provide useful information in support of these hypotheses but cannot be entirely relied upon because available dietary data are crude and because results may be subject to confounding and aggregation biases.

Case-control studies overcome some of these problems but suffer from possible biases in the selection of cases and controls and differential recall of dietary intake by cases and controls, as well as from non-differential error in the measurement of dietary intake. Prospective cohort studies avoid selection and recall biases but still rely upon food questionnaires which are known to involve substantial measurement error. These problems are compounded by the narrow range of intakes of the populations typically entering a case-control or cohort study.

Definitive studies to test the effectiveness of dietary interventions to reduce cancer incidence and mortality are not available. The proposed randomized trial will have an appropriate design and will have the power to provide a definitive answer to a question of great public health importance.

The proposed trial will at the same time provide estimates of the effectiveness of low fat dietary pattern in preventing CHD, as well as providing information on the effect of such a dietary pattern on serum cholesterol, blood pressure, and body weight. If a low fat diet does reduce the incidence of any one of the clinical outcomes of breast cancer, colorectal cancer, or coronary disease, the public health implications will be important since it can be expected to lead to an even greater emphasis on low fat dietary patterns and in public health recommendations and in clinical practice. Also, as a result of this CT, dietary guidelines (e.g. National Research Council, 1989) may be able to be refined, and the credibility of such recommendations will be much enhanced.

2.4. CALCIUM AND VITAMIN D SUPPLEMENTATION

2.4.1. Calcium, Vitamin D, and Fractures

The magnitude of the problem
See the discussion under Hormone Replacement Therapy (Section 1).
The potential role of calcium and vitamin D

Insufficient dietary calcium is one of the possible risk factors for osteoporosis and hence for fractures (e.g. Heaney 1982; Cummings et al., 1985; Cummings, 1990). An inadequate intake of calcium is common in women; the NHANES data show that calcium intake in women is 40-50% below that of men, and 75-80% of women have daily intakes below 800 mg, while 25% have intakes below 300 mg. According to the 1984 National Institutes of Health (NIH) Consensus Conference on osteoporosis, dietary calcium intake required to prevent negative calcium balance increases from around 1000 mg/day in perimenopausal women to 1500 mg/day after the menopause (Osteoporosis, 1984). Intestinal absorption of calcium declines with advancing age (Gallagher et al., 1979). An age-related intestinal resistance to the action of 1,25(OH)2D has been implicated in this impaired absorption (Heaney, 1982), as have age-related changes in parathyroid hormone and 1,25(OH)2D levels (Riggs et al., 1986). Estrogen is known to enhance intestinal calcium absorption and renal calcium conservation (Heaney, 1990). Thus, both estrogen and calcium supplementation can help reverse the negative calcium balance that accompanies aging. On the other hand, low fat diets are sometimes accompanied by a reduced intake of dairy products and of calcium and may thus increase the negative calcium balance (Holbrook et al., 1991), though reduced calcium intake has not been found in feasibility studies of the dietary modification program to be used in the WHI (Insull et al, 1990).

Even though low dietary calcium intake may be a risk factor for osteoporosis and for fractures, the data on the effectiveness of calcium supplements are conflicting (Reid, 1990; Dawson-Hughes et al., 1990; Riis et al., 1987; Prince et al., 1991). This variation may reflect differences in hormonal status and diet of the subjects. In a recent study of older postmenopausal women, calcium supplements were effective in preventing bone loss in those women with a dietary calcium intake of less than 400 mg, but not in those with higher dietary calcium intakes (Dawson-Hughes et al., 1990). The addition of vitamin D appears to increase the effect of supplemental calcium on the prevention of bone loss; it is uncertain whether this is because the absorption of calcium is enhanced, or whether vitamin D exerts an independent effect (Dawson-Hughes et al., 1991). Estrogen therapy reduces bone loss in postmenopausal women, and it is not known whether calcium supplementation in women already on estrogen will induce a significant further reduction in bone loss.

2.4.2. Calcium and Colorectal Cancer

Human observational studies (e.g. Garland et al., 1986; 1989; 1991) and animal experiments suggest that calcium may decrease the risk of colorectal cancer, possibly because increased formation of the calcium salt of bile acids decreases promotion of cancer (Lipkin et al., 1991). Data from controlled trials on the effect of calcium supplementation on colorectal cancer are not available, hence this large trial may provide valuable information.

2.4.3. The Need for a Controlled Trial of Calcium and Vitamin D

Despite the conflicting data regarding efficacy, many women are currently taking supplements of calcium and vitamin D in the hope of reducing bone loss. Only one trial of the effect of calcium and vitamin D₃ supplementation and fracture rates has been reported; hip fracture rates among healthy elderly women were reduced by 43% (P=0.05) among women completing an 18-month course of 1.2 grams of elemental calcium and 800 IU of vitamin D₃ per day (Chapuy et al., 1992). A definitive clinical trial would provide a rational basis for advising women concerning such supplementation. The CaD trial component will indicate whether supplementation is effective in reducing bone loss and fracture rates, and in reducing colorectal cancer. Subgroup analyses may provide additional information on aspects such as the effect of varying dietary intake of calcium on efficacy of supplementation in reducing bone loss, the effect of supplementation alone or in combination with estrogens on bone loss, and the effect of calcium alone or in combination with a low fat dietary pattern on colorectal cancer.
2.5. OBSERVATIONAL STUDY

2.5.1. Observational Study Potential

Observational studies have made unique and important contributions to medical knowledge. Historically, observational studies have not only generated the hypotheses which were later tested in clinical trials, but have also had a more direct impact on medical practice. For example, a valuable contribution of the Multiple Risk Factor Intervention Trial (MRFIT) was not to be found in the trial results but in the observational data on the large cohort of male screenes. The MRFIT cohort provided very stable estimates of relative and absolute risk for CHD in men by level of serum cholesterol, and these estimates have been of critical importance in the formulation of national guidelines for the prevention of CHD by lowering cholesterol. No comparable data exist for women. Cigarette smoking and lung cancer provide another example of the importance of observational data; the association was so strong that trial data was not needed to convince health authorities that action to curb smoking was desirable.

Randomized controlled trials offer a unique opportunity to evaluate the influence of preventive measures on health outcomes, since randomization eliminates the possibility that individuals otherwise at altered risk of an outcome selectively have been exposed to the measure. Nonetheless, we cannot rely on the results of randomized controlled trials for all of our information on the causes of disease and the effectiveness of health interventions. First, some potential causes of disease simply are not amenable to study via randomization. For example, in studies of long-term health outcomes it is rarely possible to randomize individuals to occupational or environmental exposures. Second, because of the costs of large randomized controlled trials, only a limited number of preventive interventions are assessable. In addition, in randomized controlled trials it is necessary to employ a relatively small number of intervention arms, e.g. treated vs. placebo, or treatment A vs. treatment B vs. placebo. Often, the range of potential interventions for a particular health problem is wider than can be encompassed in a single trial. For instance, in the randomized trial portion of the Women's Health Initiative, all women assigned to receive estrogen plus progestin will be asked to take a particular daily preparation at a given dose. Thus, the results from the trial will not speak directly to the influence of other types of progestogen, or of hormones taken at different doses or for other durations each month, on the occurrence of breast cancer, myocardial infarction, and other diseases.

Given the foregoing, it is not surprising that many of the inferences made regarding the prevention of disease are based on the results of nonrandomized studies. The latter may take the form of: a) cohort (or follow-up) studies, in which persons with or without (or at various levels of) a given characteristic are monitored for the subsequent occurrence of one or more health outcomes; or b) case-control studies, in which ill and well persons are contrasted for one or more prior exposures. The OS is designed as a cohort study. For efficiency purposes, without the risk of introducing bias, many uses of the OS will involve so-called nested case-control or case-cohort subsampling procedures.

A relative advantage of cohort over case-control studies is the ability to ascertain an individual’s exposure status prior to the presence of the outcome, thereby minimizing potential bias that can occur via retrospective ascertainment of exposure. To date, a number of cohort studies have been conducted that have been able, in one way or another, to address risk factors for health outcomes in older women. The planned Observational Study has the potential to provide information that goes well beyond that provided by existing studies. It is large (the Study will seek to recruit some 100,000 subjects) and subjects are to be followed for a relatively long time (9 years). Extensive interviews and baseline physical and laboratory examinations will be obtained on all cohort members. In addition, specimens (e.g. samples of blood, separated into its various components) will be obtained and stored for later use. Follow-up of the cohort and ascertainment of illnesses of interest will be highly complete. Finally, the range of health events identified in cohort members will be wide and will encompass the large majority of serious illnesses that occur in middle-aged and older women.
A wide variety of important clinical and public health issues will be assessed with the Observational Study. Firstly, the Observational Study will provide stable estimates of the relative and absolute risks for specific diseases posed by known risk factors such as serum cholesterol (and lipoprotein subfractions), blood pressure, smoking, hormone use, exercise, and obesity. This information will be gathered by relating information obtained on baseline characteristics to subsequent illness events and mortality. Secondly, the study is designed to address the hypothesis that underlying debility and disease is responsible for the excess mortality at low levels of body weight, cholesterol, and blood pressure. This hypothesis will be tested by relating the markers of clinical and subclinical disease, and change in weight, cholesterol, and blood pressure to subsequent mortality. Previous studies have not had the ability to address this hypothesis because of small numbers, lack of repeated measurements, inadequate ascertainment of subclinical disease, or failure to measure appropriate covariables. The third and perhaps most important purpose is the identification and testing of new hypotheses with regard to disease etiology that are not yet satisfactorily addressed in completed or ongoing studies. In addition to questionnaires and physical data, the gathering of biological specimens at baseline for storage and later analysis will allow hypotheses that arise during the course of the WHI to be examined in nested case-control or case-cohort studies. It is likely that new potential biomarkers of disease, such as protein polymorphisms and DNA markers, will be identified during the course of the WHI. The availability of stored biological material and information on other factors that might confound or modify biomarker-disease relations will facilitate epidemiologic studies of these newly identified potential determinants of disease.

The large size of the overall cohort, combined with the effort that is to be made to include sizable proportions of members of racial/ethnic minorities, will permit for a number of the more common health outcomes the identification of risk factors in individual minority groups. Minority women have not been well represented in most past or present cohort studies of cardiovascular disease, cancer, or fractures. The proposed Observational Study can be expected to enroll about 20,000 minority women as subjects. With these much greater numbers, it can begin to explore interracial differences in risk factors for conditions that occur with relatively high frequency, e.g., the major cancers, cardiovascular disease, hip or forearm fracture, and other age-related outcomes (e.g., diabetes mellitus, glaucoma, urinary incontinence). Similarly it will be possible to explore differences in risk factor impact on other subgroups; for example, those defined by age and socioeconomic characteristics.

For reasons of cost-effectiveness, the Observational Study participants at individual Clinical Centers will generally be drawn from a convenient sample rather than a population-based sample. Also, they will be screenees for the Clinical Trial. The potential loss of "representativeness" will however be mitigated by the wide geographic distribution of the 45 Clinics, which will draw on diverse populations, and by the plan to recruit about 20% minority women in the studywide sample. It is not the intent of the WHI to compare the cohort as a whole with other populations. All the comparisons will be within the cohort itself, e.g. women with and without high blood pressure, and women who do and do not use a progestogen to supplement their use of postmenopausal estrogens. Furthermore, many key risk factors for the diseases of interest will be identified in cohort members, so that a relatively unconfounded estimate of the influence of a particular risk factor should be obtainable. Thus, we believe that the generalization of results obtained from the intracohort comparisons will be no less broadly applicable than those of any other epidemiologic study.

The Observational Study capitalizes on the existence of the Clinical Trial's needs to screen a very large number of potential participants in order to obtain the targeted number of actual participants. Thus, the marginal cost of cohort identification for the Observational Study is exceedingly small - almost all of the screening costs would be incurred even if there were no Observational Study. While the added expense of following a large group of nonrandomized women for health outcomes is substantial, even this expense is considerably smaller than if the human and physical resources were not to be shared with those of the parallel Clinical Trial.
1.5.2. Need for the Observational Study

There is an urgent need for stable estimates of the magnitude of risk factor impact on health in postmenopausal women; these estimates are not nearly as complete as in men. There is a need for the identification of "new" risk factors, and the cohort design and procedures of the Observational Study allows for exploration of risk factors of uncertain status, or factors which have yet to be identified. There is a need for the elucidation of the mechanisms underlying the excess risk of mortality at low levels of weight, cholesterol, and blood pressure. Finally, there is a need 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. All of this information is important in setting health policy guidelines. It is unlikely that any of this kind of information will be obtained from clinical trials or from other existing observational studies.

3. STUDY OBJECTIVES

3.1. OBJECTIVES OF THE CLINICAL TRIAL

The overall objective of the trial will be to ascertain the benefits and risks of a number of treatments that may improve the health of postmenopausal women age 50-79. The treatments to be tested are: hormone replacement therapy, low fat dietary pattern, and supplementation with calcium and vitamin D.

The specific aims each of these treatments are:

For hormone replacement therapy:

(1) To test whether ERT and/or PERT reduces the incidence of coronary heart disease and of other cardiovascular disease.

(2) To test whether ERT and/or PERT reduces the incidence of all osteoporosis-related fractures and hip fractures separately.

(3) To assess whether ERT increases the risk of endometrial and breast cancer and whether PERT increases breast cancer risk.

For dietary modification:

(1) To test whether a low fat dietary pattern reduces the incidence of breast cancer and colorectal cancer, separately.

(2) To test whether a low fat dietary pattern reduces the incidence of coronary heart disease.

For calcium and vitamin D:

(1) To test whether supplementation with calcium and vitamin D reduces the incidence of hip fractures.

(2) To test whether supplementation with calcium and vitamin D reduces the incidence of colorectal cancer.
WHI Protocol

Sample size estimates have been based on the first aim for each treatment (see Appendix III), and power calculations have been conducted for the remaining aims. Even though the trial will generally not have sufficient power to test subgroup hypotheses unless there are unexpectedly large effects, various additional analyses will be conducted to obtain information as to whether the effects of treatments appear to vary by participant characteristics or by the presence of another treatment. Subgroup analyses that will be performed will examine:

1. The effect of HRT on the incidence of coronary and other cardiovascular disease in women with, and in women without, cardiovascular disease at baseline.


3. The effect of supplementation with calcium and vitamin D on fractures and colorectal cancer in women with low, and women with higher, intakes of dietary calcium.

4. The effect of HRT, and of a low fat dietary pattern, on breast cancer incidence in women at high and at low risk of breast cancer.

5. The effect of HRT plus low fat dietary pattern on coronary and other cardiovascular disease and on breast cancer compared to each therapy alone.

6. The effect of HRT plus calcium and vitamin D supplementation on fracture rates, compared to each therapy alone.

7. The effect of ERT on coronary and other cardiovascular disease among women with a uterus, as compared to hysterectomized women.

8. The effect of HRT, DM and CaD in subgroups of women defined by age and race/ethnicity.

The trial will also offer the opportunity to examine certain other questions such as: the effect of each treatment on perceived quality of life, on combined primary and secondary endpoints, and on total mortality; the effects of HRT and DM on lipids, lipoproteins, clotting factors, blood pressure, body mass index, waist-to-hip ratio, and blood glucose; trends in the magnitude of HRT, DM and CaD effects across age categories and across values of other participant characteristics; the relationship to clinical outcomes of (a) baseline biochemical and physical variables, (b) changes in those variables induced by treatment, and (c) adherence. The ability of changes in such intermediate variables to explain an observed relationship between treatment and disease occurrence will also be examined.

The Clinical Trial will provide valuable information on various other endpoints, even though the study design has not been motivated by considerations of power for such other endpoints. For example, DM will also be studied in relation to other cancers, including ovary and endometrium cancer, and in relation to diabetes mellitus incidence. Importantly, total mortality rates and other summary measures of benefits versus risks will be monitored in relation to each treatment and treatment combination. An important subsidiary aim is to examine the effect of each CT treatment on bone density (see Section 8).

3.2. OBJECTIVES OF THE OBSERVATIONAL STUDY

The overall objective of the Observational Study is to provide information complementary to that obtained from the Clinical Trial. Measurement of baseline characteristics, remeasurement after three years, storage of frozen blood specimens, and ascertainment of clinical events in a large cohort of postmenopausal women allow the following specific objectives to be formulated:
WHI Protocol

(1) Prediction of risk of outcome on the basis of:

(A) Questionnaires and Interview data: Women in the OS will be asked to complete the same self-administered questionnaire as CT participants. In addition, they will be asked to take part in a supplemental interview to be administered at the end of the screening visit at which a woman joins the OS (usually Screening Visit 1). This will permit the evaluation of associations that cannot be studied in the CT.

(B) Physical exam findings: The anthropometric measurements will be related to the occurrence of selected illnesses and mortality.

(C) Laboratory data: Some previously studied markers of risk can be examined in considerably greater detail than before, e.g. levels of specific lipid components, whose role in the occurrence of coronary heart disease in women is not as well understood as it is in men. Of particular interest will be analyses of stored specimens from recently-developed (or as-yet-to-be-developed) potential biomarkers, e.g. apoprotein subtypes in relation to CHD incidence, or genetic polymorphisms identifiable in stored leukocyte DNA in relation to cancer incidence.

(2) Extension of results obtained in the CT to related exposures or regimens: For example, if estrogen use (or calcium supplementation) is found to be effective in achieving a given outcome as measured in the randomized controlled trial, then one could assess whether in the Observational Study a similar relationship is present for that exact regimen, adjusting for confounding variables and exposure durations as necessary. If a similar relationship is found, a relatively high level of credibility could be given to analyses of related regimens outside those studied directly in the randomized trial. For example, if use of estrogens plus a given progestogen regimen is found to have a beneficial effect on the incidence of myocardial infarction, the data from the Observational Study can be used to assess the extent to which different progestogens/doses/durations can achieve the same effect.

(3) Assessment of temporal relationships between risk factors and disease occurrence: Changes in characteristics such as weight or serum albumin or cholesterol levels, or changes in hormone use, could be assessed for their ability to predict rates of selected clinical outcomes. By measuring and controlling for the presence of subclinical disease prior to the change in risk factor status, the ability to infer a causal relation between change in a risk factor and the subsequent incidence of diagnosed disease will be enhanced.

(4) Documentation of variation in the incidence of cardiovascular disease, cancer, osteoporosis and fracture in postmenopausal women on the basis of geographic region and other demographic characteristics, and an evaluation of the extent to which differences among demographic subgroups in the prevalence of identified risk factors account for such variation.

Appendix V provides a partial list of risk factors that will be examined in the Observational Study.

4. STUDY DESIGN

4.1. OVERVIEW

The trial will be a partially blinded, controlled clinical trial in postmenopausal women age 50-79 years. The trial will evaluate potential preventive treatments for certain clinical conditions which are important causes of morbidity and mortality in postmenopausal women.

The trial will have three main components and four active treatments. The treatments will be tested in a partial $3 \times 2 \times 2$ factorial design (Figure 1). Such a design allows the total number of participants to be
considerably less than would be required for separate experiments for each of the three CT components. The first component will test separately the efficacy of ERT and PERT vs. placebo on coronary heart disease (three arms), the second will test the efficacy of low fat dietary pattern vs. usual dietary pattern on breast and colorectal cancer (two arms), and the third will test the efficacy of calcium/vitamin D supplementation vs. placebo on fractures (two arms). In regard to safety, clinical outcomes of interest include breast cancer and endometrial cancer (HRT) and renal calculi (CaD supplementation). The HRT component will not provide a powerful test of plausible differences between ERT and PERT in respect to coronary heart disease incidence rates. Nevertheless, such differences will be examined and it may be possible to combine ERT and PERT groups in some analyses.

Sample size calculations indicate that for the HRT component 25,000 women, and for the dietary modification component 48,000 women, treated for an average of nine years would provide adequate power for the primary outcomes of interest. Assuming some overlap between the HRT and dietary modification components, it is anticipated that a total of 63,000 women would enter the Clinical Trial. It is assumed that about 45,000 (71%) of these women will be willing to subsequently enter the calcium/vitamin D component (see Appendix III for statistical power calculations). Post-trial mortality and breast and endometrial cancer incidence surveillance for a further five years is envisaged, so that total follow-up will be for an average of 14 years. The longer follow-up will protect against the possibility of missing adverse effects, such as breast cancer in relation to HRT, which may not have had sufficient time to manifest clinically during the nine year average follow-up period.

Women will be recruited on the basis of their eligibility and willingness to participate in either the HRT or the dietary modification components, or both. It is anticipated that about 40% of women who are enrolled in the hormone replacement therapy component will also be enrolled in the dietary modification component. This 40% rate is the product of 0.60, the fraction of HRT women who are expected to meet DM-specific eligibility criteria (Section 4.4), and 0.67, the fraction of HRT women who are assumed to be willing to be randomized into the DM component. A smaller proportion (21%) of women in the DM component are expected to also be eligible and willing to enter the HRT component. The distribution of women in the dietary component will be 40:60 active treatment:control, and in the hormone replacement 30:28:42 ERT:PERT:placebo as is elaborated in the following paragraph. The unequal distributions are intended to decrease study costs while maintaining statistical power. The randomization in the CaD component, which will take place at a participant's first annual visit, will be 50:50 active treatment:placebo. The total trial cohort size is projected to be 63,000.

Women who are post-hysterectomy will be randomized in the HRT between placebo and ERT in the ratio of 7:5. PERT will not be an option for such women, as the role of the progestin is primarily to protect the uterus. Women with an intact uterus will be randomized to placebo, ERT, and PERT in the ratios 7:5:8. The fraction of women with a hysterectomy at baseline will be restricted to be approximately 30%. This distribution was chosen in order to achieve adequate power for ERT vs. placebo and PERT vs. placebo in respect to coronary heart disease. Figure 1 shows the projected number of women in each cell of the CT defined by the HRT and DM randomizations.
Figure 1

Women's Health Initiative Clinical Trial
Partial Factorial Design

Projected number of women entering the various trial components

<table>
<thead>
<tr>
<th>HORMONES</th>
<th>Intact Uterus</th>
<th>Not</th>
<th>ERT</th>
<th>PERT</th>
<th>Control</th>
<th>ERT</th>
<th>Control</th>
<th>Randomized</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
<td>YES</td>
<td>4375</td>
<td>7000</td>
<td>6125</td>
<td>3125</td>
<td>4375</td>
<td>38,000</td>
<td></td>
</tr>
<tr>
<td>NO</td>
<td>YES</td>
<td>19,200</td>
<td>700*</td>
<td>1120</td>
<td>980</td>
<td>500</td>
<td>700</td>
<td>15,200</td>
</tr>
<tr>
<td>NO</td>
<td>NO</td>
<td>28,800</td>
<td>1050</td>
<td>1680</td>
<td>1470</td>
<td>750</td>
<td>1050</td>
<td>22,800</td>
</tr>
<tr>
<td>YES</td>
<td>NO</td>
<td>15,000</td>
<td>15,000</td>
<td>2625</td>
<td>4200</td>
<td>3675</td>
<td>2625</td>
<td>1875</td>
</tr>
<tr>
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<td>NO</td>
<td>63,000</td>
<td>63,000</td>
<td>2625</td>
<td>4200</td>
<td>3675</td>
<td>2625</td>
<td>-</td>
</tr>
</tbody>
</table>

*In each cell of this figure approximately 5 out of 7 women are projected to be willing to be randomized to receive calcium and vitamin supplementation (50%) or placebo (50%), while the remainder will not enter the calcium/vitamin D trial component.

The frequency of women by age group will have the following targets, with acceptable age ranges given in parentheses: 10% (0-15%) for ages 50-54; 20% (15-25%) for ages 55-59; 45% (40-50%) for ages 60-69; and 25% (20-30%) for ages 70-79. These frequencies were motivated by a desire to retain the entire age range 50-79, while paying suitable attention to overall risk versus benefit projections. Power calculations (Appendix III) have been based on the above age targets. To achieve the designated power, accrual of women into both the HRT and the DM components will be restricted to the given age-specific ranges in each clinic.

Women aged 50-79 who have been screened and found not to be eligible for the trial, or who after screening are not willing to participate in the trial, will be invited to participate in the observational component. Much of the same baseline information as for women in the trial will be collected, and mortality and morbidity surveillance will be maintained for an average of nine years. A supplemental epidemiologic questionnaire will also be administered to OS women. In addition, women will be invited to attend a second visit three years after baseline, in order to allow examination of the effects of changes in characteristics on disease outcomes, and in a subsample every three years in order to examine trends in characteristics over time. It is anticipated that 100,000 women will be recruited into the Observational Study.

4.2. CHOICE OF TREATMENTS

4.2.1. Hormones

As previously mentioned, women participating in the hormone replacement component will be randomized based on the presence or absence of a uterus.
WHI Protocol

(1) Women with a uterus will be randomized to one of three arms:

(A) Conjugated equine estrogen* (CEE) .625 mg per day

(B) Conjugated equine estrogen (CEE) .625 mg per day plus medroxyprogesterone* (MPA) 2.5 mg per day continuously

(C) Placebo estrogen or placebo estrogen plus placebo progestin

(2) Women without a uterus will be randomized to one of two arms:

(A) Conjugated equine estrogen (CEE) .625 mg per day

(B) Placebo estrogen

The drug manufacturer will provide the single and combined hormones in single tablets, so that all participants will take only one tablet per day, regardless of the arm to which they are randomized. The drugs will be distributed in six-month supplies in bottles of 215 tablets that women will return every six months for counting and replacement. The unopposed estrogens and combined tablets will be of slightly different size. Therefore, placebo tablets will be dispensed as tablets of two different sizes, so that some women with a uterus in the placebo group will get smaller tablets and others will get the larger tablets. Women in the placebo group without a uterus will get only the smaller size placebo tablets.

Drug dosages and regimes were chosen to minimize side effects and adverse effects, and provide ease of administration while maintaining clinical effectiveness.

The selected hormones and the rationale for these choices are as follows:

(1) Conjugated equine estrogens (CEE) at a dose of .625 mg/day:

This lower dose and type of estrogen is associated with favorable changes in blood lipids, bone loss, and coronary risk, and may be less likely to increase rates of breast cancer and endometrial cancer. Furthermore, conjugated equine estrogens are the most commonly prescribed estrogen preparation in the United States.

(2) Medroxyprogesterone (MPA) at a dose of 2.5 mg/day, continuous:

This agent was chosen from among the progestins because at this continuous low dose it appears to cause less reversal of the beneficial effects of estrogen on lipids than the higher dose cyclic MPA, or the 19-nortestosterone derivatives. It is the most widely prescribed progestin in the United States and is also believed to be as protective of the endometrium as higher dose cyclic MPA. Many women are reluctant to have regular menstrual periods that occur in 85% of women on cyclical regimes. In addition, there will be the benefits of ease of administration for the participants, as well as facilitation of blinding, timing of clinic visits, and drug packaging.

4.2.2. Dietary Modification Component Goals

The nutritional goals for the intervention group are to reduce the intake of total dietary fat to 20% of corresponding daily calories, reduce the intake of saturated fats to less than 7% of calories, and to increase complex carbohydrate and fiber-containing foods to five or more daily servings of vegetables and fruits and to six or more daily servings of grain products. Each participant's fat intake goals will be expressed in

* At the time of this writing of the protocol, the formulation of conjugated equine estrogens to be used in WHI is marketed as Premarin, and the formulation of medroxyprogesterone is marketed as Cycrin.
grams of fat per day. The fat gram goal will be calculated using an algorithm based on height and kilocalories as estimated from the baseline food frequency questionnaires (Table 1).

### Table 1

**Fat Gram Goals for DM Component**

Based on Screening Food Frequency Questionnaire (FFQ) Calories and Height

<table>
<thead>
<tr>
<th>Height (inches)</th>
<th>Total Calories on Screening FFQ (KCAL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;900</td>
</tr>
<tr>
<td>60-60.9</td>
<td>27</td>
</tr>
<tr>
<td>61-61.9</td>
<td>27</td>
</tr>
<tr>
<td>62-62.9</td>
<td>27</td>
</tr>
<tr>
<td>63-63.9</td>
<td>27</td>
</tr>
<tr>
<td>64-64.9</td>
<td>27</td>
</tr>
<tr>
<td>65-65.9</td>
<td>28</td>
</tr>
<tr>
<td>66-66.9</td>
<td>28</td>
</tr>
<tr>
<td>67-67.9</td>
<td>29</td>
</tr>
<tr>
<td>68-68.9</td>
<td>30</td>
</tr>
<tr>
<td>69-69.9</td>
<td>30</td>
</tr>
<tr>
<td>70+</td>
<td>31</td>
</tr>
</tbody>
</table>

**Dietary Control Group**

Women in the dietary modification control group will not be offered a nutrition intervention program since the general strategy to be adopted for this group will be minimum interference with customary diets while collecting nutritional data considered appropriate for comparison with the nutrition intervention group. Participants in the control group will be provided a standard packet of health promotion materials including information on basic nutrition principles for maintaining nutritionally adequate diets, and a copy of the USDA/DEHHS Dietary Guidelines for American (3rd Edition).

**Dietary Intervention Procedures**

Women randomized to the DM intervention arm will be assigned to a permanent group of 8-15 members led by a designated nutritionist. Each such woman will attend her first group meeting within twelve weeks of randomization. The first meeting for each group will be within four weeks of its formation. The group will meet weekly for six weeks, bi-weekly for six weeks, and monthly for nine months. Each woman will have an individual counseling session with her group nutritionist between weeks 12 and 16 from the beginning of intervention sessions. The importance of attendance at scheduled sessions will be emphasized. If a participant misses a group session she will be strongly urged to complete make-up activities. All dietary intervention women will receive a packet of health promotion materials similar to that of control participants but without dietary information.

Self-monitoring tools (Food Diary with Fat Counter and Fat Scan) will be used as educational and monitoring aids during the first year of intervention and a shorter tool (Fat Check) will be used during maintenance. For early monitoring of adherence with dietary fat goals, the Fat Scores collected from group sessions four, eight, twelve and sixteen, and from the individual counseling visit, will be entered into
the CT database. Consumption of fruits, vegetables, and grain products will be self-monitored at these same time points in the first year. The intervention integrates knowledge and skills in both nutritional and behavioral sciences. It uses a small group format and a self-reliant, self-directed approach. Self-monitoring and self-correction have been shown in extensive feasibility testing to produce dietary changes. There is individual flexibility about the exact changes in dietary composition and the rate at which they are made. The information and skills presented during the group sessions build upon the content of previous sessions and provide opportunities for necessary practice, feedback, and reinforcement. All the knowledge and skills required to bring about the dietary change goals are covered during the first year of intervention. Throughout the first year, the intervention will be delivered according to a standardized protocol in all clinics.

Weight reduction and reduction in total calories are not stated goals of the nutritional intervention. Neither body weight nor dietary caloric consumption will be controlled, but reductions in both are expected to accompany successful intervention. Maintenance of dietary change will begin in the second year and will involve about four meetings each year. The meetings will provide opportunities to update nutritional information, and review and practice skills that aid in the maintenance of dietary change. Intervention groups seeking added social support will be encouraged to meet more frequently under the guidance of "peer group leaders." "Peer-led help groups" will be discussed during the last six months of year one. In addition to the planned quarterly meetings, there will be two large group social functions yearly. The emphasis will be to promote social support among group members and between intervention groups.

After the first year, biannual newsletters will be sent to all Clinical Centers for use with their intervention participants. Some variation will be allowed during the maintenance phase in the delivery of the intervention. The Manual of Operations and Procedures (MOOP) will define the range of variation allowed.

Appendix VI provides some further detail on the intervention program and dietary assessment methods.

4.2.3. Dose and Preparation of Calcium and Vitamin D:

CT Women will be asked at their first annual visit if they are interested in joining the calcium/vitamin D trial component. If so, they will be randomized in the ratio of 1:1 to one of two arms:

(1) Calcium carbonate containing 1000 mg elemental calcium per day plus vitamin D3 400 International Units (IU) per day, with meals. This will be dispensed as two tablets, each with 500 mg elemental calcium, plus vitamin D3 200 IU.

(2) Placebo calcium and placebo vitamin D, with a meal, also dispensed as two tablets.

This dose and preparation of calcium was chosen for ease of administration, good blood absorption, and low frequency of hypercalciuria. This supplement is available over-the-counter and has been widely used in the United States for many years. Women will be encouraged, but not required, to take the two pills at different mealtimes, each day. The dose of 1000 mg per day aims to yield an average total calcium intake in excess of 1500 mg per day of elemental calcium in the active treatment group.

The dose of 400 IU of vitamin D3 is large enough to ensure adequacy (RDA is 200 IU daily), without risking toxicity. This is a typical dose for supplementation in multivitamin tablets, and has been found to raise 25-hydroxy vitamin D3 concentrations to acceptable levels (Olmdahl et al, 1982; Webb et al, 1990), and to slow bone loss (Dawson-Hughes et al, 1991). This dose can be given safely without risking hypercalciuria.
4.2.4. Exercise Advice

All randomized women will receive advice and a pamphlet encouraging them to follow a program of moderate exercise (e.g., including walking briskly for half an hour per day).

4.3. OUTCOMES OF INTEREST

4.3.1. Major Clinical Outcomes

Clinical outcomes are divided into primary outcomes for the Clinical Trial (with sufficient power for detection in a pertinent CT component), secondary outcomes of interest (but not necessarily with adequate power), and composite outcomes (combinations of primary and secondary outcomes). The primary outcome for the hormone replacement trial component is fatal and non-fatal CHD; for the dietary modification trial component, breast cancer and colorectal cancer separately; and for the calcium/vitamin D trial component, hip fractures.

Three general classifications of morbidity define major clinical outcomes for the Clinical Trial and Observational Study: cardiovascular disease, cancer, and fractures. Mortality will also be an important clinical outcome, and will include all-cause and cause-specific mortalities (e.g. coronary heart disease, other cardiovascular disease, and cancer). Clinical outcomes in the CT will be initially identified by semiannual self-administered questionnaires, and in the Observational Study by annual self-administered mailed questionnaires, with telephone follow-up as needed. After initial identification, clinical outcomes in the Observational Study will be ascertained and classified in the same way as in the Clinical Trial with some minor differences in the extent to which outcomes are centrally classified and adjudicated. Appendix II provides further detail on the outcome ascertainment and classification plan.

1. Primary outcomes:
   A. Coronary heart disease: acute myocardial infarction or coronary death
   B. Cancer
      1. Breast
      2. Colorectal
   C. Hip fracture

2. Subsidiary outcomes:
   A. Cardiovascular disease
      1. Acute (including aborted) myocardial infarction (fatal or non-fatal)
      2. Coronary death (sudden and non-sudden)
      3. Stroke (fatal and non-fatal)
      4. Congestive heart failure (requiring hospitalization)
      5. Angina pectoris (requiring hospitalization)
      6. Peripheral vascular disease (requiring hospitalization)
      7. Coronary revascularization
   B. Other Cancers
      1. Colon
      2. Rectum
      3. Endometrium
      4. Ovary
   C. All other fractures
D. Venous thromboembolic disease
   1. Pulmonary embolism
   2. Deep venous thrombosis
E. Diabetes mellitus requiring therapy
F. Other age-related outcomes
   1. Inflammatory arthritis
   2. Glaucoma
   3. Urinary incontinence
   4. Physical function status
   5. Dentation: loss of teeth
   6. Cognitive function and dementia

3. Composite outcomes:
   A. Cardiovascular disease
      1. Major: coronary heart disease, stroke, congestive heart failure requiring
         hospitalization, peripheral vascular disease with amputation
      2. Any: major CVD plus non-hospitalized congestive heart failure, other peripheral
         vascular disease, coronary revascularization, angina
   B. Cancer
      1. Diet-related: breast, colorectal, endometrial, ovarian
      2. Hormone therapy-related: breast, endometrial
      3. Total cancer (exclusive of non-melanoma skin cancer)
   C. Any fracture
   D. Any hospitalization
   E. Total mortality
   F. Cause-specific mortality
      1. Atherosclerotic cardiac
      2. Cerebrovascular disease
      3. Other cardiovascular disease
      4. Cancer
         a. Diet-related: breast, colorectal, endometrial, ovarian
         b. Hormone therapy-related: breast, endometrial
         c. All cancer
      5. Violent/Accidental/Suicide
      6. Other deaths

All clinical outcomes will be monitored in all participants in the Clinical Trial and the Observational Study. For specific trial components, specific hypotheses are related to outcomes as shown in Table 2.
Table 2

Outcome for WHI Clinical Trial
"1°" indicates primary outcomes; "2°" secondary and composite outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HRT</th>
<th>DM</th>
<th>CaD</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARDIOVASCULAR:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>1°</td>
<td>2°</td>
<td>2°</td>
</tr>
<tr>
<td>Stroke</td>
<td>2°</td>
<td>2°</td>
<td>2°</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>2°</td>
<td>2°</td>
<td>2°</td>
</tr>
<tr>
<td>Angina</td>
<td>2°</td>
<td>2°</td>
<td>2°</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>2°</td>
<td>2°</td>
<td>2°</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>2°</td>
<td>2°</td>
<td>2°</td>
</tr>
<tr>
<td>Total cardiovascular</td>
<td>2°</td>
<td>2°</td>
<td>2°</td>
</tr>
<tr>
<td>CANCER:</td>
<td></td>
<td></td>
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<tr>
<td>Breast cancer</td>
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<tr>
<td>Endometrial cancer</td>
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<td>2°</td>
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<tr>
<td>Colorectal cancer</td>
<td></td>
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<td>2°</td>
</tr>
<tr>
<td>Ovarian cancer</td>
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<td>2°</td>
<td></td>
</tr>
<tr>
<td>Total cancers</td>
<td>2°</td>
<td>2°</td>
<td>2°</td>
</tr>
<tr>
<td>FRACTURES:</td>
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<td></td>
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</tr>
<tr>
<td>Hip</td>
<td>2°</td>
<td>2°</td>
<td>1°</td>
</tr>
<tr>
<td>Other fractures</td>
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<td>Pulmonary embolism</td>
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<tr>
<td>Deep vein thrombosis</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus requiring therapy</td>
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<td>2°</td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>2°</td>
<td>2°</td>
<td>2°</td>
</tr>
</tbody>
</table>

4.3.2. Intermediate Outcomes

In addition to clinical outcomes of interest to the WHI, other findings determined by laboratory, radiologic or pathologic examination will serve as intermediate outcomes. A detailed schedule for measurement of intermediate outcomes during the follow-up period is included in Appendix I. Some of these outcomes will be ascertained in all participants and others in defined subsamples of participants.

Intermediate outcomes will be measured at baseline and one year of follow-up in all Clinical Trial participants to assess short-term effects of treatment. These outcomes will then be measured in a subsample at three, six, and nine years after randomization. Intermediate outcomes will be measured at baseline and three years of follow-up in all Observational Study participants, and then only in a subsample at six and nine years after entry. Some laboratory outcomes will only be measured in a subsample.
Table 3 describes the intermediate outcomes to be monitored in the Clinical Trial and the Observational Study:

**Table 3**

Intermediate Outcomes for WHI Clinical Trials and Observational Study

"x" indicates full sample after second measure; "s" subsample after second measure; "0" osteoporosis substudy only (see Section 8).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HRT</th>
<th>DM</th>
<th>CaD</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interview:</td>
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<td></td>
</tr>
<tr>
<td>Quality of life</td>
<td>s</td>
<td>s</td>
<td>s</td>
<td>s</td>
</tr>
<tr>
<td>Depression</td>
<td>s</td>
<td>s</td>
<td>s</td>
<td>s</td>
</tr>
<tr>
<td>Functional status</td>
<td>s</td>
<td>s</td>
<td>s</td>
<td>s</td>
</tr>
<tr>
<td>Cognitive Function</td>
<td>s</td>
<td>s</td>
<td>s</td>
<td>s</td>
</tr>
<tr>
<td>Examination:</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Height</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>s</td>
</tr>
<tr>
<td>Weight</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>s</td>
</tr>
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<td>Waist, hip circumferences</td>
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<td>x</td>
<td>s</td>
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<tr>
<td>Blood pressure</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>s</td>
</tr>
<tr>
<td>Laboratory:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematocrit, white blood cell count, platelets</td>
<td>s</td>
<td>s</td>
<td>s</td>
<td>s</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>s</td>
<td>s</td>
<td>s</td>
<td>s</td>
</tr>
<tr>
<td>Lipids/lipoproteins</td>
<td>s</td>
<td>s</td>
<td>s</td>
<td>s</td>
</tr>
<tr>
<td>Fibrinogen, factor VII</td>
<td>s</td>
<td>s</td>
<td>s</td>
<td>s</td>
</tr>
<tr>
<td>Antioxidants</td>
<td>s</td>
<td>s</td>
<td>s</td>
<td>s</td>
</tr>
<tr>
<td>Procedure/Pathology:</td>
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<td></td>
</tr>
<tr>
<td>Major ECG abnormalities</td>
<td>x</td>
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</tr>
<tr>
<td>Cervical dysplasia</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrial dysplasia</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone density/Body composition</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>Benign breast disease</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Colorectal polyps</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

4.4. STUDY POPULATION

The eligibility and exclusion criteria are as broad as possible in order to increase the generalizability of the results to the population of postmenopausal women. The trial will combine primary and secondary prevention. Thus, women with prevalent cardiovascular disease, and women with a past history of fractures, will be included (with some exclusions noted below). The study population can be drawn from a convenient population (e.g., a clinic-based sample), the general population (population-based sample), or a combination of both. In view of cost considerations and the near-impossible goal of obtaining a truly representative population sample for a clinical trial, it is anticipated that most of the participants in the CT/OS will be drawn from convenient populations. Though this does limit the generalizability of estimates of disease and risk factor prevalence, it is expected to have a minimal impact on the generalizability of treatment effects or relative risk estimates.
To maintain power, some restrictions will be made on accrual for defined subgroups. In all trial components, as mentioned above, the target fractions for randomized women will be 10%, 20%, 45%, and 25% for ages 50-54, 55-59, 60-69, and 70-79, respectively. In the HRT, hysterectomized women will represent no more than 30% of the accrued population. These distributions will be monitored by the Clinical Centers and enrollment may be temporarily closed to appropriate subgroups to achieve these goals. Minority women will be represented in the overall sample in at least the proportion that they are found in the general population of women age 50-79 (17% according to the 1990 census). Efforts will be made to ensure adequate representation of minority women and women of lower socioeconomic status, primarily by including Clinical Centers having access to large numbers of women in such population subgroups.

Inclusion Criteria for All Components

1. Postmenopausal female volunteers of all races and ethnicity, with or without a uterus or ovaries (See Manual of Operations and Procedures for detailed procedures for establishing menopausal status).
2. Ages 50-79 years, inclusive, at first screening contact.
3. Likely to be residing in study area for at least three years after randomization.
4. Providing written informed consent.

A. Exclusion Criteria for All Components

1. Competing Risk
   a. Any medical condition associated with predicted survival of less than three years in the judgment of a Clinic physician (e.g. class IV congestive heart failure, obstructive lung disease requiring long-term ventilation or supplemental oxygen in the past, severe chronic liver disease with jaundice or ascites, kidney failure requiring dialysis, sickle cell anemia)

2. Adherence or Retention Reasons
   a. alcoholism
   b. other drug dependency
   c. mental illness, including severe depression
   d. dementia
   e. active participant in any other interventional trial where participants are individually randomized to an intervention or control group

B. Additional Exclusion Criteria for All Clinical Trial Components

1. Competing Risk
   a. invasive cancer of any type in the past 10 years
   b. breast cancer at any time (in situ or invasive)
   c. any medical condition associated with predicted survival of less than three years in the judgment of a Clinic physician (e.g. class IV congestive heart failure, obstructive lung disease requiring long-term ventilation or supplemental oxygen in the past, severe chronic liver disease with jaundice or ascites, kidney failure requiring dialysis, sickle cell anemia)
   *d. baseline mammogram or clinical breast examination findings suspicious of breast cancer (see MOOP for detailed criteria)
   *e. acute myocardial infarction in past six months
   *f. stroke or transient ischemic attack (TIA) within the past six months
   g. known chronic active hepatitis or severe cirrhosis
2. Safety reasons
   a. severely underweight (BMI < 18 kg/m² or loss of 15 or more pounds in previous six months without dieting)
   b. hematocrit < 34% or hemoglobin < 11.5 gm/dl
   c. platelets < 75,000 cells/ml
   d. severe hypertension (systolic BP > 200 mmHg or diastolic BP > 105 mmHg)
   e. current use of oral daily corticosteroids for more than six months

3. Adherence or retention reasons
   a. BMI > 40 kg/m²
   b. unwilling to participate in baseline or yearly examination components such as yearly mammograms, clinical breast exams, phlebotomy, electrocardiograms, questionnaires and forms; or unable to complete baseline study requirements

C. Additional Exclusion Criteria for Hormone Replacement Component

1. Safety reasons
   a. endometrial cancer of any stage at any time
   b. endometrial hyperplasia at baseline biopsy or endometrial thickness > 5mm via ultrasonography (no recycling)
   c. malignant melanoma of any stage at any time
   d. history of non-traumatic pulmonary embolism, deep vein thrombosis or pulmonary embolism event associated with estrogen or oral contraceptive use, or deep vein thrombosis or pulmonary embolism in past six months
   e. previous osteoporosis-related fracture being treated with hormone replacement therapy
   f. history of bleeding disorder serious enough to require transfusion
   g. known history of hypertriglyceridermia, or lipemic serum leading to diagnosis of hypertriglyceridermia on baseline blood draw
   h. currently on anticoagulants
   i. currently on tamoxifen

2. Adherence or retention reasons
   a. severe menopausal symptoms that would make placebo therapy intolerable to the participant
   b. inadequate adherence with placebo run-in (less than 80% of pills taken)
   c. unable or unwilling to discontinue use of hormone replacement therapy (women must discontinue current replacement hormone therapy for at least three months in order to be eligible for the HRT)
   d. unwilling to have baseline or yearly endometrial aspirations

D. Additional Exclusion Criteria for Dietary Modification Component

1. Adherence or retention reasons
   a. special dietary requirements incompatible with the intervention diet (such as celiac sprue, other malabsorption syndromes, use of MAO inhibitors). Women will be eligible if they are following a diabetic diet or a low salt diet.
   b. colorectal cancer at any time
   c. unable to complete Four-Day Food Record adequately
   d. percent of calories from fat estimated to be 34 or less
   e. number of main meals prepared out of home ≥ 10 per week
   f. type I (insulin-requiring, ketosis-prone) diabetes mellitus
g. gastrointestinal conditions that contraindicate a high fiber diet

E. Additional Exclusion Criteria for Calcium/Vitamin D Component

1. Safety reasons
   a. history of renal calculi

2. Adherence or retention reasons
   a. unable or unwilling to discontinue use of calcium or vitamin D supplements
   b. inadequate adherence with HRT and/or DM trial components during the first year of follow-up (see Manual of Operations and Procedures for detailed criteria)

Note: An asterisk (*) in the above listing implies that a woman who is temporarily excluded may be re-evaluated for eligibility as appropriate to the excluding condition. If more than six months have elapsed since the woman's first screening visit, however, all baseline and screening activities must be repeated.

4.5. SAMPLE SIZE AND DURATION

To have sufficient power to test the primary hypotheses, it is estimated that the CT will need to randomize 25,000 women into the hormone replacement component to be followed for an average of nine years; 48,000 women into the low fat diet component to be followed for an average of nine years; and 45,000 women into the calcium/vitamin D supplementation component to be followed for an average of eight years. For details of the sample size calculations, see Appendix III. The total sample size required to achieve the above sample size targets will depend on the proportion of women willing to participate in more than one CT component. Only women who are potentially eligible and interested in the HRT or DM components will be invited for a first screening visit. The total sample size of 63,000 shown in Figure 1 is based on the assumption that 40% of the women who choose the HRT component will also be eligible and willing to be randomized to the DM. It is further assumed that about 45,000 of these 63,000 women (71%) will be eligible and willing to participate in the CaD component, for which randomization will take place at the patient's first annual visit (Figure 1). It is envisaged that CT women will be followed for mortality and for breast and endometrial cancer incidence for an additional five years beyond the end of the nine year average follow-up period mentioned above. This will allow more precise safety evaluations and total mortality comparisons for the CT.

Assuming that approximately one-third of women who attend Screening Visit 1 will be enrolled into the CT, we anticipate that approximately 100,000 women will be entered in the OS. This sample size will provide adequate power to obtain precise estimates of the strength of risk factors, since substantial numbers of clinical events can be expected to occur (Table 4, see also Appendix III).

Table 4

<table>
<thead>
<tr>
<th>Average Years of Follow-Up</th>
<th>Total Deaths</th>
<th>CHD</th>
<th>CVD</th>
<th>Breast Cancer</th>
<th>Colorectal Cancer</th>
<th>Composite *Fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>5,000</td>
<td>1,900</td>
<td>4,000</td>
<td>1,000</td>
<td>500</td>
<td>3,300</td>
</tr>
<tr>
<td>6</td>
<td>11,100</td>
<td>4,200</td>
<td>8,500</td>
<td>2,000</td>
<td>1,100</td>
<td>7,000</td>
</tr>
<tr>
<td>9</td>
<td>18,200</td>
<td>6,700</td>
<td>13,800</td>
<td>3,100</td>
<td>1,900</td>
<td>11,200</td>
</tr>
</tbody>
</table>

* Indicates hip, pelvis, vertebrae, distal radius and proximal humerus fractures
4.6. INFORMED CONSENT

The participant's full understanding of the pertinent study components is important for ethical reasons and for adherence with study protocol. Verbal consent will be obtained from each potential participant who is contacted by phone and asked screening questions. At the beginning of Screening Visit 1, screenees will be given general information about the CT components and about the OS, and a general limited informed consent will be obtained for the initial screening activities, including processing of questionnaire data, drawing blood, and obtaining medical records. Material written in large print in 6th grade level English or Spanish, that describes the study in general terms will be given to each screenee. Potential participants will be shown a video describing the study, or a closely related verbal description of the study will be provided. Toward the end of Screening Visit 1, if the woman is deemed eligible, the trial components for which she is eligible and interested will be described in detail, and written material describing each pertinent Clinical Trial component will be provided. After the potential participant has had the opportunity to read and discuss this information with the study personnel, she will be given a copy of the informed consent form to take home and review. At the beginning of Screening Visit 2, each woman continuing to be CT eligible and interested will be given an opportunity to ask additional questions. She will then be asked to make a decision regarding her participation in the HRT and DM components, and if such decision is positive, she will be asked to sign a consent form specific to the trial components she plans to enter. Written material on the CaD trial component will be provided to CT women prior to their first annual visit, along with a copy of a corresponding consent form. At the beginning of the first annual visit, each CT woman will have the opportunity to discuss the CaD component with study personnel, and to ask related questions. Eligible women will then be asked to make a decision concerning participation in the CaD component and if such a decision is positive, will be asked to sign an informed consent form specific to this CT component. Women who turn out to be ineligible or unwilling to enter the CT at any point in the screening process will be invited to participate in the OS. Interested women will be asked to sign an OS informed consent form. Model informed consent forms are listed in Appendix IV. Clinical Centers are allowed to modify these consent forms only for language and clarification. All consent forms must be submitted to the Project Office for approval.

4.7. RANDOMIZATION ASSIGNMENT BLINDING

4.7.1. Hormone Replacement Therapy

All clinic personnel and participants will be blinded to individual treatment assignments. All efforts will be made to prevent unblinding of participants for the duration of the trial. However, in some instances of unexpected or abnormal uterine bleeding, or of serious adverse experiences, it may be necessary for a clinic consulting gynecologist or a private physician to be unblinded to ensure maximal patient safety.

Some amount of spotting is expected during the first six months, particularly in the estrogen/progestin arm of the hormone replacement trial, but this may resolve. Each site will identify an individual ("designated clinic contact") who will be trained to give uniform and consistent advice to participants calling to report bleeding during the first six months of therapy. During the course of the trial, the designated clinic contact will be responsible for handling the symptom checklist and bleeding diary as well as interacting with participants to follow-up on episodes of bleeding. Because of the likely association between bleeding (and other) symptoms and treatment assignment, this individual should not be involved in ascertainment of outcomes. Should the designated clinic contact need to consult with other clinic staff who are following the participants, she/he should make every effort to describe the woman's symptoms without identifying the person.

Depending on the clinical findings, unblinding will be considered under circumstances involving either participant safety or management of side effects. Such conditions are discussed in Protocol Section 5.5 and in the Manual of Operations and Procedures. Should unblinding become necessary, the clinic
unblinding officer will exercise a database algorithm, detailed in the Manual of Operations and Procedures, that confirms that unblinding criteria have been met, and that records the unblinding activity in the database. The unblinded information will be restricted to the unblinding officer, the clinic consulting gynecologist, and only if necessary, also to the designated clinic contact. The unblinding officer will be a Clinical Center staffperson without other participant interaction responsibilities (e.g., a data coordinator or support person). As long as the unblinded information is limited to these individuals and these persons are not involved in outcome ascertainment, the potential for biasing study outcomes is minimal. Bias can further be minimized by maintaining participant blinding, even when unblinding of the designated clinic contact becomes necessary. Serious complications such as those requiring surgery will, of course, necessitate unblinding a small number of participants. There will also be a mechanism for unblinding in the event of study medication overdose by a participant or other person (see Manual of Operations and Procedures).

4.7.2. Dietary Modification

This trial will, of necessity, be unblinded. However, personnel investigating and classifying laboratory determinations and other intermediate data, as well as clinical outcomes of interest, will be blinded to the participants’ randomization group.

4.7.3. Calcium/Vitamin D

All efforts will be made to maintain double-blinding throughout. The same mechanism alluded to above will be used to unblind in the event of overdose.

4.7.4. Coordinating Center Blinding

Access to individual participant’s treatment assignment(s) by Clinical Coordinating Center personnel will be strictly limited and based on need-to-know criteria. Functions requiring treatment assignment information in the CCC include quality control and reporting. For quality control of Clinical Center unblinding, it will be necessary for CCC medical personnel to review unblinding occurrences at Clinical Centers to determine the appropriateness of unblinding and the adequacy of follow-up. For those cases, CCC medical personnel involved in these quality control procedures will be prohibited from any subsequent endpoint ascertainment or adjudication procedures for those participants whose treatment assignments were revealed to them.

For reporting purposes, access to individual treatment assignment will be limited to analytic and programming staff. The Statistical and Central Study Unit (SCSU) of the CCC will produce all routine reports on primary and intermediate endpoints, safety issues, and laboratory determinations by (coded) treatment arm for examination by the Data and Safety Monitoring Board. Distribution of these reports will be limited to the Data and Safety Monitoring Board members, appropriate NIH staff, the CCC PI, and necessary SCSU staff. To reduce further the risk of unauthorized release of information, the following steps will be taken: in preparing the analyses and reports, all SCSU staff involved will be reminded of the nature of the data and reports; working versions of all output will be shredded prior to disposal; and Clinic and Nutrition Intervention Unit (CNIU) staff and those members of the SCSU and Leadership not involved in producing reports will not be given access to these documents. After each review the reports will be collected and stored centrally. For study management purposes, summary reports accumulated across treatment arms will be presented to display overall study progress.
5. STUDY PLAN

5.1. GENERAL

The feasibility of funding and completing a study of this size and duration depends on cost-effective methods of recruitment, intervention, and follow-up. Clinic visits will be kept to a minimum frequency and duration. Only data that are essential to answering the study hypotheses and to the safety of participants will be gathered routinely. Considerable effort will be made to ensure complete and accurate ascertainment of clinical outcomes. However, for many intermediate questionnaire data, physical measurements, and biochemical variables, strategies to contain data proliferation and cost will be developed and implemented, including the freezing of samples to allow retrospective measurement among cases and controls, obtaining data on subsamples of the study population only, and obtaining data at extended intervals rather than annually.

For example, the effects of a particular treatment on an intermediate variable over time will be assessed by making observations at extended intervals or in an appropriate subsample. It is envisaged that repeated measurements on a random sample of about 100 participants in each Clinical Trial subgroup (i.e. 100 x 33 = 3,300, or about 5-6% of the total trial population) will be sufficient to provide information on trends over time for the intermediate outcomes. Similarly, small subsamples of the Observational Study cohort can be studied at three-year intervals to obtain trends over time. Secondly, to allow the relationship of change in intermediate variables to clinical outcomes to be evaluated, various observations will be made in all Clinical Trial participants at entry and after one year, and of all Observational Study women after three years. However, analyses of most samples will be confined to subsequent cases and appropriate controls.

5.2. ENROLLMENT

5.2.1. General Screening

The major activities and flow for screening are presented in Figures 2 and 3. Recruitment activities will be targeted toward women eligible for and interested in the CT. An eligibility screen is planned prior to the first clinic visit in order to minimize clinic burden.

The activities listed in Figures 2 and 3 represent a model screening scenario. Departures from this scenario may be exercised as clinic options as is elaborated in subsequent subsections, though the activities indicated for a given clinic contact or visit should be completed by the beginning of the next contact or visit, at the latest. In particular, activities may be moved forward in the screening process provided that pertinent participant consent has been obtained. CT women who do not complete all required screening activities within six months of their first screening visit will be required to provide updated baseline information prior to randomization. Women may prove to be ineligible or unwilling for CT enrollment at various points in the screening process. Such women will be offered the opportunity to participate in the OS and will be asked to complete OS baseline activities prior to leaving the clinic. In the event that a fasting blood sample has not been obtained, such women will need to return to the clinic for a fasting blood draw prior to OS enrollment.

A three-year recruitment period is anticipated for each Clinical Center. Appendix I provides a more detailed list of the measures to be collected at each clinic visit.

5.2.2. Pre-Screening

Multiple recruitment strategies may be needed at each Clinical Center. To meet the high recruitment goals of the program, it is recommended that mass mailings be used to produce a steady flow of interested, potential participants for the initial screening. Addresses for these mass mailings can be obtained from
WHI Protocol

such sources as motor vehicle registration lists, drivers' license lists, HMOs, HCFA, health insurance companies, and commercial mailing lists. These can be supplemented with the following:

(1) Media efforts: Use of newspapers, radio, T.V., newsletters
(2) Mass screening of certain high yielding communities (e.g., senior housing facilities), special social groups (churches), special occupational groups
(3) Blood banks
(4) Laboratory lists
(5) Medical referrals
(6) Mammography screening centers

The model initial contact will involve a letter and/or brochure providing basic information on the WHI and a postage-paid postcard to be returned indicating interest in participation. Age-eligible women indicating an interest will be contacted by phone by trained interviewers to identify women ineligible for the CT. Women ineligible for both the HRT and DM components will be thanked for their time and interest. Those continuing eligible for the CT will be scheduled for a First Clinic Visit (SV1), and will be instructed that a packet of materials will be mailed to them for their attention prior to SV1. The packet will include a cover letter, directions and information for travel to the clinic, a logo bag for all of their current prescriptions and regularly used over-the-counter medications and vitamin supplements, a personal information form and a food frequency questionnaire (FFQ). Women should be scheduled for Screening Visit 1 as soon as possible after their initial interview. Women given appointments before noon will be asked not to eat or drink anything except water for 12 hours before their appointment and to refrain from smoking for one hour prior to the appointment in preparation for a blood draw. Clinical Centers should schedule as many first screening visits as possible in the morning so that the blood sample can be obtained during this first visit.

There are a number of clinic options that can be exercised between the initial contact and SV1. For example, clinics wanting to maximize the HRT/DM overlap may choose to selectively invite women continuing eligible for both the HRT and DM to SV1. Clinics wanting to minimize SV1 visits that do not lead to CT enrollment could request that the FFQ be returned by mail and scanned in order to avoid visits for women who are eligible for neither CT component, or for the HRT only. Clinics concerned about the ability of women to complete an FFQ and Personal Information Form on their own could schedule pre-screening visits (SV0) in order to provide assistance with these and possibly other forms. A self-administered version of the eligibility screen will also be available for clinics that choose to obtain eligibility information by mail or in a pre-screening clinic visit. For efficiency, pre-screening visits would likely be conducted in a group setting.

Prior to a woman's first screening visit, she should be classified as continuing eligible for HRT, DM, or both. First screening visits will not be conducted for women known to be ineligible for both the HRT and DM components.
Figure 2
Women's Health Initiative Enrollment Activities and Flow: Pre-screening through First Screening Visit

Invitation:
Letter of Invitation and return postcard

Eligibility Screen:
Screening and invitation of eligibles to SV1, followed by mailing of Personal Information Q; Food Frequency Q and other materials

SCREENING VISIT 1 (SV1)
Initial screening consent; review of Personal Information Q, Interviewer Administered Q, Physical and Functional measures; Medications inventory; Fasting blood draw FFQ scan and eligibility updates for HRT and DM

CT Eligibility

Yes

CT
Detailed description of pertinent CT components; ascertain willingness

CT Willingness
Yes

Provide CT consent forms; Medical, Reproductive, and Psychosocial Q's; schedule SV2

No

OS
OS description and consent, complete Medical, Reproductive, Family History, Personal Habits, Psychosocial, and Supplementary OS Q's

No

OS
OS description and consent, complete Medical, Reproductive, Family History, Personal Habits, Psychosocial, and Supplementary OS Q's
2.3. First Screening Visit (SV1)

At Screening Visit 1, women will first be given a general description of the WHI study, and consent will be obtained to cover SV1 activities. A general medical information release form will be signed at this time. Women who have not completed a Personal Information Form or FFQ will do so at this time. Completed forms and eligibility information will be reviewed and the FFQ will be scanned. Clinic personnel will record each medication, doses indicated on the medication, and each vitamin or mineral supplement bottle a woman brings; will ask how often she takes each preparation, and will conduct a brief in-person exogenous hormone usage and psychosocial interviews.

Potential participants will then undergo limited screening measurements including systolic blood pressure, diastolic blood pressure, waist and hip circumference measures, functional status, and height and weight measurements. If they are fasting, blood will be drawn. The blood tube to be sent to a local lab will not require processing but must be refrigerated and delivered to the local lab within 12 hours. The blood to be centrally stored will be centrifuged and aliquoted within one hour, and frozen to -70 C° for forwarding to the specimen repository. Blood pressure must be measured before the blood draw is done. Women at the three selected Osteoporosis Clinical Centers will also provide a urine sample and will be referred for bone densitometry during SV1.

By this time, the completed FFQ should have been scanned and analyzed and a determination of FFQ eligibility for the DM component made. This, along with physical measurements will permit an updated assessment of continuing eligibility for the HRT and DM components. Eligible women will then be given an in-depth description of the pertinent CT components and will be asked to indicate which, if any, CT components they are willing to enter. Those indicating willingness for one or both CT components will be provided pertinent consent forms as well as Medical, Reproductive, and Psychosocial Questionnaires for filling out and return at a Second Screening Visit (SV2). As a local option, these forms could be filled out in clinic prior to the completion of SV1.

A second screening visit will be scheduled as soon as possible after SV1, allowing sufficient time to obtain local laboratory results. If blood was not drawn at Screening Visit 1, arrangements for a fasting blood draw will be made on or before Screening Visit 2.

Women who prove to be ineligible for either the HRT or the DM components at the time of eligibility updating, or women who subsequently decide that they are unwilling to be enrolled in the CT, will be invited to consider OS enrollment. As shown in Figure 2, such women will then be provided an OS description and will be asked to sign an OS consent form. They will be asked to complete Medical History, Family History, Reproductive History, Personal Habits, Psychosocial and Supplementary OS questionnaires in order to complete their baseline OS requirements. As a clinic option, some or all of these forms may be sent home with the participant for completion and return to the clinic within a two-week period.

The OS participants will be asked to keep the Clinical Center abreast of any change in address and will be told to expect to be contacted in three years for a follow-up visit, once yearly by means of a newsletter, and once yearly near the anniversary of their enrollment for completion of a self-administered questionnaire. They will be thanked for their participation and the visit will be closed.

* It is anticipated that approval by the Office of Management and Budget of OS forms may occur somewhat after the start of recruitment (09/01/93). During the interim period, screening will conclude as soon as it is determined that the screen is ineligible or is unwilling to be enrolled in the CT. During this interim period, the clinic option of mail return of the FFQ may be particularly attractive as it would allow more CT ineligible women to be screened out in advance of SV1.
WHI Protocol

Potential OS participants who have not provided a fasting blood sample (or urine sample, if appropriate) will have a clinic visit scheduled, preferably within the subsequent two weeks, for the provision of such a sample. OS enrollment will not be affected until all baseline information and specimens have been obtained.

Figure 3
Women's Health Initiative Enrollment Activities and Flow:
Second and Third Screening Visits

SCREENING VISIT 2 (SV2)
CT Eligible and Consenting

Yes

HRT DM
Review Q's x x
ECG x x
Breast Exam x x
Instruct in 4DFR x
Gynecologic Exam x
Dispense Placebo
Schedule Mammogram x x
Provide Family History x x
and Personal Habits Q's

Ineligible or Unwilling

OS
Confirm OS eligibility
OS description and consent; complete
Family History,
Personal Habits, and
OS Supplementary Q's

No

SCREENING VISIT 3 (SV3)

HRT DM
Review Q's x x
Assess 4DFR adequacy x
Assess run-in compliance x
Confirm CT eligibility x x
Randomize x x
Intervention x x

Ineligible or Unwilling

OS
Confirm OS eligibility
OS description and consent; OS
Supplementary Q

5.2.4. Second Screening Visit (SV2)
The Second Screening Visit is designed around the medical procedures required for CT participants (See Appendix I). Attempts should be made to complete and evaluate all First Screening Visit activities prior to a woman's second visit. Women who are found to be ineligible in the interim should be notified and invited to join the OS. Those agreeing will have a clinic visit scheduled to afford completion of OS baseline activities as shown in Figure 3.
At the beginning of SV2 each woman will be given an opportunity to ask additional questions about the CT and the informed consent. Women who are still interested will be asked to sign the informed consent for each trial component to be entered. The Medical, Reproductive, and Psychosocial questionnaires will be collected and reviewed if they have not been reviewed previously.

Women with continued eligibility for the Clinical Trial will have a resting 12-lead electrocardiogram. The electrocardiogram and complete blood count reports will be reviewed by a health care provider (nurse practitioner, physician assistant, or physician), who will also perform a clinical breast exam and provide breast self-examination instruction.

Women who have had a mammogram within 12 months of Screening Visit 2 will be asked the name of the mammographer and facility so that results can be obtained. If more than 12 months have elapsed since the last mammogram, a mammogram will be scheduled.

During this part of the second visit, all potential participants of the Hormone Replacement Therapy component will receive a pelvic exam and pap smear. Those women without prior hysterectomy will also have an endometrial aspiration. Women who have had a pap smear, endometrial biopsy (or diagnostic D&C) within 12 months prior to SV1 may not need to have these tests at baseline. Women for whom an endometrial biopsy was not successful due to cervical stenosis will have a transvaginal uterine ultrasound as their baseline endometrial evaluation.

Women eligible for, and planning to enroll in the HRT component, will receive the run-in placebo tablets dispensed in a bottle containing 50 tablets. The potential HRT participants will be instructed carefully regarding steps they should take should they experience vaginal bleeding and will be instructed on keeping a bleeding journal that they will bring with them to Screening Visit 3.

For those women wanting to enroll in the Dietary Modification component, training in completing the Four Day Food Record will be given with the help of an instructional video. Potential participants will then be given time to practice recording a meal, and the dates for completion of the four day food record will be assigned.

A third clinic visit will be scheduled for all women interested in and eligible for either or both the HRT and DM trial components. To ensure mammmography and gynecologic pathology results are available, up to six weeks should be allowed between Screening Visits 2 and 3. These women will be provided with Family History and Personal Habits questionnaires for completion and return at SV3.

Women who do not provide CT consent, or who are found to be ineligible or unwilling during the course of SV2 will be invited to join the OS. As shown in Figure 3, consenting women will be asked to complete the remainder of the OS baseline activities as were detailed in the SV1 description.

5.2.5. Third Screening Visit (SV3)

Final evaluation of CT eligibility and subsequent randomization are the primary activities of Screening Visit 3. All Screening Visit 1 and Screening Visit 2 activities should be completed and evaluated prior to a woman's third visit. Women found to be ineligible between SV2 and SV3 will be notified and invited to join the OS. Those agreeing will have a clinic visit scheduled to allow completion of OS activities.

At the beginning of SV3, the Family History and Personal Habits questionnaires will be reviewed. Other SV3 activities are specific to the CT components in which the woman intends to participate. Women planning to enter both the HRT and DM components must complete both sets of activities as follows:
(1) HRT

Before Screening Visit 3, the clinic physician, nurse practitioner, or physician assistant will review the results of the mammogram, the Pap smear and, for non-hysterectomized women, the endometrial aspiration. The women in the HRT component will be asked to bring their WHI tablet containers, with any remaining tablets, to this visit. When the women arrive at the clinic, medication adherence will be assessed by counting remaining tablets. HRT-only women judged ineligible or declaring themselves unwilling to be randomized will be invited to participate in the OS and, if interested, will complete OS activities as shown in Figure 3. Women with any abnormal mammogram, Pap smear, or endometrial biopsy results will be referred back to their primary physician for further evaluation.

Women still eligible for the Hormone Replacement component will be randomized as described in Section 5.2.6., instructed in the use of medications, and their first six-month supply of tablets will be dispensed. They will be instructed carefully regarding steps to take should they experience vaginal bleeding and will be instructed on keeping a bleeding journal that they will bring with them on each six-month visit. They will also be asked to contact their Clinical Center should they see a physician or be hospitalized for any of the relevant potential adverse effects. All HRT component participants will be given a randomization packet containing general health information and written material describing their role in the trial.

(2) DM

Women interested in the Dietary Modification component will have completed their Four Day Food Records and will bring them to this visit for review by a diet technician. Their mammogram reports will be reviewed and final eligibility determined. Those still eligible for this trial component will be randomized at this time. Women assigned to the Dietary Modification control group will have the importance of their role described and emphasized. Enrollees assigned to the Dietary Modification intervention will be assigned to a dietary intervention group. All DM participants will receive a randomization packet that includes general health information and written material describing their role in the trial. DM-only women who became ineligible or unwilling to participate in the DM component will be invited to participate in the OS and, if interested, will complete OS activities.

Women interested in both the HRT and DM components who become ineligible or unwilling to participate in either CT component will be invited to participate in the OS, and, if interested, will complete OS activities.

5.2.6. Study Registration and Randomization

Women who express interest in the Dietary Modification component, the Hormone Replacement Therapy component, or both will be screened to assess their eligibility for the designated component(s) and all necessary data will be entered into the clinic database during the time between Screening Visits 1 and 3. In each case, informed consent will be obtained according to relevant institutional and legal requirements and recorded in the database. When a woman has completed the necessary screening and provided consent, the data coordinator or designated clinic staff person will execute a database function that will verify eligibility for the designated trial component, assign the woman to a trial arm according to the algorithm described below, determine membership(s) in appropriate subsamples, and produce a confirmation of randomization report. Once a woman has been randomized into a trial arm, she will be followed in that arm regardless of her adherence to her assigned treatment.
WHI Protocol

Women who participate in the DM component, the HRT component or both will be screened and given the opportunity to participate in the calcium/vitamin D trial at their first annual visit.

CT randomization will use a randomized permuted block algorithm, stratified by clinic, age (50-54, 55-59, 60-69, 70-79), and, for the HRT, by hysterectomy status. Treatment assignments for all participants in each Clinical Trial will be generated in the proportions described in Figure 1. Block size will be allowed to vary randomly to preclude further any exercise in judgment in the assignment of participants to Trial arms. Enrollment into certain cells (e.g. younger ages or post-hysterectomy women) may be closed from time to time in order to meet the design criteria for distributions on these key factors.

Observational Study

Women attending at least one clinic visit who are not eligible for or willing to participate in the Dietary Modification or the Hormone Replacement CT components will be offered the opportunity to participate in the Observational Study. Informed consent will be obtained and all necessary data entered into the clinic database. When this has been completed (including the provision of a blood specimen and, if appropriate, a urine specimen), the data coordinator will execute a database function that will register the woman in the Observational Study, determine membership in appropriate subsamples, and generate a registration confirmation report.

Sampling for Substudies

Some intermediate effects of Trial interventions will be assessed in blood specimens drawn at the first annual visit in the CT and the three-year visit in the OS. For these measures, a cohort of approximately 5-6% of Trial enrollees stratified by treatment arm and age will be selected at the time of randomization for routine laboratory analyses. The subcohort sampling rates will also be selected to ensure adequate representation by racial/ethnic groups and socioeconomic groups. These selections will not be revealed to Clinical Center personnel but will be flagged in the database as specimens requiring routine analyses. Sampling schemes for other studies will be developed and implemented in the database as appropriate following Executive Committee and Project Office approval.

5.3. FOLLOW-UP

5.3.1. Clinical Trial

   (1) General CT Follow-Up

Clinical Trial participants will be followed through regularly scheduled examinations to collect data on study variables, to monitor the occurrence of possible side effects, and to promote adherence to study protocol. Annual visits will be scheduled for the four-week interval surrounding the anniversary of their randomization into the CT. Interim six-month follow-up visits will be scheduled within the four-week interval surrounding the midpoint of the participant’s follow-up year. In the event that the annual or six-month visit cannot be conducted within the target time interval, such a visit will be conducted as close as possible to the time window, and all participant data will be entered into the database.

Before each annual and interim six-month visit, all CT participants will be mailed a questionnaire packet to be completed at home and brought with them to their clinic appointment. The questionnaires for each visit (listed in Appendix I) will include: interim medical history (including the occurrence of any outcomes of interest) and side effects questionnaire. They will also be asked to bring in all their medications and vitamin supplements for an updated inventory. A food frequency questionnaire will also be collected at selected annual visits on all CT
participants. A small subsample of women providing a food frequency questionnaire will also be asked to provide a four day food record. At the six-month interim visit, all CT participants will have their questionnaires reviewed and will answer brief questions regarding their current medications to update the medication database. If the participant has any concerns or symptoms, she will be seen by a Clinic physician, nurse practitioner, or physician assistant. If any potential outcomes are reported, the clinic will initiate the outcome's ascertainment and classification protocol. An appointment will be made for the participant's annual visit.

At least six weeks prior to each CT participant's anniversary of her most recent mammogram, the Clinical Center will request that the woman have a mammogram, thereby ensuring that the results will be available at the annual clinic visit.

During the annual clinic visit, participants will undergo the same activities as the six-month visit. In addition, all CT participants will have a physical exam including: blood pressure, resting pulse rate, height, weight, functional status, waist and hip measurements, clinical breast exam, and training in breast self-exam.

At the first annual visit all CT participants will have their blood drawn and stored. Blood will be drawn and stored on a 5-6% subsample of women at the third annual visit and at every subsequent third annual visit. CT women will also have a resting 12-lead electrocardiogram every three years. For women randomized at clinics participating in the osteoporosis substudy, bone densitometry studies and urine collection will be done at the first and third annual visit and every three years thereafter.

Certain behavioral questionnaires will be re-applied to all CT participants at their first annual visit and in a subsample every three years thereafter (quality of life, treatment specific effects) while others will be re-administered at one year only (predictors of retention).

(2) Hormone Replacement Component Specific Follow-Up

At three months after randomization, HRT participants will be contacted by phone by Clinical Center personnel in order to answer questions the participant may have and to identify any major adverse experiences that have not been self-reported.

At both the six-month interim and annual visits, HRT participants will be asked to return their unused HRT tablets and their adherence will be assessed by counting remaining tablets. Their bleeding diaries will be reviewed by the designated clinic contact. A brief questionnaire will be administered to each participant to identify potential adverse effects. If there has been any bleeding, or if the participant has had any side effects other than minor symptoms, the participants will be seen by the designated clinic contact and the bleeding/side effects issues will be reviewed. The contact may decide at this time that other work-up or referral is necessary. After the participant is cleared, she will be dispensed a new six-month supply of tablets and a new bleeding/side effects diary.

For HRT participants with a uterus the annual physical exam will include: a pelvic exam, Pap smear, and (for all ERT, 5% PERT, 5% Placebo) an endometrial aspiration. A transvaginal ultrasound will be performed if an endometrial aspiration proves impractical (see Section 5.5.2.2.).
(3) Dietary Modification Component Specific Follow-Up

A small (age, racial/ethnic and socioeconomically stratified) sample of women (5-6%) will be selected on an annual basis to complete a four day food record. A similarly stratified small sample will be chosen for unannounced 24-hour dietary recalls at selected time points.

(4) Calcium/Vitamin D Trial Component Follow-Up

Women participating in the calcium/vitamin D trial component will be asked to return their unused tablets at each follow-up visit. Adherence will be measured by counting remaining tablets. Unless contraindicated by a report of renal calculi or other adverse experiences as described in Section 5.5., a new six-month supply of tablets will be dispensed.

5.3.2. Observational Study

Routine follow-up for Observational Study participants consists of mailed newsletters and self-administered questionnaires and limited clinic visits. Additional measures may be incorporated through the ancillary study mechanism.

Approximately two weeks before the anniversary of their enrollment in the Observational Study, OS participants will be mailed a self-administered Medical History Update questionnaire and a postage prepaid return envelope. If no response to this mailing is received within three weeks, an attempt will be made to contact the participant by telephone.

OS participants will also be mailed an annual newsletter prepared by the CCC at about six months following their OS enrollment or their OS enrollment anniversary. The purpose of the newsletter is to further bond participants to the study and to obtain updated addresses.

Three years after enrollment into the study, all OS participants will be invited to a follow-up clinic visit. Before this visit they will be mailed a packet of questionnaires that will include questions on health habits, medical history and outcomes, as well as psychosocial and food frequency questionnaires. Participants will have the option of completing forms at the clinic. At the clinic visit, they will have blood drawn, and the following measurements will be taken: height, weight, functional status, waist and hip measurements, and blood pressure. A 5-6% subsample of participants will be similarly followed in clinic every three years, with the same measures as for the first three-year visit. At the three osteoporosis substudy centers, bone densitometry studies and urine samples will be completed for all OS women every three years. If no response is received to the 3-year visit invitation, every effort will be made to contact the participant by phone and to schedule a clinic visit.

5.3.3. Study Closeout

Assuming that one or more CT components are not terminated early, planning for closeout will begin four years prior to the actual closeout year. This will begin first with the formation of a closeout committee, consisting of representatives from NIH, the CCC, and the Clinical Centers. This committee will consider the issues involved in the scheduled termination of clinical activities, and will present detailed plans to the Executive Committee. During the three years prior to the closeout year, efforts will be intensified to locate lost-to-follow-up participants at the time of their anniversary date and last scheduled follow-up visit.

CT participants who attend the annual visit prior to their final closeout visit will be notified that the study termination will be approaching, and efforts to lessen the psychological effects of study termination will be initiated. Six months before their closeout visit, participants will be sent literature about the study closeout, and reminded to expect their closeout visit. The closeout contacts will consist of a visit around the calendar time of the annual visit, followed by a phone contact six weeks later.
The closeout visit will have many of the same elements as an annual visit, that is, participants will be mailed questionnaires to complete and bring to the visit. They will be asked to bring in their study medications for tablet-counting. They will also bring in their current prescription medications and currently used over-the-counter medications, for updating the medication inventory. The usual anthropometric measurements will be taken. Women in the HRT component will have a pelvic exam, Pap, and endometrial aspiration (women with a uterus). All CT women will have a mammogram (unless contraindicated) and breast exam. A detailed personal data form will be completed at this time, so that all contact information can be updated. Additional closeout procedures for each specific CT component will be as follows:

A. HRT

Both participants and providers will continue to be blinded at the closeout visit. Study medications will be discontinued, and participants will be carefully instructed regarding symptoms they might expect from discontinuation of hormones. A list of common symptoms and suggested steps to alleviate symptoms will be provided. Participants will be advised to call the clinic physician, nurse practitioner, or physician’s assistant if they have any severe symptoms, or any significant vaginal bleeding. It may be necessary for the designated clinic contact to consult with the consulting gynecologist before the next scheduled contact, if it appears that a participant will require ongoing hormone replacement. In this case, the designated clinic contact will contact the participant’s primary physician, and make arrangements for the participant to be treated by the primary physician, after speaking with the clinic consulting gynecologist.

Participants will also fill out a form to record their best guess of what treatment group they were assigned to, to assess the degree of the double-blind. A form will also be completed to ascertain if the participant has a continuing source of medical care and whether all study medications have been returned.

A closeout telephone contact will take place approximately six weeks after the closeout visit. This may be done at the clinic for participants without phones. Both participants and clinic staff will be unblinded at this time. At this contact, participants will be asked questions regarding symptoms since discontinuing study medications. Questions to be addressed will include:

- Whether symptoms thought to be associated with study drugs have been relieved once medication was discontinued.
- Whether new problems have arisen that could be associated with stopping study medications.
- Whether the participant has been prescribed hormones by an outside physician since her closeout visit.

B. DM

Participants in the dietary modification trial will be told that the formal trial will end. The intervention group participants will be told that dietary supervision and meetings arranged by clinic staff will end but they will be given every possible assistance to maintain their low fat, high fruit and vegetable eating patterns and to arrange their own meetings before their final visits. Women in the control group will be told that official dietary intervention for the other group will end and that control group participants will be given an opportunity to attend one or two special instructional sessions on ways to lower the fat in their diets and will be offered self-help materials to help them to modify their eating patterns. These materials will be based on the
most successful components of the WHI intervention. Any new dietary advice that becomes available during the conduct of the trial will be shared with both groups of women.

C. CaD

Women in the calcium/vitamin D component will be participants in at least one of the two other clinical trials, and the measurements taken during their closeout visit will follow those for the HRT and DM components. At the closeout visit their adherence to study medications will be assessed by tablet counts, and their drugs will be discontinued. Participants will be asked to provide their best guess of their treatment assignment. It is unlikely that they will experience any significant symptoms from stopping treatment, and they will be informed of this. At this contact, forms will be completed to document participants' continuing source of medical care, and to document that study drugs have been returned. At their closeout phone contact six weeks later participants and clinics will be unblinded. If participants on the calcium/vitamin D replacement choose to continue treatment, drug and dosage information will be provided to them and their primary physician.

D. Training and Trial Documentation

Training will be provided for Clinical Center staff to counsel CT participants as they exit from the study. At the conclusion of the CT, each participant will be provided with a summary of overall trial results as appropriate and selected results from their clinical exams and laboratory tests. The Clinical Coordinating Center, in accordance with guidelines developed by the Project Office and the Executive Committee, will prepare and document the final data tape.

E. OS

Two months prior to study closeout, participants in the OS will receive notification by mail that the study is coming to a close. At this time they will be sent a final interim medical history questionnaire to complete and return to the Clinical Center. They will also be sent literature about the study closeout.

5.4. ADHERENCE AND RETENTION

Retention of study participants and their adherence with the study protocol is a dominant focus after the participant is enrolled. Retention has several components: Adherence (taking study drugs), Performance (maintaining low fat dietary consumption), and Participation (attending follow-up visits, and accepting telephone calls). The evidence from randomized evaluations and evidence from observational studies of participant accrual and follow-up suggest that personal attention from staff and specific and reassuring feedback about required follow-up activities are themselves useful retention strategies. Correlational evidence indicates that freedom from worries about health, comfort with the intervention materials, and higher SES are related to retention. Taken together, these studies suggest that a retention protocol that will increase social support and positive interactions while minimizing unnecessary health concerns and worry, will maximize retention in WHI.

The CCC will provide each Clinical Center with a package of core study-wide retention enhancements. Personal contacts, visits, and follow-up phone calls will be the cornerstone of Clinical Center specific retention efforts, while making sure to avoid the introduction of any contamination or bias. The CCC will coordinate scripts and provide interviewer and staff training and guidelines for standardized contacts using social support and health-related messages. Each Clinical Center will continue to implement its own local additional retention efforts to complement study-wide functions. The following strategies exemplify those that may be included:
WHI Protocol

- Appointment reminders (postcards and telephone contacts)
- Newsletters
- Methods for involving family members
- Special events
- Local Participant Ombudsman
- Modest incentives (pins, mugs, calendars, etc.)
- Health-related informational materials
- Weekly tablet containers
- Physician letters
- Family and friend involvement

5.5. EVALUATION AND MANAGEMENT OF ADVERSE EXPERIENCES IN THE CT

5.5.1. Adverse Experience Monitoring

When informed consent is obtained, potential adverse effects of study treatments will be explained to each prospective participant. Written material outlining these adverse effects will be provided and the women will be instructed to notify the Clinical Center of any adverse experiences, illnesses or hospitalizations. Information on the nature, duration, and intensity of the adverse reaction will be recorded along with information on any remedial action to be taken. These adverse experiences will be collected and reported under all circumstances and without the assumption that they are related to study treatment. Participants will be appropriately monitored until the end of the Trial.

All adverse experiences will be reported to the Clinical Coordinating Center. Serious and life-threatening experiences will be reported by telephone or fax within 24 hours, as well as by routine methods. Serious adverse experiences include those that are fatal or life threatening, permanently disabling, those that require inpatient hospitalization, or a cancer diagnosis, or overdose. The Manual of Operations and Procedures will provide greater detail concerning procedures for defining and reporting adverse experiences, including FDA guidelines.

The independent Data and Safety Monitoring Board (Section 10) will periodically monitor all potential side effects and make appropriate recommendations to ensure participant safety.

5.5.2. HRT

5.5.2.1. General

Prior to randomization, HRT participants will be briefed on the possible side effects from the study drugs and the medical significance of these possible side effects. Written material outlining these adverse effects will be provided. Participants will be instructed to record any vaginal bleeding or spotting in a bleeding diary and to notify the designated clinic contact (see Section 4.7) at the time vaginal bleeding first occurs. Routine endometrial aspiration biopsies will be performed prior to randomization and, for appropriate subsamples of HRT participants, at regularly scheduled intervals during the trial. Diagnostic endometrial evaluation will be performed at the request of the clinic consulting gynecologist.
2.2. Endometrial Evaluation

Routine endometrial evaluation will be performed in all women with a uterus at baseline, selectively at annual follow-up visits (all ERT, 5% PERT, 5% placebo), and at the end of treatment. Women with abnormal baseline biopsies will be excluded from HRT.

Diagnostic endometrial evaluation will be performed at the request of the clinic consulting gynecologist, who will maintain a copy of all records concerning vaginal bleeding and baseline, follow-up and diagnostic endometrial evaluations. The clinic consulting gynecologist will record this information on the study forms along with any unblinding action to be taken, should this be necessary. All follow-up endometrial biopsy samplings will be evaluated locally. All abnormal findings on follow-up biopsies will be reviewed by a central pathologist, along with 5% of normal samplings. Baseline endometrial biopsies will not be reviewed centrally. A standardized classification system will be used (see Manual of Operations and Procedures).

All endometrial aspiration biopsies (routine or diagnostic) will be performed with a flexible aspirator device. Entry into the uterus, by definition, will indicate a successful procedure, regardless of whether or not adequate tissue is obtained. If the uterus cannot be entered with the flexible aspirator device, a second attempt will be made by a different operator, using cervical block anesthesia. If these two attempts fail at passing the cervical os, a transvaginal uterine ultrasound will be performed.

Normal endometrium refers to any pathologic finding from tissue biopsy that is compatible with atrophic, proliferative or secretory endometrium. Insufficient tissue obtained for diagnosis also qualifies as normal endometrium. Other biopsy findings require evaluation and management or referral to the primary physician by the clinic gynecologist. Endometrium with a thickness ≤ 5 mm on transvaginal uterine ultrasound is considered normal.

Abnormal endometrial findings refer to:

1) simple hyperplasia or
2) adenomatous, complex or atypical hyperplasia or endometrial cancer.

If the transvaginal uterine ultrasound shows a thickness of the endometrium > 5 mm, the participant will be referred to her primary physician for further evaluation. The woman may be eligible to enter or continue in the HRT if this evaluation shows that the endometrium is normal.

5.5.2.3. Management of Vaginal Bleeding

The management of vaginal bleeding will depend on (a) severity of bleeding, (b) time since randomization, (c) treatment assignment, and (d) endometrial histology.

- When to Biopsy

Effort will be made to avoid breaking the blind whenever possible and to minimize the staff to be unblinded. Light bleeding or spotting during the first six months post randomization will be assessed and managed without unblinding. Heavy bleeding at any time will require a biopsy, and blinding will be maintained. Spotting or light bleeding occurring after six months post-randomization will be referred to the consulting clinic gynecologist. This gynecologist will review the participant's bleeding diary and biopsy record, will be unblinded to her treatment arm, and will decide whether an unscheduled biopsy is necessary.
WHI Protocol

a) **Bleeding during first six months post-randomization**:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heavy bleeding (&gt; usual menstrual bleeding)</td>
<td>Biopsy</td>
</tr>
<tr>
<td>Spotting or light bleeding</td>
<td>Reassure, reassess at six month visit</td>
</tr>
</tbody>
</table>

b) **Bleeding after first six months post-randomization**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heavy bleeding (&gt; usual menstrual bleeding)</td>
<td>Biopsy</td>
</tr>
<tr>
<td>Spotting or light bleeding</td>
<td>Biopsy</td>
</tr>
<tr>
<td>PLACEBO</td>
<td>Biopsy</td>
</tr>
<tr>
<td>PERT</td>
<td>Gynecologist decides</td>
</tr>
<tr>
<td>ERT</td>
<td>Biopsy. (May be possible to delay a few months or advance yearly biopsy date.)</td>
</tr>
</tbody>
</table>

- Management According to Endometrial Histology*

Results of unscheduled and annual biopsies will be referred to the consulting gynecologist who will use the following algorithm, and direct the designated clinic contact in further management without unblinding, when possible. Thus, blinding of clinic personnel except for the consultant gynecologist and unblinding officer will be preserved.

<table>
<thead>
<tr>
<th>ALL ARMS:</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrophy or Normal</td>
<td>Continue HRT for three months and reassess. If bleeding persists, refer to primary physician for further evaluation.</td>
</tr>
</tbody>
</table>

**PLACEBO:**

| Simple or adenomatous hyperplasia; atypia; or cancer | Discontinue placebo and refer to primary physician** |

**PERT or ERT:**

| Simple hyperplasia                   | Continue HRT, add MPA 20 mg/day for three months, then rebiopsy. If simple hyperplasia continues, increase MPA to 30 mg/day for three months, then rebiopsy. |
| Adenomatous hyperplasia              | Discontinue HRT, add MPA 20 mg/day for three months, then rebiopsy. If adenomatous hyperplasia persists, increase MPA to 30 mg/day for three months and rebiopsy. |
| Atypia or cancer                     | Discontinue HRT and refer to primary physician.** |

* See Manual of Operations for detailed protocol for management according to endometrial histology and treatment arm.

** If atypia or cancer is diagnosed by the local pathologist, a copy of the path report will be sent to the participant’s primary physician, to be followed by a copy of the central review pathologist’s report.
5.5.2.4. **Discontinuation of HRT Treatment**

Pathologic biopsy findings will result in modification of the study treatment as follows:

- If pathologic findings of simple hyperplasia persist after appropriate management as outlined above and in the Manual of Operations and Procedures, the medications will be permanently discontinued, and the participant will be referred to her primary physician for evaluation and treatment. If a woman has a hysterectomy as part of her treatment, she may re-enter the study, but may need to be put on a different regimen (i.e., women originally randomized to the PERT arm who have a hysterectomy will be given ERT but will continue to be followed for outcomes in the PERT arm).

- If pathologic findings are atypia or endometrial cancer, HRT medications will be permanently discontinued and the participant will be referred to her primary physician for evaluation and management.

- If a woman develops breast cancer, her HRT study medication will be discontinued.

Refusal of scheduled endometrial biopsy or mammography after randomization will result in discontinuation of HRT medications with continued follow-up of the woman. If the participant later agrees to the procedure, HRT medications will be resumed. Inability to obtain a biopsy due to stenosis of the cervix is not an indication for discontinuing HRT medications after randomization.

In addition, the following adverse experiences may result in temporary discontinuation of the HRT treatment:

a) Any hospitalization
b) Myocardial infarction
c) Stroke
d) Any severe illness in which HRT is temporarily inappropriate

5.5.2.5. **Changing the HRT Arm**

Women who are randomized to the PERT arm but who subsequently have a hysterectomy for reasons other than cancer will be eligible to continue on active hormone replacement therapy. Since there is no clinical indication for women without a uterus to be given progestins, women who have a hysterectomy during the trial follow-up will be changed from PERT to ERT. They will be followed in the PERT arm for outcomes, however. Similarly, women who are randomized to ERT may be changed to PERT as required for management of adverse effects of HRT (see Section 5.5.2.). These women will be followed in the ERT arm for outcomes.

5.5.3. **Dietary Modification Component**

Any experiences that require a special diet may result in the temporary or permanent discontinuation of the dietary intervention, including:
WHI Protocol

a) Newly developed Type I (ketosis prone) insulin-requiring diabetes,
b) Gastrointestinal disease or surgery, such as malabsorption syndrome, short gut syndrome, etc.
c) Acute or chronic pancreatitis
Such discontinuation will be decided by the clinic physician in conjunction with the participant’s primary physician and notification will be sent to the CCC on the Participant Status Form. All such women will continue to be followed for outcomes in their assigned randomization group.

5.5.4. Calcium/Vitamin D Component

The following adverse experiences may result in the temporary discontinuation of the calcium/vitamin D therapy:

a) Any hospitalization
b) Accidents resulting in immobilization
c) Myocardial infarction
d) Stroke
e) Any severe illness in which the administration of calcium/vitamin D is temporarily inappropriate.

Women who develop renal calculi will have calcium/vitamin D pills permanently discontinued.

5.5.5. Notifications

5.5.5.1. Immediate and Urgent Referrals

Immediate referrals are medical emergencies which require immediate notification of both the participant and her primary physician. Immediate notification of the participant should occur during the clinic visit. Immediate notification of the participant’s physician should be accomplished by telephone, to be completed before the participant leaves the Clinical Center. A follow-up letter documenting information discussed by phone should also be sent to the participant’s physician.

Urgent referrals are made for abnormalities detected which require medical attention but not on an emergency basis. Urgent notification of the participant should occur before the participant leaves the Clinical Center, or immediately upon receipt of the finding from the central laboratory. Urgent notification of the participant’s physician should be sent within the week. Findings requiring immediate/urgent referral are as follows:

- Medical history
  severe depression
  severe vaginal bleeding*

- Physical Examination
  resting pulse rate < 40/min or > 130/min
  SBP > 200 mm Hg
  DBP > 105 mm Hg
  suspicious breast mass
  pelvic mass
  any other problem the Clinical Center physician feels requires attention immediately (for example, exacerbation of congestive heart failure, acute asthma episode, etc.)

- Endometrial Evaluation
  cancer or atypia*
WHI Protocol

- Mammography
  finding suspicious for cancer
- Electrocardiogram (CT only)
  acute myocardial ischemia/injury
  atrial flutter or fibrillation (new onset)
  sustained ventricular tachycardia
  3rd degree AV block
  Mobitz type II AV block
- Hematology
  hematocrit < 30% or hemoglobin < 10 gm/dl
  WBC < 1,000 cells/mm³
  platelet count < 50,000 cells/ml

5.5.5.2. Routine Referrals

Physical findings and laboratory values as well as copies of electrocardiograms and Pap smear, endometrial aspiration and mammography reports could be sent routinely to participant's physicians. Decisions regarding specific reporting should be made at the Clinical Center level in the context of community referral practices and participant's preferences. Participants will be asked at the beginning of the study for their permission to send such reports to their physician.

The following findings may be considered for reporting:

- Medical history
  unexplained weight loss
  cognitive decline
  angina (new or uncontrolled)
- Physical examination
  blood pressure
  weight
- Bone densitometry (baseline bone mineral density at hip more than 3 standard deviations below mean for age)
  rapid bone loss (>15% per year, or >30% over 3 years)
- Chemistry
  lipids

Note: Asterisks (*) in the above listing imply that the finding is evaluated and referred by the clinic gynecologist.

6. CENTRALIZED STUDY OPERATIONS

6.1. DATA MANAGEMENT

All routine data will be collected and entered by the Clinical Centers using certified data collection staff and data collection forms or direct entry screens provided by the CCC. For data and clinic management purposes, each Clinical Center will be equipped with a local area network (LAN) consisting of a Novell
fileservers, five personal computers (PC), a printer, two barcode readers, and a mark-sense reader (scanner). Each fileserver will be loaded with software for the following functions: network management (Novell Netware), graphical user interface (Windows), data management (developed by the CCC in Oracle), word processing (Word for Windows), spreadsheet (Excel for Windows), and electronic mail (DaVinci Mail). Each Clinical Center PC will be connected to the file server through the LAN in order to provide shared access to clinic data and software. Each Clinical Center LAN will be connected to the CCC by a wide area network (WAN). The WAN will link all WHI file servers over dedicated communications lines and will provide continuous communications abilities. Most equipment will be delivered directly to the Clinical Centers. The file server and WAN equipment will be delivered to the CCC for configuration. The CCC will be responsible for daily incremental back-ups of all study-wide data over the WAN. Additional aspects of the data management system will be specified in the data systems manual.

6.2. QUALITY ASSURANCE

The quality of study-wide operations, data, and products will be assured by a variety of methods including clear and complete documentation, centrally managed training and certification, routine reports, annual quality assurance site visits and task specific quality assurance measures (e.g., routine observation, chart audits, duplicate data entry, split duplicate specimen analyses) as deemed appropriate by the Executive Committee and Project Officer. 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 Clinical Centers for resolution, and a systematic means of updating the central database based on their responses will be established. To assist in addressing these queries, the Clinical Centers will be required to store hard copies of their data collection forms in a readily accessible manner, and to respond to queries in a timely fashion. Standards for performance will be proposed by the Operations Subcommittee (see Section 10), approved by the Executive Committee, and documented in the Manual of Operations and Procedures. Study units determined by the guidelines of the Operations Subcommittee to be operating below acceptable performance levels will be required to submit plans for remedial action to the Executive Committee for approval and will be subject to more intensive monitoring.

6.3. DRUG DISTRIBUTION

Study medications will be shipped to the Clinical Centers on a regular basis by the CCC drug distribution center located at Ogden BioServices. Study medications will come in several forms: placebos for the run-in period of the HRT; blinded medications for the HRT (Placebos, ERT and PERT); open label conjugated equine estrogen and medroxyprogesterone for management of some adverse and side effects of HRT; and blinded medications for the calcium/vitamin D component. Bottles for the run-in period will contain 50 tablets; for follow-up, HRT bottles will contain 215 tablets. Calcium/vitamin D trial preparations will be bottled in quantities of 60 tablets. All medications will be identified with a unique bottle number for tracking and inventory purposes. Clinical Centers will log each incoming shipment and each bottle dispensed or returned into the Clinical Center database upon receipt or dispensation. For blinded study medications, the bottle number will be linked to trial arm in the Clinical Center database. This link will not be accessible to Clinical Center database users. To dispense blinded study medications, the data coordinator or other authorized clinic staff member will execute a database function that will identify an appropriate bottle in the drug inventory at the clinic site. Clinical Centers will be responsible for labeling each bottle with the participant's name, identification number, and Clinical Center information.

6.4. OUTCOME ADJUDICATION

For purposes of attaining high quality outcome data for each CT component, the primary outcome diagnosis will be analyzed by local Clinical Center physician representatives and the data packets, including discharge summary and respective data reports, will be sent to the CCC for central adjudication.
WHI Protocol

The specifics for each scheme of adjudication within the cardiovascular, cancer and fracture outcomes is detailed in Appendix II. In general, while central adjudication may be part of outcome assignment for each study component in the Clinical Trial, the expectation is that for the Observational Study only a portion of diagnoses will be reviewed centrally for quality assurance purposes.

7. STUDY MONITORING AND DATA ANALYSIS

7.1. GENERAL

Progress in the CT and OS will be monitored in several ways: reports on subject accrual, adherence to follow-up procedures, and on intervention adherence rates in the CT will be provided by the CCC to the Executive Committee, as well as to the Data and Safety Monitoring Board (DSMB) and the NIH on a regular basis. Reports on adverse effects and on clinical outcomes by randomization group will be provided on a regular basis to the DSMB. These reports will provide the basis for considerations of remedial actions or protocol changes, and for considerations of early stoppage of CT components.

7.2. ACCRUAL, ADHERENCE AND ACCUMULATED ENDPOINT EVENTS

Developing information on subject accrual, and hence average follow-up duration at planned study termination, on adherence, and on the total number of primary outcome events among women randomized to each CT component will be used to produce updated primary outcome power projections, of the type shown in Appendix III. The design assumptions concerning intervention effect on primary endpoint rates will be retained in these power calculations, the results of which will be provided annually to the DSMB and the NIH. Remedial action may be indicated if powers (about 90% or greater) under CT or OS design assumptions are projected to fall as low as 80%. Reports on accrual, intervention adherence in the CT, completeness of participation in follow-up and outcome ascertainment activities, and on other aspects of quality control, will be provided regularly to the Executive Committee and the NIH for each active Clinical Center in order to allow early identification of potential problems.

Accrual information by age, racial/ethnic subgroup, and socioeconomic subgroup will also be monitored in the CT and OS, as will be the fraction of women who are post-hysterectomy in the HRT component of the CT. Noteworthy departures from targeted fractions may give rise to specialized recruitment efforts to recover the desired distributions, or to the temporary closure of some enrollment categories. Adherence in the CT will also be monitored by age, racial/ethnic, and socioeconomic subgroups.

7.3. MONITORING OF CLINICAL EVENTS BY RANDOMIZATION GROUP IN THE CT

The development of procedures for monitoring the CT for possible early stoppage poses specific challenges, some of which are unique to the WHI. There is the danger of over-interpreting treatment effects for a CT component early in the trial follow-up period, without adequately acknowledging the fact that multiple outcomes are being monitored and hence chance differences are more probable, and without adequately acknowledging that hypothesized (beneficial or adverse) effects for some outcomes have a substantially later time course than others. Along the same lines there is a danger in over-interpreting a beneficial effect of a treatment on a given CT outcome since the CT treatments have hypothesized benefits and risks for a number of important diseases. For example, early stoppage of the HRT component on the basis of evidence of hip fracture prevention, without definitive data on coronary heart disease or breast cancer effects would leave unanswered some of the most important public health issues surrounding HRT. Similarly, if a CT treatment is observed to have both beneficial and adverse effects then trial monitoring procedures need to rely on some suitable composite or summary outcomes, in order that the public health implications be as unequivocal as possible, while simultaneously paying all due attention to the safety of participating women.
WHI Protocol

To address these issues an independent Data and Safety Monitoring Board (DSMB) for the WHI will be appointed by the NIH Director. Information on the occurrence of outcomes of interest (Section 4.3) by treatment group will be presented at regular meetings of the DSMB. Evidence of adverse effects, or of adverse risk to benefit profile, may give rise to recommendations for protocol changes (e.g., concerning dosages or dosage modification procedures in the HRT or CaD components, or concerning dietary goals in the DM component), or in the event of a serious adverse effect or a compelling favorable benefit to risk profile, to a recommendation of early stoppage of a CT component, or of certain treatment arms of a CT component.

The specific procedures for accomplishing such monitoring will be developed in collaboration with the DSMB. Elements of the plan are expected to include a major reliance on total mortality, with due consideration of the likely time course of outcomes that may contribute significantly to total mortality. The occurrence of non-fatal events will contribute informative censorship information to the mortality analyses. In order to allow greater sensitivity to evolving morbidity data, consideration will also be given to multivariate comparisons, and to the construction of a composite disease outcome variable that would combine incidence information from several diseases, probably in a weighted manner. Each such outcome analysis will make appropriate provision for the multiple time points of interim analyses, and for the hypothesized time course of treatment effects in a manner that attempts to avoid premature stoppage while ensuring participant safety.

7.4. DATA ANALYSIS

Clinical Trial

The basic test statistic to be used to compare an intervention group to a corresponding control group, both for CT monitoring and for periodic analysis, will be a weighted (two-sided) logrank statistic. Such a statistic can be written

\[ T = \sum w_i (O_i - E_i) \]

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 \( \sigma^2 \) represents the conditional variance of \( O_i \), then it follows that the variance \( (\sigma^2) \) of \( T \) is estimated by \( \sigma^2 = \sum w_i^2 V_i \) and the test for differences between groups is then made by referring \( T^2/\sigma^2 \) to the 95th percentile of a chi-square distribution on one degree of freedom.

The weighting is intended to enhance test power. Since it is anticipated that intervention versus control disease incidence ratios will vary approximately linearly as a function of time since randomization, the weights \( w_i \) will be chosen to equal time from randomization up to a disease-specific maximum (three years for vascular disease and fracture occurrence, 10 years for cancer occurrence and total mortality) and to be constant thereafter.

The test statistic will be modified slightly for outcome categories that rely on centralized ECG assessments. Since ECG readings are obtained every three years during follow-up, the test statistic will be replaced by a weighted combination of binomial proportions at three, six, and nine years and at close-out for these outcomes. The weights will be averages of those previously described over the pertinent follow-up period.

In acknowledgment of the partial factorial design the (four) primary endpoint tests will be stratified on the categories of the other interventions, baseline age (50-54, 55-59, 60-69, 70-79), and self-reported prevalent disease (if applicable) for that outcome. The HRT comparisons will, in addition, stratify on hysterectomy
status. In these and other analyses, the times from randomization to disease occurrence will be censored at the time of death from other disease or loss to follow-up. The primary endpoint tests will not be adjusted for multiple testing since each trial component merits a separate hypothesis test. Corresponding to each of these tests, we will estimate intervention versus control group relative risks as a function of time from randomization using relative risk (Cox) regression methods (Cox, 1972) stratified as just described with suitably defined time-dependent covariates (e.g. Kalbfleisch and Prentice, 1980; Cox and Oakes, 1984). Closely related analyses will also be carried out to estimate a 'full adherence' relative risk function for each intervention in relation to its primary endpoint.

The same statistical methods will be used for testing and estimation of the secondary and composite outcomes, as well as the subgroup associations listed in Section 3.1. The same methods will also be used to compare total mortality rates between intervention and control groups. The manner in which these analyses will acknowledge the sequential monitoring aspect of the CT will be described in a separate document, to be developed in conjunction with the DSMB.

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 for the outcomes of interest reliably 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 will have 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 will provide information of the reproducibility of the measurements taken, 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 will be stratified on age, racial/ethnic group, and socioeconomic group, and will be a subset of the 5-6% sample that will be followed for trends in risk factors beyond the three year visit by OS participants. The size of the OS cohort, and the comprehensive set of measurements to be obtained will 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 sampling provides the only practical approach to reducing the number of OS women whose blood specimens and complicated questionnaires 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 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. Specifically, in the OS data and specimens from the 5-6% sample, that will be used to monitor relative risk factor trends at baseline and three years, can provide an efficient subcohort for a range of OS analyses. Since those materials will be analyzed routinely for the purpose just mentioned, the marginal cost involved in case-cohort analyses will arise only from the corresponding analysis of materials from the cases who develop the outcome 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 will provide 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-vascular 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 III 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 near identity 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. As indicated earlier (3.2) under circumstances in which careful analyses of this type lead to substantial agreement between CT and OS results, it may often be reasonable to extrapolate the relative risk results beyond those examined in the CT, using the OS.

8. OSTEOPOROSIS SUBSTUDY

In order to ensure standardization of equipment and procedures used in bone mineral density measurements (BMD), such measurements will be restricted to the CT and OS participants at three VCCs. Urine samples will also be collected from these women. Changes in bone densities from baseline to prescribed follow-up times in the CT will be examined in relation to each CT component. The ability of such BMD changes to explain the relation between CT treatments and fracture occurrence will also be examined. In the OS, changes in BMD between baseline and three years will be studied in relation to baseline measurements, and the impact of including BMD measurements and changes in analyses of the relationship between fracture and corresponding risk factors will be examined.

9. ANCILLARY STUDIES

Ancillary studies will involve CT or OS participants, and will involve the collection of data or specimens that are not part of the core study materials. Such studies may involve all or as few as one of the WHI Clinical Centers. Ancillary studies must not interfere with the basic objectives of the CT and OS. 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 Subcommittee of the Executive Committee, and following a favorable recommendation, approved by the Executive Committee, the Data and Safety Monitoring Board, and the NIH Project Office. Separate informed consent must be obtained as needed for each ancillary study, as must approval of the institutional review boards of the participating institution(s). External funding will typically be required.

10. STUDY ORGANIZATION

The study organization includes a Project Office within the Office of the NIH Director, Vanguard and Additional Clinical Centers, a Clinical Coordinating Center (including core laboratories), a Management Committee, an Investigators Committee, and an Executive Committee with various subcommittees and working groups. There is also a WHI Program Advisory Committee and a Data and Safety Monitoring Board, with memberships drawn from outside the study hierarchy. Some aspects of the study organization are shown in Figure 3.

Project Office

The study is being conducted out of the NIH Director's Office with the participation of several of the categorical NIH institutes. The NIH Project Office is responsible for oversight of the scientific, administrative, and fiscal aspects of the WHI, and for the integration of participating NIH institutes.
WHI Program Advisory Committee

This Committee was appointed by the NIH Director to provide liaison with groups having a special expertise or interest in women's health, and with the community-at-large. It will advise the Project Office and NIH Director concerning potential problem areas within or outside of the WHI. Membership is drawn from public, lay, and scientific leaders, with the ex-officio participation of the Project Office and selected other WHI units.

Data and Safety Monitoring Board (DSMB)

An independent DSMB has been appointed by the NIH Director to monitor study progress, outcomes, and safety and to make recommendations in regard to protocol changes. The DSMB approves the procedures used to monitor the study for consideration of early stoppage of any of its components, and will make corresponding recommendations, when appropriate, based on the regular review of all pertinent study data, including adverse effects and unblinded outcome data in the CT. The Clinical Coordinating Center will provide study data for review by the DSMB. The DSMB will report its recommendations to the NIH Director.

Investigators Committee

The Investigators Committee meets annually in person, and as necessary by (regional) conference call, to review the progress of the study and to vote on major issues. This committee represents all of the centers participating in the WHI, including the PIs of the Clinical Centers, the PI and a Co-PI of the CCC, and two representatives from the NIH Project Office. The chair and co-chair of the Investigators Committee are appointed by the NIH Project Office for three-year terms. Other personnel who attend the annual meetings are non-voting members.

Executive Committee

The Executive Committee provides scientific direction for the WHI at the operational level. Its 12 members meet quarterly, if necessary, and have monthly conference calls. The two permanent members of the Executive Committee are the CCC PI and the NIH Project Officer. Eight other members serve three-year terms that are concurrent with their tenures as chairs of the eight Executive Committee subcommittees.
(see below). Other members of the Executive Committee include the NIH-appointed Chair and Co-Chair of the Investigators Committee.

**Management Committee**

The Management Committee meets weekly, or as necessary, by conference call to deal with interim business (between Executive Committee meetings) and to discuss the day-to-day and logistical needs of the study. The Management Committee consists of the NIH Project Officer, the CCC PI, the Executive Committee Chair and one other investigator from the Executive Committee who is appointed by the Project Office.

**Executive Committee Subcommittees:**

Eight subcommittees function as subunits of the Executive Committee and are charged with specific functions that are critical to the study. These subcommittees make recommendations to the Investigators Committee and the Executive Committee. They have about 8-10 members including a chair and co-chair, all appointed by the Project Office. The members, who are appointed by NIH for three-year terms, meet semiannually, if necessary, with one semiannual meeting to be held in conjunction with the annual Investigators Committee meeting. The subcommittees may have special working groups, some of which may be unnecessary after the Planning Phase. The eight subcommittees and their general responsibilities are as follows:

**Intervention Subcommittee**

This subcommittee is responsible to the Executive Committee for the development, implementation and monitoring of the intervention protocols. It also addresses the coordination of the interventions. Its initial membership is composed of the chair and co-chair of three Working Groups - Hormone Replacement, Dietary Modification, and Calcium/Vitamin D - and one representative each from both the CCC and the Project Office.

The Hormone Replacement Working Group may make proposals related to any aspect of this trial component -- protocol issues, data collection, blinding, safety monitoring, notifications, and evaluations and management of adverse experiences. During the Planning Phase, it reviews all relevant sections of the protocol and the Manual of Operations and Procedures and the relevant data collection forms. It also collaborates with the Laboratory Operations Working Group of the Operations Subcommittee in proposing standardized procedures for endometrial aspiration, Pap smear, mammography and transvaginal uterine ultrasound and for the reading of endometrial tissue biopsy samples.

The Dietary Modification Working Group may make proposals concerning any aspect of this trial component -- protocol issues, data collection, counseling, educational material including newsletters, monitoring, and certification. During the Planning Phase, it reviews all relevant sections of the protocol and the Manual of Operations and Procedures and the relevant data collection forms. It also reviews nutritional training and certification procedures.

The Calcium/Vitamin D Working Group may make proposals concerning any aspect of this trial component -- protocol issues, data collection, blinding, safety monitoring, notifications, and evaluations and management of adverse experiences. During the Planning Phase, it reviews all relevant sections of the protocol and the Manual of Operations and Procedures and the relevant data collection forms.

Each Working Group has about 6-8 members including a chair and co-chair, all appointed by the Project Office.
WHI Protocol

Morbidity and Mortality Subcommittee

This subcommittee is responsible to the Executive Committee for the development, implementation and monitoring of the events classification protocols. It also addresses the standardization and coordination of data collection and assessment among working groups. Its initial membership includes the chair and co-chair of four Working Groups - Cardiovascular Disease, Cancer, Fractures, and Other Age-Related Events.

The Cardiovascular Events Working Group may make proposals concerning any aspect of data collection and classification of cardiovascular events, including myocardial infarction, angina, stroke/TIA, congestive heart failure, peripheral vascular disease and venous thromboembolism. It may develop smaller working groups specifically devoted to stroke or coronary disease if needed. During the Planning Phase, it reviews all relevant sections of the protocol and the Manual of Operations and Procedures and reviews tests of relevant data collection forms.

The Cancer Events Working Group may make proposals concerning any aspect of data collections and classification of cancer events, including breast, endometrial, ovarian, colon, rectal, and other cancers. It may develop smaller working groups devoted to specific cancers if needed. During the Planning Phase, it reviews all relevant sections of the protocol and the Manual of Operations and Procedures and reviews tests of relevant data collection forms.

The Fracture Events Working Group may make proposals concerning any aspect of data collection and classification of fractures, including osteoporotic and non-osteoporotic fractures. It may develop smaller working groups devoted to specific fractures if needed. During the Planning Phase, it reviews all relevant sections of the protocol and the Manual of Operations and Procedures and reviews tests of relevant data collection forms.

The Other Age-Related Events Working Group may make proposals concerning data collection on, and classification of, the following outcomes: glaucoma, cataracts, arthritis, diabetes mellitus and tooth loss. They will, in collaboration with the Behavioral subcommittee, make proposals concerning the data collection and classification for the following outcomes: physical disability, dementia, depression and incontinence. It may develop smaller working groups devoted to each of these several specific outcomes if needed. During the Planning Phase, it reviews relevant sections of the protocol and the Manual of Operations and Procedures and reviews tests of relevant forms.

Each Working Group has about 6-8 members including a chair and co-chair, all appointed by the Project Office.

Operations Subcommittee

This subcommittee is responsible to the Executive Committee for the development, implementation and monitoring of the procedures for recruitment, retention, consent, and follow-up and of approaches pertinent to special populations. It is also responsible to the Executive Committee for standardized staff training, retraining, certification, and other quality control procedures related to the Clinical Centers and the Central Units. Its membership includes the chair and co-chair of five working groups -- Recruitment and Retention, Training and Certification, Clinic Operations, Data Management, and Laboratory Operations. Its work on recruitment and retention will be coordinated with that of the Special Populations and Behavioral Subcommittees, described below.

The Recruitment and Retention Working Group may make proposals concerning the development of common approaches to participant recruitment and long-term retention that may be adapted for use by individual Clinical Centers. It also may propose methods for monitoring recruitment and retention to assure adequate representation in pre-determined strata such as those determined by age, hysterectomy
status and ethnic/racial origin. Retention proposals will be coordinated with the Retention Working Group of the Behavioral Subcommittee. During the Planning Phase it reviews all relevant sections of the protocol and the Manual of Operations and Procedures and proposes informational and promotional materials such as brochures, press releases, posters and videotapes.

The Training and Certification Working Group may make proposals concerning the development of initial strategies for training of clinic personnel in any aspect of clinic operations, such as data collection, randomization, safety monitoring and data management. It also may propose methods for monitoring quality of training, needs for retraining and awarding and withdrawing certification. During the Planning Phase it reviews all relevant sections of the protocol and the Manual of Operations and Procedures and reviews criteria for certifying Clinical Center technicians and other personnel in specific procedures.

The Clinic Operations Working Group may make proposals concerning the development, implementation and monitoring of clinic procedures including the administration of data collection forms, performance of physical examinations and procedures, management of referral and adverse effects, and maintenance of regular communications between the Clinical Centers and the Coordinating Center. During the Planning Phase it reviews all relevant sections of the protocol and develops common approaches to clinic operations that may be adapted for use by individual Clinical Centers.

The Data Management Working Group may make proposals for developing, implementing and monitoring data capture and management methods and procedures, data quality, computer hardware and software needs. During the Planning Phase it reviews the WHI Data Systems Manual, the data management sections of the Protocol, Manual of Operations and Procedures and the database development priorities.

The Laboratory Operations Working Group may make proposals for the development, implementation and monitoring of specimen collection, processing and tracking, analysis, and quality control procedures. In addition to blood and urine specimens, the procedural aspects and quality control of pelvic exams and pap smears, endometrial aspirations, mammography and clinical breast exams, ECGs and bone densitometry will be proposed by this Working Group in collaboration with other pertinent Working Groups (e.g., HRT Working Group of the Intervention Subcommittee). During the Planning Phase it reviews all relevant sections of the Protocol, and Manual of Operations and Procedures.

**Behavioral Subcommittee**

This subcommittee is responsible to the Executive Committee for all behavioral aspects of the interventions, including enhancement and assessment. In addition, this subcommittee makes proposals for the health-related quality of life (HRQL) and other psychosocial components of the clinical trial. It serves as a resource to all other subcommittees or working groups on behavioral and psychosocial issues, and coordinates relevant measures with the Observational Study Subcommittee. During the Planning Phase it reviews all relevant sections of the protocol and the Manual of Operations and Procedures. In addition, it reviews relevant forms, and quality control issues for the behavioral data (i.e., adherence, HRQL, and other psychosocial measures). The Subcommittee reviews plans for training on, and administration and collection of, behavioral data and on adherence. It is composed of about 6-8 members including the chair and co-chair of Assessment and Retention Working Groups.

The Assessment Working Group may make proposals concerning psychosocial assessment in the WHI. Its members will propose measures of psychosocial variables at baseline and follow-up sessions. This working group will review all forms for readability and literacy levels, and will advise on form design and cognitive issues related to survey research. The members will advise on training modules for psychosocial form completion and interviewer competency. The members will recommend variables from the
psychosocial forms that should be monitored trial-wide for safety and treatment effects and will recommend a timeline and format for monitoring.

The Retention Working Group may make proposals for the design and monitoring of retention and adherence to the three interventions in the WHI in collaboration with the Recruitment and Retention Working Group of the Operations Subcommittee. This will include activities to promote attendance at follow-up contacts, taking pills according to the trials' schedules, and maintaining dietary change across the course of the trials. This working group will propose data to be monitored at regular intervals to identify retention and adherence problems. Its members may recommend strategies to overcome these problems once identified.

Special Populations Subcommittee

This subcommittee is responsible to the Executive Committee for addressing issues of cultural sensitivity and applicability to diverse minority populations. It collaborates with other subcommittees to develop, implement, and monitor specific recruitment, retention and substudy strategies for minority women, and works with the Interventions Subcommittee to enhance the applicability of the study methods to minority women. During the Planning Phase it reviews relevant sections of the protocol, manual and forms to improve cultural sensitivity. It also reviews and monitors the development of Spanish-language forms. It may also propose supplementary training material as needed to improve the ability of clinic staff to recruit, retain, and provide interventions and follow-up to minority and low socioeconomic status women. It is composed of about 6-8 members including a chair and co-chair, all appointed by the Project Office.

Observational Study Subcommittee

This subcommittee is responsible to the Executive Committee for the development, implementation and monitoring of all aspects of the Observational Study, including development of supplementary questionnaires and selection of subsets for study in future years. It also reviews recruitment of participants into the OS to insure adequate representation of predetermined strata such as those determined by age, hysterectomy status and ethnic/racial origin. During the Planning Phase it reviews all relevant sections of the protocol, manual and forms. It collects and prioritizes suggested additional questions and advises concerning the baseline OS supplementary questionnaire. It is composed of about 10-12 members including a chair and co-chair, all appointed by the Project Office. It has three working groups -- the Cardiovascular Working Group, the Cancer Working Group, and the Osteoporosis Working Group.

The Cardiovascular Working Group may make proposals concerning the development, implementation and monitoring of cardiovascular epidemiology aspects of the Observational Study. During the Planning Phase it reviews all relevant sections of the protocol, forms and the Manual of Operations and Procedures. The working group has about 6-7 members including a chair and co-chair, all appointed by the Project Office.

The Cancer Working Group may make proposals concerning the development, implementation and monitoring of all cancer epidemiology aspects of the Observational Study. During the Planning Phase it reviews all relevant sections of the protocol, forms and the Manual of Operations and Procedures. The working group has about 6-7 members including a chair and co-chair, all appointed by the Project Office.

The Osteoporosis Working Group may make proposals concerning the development, implementation and monitoring of all aspects of the Osteoporosis Substudy. During the Planning Phase it reviews all relevant sections of the protocol, forms and the Manual of Operations and Procedures. The working group has about 6-7 members including a chair and co-chair, all appointed by the Project Office.
WHI Protocol

Publications and Presentations Subcommittee

This subcommittee is responsible to the Executive Committee for the timely dissemination of WHI findings through publications and presentations.

The Subcommittee will encourage investigators, particularly young faculty, to submit plans for publications and presentations. These plans will be coordinated and integrated into a "production schedule". Adherence to prespecified delivery dates by the first author and the CCC will be monitored and corrective actions recommended, if necessary. This subcommittee is also involved in the WHI review and approval process for manuscripts and abstracts. The members of the Subcommittee will actively identify opportunities for presentations, and in a fair and equitable way, involve all WHI investigators in the dissemination process.

During the Planning Phase, this Subcommittee will propose a publication and presentations policy and present it to the Investigators and Executive Committees for approval. It will also develop a schedule of topics for presentations and publications at the various phases of the WHI. The members of this subcommittee will be mostly senior scientists representing diverse disciplines. The subcommittee will have about 8-10 members, including a chair and co-chair, all appointed by the Project Office.

Design and Analysis Subcommittee

This subcommittee is responsible to the Executive Committee for the overall design, integrity and analysis of the study. It also monitors and reviews protocol amendments, ancillary studies and proposes procedures for data quality control and data monitoring. The members should have special expertise in the different aspects of clinical trial design and analysis.

Throughout the trial, this subcommittee makes recommendations to the Investigators Committee and the Executive Committee regarding suggested amendments to the trial protocol and approval of ancillary study proposals. In addition, it regularly monitors the quality of key trial data and addresses general analysis issues.

During the Planning Phase, this subcommittee is charged with making proposals for 1) a policy for ancillary studies, 2) a plan for monitoring data quality control at the Clinical Coordinating Center and its subcontractors and at the Clinical Centers and 3) a plan for data monitoring and analysis of trial data. The latter will be presented to the Data and Safety Monitoring Board for review and approval.

The subcommittee will have about 8-10 members and a chair and co-chair, all appointed by the Project Office.
11. **TIMETABLE**

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<th>End Date</th>
<th>Duration</th>
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<td>Phase 2F - Data Analysis</td>
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<td>09/29/07</td>
<td>(2 years, 2 weeks)</td>
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* Assuming that recruitment is uniform over the designated three-year periods and that closeout visits occur on average three months prior to the end of Phase 2D, the average follow-up period will be 10 years in the VCCs and eight years, seven months in the other CCs for an overall average of 8.9 years, exclusive of the additional five years of follow-up for mortality and for breast and endometrial cancer incidence.
APPENDIX I

Baseline and Follow-up Variables

1. AT BASELINE

INITIAL CONTACT (CT and OS)

Questionnaire: Eligibility -- birthdate; current involvement in other research studies; ability to get to clinic (help needed); residing in area for next three years; number of meals prepared away from home; special diets (gluten-free, low-fiber); loss of 15 pounds in last six months; diabetes history; menopausal status (age of menopause, date of last bleeding, menopausal symptoms); history of hysterectomy; use of tamoxifen; estrogen and progestin use (date of last use, indications, willingness to discontinue); history of deep vein thrombosis and pulmonary embolus (concurrent hormone use, occurrence in last six months); history of cancer (site, diagnosis in last 10 years); history of heart failure, high triglycerides, lung disease requiring oxygen, bleeding problem, liver disease, jaundice, renal failure requiring dialysis; other chronic illness; history of stroke, transient ischemic attack, or myocardial infarction (ever, last 6 months); ethnicity.

VISIT I (CT and OS)

Questionnaire: Personal Information Questionnaire -- name (legal name, other names used, name as listed in the phone book); address; telephone numbers (home, work, other); best time to contact; marital status; name, address and telephone number of friends or relatives not living with participant; social security number; employment status; education; partner's name, social security number, occupation, and education; income; name, address and telephone number of physician, date physician last seen; date of last mammogram, Pap smear, and endometrial aspiration and where obtained; insurance coverage.

Semi-quantitative food frequency.

Hormone Interview -- current and past hormone replacement and oral contraceptive use.

Psychosocial Interview -- depression, mental status.

Medical History -- hospitalization for more than three days in last two years; diagnosis of cardiovascular diseases (hypertension, angina, MI, intermittent claudication, cardiac arrest, atrial fibrillation, aortic aneurysm, CHF); cardiovascular procedures (CABG, PTCA, cardiac catheterization, carotid endarterectomy, pacemaker); fracture (site); renal stones; osteoporosis; major abdominal surgeries; productive cough for three months; pancreatitis; ulcers; ulcerative colitis; irritable bowel syndrome; intestinal polyps; rheumatoid osteoarthritis; systemic lupus erythematosus; asthma; gall bladder disease; thyroid disease; peripheral arterial disease and surgery; fractures after age 40; history of high blood cholesterol; vision; and hearing.

Reproductive History -- age at menarche, history of amenorrhea and menstrual irregularity; number of pregnancies; pregnancy outcomes; infertility; lactation; gynecologic surgery; breast surgeries.

Psychosocial -- quality of life (physical function, emotional function, social function, sexual activity, symptoms, health perceptions, diet-related changes, urinary function, sleep patterns); psychological predictors (life events, social resources, stress, optimism, hostility,
WHI Protocol - Appendices

emotional expressiveness, reasons for being in the study, barriers to adherence, self-efficacy).

Medication and vitamin supplement inventory.

Observational Study -- birth weight, prematurity, multiple births, breast fed as an infant; magnitude of weight fluctuations in the last 20 years, use of powders, religion, residential history, work history (history of farm or beautician work; three jobs held longest); electromagnetic exposures. Also Family History and Personal Habits Questionnaires (See Visit 2 below for listing of content.).

**Physical:**
- Height, weight, functional status (grip strength, chair stand, timed walk).
- Circumference of waist, hip.
- Blood pressure, resting pulse.

**Laboratory:**
- Plasma (citrate and EDTA), serum, buffy coat, RBCs for storage.
- FSH (as needed for eligibility).
- Hematocrit, white blood cell count, platelet count.
- Fasting plasma glucose (subsample).
- Fasting TC, HDLC, TG, LDLC, HDL2, HDL3, Lp(a) (subsample).
- Fibrinogen, activated factor VII (subsample).
- Antioxidants (tocopherol, carotenoids, selenium, vitamin C) (subsample).
- Urine for storage (osteoporosis substudy sites only).
- Bone density (osteoporosis substudy sites only).

**VISIT 2 (CT only)**

**Questionnaire:**
- Family History -- number of full-blooded primary relatives; diabetes; myocardial infarction; cervical cancer; prostate cancer; breast cancer; colorectal cancer; endometrial cancer; ovarian cancer; prostate cancer; stroke; fractures; parental age at death.
- Personal Habits -- smoking history (never, past, current cigarettes/day, years smoked, smoking for weight control, quitting for health reasons); passive smoking (as a child, as an adult, current exposure, at work); alcohol consumption (never, past, current quitting for health reasons); coffee consumption (never, current cups/day); physical activity and exercise (current and past strenuous activity, sedentary activities, walking, exercising for more than 15 minutes); special diets; health screening; (BSE; CBE, mammogram, Pap smear, sigmoidoscopy/colonoscopy, stool guaiac); height and weight changes (height at 18; weight at 18, 35 and 50; maximum and minimum weight, weight fluctuation)
- Four-day food record instructions. (DM only)
- HRT Diary instructions. (HRT only)

**Physical:**
- Clinical breast exam and breast self-exam instruction.
- Pelvic exam (HRT), Pap smear (HRT in women with uterus).
- Endometrial aspiration (HRT in women with uterus).
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Procedure: Mammography.
Resting 12-lead electrocardiogram.

VISIT 3 (CT only)

Questionnaire: Final eligibility check.
Medication and vitamin supplement inventory.
Placebo run-in adherence check (HRT only).
Four-day food record (DM only).

2. EVERY SIX MONTHS (CT ONLY)

Questionnaire: Medical history update, including:
Clinical outcomes of interest.
Side effects (symptoms pertinent to specific CT components).
Medication and vitamin supplements inventory.
HRT Diary (HRT).
Adherence to medications (HRT and CaD).

3. AT 12 MONTHS (CT ONLY)

Questionnaire: Psychosocial -- quality of life.
Psychosocial Interview.

Laboratory: Plasma (citrate and EDTA), serum, and RBCs for storage.
Fasting plasma glucose (subsample).
Fasting TC, HDLC, TG, LDLC, HDL2, HDL3, Lp(a) (subsample).
Fibrinogen, activated factor VII (subsample).
Antioxidants (tocopherol, carotenoids, selenium, vitamin C) (subsample).
Urine for storage (osteoporosis substudy sites only).
Bone density (osteoporosis substudy sites).

4. EVERY 12 MONTHS (CT ONLY)

Questionnaire: Dietary Assessment -- semi-quantitative food frequency questionnaire (subsample of CT cohort).
Twenty-four hour dietary recall (subsample of DM only).
Four-day food record (subsample of DM only).

Physical: Weight, height, functional status.
Circumference of waist, hip.
Blood pressure, resting heart rate.
Clinical breast exam and breast self-exam instructions.
Pelvic exam, Pap smear (HRT in women with a uterus).
Endometrial aspiration (ERT, subsample of PERT and placebo among HRT women with a uterus).
Mammography.

5. EVERY THREE YEARS (CT ONLY)

Questionnaire: Psychosocial -- quality of life (subsample).
               Psychosocial Interview (subsample).
Laboratory:   Fasting plasma glucose (subsample).
               Hematocrit, platelet count, white blood cell count.
               Fasting TC, HDLC, TG, LDLC, HDL2, HDL3, Lp(a) (subsample).
               Fibrinogen, activated factor VII (subsample).
               Antioxidants (tocopherol, carotenoids, selenium, vitamin C) (subsample).
               Urine for storage (osteoporosis substudy sites only).
               Bone density (osteoporosis substudy sites only).
               Resting 12-lead electrocardiogram.

6. AT THREE YEARS (OS ONLY)

Questionnaire: Personal Habits -- smoking, alcohol, caffeine, exercise.
               Medical history update.
               Semi-quantitative food frequency.
               Psychosocial -- quality of life.
               Psychosocial Interview.
Physical:     Height, weight, functional status.
               Circumference of waist, hip.
               Blood pressure, resting heart rate.
Laboratory:   Plasma (citrate and EDTA), serum, and RBCs for storage.
               Hematocrit, platelet count, white blood cell count.
               Fasting plasma glucose (subsample).
               Fasting TC, HDLC, TG, LDLC, HDL2, HDL3, Lp(a) (subsample).
               Fibrinogen, activated factor VII (subsample).
               Antioxidants (tocopherol, carotenoids, selenium, vitamin C) (subsample).
               Urine collection (osteoporosis substudy sites only).
               Bone density (osteoporosis substudy sites only)
EVERY THREE YEARS (SUBSAMPLE OF OS)

Questionnaire: Personal habits.
Medical history update.
Semi-quantitative food frequency.
Psychosocial -- quality of life.
Psychosocial Interview.

Physical: Height, weight, functional status.
Circumference of waist, hip.
Blood pressure, resting heart rate.

Laboratory: Plasma (citrate and EDTA), serum, RBCs for storage.
Fasting plasma glucose.
Fasting TC, HDLC, TG, LDLC HDL2, HDL3, Lp(a).
Fibrinogen, activated factor VII.
Antioxidants (tocopherol, carotenoids, selenium, vitamin C)
Urine collection (osteoporosis substudy sites only).
Bone density (osteoporosis substudy sites only).

(Note: Bloods from the subsample [usually five to six percent] will be analyzed immediately; in addition plasma, serum, buffy coat, RBCs will be obtained at specified times and stored at -70°C for subsequent case-control analyses.)
APPENDIX II

Overview of Classification Procedures
and Definitions of Clinical Outcomes

1. Identification of Clinical Outcomes

A. Clinical Trial

Clinical outcomes will be identified initially through self-administered mailed questionnaires regarding recent symptoms, diagnoses, medications, hospitalizations and procedures. These questionnaires will be mailed to CT participants semi-annually, with follow-up as needed for unreturned questionnaires. When the semi-annual questionnaire coincides with an annual clinic visit, participants will be asked to bring completed forms with them to the visit.

B. Observational Study

The same self-administered mailed questionnaires on recent symptoms, diagnoses, medications, hospitalizations and procedures will be mailed to OS participants annually, with telephone follow-up as needed for unreturned questionnaires.

2. Outcomes Information to be Collected

A. All deaths: death certificate; next-of-kin or physician interview if needed to determine cause of death in out-of-hospital deaths; autopsy or coroner's report if available; emergency medical services data if available.

B. All hospitalizations: discharge summary and face sheet with ICD-9 diagnosis and procedure codes (additional information for specific diagnoses to be collected as in sections C-F below).

C. Cardiovascular disease requiring hospitalization

1. Angina pectoris or myocardial infarction: electrocardiograms, cardiac enzymes, hospital discharge summary for report of symptoms and therapy (thrombolytic therapy, angioplasty, coronary bypass surgery, cardiac catheterization, exercise stress test or thallium studies).

2. Stroke/TIA: report of cerebral CT or MRI scan; hospital discharge summary for neurologic exam.

3. Congestive heart failure: chest X-ray report; hospital discharge summary for signs and symptoms, electrocardiograms and enzyme reports.

4. Carotid artery disease or peripheral vascular disease: angioplasty, hospital discharge summary for signs and symptoms; report of angiogram or ankle-arm blood pressures procedure; or operative report.

D. Cancer:

1. Breast, endometrium, ovary, colon, rectum: pathology report; surgical/operative report; radiology reports (diagnostic x-rays and nuclear medicine reports, i.e., bone scan); oncology/radiology consult summary if available (corresponding to first course of cancer treatment); TNM staging form if available; hormone receptor (estrogen and progesterone) assay results for all breast cancers.

2. All other cancers (excluding non-melanoma skin cancers): pathology report.

E. Fractures: X-ray report; discharge summary for hip fracture.
WHI Protocol - Appendices

F. Venous thromboembolic disease

1. Pulmonary embolism: arteriogram or lung scan report, hospital discharge summary.


3. Outcomes Data Storage

All outcomes information will be stored centrally to ensure uniform content, secure storage and ease of access during analyses and performance of case control studies.

4. Classification of Endpoints

The physician responsible for classifying cardiovascular events at each Clinical Center will be a member of a Cardiovascular Morbidity and Mortality Endpoints Committee. All potential ischemic hospitalized events related to coronary heart disease including myocardial infarction, angina pectoris and congestive heart failure will have an event package completed including the hospital discharge summary, reports of cardiac enzyme levels and the 1st day, 3rd day and last ECG collected. These will be sent to the CCC and the materials sent to the Endpoints Committee member of three other clinics. Upon review if two of the three Endpoints Committee members agree with the original diagnosis then no further adjudication will be necessary. If not, then that endpoint packet will be adjudicated by a subset of the Endpoints Committee at regular intervals.

Although packets will be made up for these events for both the Clinical Trial and Observational Study, only a 5% random sample will be reviewed in the Observational Study at the beginning of the study. If specified quality control criteria can be met the percentage reviewed will be reduced to 2% in the Observational Study.

The five primary cancer outcomes (breast, endometrium, ovary, colon and rectum) will have documentation collected at the Clinical Center and materials sent to the CCC. Materials to be collected will allow for tumor node metastases (TNM) staging to be done at the CCC. Data regarding estrogen and progesterone receptor will be collected for all breast tumors. All other cancers will have coding (ICD) done according to the hospital face sheet status. As a quality control measure 5% of the cancer outcomes will be resubmitted for verification. This will go to 2% as quality control criteria are met.

All fractures will be ascertained by self report of the fracture and hospitalization. At the beginning of the study, for participants in the Clinical Trial and those in the Observational Study who are participating in the Osteoporosis substudy, hip fractures will be confirmed by a radiologist's report and hospital discharge summary, reviewed at the CCC. All other fractures will be confirmed from an x-ray report reviewed at the CCC. A subsample of the hip fractures (5% and 2% later if good quality control is demonstrated) will be reviewed at the CCC thereafter. For women in the OS but who are not in the Osteoporosis substudy, fractures will be based on self-report of a physician's diagnosis of a new fracture or a hospital discharge summary indicating a new diagnosis of a new fracture reviewed at local clinics.

All strokes in both the Clinical Trial and the Observational Study will have endpoint packets completed consisting of a discharge summary and either a cerebral MRI or CT scan report. These will be assigned diagnosis by the clinic personnel, and a copy of the packet sent to the CCC. Further adjudication of these endpoints for the Clinical Trial may be done as part of an ancillary study.

All outcomes of other age-related diseases will be collected as part of the responses to questionnaires or limited physical examination and will have no adjudication centrally and no special storage considerations.
5. Classification of Prevalent Disease at Baseline

Prevalent disease will be defined by participant report, without relying on further confirmation by physician's or hospital records. The only exception to this general rule is a diagnosis of prevalent diabetes, which also requires, in addition to diagnosis, current treatment with insulin or oral hypoglycemic agents. In addition, evidence of silent disease such as myocardial infarction by electrocardiogram will be used to define prevalent disease.

Prevalent coronary heart disease will include reported coronary revascularization procedures, and prevalent peripheral vascular disease will include reported aortic aneurysm, aortic aneurysm repair, arterial revascularization in lower extremities, or lower extremity amputation for gangrene or impaired circulation.

6. Definition of Endpoints

A. Cardiovascular Disease: A hierarchy of cardiovascular endpoints may be developed if needed for identification of a single endpoint per participant for purposes of analysis.

1. Myocardial infarction:

   a. Completed myocardial infarction: Death of part of the myocardium due to occlusion of a coronary artery from any cause, including spasm, embolism, thrombosis or plaque rupture. Myocardial infarctions are classified as definite, or probable, based on the triad of electrocardiographic changes, cardiac enzymes and symptoms as shown below [adapted from Rautaharju, J Electrocardiol 1992;24 (suppl):179-187]:

<table>
<thead>
<tr>
<th>ECG Pattern/Symptoms</th>
<th>Abnormal</th>
<th>Equivocal</th>
<th>Incomplete</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac pain present:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evolving Q-wave MI or evolving profound ST-T abnormalities</td>
<td>Definite MI</td>
<td>Definite MI</td>
<td>Definite MI</td>
<td>Definite MI</td>
</tr>
<tr>
<td>Equivocal Q wave evolution or evolving major ST-T abnormalities</td>
<td>Definite MI</td>
<td>Definite MI</td>
<td>Probable MI</td>
<td>Probable MI</td>
</tr>
<tr>
<td>Non-evolving major or minor Q waves or non-evolving major or minor ST-T abnormalities</td>
<td>Definite MI</td>
<td>Probable MI</td>
<td>No MI</td>
<td>No MI</td>
</tr>
<tr>
<td>Other ECG, ECG absent or uncodable</td>
<td>Probable MI</td>
<td>No MI</td>
<td>No MI</td>
<td>No MI</td>
</tr>
<tr>
<td><strong>Cardiac Pain absent:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evolving Q-wave MI or evolving profound ST-T abnormalities</td>
<td>Definite MI</td>
<td>Definite MI</td>
<td>Definite MI</td>
<td>Probable MI</td>
</tr>
<tr>
<td>Equivocal Q wave evolution or evolving major ST-T abnormalities</td>
<td>Probable MI</td>
<td>Probable MI</td>
<td>No MI</td>
<td>No MI</td>
</tr>
<tr>
<td>Non-evolving major or minor Q waves or non-evolving major or minor ST-T abnormalities</td>
<td>Probable MI</td>
<td>No MI</td>
<td>No MI</td>
<td>No MI</td>
</tr>
<tr>
<td>Other ECG, ECG absent or uncodable</td>
<td>No MI</td>
<td>No MI</td>
<td>No MI</td>
<td>No MI</td>
</tr>
</tbody>
</table>
Cardiac pain is defined as pain occurring anywhere in the anterior chest, left arm or jaw in the absence of a definite non-cardiac cause of chest pain. Supportive evidence of cardiac pain includes dull or visceral quality to the pain, precipitation by effort and relief with rest or nitroglycerin.

Cardiac enzymes are "abnormal" in the absence of known non-ischemic cause for enzyme elevation if: 1) creatine kinase MB isoenzyme (CK-MB) is reported as "present" without further quantification or CK-MB is twice the upper limits of normal or CK-MB is ≥ 10% of total CK value in absence of normal range; or 2) the ratio of lactate dehydrogenase (LDH)1:LDH2 > 1 or LDH1 is twice the upper limit of normal in absence of LDH2; or 3) total CK and LDH are both at least twice the upper limit of normal.

Cardiac enzymes are "equivocal" if criteria for abnormal enzymes are not met and if: 1) either total CK or total LDH are at least twice the upper limit of normal; 2) both total CK and total LDH are between the upper limit of normal and twice the upper limit of normal; 3) CK-MB is "weakly present" or between the upper limit of normal and twice the upper limit of normal or 5-9% of total CK; or 4) if LDH1 is present and LDH2 is missing, and LDH1 is between the upper limit of normal and twice the upper limit of normal.

Enzyme diagnostic criteria can be tabulated as follows:

<table>
<thead>
<tr>
<th>TOTAL CK</th>
<th>Twice Upper Limit of Normal</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal</td>
<td>Equivocal</td>
<td></td>
</tr>
<tr>
<td>Equivocal</td>
<td>Equivocal</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

b. Aborted myocardial infarction; treated with thrombolytic therapy with or without "cardiac pain" (protocol definition), with or without abnormal cardiac enzymes, but having ECG changes of major or minor Q waves and/or major or minor ST-T wave abnormalities.

2. Coronary death: Death consistent with coronary heart disease (CHD) as underlying or immediate cause, plus any one of the following:

a. pre-terminal hospitalization with myocardial infarction, fatal MI within 28 days, or

b. previous angina or myocardial infarction and no known potentially lethal non-coronary disease process, or

c. CHD diagnosed as cause of death at post-mortem examination, or

d. death resulting from a procedure related to coronary artery disease such as coronary bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA).
Coronary death will be subclassified as:

a. Definite fatal MI: no known non-atherosclerotic cause and definite MI within 4 weeks of death

b. Definite fatal CHD: no known non-atherosclerotic cause and one or both of the following: chest pain within 72 hours of death or a history of chronic ischemic heart disease in the absence of valvular heart disease or non-ischemic cardiomyopathy

c. Possible fatal CHD: no known non-atherosclerotic cause, and death certificate consistent with underlying cause

Timing of coronary death will be classified as "sudden" when death occurs within 1 hour after onset of symptoms or having been last seen without them, and in the absence of potentially lethal non-coronary disease process. It will be classified as "rapid" when death occurs within one-24 hours of symptom onset.

3. Stroke: Rapid onset of persistent neurologic deficit attributable to an obstruction or rupture of the arterial system, including stroke occurring during surgery, that is not known to be secondary to brain trauma, tumor, infection, or other non-ischemic cause. The deficit must last more than 24 hours unless death supervenes or there is a demonstrable lesion compatible with acute stroke on CT or MRI scan.

a. Non-fatal stroke (either of the following):

1. Recent onset of severe headache, loss of consciousness, or unequivocal objective findings of a localizing neurologic deficit and duration longer than 24 hours and absence of other disease process causing neurologic deficit such as neoplasm, subdural hematoma, cerebral angiography, or metabolic disorder;

2. Diagnosis of stroke based on abnormality demonstrated by CT or MRI consistent with current neurologic symptoms or signs, or positive lumbar puncture (for subarachnoid hemorrhage)

Strokes will be subclassified if criteria are met on the basis of compatible findings on CT or MRI scan or lumbar puncture to the following types:

A. Hemorrhagic
B. Ischaemic
C. Unknown type Stroke

b. Fatal stroke: death certificate listing stroke as consistent with, underlying, or immediate cause of death, plus any one or more of the following:

1. preterminal hospitalization with stroke as defined above, or fatal stroke within 28 days, or
2. previous stroke and no known potentially lethal non-cerebrovascular disease process, or
3. stroke diagnosed as cause of death at post-mortem examination.

4. Congestive heart failure (hospitalization only): cardiac output insufficient to meet metabolic needs despite adequate filling pressures, as defined by any one of the following:

a. cardiomegaly and pulmonary edema on chest X-ray, or

b. dilated ventricle and wall-motion abnormalities by echocardiography or contrast ventriculography, or
5. Angina pectoris (hospitalization only): chest pain, tightness or shortness of breath produced by myocardial ischemia that lasts for less than 20 minutes and does not result in infarction, usually caused by coronary arterial insufficiency, as defined by any one of the following:
   a. coronary artery bypass graft surgery or angioplasty, or
   b. 70% or greater obstruction of any coronary artery, or
   c. ST depression > 1mm on exercise testing, or
   d. angina diagnosed by physician plus receiving medical treatment for angina (nitrates, beta-blockers or calcium-channel blockers)

6. Peripheral arterial disease: intermittent claudication, ischemic ulcers or gangrene due to arterial insufficiency in the lower extremity as defined by any one of the following:
   - Discharge summary and records of bypass surgery, angioplasty or thrombolysis for peripheral arterial disease

7. Carotid artery disease: requires hospitalization with a discharge summary and report of angioplasty or surgical procedure.

8. Coronary revascularization: coronary bypass grafting (CABG), percutaneous transluminal coronary angioplasty (PTCA), or atherectomy, pacemakers and defibrillator.

B. Cancer: primary malignant tumor, invasive or in situ, with or without pathologic confirmation including all histologic subtypes. Information to be collected for the five major cancer sites (breast, endometrium, ovary, colon, and rectum) includes primary site, anatomic subsite, stage of disease, histology, tumor behavior and grade. Of these six data items, only primary site will be recorded for all other cancers. In addition, estrogen and progesterone receptor status of the primary tumor will be recorded whenever available for all primary breast cancers. Cancer diagnoses of interest include the following:

1. Breast
2. Endometrium (including corpus uteri)
3. Ovary (including borderline malignant tumors)
4. Colon
5. Rectum
6. All other cancers (excluding non-melanoma skin cancers)

Self-reports of any cancer diagnosis will be collected by annual mailed questionnaires and at all follow-up visits, and will be confirmed as follows:

a. Pathology report stating the diagnosis as cancer or use of specific terms that are synonymous with cancer: malignancy, malignant tumor, malignant neoplasm, carcinoma, CA, or a specific histology that defines malignant tumor morphology. The ambiguous terms "probably, suspect, suspicious,
compatible with, most likely, and consistent with" cancer ARE NOT diagnostic of cancer. The term "neoplasm" or "tumor" must be preceded by the word "malignant" to be diagnostic of cancer.

b. Without pathologic confirmation, the diagnosis of cancer will be adjudicated by the Mortality and Morbidity Classification Committee.

C. Fractures

1. Hip fractures: for all participants in the Clinical Trial and Observational Study, hip fractures will be defined as radiographically confirmed fracture of the proximal femur, including fractures of the femoral neck and intertrochanteric region. Self-report of fractures will be collected on the Medical history Update Form and at all follow-up visits. Hip fractures will be confirmed as follows:

a. Written report by a radiologist based on a preoperative radiograph, stating that a new, acute, or healing fracture of the proximal femur (or one of its regions: the femoral neck or intertrochanteric region) is present. Written reports not by a radiologist may be accepted after review and confirmation by the UCSF Osteoporosis Coordinating Center radiologist.

b. Alternatively, a combination of the following: 1) a negative or equivocal report of a preoperative radiograph of the hip (e.g. "possible" or "probable" or "suspected" hip fracture), combined with 2) a hospital discharge summary listing fracture of the proximal femur, femoral neck fracture, intertrochanteric fracture, or hip fracture and a written radiologist's report of either a bone scan or MRI scan unequivocally stating that a new hip fracture, or healing hip fracture, is present.

c. Alternatively, a combination of the following: 1) an equivocal written report of a radiograph of the hip (e.g. "possible" or "probable" or "suspected" hip fracture), combined with 2) confirmation of the diagnosis by the UCSF Osteoporosis Coordinating Center radiologist, based on the review of preoperative radiographs of the hip and other imaging studies and clinical findings from the hospital record.

2. All fractures other than hip: for participants in the Clinical Trial and Osteoporosis substudy, fractures will be defined as a radiographically confirmed new or acute fracture of any bone. Self reports of fractures will be collected on the Medical History Update Form and at all follow-up visits. Self-reports will be confirmed as follows:

a. Written x-ray report stating that a new, acute or healing fracture of a bone is present.

b. Vertebral fractures usually cannot be diagnosed as new or acute with certainty based on nonserial radiographs alone. Although the criteria listed in 2.a. will be used to confirm the presence of a vertebral fracture, these fractures will be categorized and analyzed separately.

3. For hip fractures in all participants, and all fractures other than hip in participants in the Clinical Trial and Osteoporosis substudy:

a. Fractures reported by participants but accompanied by an x-ray report indicating a normal radiograph of that site will be classified as "confirmed non-fracture."

b. Fractures reported by the participant but found to be "uncertain" by x-ray report (e.g., possible" or "probable" or "suspected") will also be recorded but will classified as "uncertain."
D. Venous thromboembolic disease

1. Pulmonary embolism: embolic obstruction of pulmonary arteries usually accompanied by acute onset of chest pain and dyspnea accompanied by tachycardia, tachypnea and hypoxemia. Diagnosis of pulmonary embolism will be confirmed by any of the following:

   a. characteristic signs and symptoms in the presence of documented deep venous thrombosis (defined below), or

   b. positive ventilation-perfusion lung scan, or

   c. embolism demonstrated on pulmonary angiography.

2. Deep venous thrombosis: thrombotic obstruction of deep veins of calf, thigh or pelvis usually accompanied by pain, tenderness and swelling at the site of obstruction. Diagnosis of deep venous thrombosis will be confirmed by positive venography, impedance plethysmography, doppler examination, or isotope scanning.

E. Treated diabetes mellitus: physician diagnosis of diabetes plus current treatment with insulin or oral hypoglycemic agents.

F. All Deaths: must be classified by underlying cause of death and death certificate obtained. They will be subclassified as follows:

1. Atherosclerotic cardiac

2. Cerebrovascular disease

3. Other cardiovascular disease

4. Cancer

5. Violent/Accident/Suicide

6. Other
APPENDIX III

Statistical Power for Women’s Health Initiative
Clinical Trial and Observational Study

1. CLINICAL TRIAL

Introduction

As described in the main text there are three components of the Clinical Trial: dietary intervention (A), hormone replacement therapy (B) and calcium/vitamin D supplementation (C). Women who are eligible and willing to participate in either the dietary or the hormone component may enter the trial but each woman will be encouraged to participate in all three components. Thus a woman may participate in component A alone, B alone, A and B, A and C, B and C, or in all three components. We envisage that approximately 21% of the women who are willing and eligible to participate in the dietary component will also be willing and eligible to participate in the hormone component. We also envisage that at about 70% of women who enter the trial will accept participation in the calcium/vitamin D component.

In the following three subsections we describe the statistical power calculations for each of the three components. In the final subsection we pull together the results for each component and give an estimated sample size for the three components and the complete trial.

A. Dietary Intervention

The two main hypotheses of the dietary intervention component are that breast cancer incidence and colorectal cancer incidence will be reduced. A secondary hypothesis is that the incidence of coronary heart disease (CHD) will be reduced. Power calculations are presented for each of these hypotheses. Assumptions for these power calculations are described below.

Randomization Ratio. We propose to randomize 40% of the eligible women to dietary counseling and the remaining 60% to standard dietary advice. This ratio is chosen to reduce the costs of dietary counseling in the trial while maintaining statistical power.

Significance Level. Power is calculated for a one-sided test at significance level \( \alpha = 0.025 \). One-sided tests for the dietary hypotheses are warranted by the preponderance of preliminary evidence against any increase in incidence of breast or colorectal cancer or coronary heart disease as a result of the dietary counseling.

Statistical Test. For breast cancer and colorectal cancer, we assume that a comparison of rates of new cases of disease in the two randomized groups, based upon a weighted logrank test, will be conducted as the main analysis. For coronary heart disease, we use a weighted binominal test, dividing the follow-up interval into three periods: 0-3 years, 3-6 years, and 6-9 years. This test accounts for the fact that complete data on CHD events will be available for individuals at three-yearly intervals, corresponding to the timing of the ECG examinations. The power calculations are performed using a modified version of a program written by Lakatos (Lakatos, Biometrics, 44, 229-241, 1988). For breast and colorectal cancer the weights increase linearly up to 10 years, corresponding to the model of Self et al (Controlled Clinical Trials, 9, 119-136, 1988). For coronary heart disease the weights for the three periods are one, two, and two, corresponding to an intervention effect that increases linearly up to three years and remains constant thereafter. These weights are chosen to maximize the statistical power of the study under time patterns of intervention effect that may be anticipated from dietary modification.

Trial Duration. Calculations are presented for average follow-up durations of six years and nine years.
Sample Size. Preliminary calculations indicated that adequate power would be obtained with a sample size of between 40,000 to 60,000. We present results for 42,000, 48,000 and 54,000 women.

Age Distribution. We assume women aged 50-54, 55-59, 60-69 and 70-79 years will enter the trial in the ratio 2:4:9:5.

Loss to Follow-up/Competing Risk. We assume a 3.0% per annum loss to follow-up due to deaths from other causes or disappearance, but only 2.0% per annum for the CHD endpoint, since about one third of deaths in the trial will be due to CHD.

Anticipated Intervention Effect.

(i) Breast Cancer. Self et al (Controlled Clinical Trials, 9, 119-136, 1988) discuss in detail the determination of the anticipated effect of a low-fat dietary intervention upon breast cancer incidence in a clinical trial. Their calculations involved assumptions regarding compliance, the magnitude of the dietary effect and the extent of the lag in this effect (described below). These assumptions led to an estimated 17% reduction in breast cancer incidence over an average follow-up period of approximately eight years.

Their compliance assumptions were based on data collected in the pilot study for the Women's Health Trial (1985-1986). The women in the intervention group in this trial decreased their average percent calories from fat from a baseline level of 39.5% to a level of 21.0% at six months, increasing to 21.7% at one year and to 22.6% at two years. It was assumed that their average level at 10 years would increase linearly to 26%. The women in the control group had corresponding average levels of 39.4%, 38.8%, 37.8% and 37.2% at baseline, six months, one year and two years. It was assumed that a total reduction of 4% in percent calories from fat would occur over the 10 years of the trial in these women. We assume the same pattern of non-compliance, except that the women in the control group are expected to have an average intake of 38.0% calories from fat at baseline since women consuming more than 34% calories from fat at entry will be eligible and the current mean intake in the population is assumed to be 36%.

The magnitude of the dietary intervention effect was estimated from international correlations between dietary fat 'disappearance' data and breast cancer incidence rates. These data suggest a relative risk of 0.33 for lifetime consumption of 20% compared to 40% calories from fat. It was assumed that by the end of 10 years of intervention a relative risk of 0.50 would be achieved by fully compliant women, and that the relative risk would decrease linearly from 1.0 over this period. This gradually changing relative risk, from 1.0 at baseline to 0.5 at 10 years, leads, when averaged over the nine-year average follow-up period and taking non-compliance into account, to a projected 14% reduction in breast cancer incidence.

We calculate the power in our trial for detecting not only a 14% reduction but also a 12% or 11% reduction in breast cancer incidence.

(ii) Colorectal Cancer. International correlations show similar relationships between total fat disappearance data and colorectal cancer incidence as with breast cancer incidence. However, in contrast to breast cancer, the relationship between fat and colorectal cancer is supported by prospective observational cohort studies (Willett, W. C., et al, New England Journal of Medicine, 323, 1664-1672, 1990). Moreover, migrant studies suggest their more rapid adoption of indigenous incidence rates of colorectal cancer than of breast cancer (e.g. McMichael, A. J., Giles, G. G., Cancer Research, 48, 751-756, 1988). In addition, increases in dietary fiber, besides decreases in fat, are postulated to reduce colorectal cancer incidence. Thus, we would expect a greater effect of dietary intervention upon colorectal cancer incidence than upon breast cancer incidence, and a possibly shorter lag in this effect. For these reasons we anticipate a reduction of approximately 18-22% in colorectal cancer incidence in this trial and present power calculations for 18%, 20% and 22% reductions.

(iii) Coronary Heart Disease. Data from the pilot study of the Women's Health Trial (Henderson et al, Preventive Medicine, 19, 115-133, 1990) indicate that the serum cholesterol levels of women in the intervention
group fell on average by 6-7% over the initial two years. This occurred in the presence of the non-compliance levels described above. In addition results from the Lipid Research Clinics Coronary Primary Prevention Trial (LRC Program, JAMA, 251, 351-364, 1984) suggest that CHD incidence is reduced over a period of seven to eight years by approximately two times the percent reduction in serum cholesterol. Although the period of our trial is longer (nine years average follow-up), and we might therefore expect larger effects, we conservatively apply this two-fold factor to the 6-7% reduction in serum cholesterol achieved in the Women's Health Trial pilot study. Hence we investigate the power in this study to detect reductions of 11%, 12% or 14% in CHD incidence.

**Incidence Rates.**

(i) & (ii) *Breast Cancer and Colorectal Cancer.* We have used the age-specific incidence rates published from the SEER program for the years 1985-1989. No healthy volunteer correction is applied to the cancer incidence figures, since neither disease is thought to be strongly related to socioeconomic status or previous ill-health. Although there has been an increasing incidence of breast cancer in recent years, we conservatively assume that population incidence rates will remain steady during the trial.

(iii) *Coronary Heart Disease.* To account for the strong secular decrease in CHD-ID mortality (and, by inference, CHD morbidity) the published USA age-specific mortality rates for the years 1980-88 were projected forwards into the trial period, assuming that the linear trends would continue for a further 10 years and would thereafter stabilize. The incidence rates were obtained by multiplying the mortality rates by 2.5. They were then reduced by 33% to account for the healthy volunteer effect, i.e. the anticipation that women volunteering for the trial will have considerably lower CHD rates than in the general population.

**Statistical Power.**

(i) *Dietary Modification: Breast Cancer.*

<table>
<thead>
<tr>
<th>Average follow-up (y)</th>
<th>Intervention effect (%)</th>
<th>Percentage of cases</th>
<th>Power (%)</th>
</tr>
</thead>
<tbody>
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(ii) *Dietary Modification: Colorectal Cancer.*

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<th>Power (%)</th>
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(iii) **Dietary Modification: Coronary Heart Disease.**

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<th>Average follow-up (y)</th>
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<th>Percentage of cases</th>
<th>Power (%)</th>
<th>Sample size</th>
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**B. Hormone Replacement Therapy**

Women with a uterus will be randomized to one of three groups: Estrogen Replacement Therapy (ERT), Progestin/Estrogen Replacement Therapy (PERT) or Control (C). Those without a uterus will be randomized to ERT or Control.

The main hypotheses are that ERT (or PERT) reduces coronary heart disease incidence. A secondary hypothesis is that ERT (or PERT) reduces the incidence of fractures. With regard to undesirable effects there is interest in testing for a possible increase due to ERT (or PERT) in the incidence of breast cancer. Estimated powers for each of these hypotheses are presented. Assumptions for these power calculations are described below.

**Randomization Ratio.** We propose to randomize 25% of the eligible women with a uterus to ERT, 40% to PERT and 35% to Control; and 42% of the women without a uterus to ERT and 58% to Control. These ratios are chosen to maximize statistical power and reduce costs associated with monitoring women receiving ERT. We will restrict entry to ensure that not more than 30% of the women in the trial are without a uterus.

**Significance Level.** Power is calculated for a two-sided test at significance level $\alpha = 0.05$.

**Statistical Test.** As for dietary intervention. The weights for the weighted logrank tests for the effect on fractures are assumed to increase linearly up to three years of follow-up and remain constant thereafter. Separate tests will be made comparing ERT with Control and PERT with Control. The test for PERT will be interpreted conditionally on the results of the ERT test, since it is currently thought unlikely that PERT would achieve a greater reduction in CHD incidence than ERT.

**Trial Duration.** As for dietary intervention.

**Sample Size.** Preliminary calculations indicated that adequate power for the main hypothesis would be obtained with a total sample size of between 20,000 to 30,000. We present results for 20,000, 25,000 and 30,000 women.

**Age Distribution.** As for dietary intervention.

**Loss to Follow-up/Competing Risk.** As for dietary intervention.

**Drop-Out.** We assume that in year one of follow-up 6% of women in the ERT (PERT) group will switch to Control and 3% per year thereafter up to year 10.

**Drop-In.** We assume that up to and including year five, 1.5% of women in the Control group per year will switch to ERT or PERT. For years 6 to 10 this annual rate win fall to 1.0%.
Lag. We assume that there will be a three-year lag in the effects of ERT or PERT on each of the disease incidences considered, except for breast cancer where the lag will be 10 years. Our assumption is that the treatment effect (on the hazard scale) increases linearly from zero at randomization to its full effect at the end of the lag period.

Anticipated Intervention Effect.

(i) & (ii) Coronary Heart Disease. As documented in the protocol, results from observational studies lead us to expect a reduction in incidence of approximately 50% in CHD for women taking ERT over a 10-year period. We assume that ERT and PERT will have similar intervention effects. Because of the likely existence of biases in the observational studies, we present estimated power for detecting a 25% or 30% reduction.

(iii) Fractures. Observational studies suggest that ERT may reduce hip fracture rates and "combined-site" fracture rates by 50%. Because of the likely existence of biases in observational studies, we present estimated power for detecting a 25%, 30%, or 35% reduction.

"Combined-site" fractures include those sites thought likely to fracture mainly due to osteoporosis in women over age 50 years. These are proximal femur (hip), distal forearm, proximal humerus, pelvis and vertebra. Hip is chosen as a separate endpoint because of the serious morbidity caused by this fracture.

(iv) Breast Cancer. Observational studies suggest that there may be an increased relative risk of breast cancer for women taking ERT. We present the estimated power for detecting a 20% or 30% increase.

Incidence Rates.

(i) Coronary Heart Disease. As for dietary intervention.

(ii) Fractures. Incidence figures of first fractures in five anatomical sites (proximal femur, distal forearm, proximal humerus, pelvis, vertebra) from Rochester, Minnesota study were provided by Dr. J. Melton. To obtain incidence for the combined sites, we summed the incidence figures for each individual site but then applied a multiplicative factor 0.8 to account for possible fractures at multiple sites that may occur in some women. We also applied a healthy volunteer effect of 0.8 to take account of the possible selection into the trial of women less likely to fracture. For hip fracture incidence we applied the same healthy volunteer correction.

(iii) Breast Cancer. As for dietary intervention. (Unlike dietary intervention, there may possibly be a healthy volunteer effect for breast cancer in the hormone replacement component due to some women with a family history of breast cancer being unwilling to participate. However, there is also an increasing rate of breast cancer in the general population. Neither of these phenomena are included in our calculations, but their effects are likely to cancel each other.)

Statistical Power (%).

(i) ERT versus Control: Coronary Heart Disease.

<table>
<thead>
<tr>
<th>Average follow-up (y)</th>
<th>Intervention effect (%)</th>
<th>Percentage cases</th>
<th>Power (%)</th>
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</table>
(ia) PERT versus Control: Coronary Heart Disease.

<table>
<thead>
<tr>
<th>Average follow-up (y)</th>
<th>Intervention effect (%)</th>
<th>Percentage cases</th>
<th>Power (%)</th>
<th>Total sample size</th>
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(ii) ERT versus Control: Combined Fractures.

(The percentage of cases and the powers in this table are based upon our original age distribution assumptions, i.e., 50-50 60-69, 70-79 year olds enter in the ratio 2:2:1, and hence are conservative estimates.

<table>
<thead>
<tr>
<th>Average follow-up (y)</th>
<th>Intervention effect (%)</th>
<th>Percentage cases</th>
<th>Power (%)</th>
<th>Total sample size</th>
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(iia) PERT versus Control: Combined Fractures.

(The percentage of cases and the powers in this table are based upon our original age distribution assumptions, i.e., 50-50 60-69, 70-79 year olds enter in the ratio 2:2:1, and hence are conservative estimates.

<table>
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<th>Percentage cases</th>
<th>Power (%)</th>
<th>Total sample size</th>
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(iii) ERT versus Control: Hip Fractures.

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<th>Average follow-up (y)</th>
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<th>ERT</th>
<th>Power (%) Total sample size</th>
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(iiiia) PERT versus Control: Hip Fractures.

<table>
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<th>Average follow-up (y)</th>
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(iv) ERT versus Control: Breast Cancer.

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(iva) PERT versus Control: Breast Cancer.

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C. Calcium/Vitamin D.

Calcium/Vitamin D. Women will be randomized to one of two groups: Calcium/Vitamin D supplementation (CaD) or Placebo. The main hypothesis is that CaD reduces fracture rates.

Estimated powers for the main hypothesis are greatly in excess of those calculated for the effect of ERT on fracture rates, as shown below.

Randomization Ratio. We will randomize 50% of eligible women to CaD and 50% to Placebo.

Significance Level. As for hormone replacement.

Statistical Test. As for hormone replacement.

Trial Duration. Average follow-up for this component will be one year less than for the other components. We tabulate powers for five years and eight years follow-up.

Sample Size. We calculate power for sample sizes of 25,000, 35,000, and 45,000.

Age Distribution. As above.

Loss to Follow-up/Competing Risk. As above.

Drop-Out and Drop-In. These rates should be considerably lower than for hormone replacement. However we assume, conservatively, that they are the same.

Lag. As for Hormone Replacement for Fractures, and 10 years for Colorectal Cancer.

Anticipated Effect. Observational studies suggest the same level of effect on the incidence of fractures as ERT. We therefore adopt the same effects as for hormone replacement. We calculate power for a reduction of 18-22% in the incidence of colorectal cancer.

Incidence Rates. As above.
Statistical Power.

(i) Calcium/Vitamin D versus Control: Hip Fractures

<table>
<thead>
<tr>
<th>Average Follow-up (y)</th>
<th>Intervention effect (%)</th>
<th>Control</th>
<th>Calcium/Vitamin D</th>
<th>Power (%)</th>
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(ii) Calcium/Vitamin D versus Control: Combined Fractures

(The percentages of cases and powers in this table are based upon our original age distribution assumptions, i.e., 50-59, 60-69, 70-79 year olds enter in the ratio 2.2.1 and hence are conservative estimates.)

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<tr>
<th>Average Follow-up (y)</th>
<th>Intervention effect (%)</th>
<th>Control</th>
<th>Calcium/Vitamin D</th>
<th>Power (%)</th>
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(iii) Calcium/Vitamin D versus Control: Colorectal Cancer

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Conclusion

From these power calculations we propose a trial with an average nine years follow-up and the following sample size:

(A) For the dietary intervention component, 48,000 women
(B) For the hormone replacement component, 25,000 women
(C) For the calcium/vitamin D component, 45,000 women.

These sample sizes provide good power for all the main hypotheses: Diet versus Breast Cancer (86% for a 14% reduction), Diet versus Colorectal Cancer (90% for a 20% reduction), Hormone Replacement versus Coronary Heart Disease (91-92% for a 30% reduction), Calcium/Vitamin D versus Fractures (97% for a 25% reduction in Hip Fractures) and good power also for some secondary hypotheses: Diet versus Coronary Heart Disease (86% for a 14% reduction), Hormone Replacement versus Fractures (85-87% for a 25% reduction in Hip Fractures) and Calcium versus Colorectal Cancer (85% for a 20% reduction).

There is 61% power for picking up a 30% increase in breast cancer risk from hormone replacement therapy should it exist, and a 33% possibility of detecting even a 20% increase. A further five years follow-up of women in the hormone replacement component is planned to increase the power in monitoring for this potential adverse effect. The power for detecting a 30% increase after 14 years average follow-up is 91-92%, and for a 20% increase is 60-62%.

According to our estimate that 21% of the 48,000 women participating in the dietary component will also participate in the hormone component, the total number of women anticipated in the trial will be 63,000.

2. OBSERVATIONAL STUDY

There are a number of factors to be considered in describing the power of the Observational Study to elucidate relationships between baseline measurements and subsequent disease risk, as well as relationships between changes in measurements from baseline and three years and subsequent disease risk. These include:

(i) Incidence rates for diseases of interest - as described in Section 2 of the protocol and in the earlier part of this Appendix, incidence rates are quite variable for the diseases of interest in the WHI. For example, the annual incidence rates for some key outcome categories, assuming that 10%, 20%, 45% and 25% of OS enrollees are in the age categories 50-54, 55-59, 60-69 and 70-79, respectively, are approximately 5.0 for coronary heart disease, 3.0 for breast cancer, 1.8 for colorectal cancer, and 4.0 for hip fractures, per 1,000 enrollees. Naturally, it will be desirable to use the OS for studies of less common outcomes, including specific cancers (e.g., endometrial, ovarian), selected vascular diseases (e.g., hemorrhagic stroke, deep vein thrombosis), and fractures at specific, less common sites. The annual incidence rates for such diseases may be less than 1.0, or even less than 0.5 per thousand. Hence, generic power calculations have been conducted for annual incidence rates of 0.1, 0.5, 1.0, 2.0 and 5.0 per thousand.

(ii) Follow-up durations - it is particularly important that the OS begin to generate research reports as early as possible during the course of the WHI program. Hence, power calculations have been performed for average cohort follow-up durations of 3, 6 and 9 years. The three-year power calculations, for example, can be applied to studies of baseline characteristics when the average follow-up time for the OS (or a subset thereof) is three years, or to the study of changes in characteristics between baseline and three years when the average follow-up time is six years, since outcomes prior to a participants three-year visit do not contribute to these latter analyses.

(iii) Sample size and subset analyses - power calculations based on the entire intended OS sample size of 100,000 are perhaps of most interest, but there is also considerable interest in analyses based on various OS subsets. For example, separate analyses for each decade of baseline age would require power calculations for
cohorts in the range of 25,000 to 45,000 subjects in view of the anticipated OS age distribution mentioned above. Similarly, the anticipated OS enrollment by racial/ethnic subgroup is as follows: non-Hispanic, white - 80,000; African American - 10,000; Hispanic - 6,000; Native American - 2,000; Asian Pacific Islander - 2,000. Other analyses may be restricted to OS women for whom a certain measurement falls within selected percentiles relative to the overall OS distribution. For example, an important goal of the OS pertains to further elucidation of the relationship between a low-blood cholesterol or a recent reduction in blood cholesterol and subsequent mortality. Analyses restricted to the approximately 40,000 women with baseline blood cholesterol in the lowest two quintiles may provide particular insights. For example, one will be able to compare the mortality rates of women with blood cholesterol measurements in the lowest quintile at both baseline and three years, to those whose cholesterol has dropped from the second lowest to the lowest quintile between baseline and their three-year visit.

Power calculations were conducted for sample sizes of 100,000; 80,000; 40,000; 20,000; 10,000; 6,000 and 2,000 in order to explore the relationship between power and subset sample size.

(iv) Distribution of exposures or characteristics - the characteristics or exposures to be related to disease risk may involve a variety of types of measurements, including binary, categorical and continuous variates, and mixtures thereof. However, most analyses, especially exploratory analyses, will involve the comparison of disease risks between two groups of OS members distinguished by their values of one or more characteristics. For example, one may compare current ERT users to non-users; or may compare women in the highest quintile of baseline blood cholesterol, or baseline dietary fat intake, to corresponding women in the lowest quintile. Hence, power calculations were conducted as a function of the frequency of a binary characteristic or exposure, with 'exposure' frequencies taking values of 0.5%, 1%, 10%, 30% and 50%. For example, to obtain the power of a comparison of the highest quintile to lowest quintile of blood cholesterol in the entire OS cohort one can examine the following tables for a sample size of 40,000 (the highest and lowest quintiles combined) with an exposure frequency of 50% (one-half of the 40,000 women will be in the highest quintile).

(v) Odds ratio - there are a range of odds ratio values that may be pertinent to associations of interest in the OS. Odds ratios of 2.0 or above may have particular public health importance, particularly if the characteristic under study is fairly common. Note that odds ratios and relative risks are virtually identical for the range of disease incidence rates mentioned above.

In considering the range of odds ratios pertinent to the OS, it is important to consider the regression attenuation that arises from random measurement error in the assessment of characteristics of interest. For example, the slope of the regression line that relates the log-disease incidence (e.g., log-coronary heart disease incidence) to a single blood cholesterol measurement are attenuated by a factor of about 2/3 on the basis of such random measurement error, so that an odds ratio of 2 is reduced to \( \exp\{2/3 \log 2\} = 1.59 \) by (non-differential) measurement error. The corresponding attenuation factor for estimates of nutrient intakes based on a food frequency instrument may be in the vicinity of 1/3 depending upon the nutrient and assessment instrument, so that an odds ratio of 2 is attenuated to about 1.26 based on random measurement error for such exposures. Hence, to explore the power of the OS under various configurations of association strength and regression dilution, power calculations have been conducted for odds ratios of 1.25, 1.50, 1.75, 2.0 and 3.0.

(vi) Sampling procedures, and confounding factor control - the power calculations that follow assume the characteristic or exposure under study to be available on all pertinent study subjects, and uses the asymptotic distribution of a simple odds ratio statistic. However, many of the OS analyses will use time-matched case-control, or stratified case-cohort, sampling to reduce the number of women for whom expensive analysis of stored specimens or complicated questionnaires must be carried out. The efficiency of a time-matched case-control analysis as compared to a full cohort analysis is approximately \( k(k+1)^{-1} \), where \( k \) is the number of controls matched to each case. Hence, a one-to-\( k \) matched case-control study based on a cohort of size \( n \) has power approximately equal to a full-cohort analyses based on a sample of size \( nk(k+1)^{-1} \).
The following array can be used to approximately convert full-cohort sample size to corresponding \(1:k\) matched case-control effective sample size for \(k = 1, 2, 3, 5\).

**Effective Cohort Sizes for 1:k Matched Case-Control Analysis**

**Full Cohort Sample Sizes**

<table>
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<th>Controls (k) per case</th>
<th>Controls (k) per case</th>
</tr>
</thead>
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<tr>
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<td>3</td>
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<tr>
<td>5</td>
<td>83,333</td>
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</table>

Most OS analyses will also make provision, via stratification, matching or regression modeling, for factors that have potential to confound the association under study. Such control is essential to accurate odds ratio, or relative risk estimation, and corresponding more complex tests will tend to have reduced power, relative to the corresponding test in which confounding control is unnecessary. However, the power reduction is likely to be quite minor in most OS analyses so that no provision for confounding control is included in the OS power calculations.

The following tables present the power calculations for the configurations listed above, with the exception that combinations of factors for which the power is less than 50% are omitted for brevity.

Table 1 provides power calculations for analyses based on the entire cohort of size 100,000. For example, from the lower section of Table 1 one can see that the power for detecting a relative risk of 1.5 associated with a characteristic present in 50% of the cohort is 72% after an average 3 years of follow-up, and 95% after an average of 6 years of follow-up, even for a disease with annual disease incidence of .05% per year, which is close to that for cancers of the endometrium and ovary, for example. An odds ratio of about 1.5 for above versus below the median fat intake can be projected from international correlation analyses for endometrial and ovarian cancer, after accounting for regression dilution. Similarly, an odds ratio of 2.0 associated with a characteristic arising in only 1% of the cohort can be detected with adequate power for diseases as common as breast cancer or hip fractures, and can be detected with power 83% after an average of only 3 years of follow-up for a disease such as coronary heart disease having an annual incidence of about .5% per year or greater.

Table 2 presents corresponding analyses for a subsample of the OS of size 80,000. As such, it gives projected power for OS analyses restricted to non-Hispanic white women or for analyses on the entire 100,000 women based on a case-control analysis with four controls per case. Note that the power reductions in moving from Table 1 to Table 2 tend to be fairly modest. Consider two specific associations which could be examined in the OS: About 5-10% of postmenopausal women have serum ferritin concentrations about 200µg/liter. A study in Finnish men indicates that such elevated concentrations may convey an odds ratio of about 2.2 for coronary heart disease. Table 2 indicates that a 1:4 matched case-control study in the OS cohort would have power in the vicinity of 90% for detecting an elevated serum ferritin and CHD association, even if the odds ratio is as small as 1.25. As a second example, suppose that a particular occupational group, such as a lab technician or hair dresser, constitutes only .5% of the OS cohort. Table 2 indicates that a 1:4 matched case-control study based on the OS would have power of at least 76% by an average 6 years of follow-up, or 94% by an average of 9 years of follow-up, for detecting an odds ratio of 3.0 for a disease such as breast cancer with an annual incidence rate of 2 per 1,000 or greater. In fact, a British Columbia study suggests a breast cancer odds ratio of about 4 for these occupational groups.
Table 3 shows corresponding power calculations for a subsample of size 40,000, as corresponds, for example, to studies restricted to extreme quintiles of a measured characteristic. A relative risk as small as 1.50 between extreme quintiles of a nutrient intake variable, for example, will be able to be detected with power 90% or greater by an average of three years of follow-up for diseases such as breast cancer, hip fractures or coronary heart disease having an annual incidence of at least .2%. Such an odds ratio can be detected with a power of 80% for a much rarer disease with incidence of .05% per year, by an average of 9 years of follow-up. Table 4 gives corresponding power calculations for a subsample of size 20,000. These entries are pertinent to full-cohort analyses restricted to the subset of women in the age range 70-79 at baseline, and to subsamples of size 40,000 under 1:1 matched case-control sampling.

Table 5 gives power calculations for a subsample of size 10,000 - the anticipated number of African Americans in the OS. Note that there will be adequate power to detect an odds ratio of 1.50 or larger for diseases of annual incidence of .2% or larger, provided the characteristics or exposure arises in about half of the women in the subsample. Table 6 gives power calculations for a subsample of size 6,000 - the anticipated number of Hispanic American women in the OS. There is adequate power to detect an odds ratio of 1.75 or larger for diseases of annual incidence of .2% per year or larger, again provided the characteristic arises in about 50% of the subsample. Finally, Table 7 gives power calculations for a subsample of size 2,000 - the anticipated number of Native American, and of Asian and Pacific Islander American women in the OS. Odds ratios of 3.0 will be able to be detected for diseases having annual incidence of about .2% per year or greater, provided the characteristic under study arises in about 50% of the subsample.

Acknowledgment: The CT power calculations given in Appendix III Section 1 were developed by Larry Freedman, Nancy Geller, Ed Lakatos, Victor Kipnis, and David Pee.
### Appendix III, Table 1.
**OS Power Calculations for a Cohort Size of 100,000**

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<td>Odds</td>
<td>Odds</td>
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<td>0.66</td>
<td>0.79</td>
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<tr>
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### Appendix III, Table 4.

**OS Power Calculations for a Subsample Size of 20,000**

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<td>Odds</td>
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OS Power Calculations for a Subsample Size of 10,000

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### Appendix III, Table 6.
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### Appendix III, Table 7.
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<tr>
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<td>0.80</td>
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<tr>
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APPENDIX IV

Informed Consent Guidelines

1. INTRODUCTION

This Appendix consists of model informed consent documents for use at the Clinical Centers. The CC's may modify the model consent forms only for language and clarification, plus additions required by their own Institutional Review Board. CC's may not delete any topics covered in the model forms. All informed consent documents will be centrally reviewed and approved by the Project Office prior to their use in the WHI program.

The model informed consent documents given here consist of (i) initial consent to take part in the WHI, (ii) consent form for the Hormone Replacement Therapy part of the WHI Clinical Trial, (iii) consent form for the Dietary Change part of the WHI Clinical Trial, (iv) consent form for the calcium/vitamin D part of the WHI Clinical Trial, and (v) consent form for the Observational Study part of the WHI.
2. INITIAL CONSENT TO TAKE PART IN THE WOMEN'S HEALTH INITIATIVE

[Clinical Center]
[Principal Investigator]
[24-Hour Contact]

Consent to Participate in First Screening Clinic Visit

Reason for the Study

There are many questions about the best ways to prevent some of the major diseases that women may have as they get older. The WHI has been set up to study some of these major diseases; namely, heart disease, breast cancer, colon and rectum cancer, and bone fractures (breaks) due to weakened bones (osteoporosis).

Heart disease is the most common cause of death in women aged 50 to 79. About 1 out of every 8 women in the U.S. will get breast cancer in her lifetime. Cancers of the colon and rectum are the third most common major cancer. Hip fractures occur commonly in older women; about 1 out of 6 women aged 50 and over will have a hip fracture in her lifetime.

The goal of the WHI is to study ways to decrease women's chances of getting these diseases, and to improve their quality and length of life.

Purpose

The Women's Health Initiative (WHI), funded by the National Institutes of Health, is a study of ways to prevent breast cancer, colon and rectum cancer, heart disease, and fractures. About 160,000 women from approximately 45 centers in the United States will take part in this study. The WHI will investigate the possibility of improving the health of women aged 50 to 79. Women will be followed in the study for 8-12 years. (How long you are in the study will depend on when you join. Women who enter the study in 1993 will be followed for up to 12 years, while women who join later will be followed for less time.)
Study Parts

There are two major parts to the WHI, a Clinical Trial and an Observational Study. The Clinical Trial will try to find out if there is a benefit to taking hormone replacement therapy, or to changing one’s diet to a low-fat, high fiber, high fruit and vegetable eating pattern, or to taking daily calcium and vitamin D. By joining this part of the study, you may help to answer the question of whether these various changes will improve health. You may choose to take part in 1, 2, or 3 parts of the Clinical Trial. The Observational Study part of the WHI will include women who do not join the Clinical Trial, but who are examined and followed for 8–12 years to provide more information about women’s health, and to learn more about causes of disease in older women.

Procedures

Activities of the First Clinic Visit

The results of your first clinic visit will help to determine if you are able to join in the WHI. All of the activities are to see if you will be able to join either the Hormone Replacement part or the Dietary Change part of the study, or both. The WHI staff will be able to give you an idea of whether you might be able to join toward the end of the visit.

At this visit:

- The questionnaires you completed before the visit will be reviewed, or you will complete questionnaires in the clinic.
- Clinic staff will record the names and dosages of medications you are currently taking.
- Your pulse will be measured.
- Your blood pressure will be measured.
- Your height and weight will be measured.
- The distance around your hips and waist will be measured.
- You will be given some questionnaires about your personal qualities and lifestyle to complete, either in the clinic or at home.
- You will be briefly interviewed about how you are feeling, and about female hormones you may have used in the past.
- Physical strength measures will be made twice:
  1) **Grip Strength:** You will be asked to squeeze 2 handles together with your hand, which will measure your hand strength.
  2) **Chair Stand:** You will be asked to stand several times from a sitting position on a chair. This will measure the strength of your leg muscles.
  3) **Time to Walk 18 Feet:** You will be asked to walk a distance of 18 feet and a Clinic staff member will measure how long it takes you to walk that far. This will measure your walking strength.
- About 3 tablespoons of blood will be drawn for laboratory tests. You will need to take nothing by mouth except water and your regular medications for 12 hours before the blood test.

Osteoporosis Substudy Clinical Centers only:

- You will be asked to provide a urine sample (at least 1 tablespoon) which will be stored for laboratory tests at a later date.
- Your bone density will be measured in your hip, spine and in your whole body. The test is painless and takes about 30 minutes.

All of the tests of this first clinic visit should take approximately 2–4 hours to complete.

You will be told if you have an abnormal blood pressure, and if you have abnormal blood test results for anemia done through your Clinical Center, and if you want, your doctor will also be told. Some of the blood drawn will be stored for tests at a later date. These blood tests will not replace your usual medical care (for example, your cholesterol level will not be reported to you or your doctor). [Clinics may change per their procedure.]

Risks

Blood pressure, urine sample, height, weight, hip, waist, and physical strength measures:

There should be no risks with these tests.

Blood draw:

There is a small risk with drawing blood. You may feel a little discomfort as the needle goes through the skin. There may be some bruising at the site where blood is drawn. Pressing hard on the spot for 1 or 2 minutes after the needle is removed will help to prevent a bruise. On very rare occasions, the arm may become infected.

Bone density measurement (Osteoporosis Substudy Clinical Centers only):

The bone density measurement involves a small amount of radiation. Small amounts of radiation may have potential harm, but the risk is difficult to measure and is probably very small. The total radiation from the bone density measurements is less than 1% of the natural background radiation a person receives living in a typical American community for one year. It is less than half the radiation from a round-trip airline flight from the east to the west coast.

Benefits

By taking part in this study, you will help increase scientific knowledge about the prevention of breast cancer, colon and rectum cancer, heart disease, and fractures (broken bones) in women, and ways to prevent disease and promote the health of women from all backgrounds and lifestyles.

Alternate Treatments
WHI Protocol - Appendices

There are no treatments in the first screening visit, and therefore no alternate treatments.

Costs

The first clinic visit and laboratory test will cost you nothing other than your time and travel costs. You will not be paid for being in the study. It is unlikely that any unfavorable effects will occur as a result of your completing the first visit. However, any problems that might occur during the course of this study would need to be covered by your medical insurance [or clinic inserts their alternate source of medical care for participants without medical insurance]. The Clinical Center will not pay you for any such medical conditions you may develop. You will not be reimbursed for any wages lost from taking part in this study.

Confidentiality

All of your study records will be kept strictly confidential as provided by law. Your personal identity will not be revealed in any publication or release of results. Only WHI staff at the [name] Clinical Center and the Clinical Coordinating Center at the Fred Hutchinson Cancer Research Center in Seattle, Washington will have access to your personal data (i.e. study number, name, social security number and address) for the purpose of study wide mailings as well as maintaining and updating your study records. The Food and Drug Administration will be allowed to examine your study records for safety reasons.

Right to Withdraw

Your decision to join in this study is voluntary. You may drop out at any time, for any reason, without notice. However, we hope you will take part for the entire time of the study because all of the information is needed to be able to get correct answers to our questions. If you decide to leave the study, we hope to be able to contact you yearly to see how you are doing.

Voluntary Consent

If you have any questions about any part of the study or your rights as a volunteer, a WHI staff person will be on hand to answer them before you sign this consent form. Also, if you have any questions about your rights as a participant in this study, please call ______________________ in the Institutional Review Board Office of [Clinical Center] at [phone number]. If you have any questions at any time, you may call: [Clinical Center name and phone number] or any of the investigators listed at the head of this statement. Before you sign this form, please ask any questions on any part of this study that are unclear to you.
Other Information

Your joining is important to the success of this study. Unless many volunteers such as yourself agree to join, this type of study will not be possible. If, as a result, we learn that a low fat diet reduces the risk of breast cancer, colon or rectum cancer, or coronary heart disease, or that hormone replacement therapy reduces the risk of heart disease or broken bones, many women may benefit.

We have tried to make joining the study as easy as possible for you. Please let us know if there are ways you think it would be easier for you and others to join this study.

In order for this study to be valid, you should not join other health studies where you would be placed by chance into a group.

Whether or not you choose to join this study will not affect your personal medical care or your medical insurance coverage.

An independent committee of experts in medical research will be reviewing study results on a routine basis to consider whether any changes should be made in the study to assure the safety of the treatments and to evaluate the overall risks and benefits of each treatment.

Investigator's Statement

I have provided an explanation of the above research program. The subject was given an opportunity to discuss this procedures, including possible alternatives, and to ask any additional questions. A signed copy of the consent form has been given to the subject.

______________________________  _______________________
Signature of Principal Investigator or Designee             Date

PARTICIPANT STATEMENT

I have read the WHI study description and I voluntarily consent to take part in this study. I understand that I may drop out of the study at any time. I have had a chance to ask questions and have had my questions answered. I understand that I may ask further questions at any time and that I will receive a copy of this signed consent form for my records.

______________________________  _______________________
Signature of Participant             Date
3. CONSENT FORM FOR THE HORMONE REPLACEMENT THERAPY PART OF THE WOMEN'S HEALTH INITIATIVE CLINICAL TRIAL

[Clinical Center]

[Principal Investigator]

[24-Hour Contact]

This form is to ask you to think about joining the Hormone Replacement Therapy part of the Women's Health Initiative (WHI) Clinical Trial. If you are able, you may choose to be in this part of the study. You may also be able to be in the Dietary Change part of the Clinical Trial, whether or not you choose to enter the Hormone Replacement Therapy part. We expect thousands of woman across the United States to be part of this study.

Reasons for the Hormone Replacement Therapy Part of the WHI

There are many questions about the best ways to prevent some of the major diseases that women many have as they get older. The WHI has been set up to study some of these major diseases; namely, heart disease, breast cancer, colon and rectum cancer, and bone fractures (breaks) due to weakened bones (osteoporosis).

Heart disease is the most common cause of death in women aged 50 to 79. About 1 out of every 8 women in the U.S. will get breast cancer in her lifetime. Cancers of the colon and rectum are the third most common cancer. Hip fractures occur commonly in older women; about 1 out of 6 women aged 50 and over will have a hip fracture in her lifetime.

The goal of the WHI is to study ways to decrease women's chances of getting these diseases, and to improve their quality and length of life.

As women go through menopause ("change of life"), their bodies stop making some female hormones. These hormones are thought to protect against heart disease and fractures. Past studies have suggested that taking female hormone pills may decrease the chances of getting heart disease or fractures. However, it is not clear from those studies whether women who take female hormones may already be healthier than those who don't, or whether the hormones themselves protect against heart disease or fractures. The WHI is specially set up to find out if the female hormone pills themselves improve women's health by protecting against these diseases.

Two ways of taking hormone therapy will be studied. The first way is to give estrogen by itself. This is the way hormones used to be given all the time. Therefore, most of what we know about the possible benefits of hormone therapy in preventing heart attacks and bone fractures comes from studies in which women took only estrogen.

In the past few years, doctors have commonly given a second hormone to women who have not had their uterus (womb) removed. This is because there is an increased chance of cancer of the endometrium (lining of the uterus) in women who take estrogen only. The second hormone, progesterone, prevents this increased chance of cancer of the endometrium. However, it may be that the progesterone hormone takes away from the good effects of estrogen in reducing heart attacks. Because heart attacks are much more common than endometrial cancer, this would be a problem.

Doctors now prescribe both these ways of taking hormones; some women are given estrogen by itself, whereas other women are given estrogen and progesterone. (Estrogen alone can be given to a woman with a uterus if regular tests of the lining of the uterus—called "endometrial aspirations" are done to look for early signs of cancer or "pre" cancers.) We do not know which of these ways is best in terms of overall risks and benefits, and
so another purpose of the Hormone Replacement Therapy part of the study is to find out which is best: no hormones at all, estrogen only or estrogen and progesterone.

**Purpose**

The main purpose of the Hormone Replacement Therapy (HRT) part of the WHI Clinical Trial is to see if taking 1 of 2 different female hormone pills will improve women's health by lowering the risk of heart disease, hip fractures, and other bone fractures.

**Procedures**

If you decide to join in the HRT, you will be asked to fill out some health forms and have some tests to see if you are able to join the study. These tests will include:

- mammogram
- pelvic exam and Pap smear
- tests of your uterus

(If you have had a mammogram, Pap smear, or tests of the uterus in the past year, you may not need to have these tests repeated before entering the study.) These tests are described in more detail below.

If you are found to be able to join the HRT part, and want to join, you will be placed by chance into 1 of 3 groups, depending on whether you have had your uterus removed.

If you have **NOT** had your uterus removed, you will be placed by chance into 1 of the following 3 groups:

1) A group given pills of Estrogen alone;
2) A group given pills of Estrogen + Progesterone combined; or
3) A group given inactive pills (a placebo, like "sugar pills").

The chance of being placed in group 2, or of being placed in group 1, is slightly higher than of being placed in group 3.

If you **HAVE** had your uterus removed, you will be placed by chance into 1 of the following 2 groups:

1) A group given pills of Estrogen alone, or
2) A group given inactive pills (a placebo, like "sugar pills").

The chance of being placed in group 2 is slightly higher than that of being placed in group 1.

The estrogen to be used is Conjugated Equine Estrogen .625 mg daily. The progesterone to be used is Medroxyprogesterone 2.5 mg daily. The types and strengths of estrogen and progesterone to be used in this study have been used for several years in hundreds of thousands of women in the U.S. These are not considered experimental medications.

Your placement into these groups will be by chance and will be done by the computer. None of the WHI Clinical staff or doctors will know to what group you have been assigned. You will also not know whether your study pills are estrogen, or estrogen + progesterone, or inactive pills (a placebo, like "sugar pills").
One study pill will be taken each day, by mouth. While you are in the study, you will not be able to take any additional female hormones other than those prescribed by WHI clinic doctors for symptoms or for bleeding from your vagina.

If you join in the HRT part of the study, you will be asked to visit the clinic every 6 months for 8–12 years. (The length of time you will be in the study depends on the year you join. For example, women joining in 1993 will be followed for up to 12 years, while women joining in 1997 will be followed for about 8 years.) You will also be asked to phone the clinic if you have problems and to keep a diary of special problems and vaginal bleeding while you are taking the study pills. In the beginning years of the study, clinic staff may call you between visits to make sure you are not having any problems.

The amount of time asked of you to join in the HRT part of the study will be about:

<table>
<thead>
<tr>
<th>Activity</th>
<th>Total Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 or more Screening Visits</td>
<td>4 to 8 hours, plus travel to clinic</td>
</tr>
<tr>
<td>Writing in your Bleeding Diary (during the 1st year) and taking study pills</td>
<td>Less than 5 minutes/day</td>
</tr>
<tr>
<td>Clinic visits: Every 6 months</td>
<td>3 hours/year, plus travel to clinic</td>
</tr>
<tr>
<td>Completing questionnaires before or at each clinic visit</td>
<td>2 hours/year</td>
</tr>
<tr>
<td>Talking with Clinic Staff by phone between clinic visits</td>
<td>½ hour/year</td>
</tr>
</tbody>
</table>

If you decide to join the Dietary Change part of the study as well as the HRT part, you may be asked to spend an additional 30 hours in the first year and 8 hours per year throughout the rest of the study.

Description of Procedures During HRT Study

Yearly Visits

During the 8–12 years you are in the HRT study, you will have clinic visits every 6 months. At each yearly visit you will have the following activities:

- Your Symptom & Bleeding Diary will be reviewed.
- Your remaining study pills will be collected and you will be given a new bottle of pills.
- The questionnaire you completed before or at the clinic visit will be reviewed by the clinic staff.
- Clinic staff will record the names and dosages of any medications you are currently taking.
- Your pulse will be measured.
- Your blood pressure will be measured.
- Your height and weight will be measured.
The distance around your hips and waist will be measured.

Physical strength measures will be made twice:

1) **Grip Strength:** You will be asked to squeeze 2 handles together with your hand, to measure your hand strength.

2) **Chair Stand:** You will be asked to stand several times from a sitting position on a chair. This will measure the strength of your leg muscles.

3) **Time to Walk 18 Feet:** You will be asked to walk a distance of 18 feet and a Clinic staff member will measure how long it takes you to walk that far. This will measure your walking strength.

You may be given some questionnaires about your personal qualities and lifestyle to complete either in the clinic or at home.

You may be briefly interviewed about how you are feeling and about female hormones you may have used in the past.

You will be given a clinical breast exam by a clinic doctor or nurse and will be taught to examine your own breasts.

After 1 year, and for some women, every 3 years, about 3 tablespoons of blood will be drawn for laboratory tests. You will not be able to eat or drink anything but water and your regular medications for 12 hours prior to the blood test.

You will be given a pelvic exam and Pap smear before being started on study pills and yearly after that if you have not had your uterus removed. If you have not had your uterus removed, you will also be given a test of the lining of your uterus (endometrial aspiration) before you start the study pills. You may be given an endometrial test once a year. (If you have had a Pap smear or an endometrial aspiration within the past year, you may not need to have these tests repeated before entering the study.)

The pelvic exam and Pap smear will be the same as those done by gynecologists or other doctors you may have seen. During this exam, the clinic doctors (or nurse practitioner or physician's assistant) will insert a plastic or metal instrument in your vagina so that your cervix can be seen, take scrapings from your cervix for the Pap smear, and do an examination of your uterus and ovaries with her/his gloved hands.

Testing the lining of the uterus (endometrium) includes taking a small piece of the lining of your uterus. This is called an endometrial aspiration. After inserting an instrument into your vagina, the doctor (or nurse practitioner or physician assistant) will insert a thin tube through your cervix and take samples from the lining of your uterus. You may feel cramping of your uterus during and after the test, which can be treated with medicine. If you find the test uncomfortable, a pain medication can be applied around your cervix.

If it is not possible to do an endometrial aspiration, an ultrasound exam of your uterus will be done. In this test, a thin probe (about the size of a tampon) is put into your vagina, and a sound-
wave picture of your uterus is taken. This test should be no more uncomfortable than a pelvic exam. If further investigation is needed, you will be referred to your usual health care provider.

- You will be required to have a mammogram each year throughout the trial.
- You will be given an electrocardiogram heart examination (ECG) every 3 years. This consists of placing wires on your chest while you are lying down, and recording your heart's activity. If you smoke, you will not be able to have a cigarette for 2 hours prior to the test.

For Osteoporosis Substudy Clinical Centers only:

- You will be asked to provide a urine sample (at least 1 tablespoon) which will be stored for laboratory tests at a later date.
- At the first yearly visit and at the 3rd, 6th and 9th yearly visit, your bone density will be measured in your hip, spine and in your whole body. The test is painless and takes about 30 minutes.

Abnormal findings of the following tests will be told to you or your doctor or clinic: blood pressure, blood test for anemia done at your Clinical Center; mammogram, pelvic exam, Pap smear, endometrial aspiration, uterine ultrasound and ECG. Some abnormal findings may exclude you from joining the HRT part of the study. If this should occur, the reasons why you are not able to join will be fully explained by the Clinic staff.

Some of the blood drawn will be stored for tests at a later date. These blood tests will not replace your usual medical care (for example, your cholesterol level will not be reported to you or your doctor). [Clinics may change per their procedures.]

Six-month visits

At the 6-month visits the following activities will occur:

- Your Symptom & Bleeding Diary will be reviewed.
- Your remaining study pills will be collected and you will be given a new bottle of pills.
- The questionnaire you completed before or at the clinic visit will be reviewed by the clinic staff.
- Clinic staff will record the names and dosages of any medications you are currently taking.

Risks

Hormone Replacement Therapy

The use of estrogen pills may in rare cases cause cancer of the lining of the uterus (endometrium), and more rarely, it could possibly slightly increase the risk of breast cancer, a blood clot in the legs or lung, or gallstones. In other studies of women who have used estrogens but have not had routine tests of their uterus, the risk of cancer increased with more years of use and even continued after they stopped taking estrogens. In this study, if the routine tests find changes that may lead to cancer, your treatment will be changed. The addition of progesterone
may decrease the risk of cancer of the lining of the uterus, but we are not sure about how it may affect the risk of heart disease or breast cancer. The use of estrogen or progesterone could cause bleeding from the vagina, water bloating, weight gain, breast swelling and tenderness, abdominal bloating, nausea, headache, irritability, mild depression, mild increased skin color and increased vaginal discharge.

If you experience vaginal bleeding or spotting, it may require an extra endometrial test and possibly treatment with changed doses of female hormones or even stopping study pills. If bleeding continues, or if the endometrial test is abnormal, you may need more tests, including a D & C. These further tests will need to be done by your doctor, and will not be done by WHI doctors. Other symptoms can be managed in several ways, but may require some change of medication dosage, or even stopping study pills. Even if you have to stop taking study pills, you will still come to clinic visits and will be followed to the end of the study.

A more serious possible side effect is a change in the lining of the uterus that would require that you stop taking the study medications or be treated with changed doses of female hormones. In rare cases, cancer of the uterus may develop in women on hormones. In very rare cases, cancer of the uterus may also develop in women who are not on hormones. Surgery to remove the uterus could be necessary for uterus cancer, for very severe vaginal bleeding, or for other disease of the uterus.

**Pulse; blood pressure; height, weight, hip, waist measures and physical strength; and clinical breast exams:**

There should be no risks with these activities.

**Blood draw**

There is a small risk with the process of drawing blood. You may feel a little discomfort as the needle goes through the skin. There may be some bruising of the site where blood is drawn. Pressing hard on the spot for 1 or 2 minutes after the needle is removed will help to prevent a bruise. Very rarely, the arm may become infected.

**Pelvic exam and Pap smear**

There should be no risks with this examination, but some women may find it unpleasant or uncomfortable.

**Evaluation of the lining of the uterus**

The risks of this procedure are minimal but in rare cases include tearing of the uterus, bleeding from the vagina, or an allergic reaction to the pain killer injection.

**Ultrasound exam of uterus**

This procedure should not be associated with any risk, but some women may find it unpleasant or uncomfortable, as with the pelvic examination.
Mammogram

A mammogram involves the use of radiation which may slightly increase the risk of developing breast cancer. Scientists of the WHI and the National Cancer Institute believe, however, that this small risk is outweighed by the benefit of finding of breast cancer early, and recommend yearly screening for all women in your age group.

ECG

There should be no risk with this procedure.

Bone Density Measurement (Osteoporosis Substudy Clinical Centers only)

The bone density measurement involves a small amount of radiation. Small amounts of radiation may have potential harm, but the risk is difficult to measure and is probably very small. The total radiation dose from the bone density measurements is less than 5% of the natural background radiation a person receives living in a typical American community for one year. It is about the same as the radiation from 3 coast-to-coast airline flights from the east to the west coast.

Benefits

By taking part in this study, you will help further scientific knowledge about the prevention of heart disease and broken bones in women.

Alternate Treatments

Prevention of heart disease

Some studies have suggested that taking regular aspirin may decrease heart attack risk. At the present time, the standard treatment would be routine physical exams, controlling blood cholesterol, blood pressure, and weight, and keeping a healthy lifestyle including regular exercise, a moderate diet and not smoking cigarettes.

Prevention of fractures due to weakened bones

Some treatments, such as estrogens, calcium and vitamin D supplements, Tamoxifen, and some other treatments to prevent weakened bones are being tested for their ability to prevent broken bones. At the present time, the standard treatment would be to have routine physical exams, engage in regular physical activity, and maintain a diet that includes adequate amounts of calcium and vitamin D.

Costs

The tests, medications, and visits that are part of this study will cost you nothing other than your time and travel cost. The clinic visits, ECGs, laboratory tests and study medications are provided free of charge by the study. The mammogram will be provided at no cost to you. The cost of the mammogram may be charged to your insurance. If you do not have insurance, or if your insurance will not pay the costs, any remaining costs of the
mammogram will be paid for by the study. You will not be paid for being in the study. [Note: Clinical Centers may modify this section based on their contract regarding charging 3rd-party payers.]

Any problems that might occur during the course of this study would need to be covered by your medical insurance [or clinic inserts their alternate source of medical care for participants without medical insurance]. The Clinical Center will not pay for any such medical conditions you may develop. You will not be reimbursed for any wages lost from taking part in this study.

Confidentiality

All of your study records will be kept strictly confidential as provided by law. Your personal identity will not be revealed in any publication or release of results. Only WHI staff at the [name] Clinical Center and the Clinical Coordinating Center at the Fred Hutchinson Cancer Research Center in Seattle, Washington, will have access to your personal data (i.e. study number, name, social security number and address) for the purpose of study wide mailings as well as maintaining and updating your study records. The Food and Drug Administration will be allowed to examine your study records for safety reasons. Study records will be kept indefinitely for analysis and follow-up.

Right to Withdraw

Your decision to be in the study is voluntary. You may drop out at any time, for any reason, without notice. However, we hope that you will take part for the entire time of the study because all of this information is needed to be able to draw correct conclusions. If you decide to leave the study, we hope to be able to contact you yearly to see how you are doing. If you decide to leave the study it will not affect your regular medical care.

Voluntary Consent

If you have any questions about any part of the study or your rights as a volunteer, a WHI staff person will be on hand to answer them before you sign this consent form. Also, if you have any questions about your rights as a participant of this study, please call ______________ in the Institutional Review Board Office of [Clinical Center] at [phone number]. If you have any questions at any time, you may call: [Clinical Center name and phone number] or any of the investigators listed at the head of this statement. Before you sign this form, please ask any questions on any part of this study that are unclear to you.

Other Information

Your joining is important to the success of this study. Unless many volunteers such as yourself agree to join, this type of study will not be possible. If, as a result, we learn that hormone replacement therapy reduces the risk of heart disease or broken bones in women, many women may benefit.

We have tried to make joining the study as easy as possible for you. Please let us know if there are ways you think it would be easier for you and others to join this study.

In order for this study to be valid, you should not join other health studies where you would be placed by chance into a group.

A doctor, nurse, or physician assistant will review your health history and test results to make sure there is no medical reason why you should not join in the Hormone Replacement Therapy part of the WHI. If you agree to join, you will be asked for the name of your doctor or clinic, so that he or she can be told of your joining in the WHI.
If any study test suggests that a health problem needs further study, you will be sent back to your doctors or clinic, who will evaluate the need for further study. Copies of reports and hospital records of your doctor's follow-up may be requested by the WHI and become part of your study record at the [Clinical Center]. Whether or not you choose to join the Hormone Replacement Therapy Study will not affect your personal medical care or your medical insurance coverage.

An independent committee of experts in medical research will be reviewing study results on a routine basis to consider whether any changes should be made in the study to assure the safety of the treatments and to evaluate the overall risks and benefits of each treatment.

**Investigator's Statement**

I have provided an explanation of the above research program. The subject was given an opportunity to discuss this procedures, including possible alternatives, and to ask any additional questions. A signed copy of the consent form has been given to the subject.

______________________________  
Signature of Principal Investigator or Designee  
______________________________  
Date

**PARTICIPANT STATEMENT**

I have read the description of the Hormone Replacement Therapy part of the WHI. I voluntarily consent to join in this part of the study. I understand that I may drop out of the study at any time. I have had a chance to ask questions about the Hormone Replacement Therapy part of the Study. I understand that I may ask further questions at any time and that I will receive a copy of this signed consent form for my records.

______________________________  
Signature of Participant  
______________________________  
Date

______________________________  
Signature of Witness  
______________________________  
Date
4. CONSENT FORM FOR THE DIETARY CHANGE PART OF THE WOMEN'S HEALTH INITIATIVE CLINICAL TRIAL

[Clinical Center]
[Principal Investigator]
[24-Hour Contact]

This form asks you to think about joining in the Dietary Change part of the Women's Health Initiative (WHI) Clinical Trial. If you are able, you may choose to join in this part of the study. You may also be able to join in the Hormone Replacement Therapy part of the Clinical Trial, whether or not you choose to enter the Dietary Change part. We expect thousands of women across the U.S. to be part of this study.

Reasons for the Dietary Change Part of the WHI

There are many questions about the best ways to prevent some of the major diseases that women many have as they get older. The WHI has been set up to study some of these major diseases; namely, heart disease, breast cancer, colon and rectum cancer, and bone fractures (breaks) due to weakened bones (osteoporosis).

Heart disease is the most common cause of death in women aged 50 to 79. About 1 out of every 8 women in the U.S. will get breast cancer in her lifetime. Cancers of the colon and rectum are the third most common major cancer. Hip fractures occur commonly in older women; about 1 out of 6 women aged 50 and over will have a hip fracture in her lifetime.

The goal of the WHI is to study ways to decrease women's chances of getting these diseases, and to improve their quality and length of life.

Some past studies have found that having a diet that is high in fat may increase the chance of getting cancers of the breast, colon, or rectum, or of getting heart disease. Not all studies have found this, however. The WHI has been specially set up to include a very large number of women, with a low-fat, high fruits and vegetables dietary change program, so that we will have clear answers about whether following a low-fat diet will increase the quality and length of women's lives by decreasing women's chances of getting these cancers and heart disease.

Purpose

The main purpose of the Dietary Change (also called Dietary Modification – DM) part of the WHI Clinical Trial is to see if greatly reducing the amount of fat and increasing the amount of grains, fruits, and vegetables in the diet will reduce the risk of breast cancer, colon and rectum cancer, and heart disease in women, and increase the quality and length of life.

If you decide to join in the Dietary Change part, you will be asked to complete a Four Day Food Record to determine if you are still able to join this part of the study.

If you are found to be able to join the Dietary Change part, and want to join, you will be placed by chance into 1 of 2 groups:
1) A Dietary Change Group, where you will be taught ways to greatly reduce your daily dietary fat intake and to increase your intake of grains, fruits, and vegetables.

2) A Comparison Group, where no special dietary change teaching or effort will be required.

Your placement into one of these groups will occur by chance, and will be done by a computer, not by a WHI staff member. There will be a slightly greater chance of being assigned to the Comparison Group than to the Dietary Change Group.

Procedures

Dietary Change Group

If you are placed in the Dietary Change Group, you will be taught how to lower the fat in your diet to 20% of total calories and to increase your intake of grains, fruits, and vegetables. (In the average American diet, fat is 36% to 38% of total calories.)

You will be asked to come to group instructional sessions led by a nutritionist. At the beginning, the groups will meet once a week for 6 weeks, once every two weeks for the next 6 weeks, and once a month for 9 months. After the first year they will meet 3–4 times a year until the study ends in about 8–12 years. During these sessions, the nutritionist will help you learn how to plan and shop for low-fat foods and to prepare low fat meals. At times you will also be asked to keep careful records of the food you eat.

You will be asked to visit the clinic every 6 months and to phone the clinic if you have problems. You will spend about 40 to 45 hours of your time in the Dietary Change study during the first year, and from 20 to 25 hours a year after that until the study ends.

Comparison Group

If you are placed into the Comparison Group, you will not be asked to make any changes in what you normally eat. If you are in this group, you will spend less than 10 hours a year on the study.

Both Groups

The amount of time asked of you in the Dietary Change part will be about:

<table>
<thead>
<tr>
<th>Activity</th>
<th>Total Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Three or more Clinic visits at the beginning for enrollment</td>
<td>4–8 hours, plus travel to clinic</td>
</tr>
<tr>
<td>Clinic visits: Every 6 months</td>
<td>3 hours/year, plus travel to clinic</td>
</tr>
<tr>
<td>Completing questionnaires before (or at) each clinic visit</td>
<td>2 hours/year</td>
</tr>
<tr>
<td>For women in the Dietary Change Group only</td>
<td>30 session hours in Year 1; 8 session hours/year, Years 2–9</td>
</tr>
</tbody>
</table>
If you decide to join the Dietary Change Group, you will be asked to do several clinic activities and have tests to see if you are able to join the study including a mammogram if you have not had one in the past year.

You will be asked to visit the clinic every 6 months for about 8–12 years and to phone the clinic if problems occur. You will be advised to do moderate exercise for ½ hour each day.

If you decide to join the HRT part of the study as well as the Dietary Change part, you will be asked to spend an additional 5 minutes a day for the first year, plus an extra ½ hour per year throughout most of the study.

**Description of Activities**

During the 8–12 years you are in the Dietary Change study, you will have clinic visits every 6 months. At each yearly visit you will have the following activities:

- The questionnaires you completed before the visit will be reviewed by the Clinic Staff, or you will complete the questionnaires in the clinic.

- Clinic Staff will record the names and dosages of any medications you are currently taking.

- Your pulse will be measured.

- Your blood pressure will be measured.

- Your height and weight will be measured.

- The distance around your hips and waist will be measured.

- Physical strength measures will be made twice:

  1) **Grip Strength**: You will be asked to squeeze 2 handles together with your hand, which will measure your hand strength.

  2) **Chair Stand**: You will be asked to stand several times from a sitting position in a chair. This will measure the strength of your leg muscles.

  3) **Time to Walk 18 Feet**: You will be asked to walk a distance of 18 feet and a Clinic staff member will measure how long it takes you to walk that far. This will measure your walking strength.

- You will be given some questionnaires about your personal qualities and lifestyle to complete either in the clinic or at home.

- You will be briefly interviewed about how you are feeling and about female hormones you may have used in the past.
WHI Protocol - Appendices

- You will be given a clinical breast exam by a clinic doctor or nurse and will be taught how to examine your own breasts.

- After 1 year and at 3, 6, and 9 years, about 3 tablespoons of blood will be drawn for laboratory tests. You will not be able to eat or drink anything but water and your regular medications for 12 hours prior to the blood test.

- You will be required to have a mammogram each year throughout the trial. (If you have had a mammogram in the past year, you may not need to have one before entering the study.)

- You will be given an electrocardiogram heart examination (ECG) every 3 years. This consists of placing wires on your chest while you are lying down, and recording your heart's activity. If you smoke, you will not be able to smoke for 2 hours before the test.

For Osteoporosis Substudy Clinical Centers only:

- You will be asked to provide a urine sample (at least 1 tablespoon) which will be stored for laboratory tests at a later date.

- At the first yearly visit and at the 3rd, 6th and 9th yearly visit, your bone density will be measured in your hip, spine and in your whole body. The test is painless and takes about 30 minutes.

Abnormal findings of the following tests or procedures will be told to you or your doctor or clinic: blood pressure; blood test for anemia done at your Clinical Center; mammogram; and ECG. Some abnormal findings may exclude you from joining in the Dietary Change part of the study. If this should occur, the reasons why you are not able to join will be fully explained by the Clinic staff. These blood tests will not replace your usual medical care (for example, your cholesterol will not be reported to you or your doctor). [Clinics may change per their procedures.]

Six-Month Visits

At the six-month visits, the following activities will occur:

- The questionnaire you completed before or at the clinic visit will be reviewed by the Clinic staff.

- Clinic staff will record the names and dosages of any medications you are currently taking.

Risks

Dietary Change

The dietary changes to be made by women in the Dietary Change Group have no known risks for health in women who keep a well-balanced diet. However, it is possible that a strict low-fat diet may have effects that are not known at this time. If you are in the Dietary Change Group, a nutritionist will review several times what you are eating to be sure it meets your nutritional needs. Changes in your diet may lead to minor discomforts: occasional diarrhea or constipation, or increased gas. You will be advised on ways to avoid these problems or to make the changes easier to tolerate. You may also experience a small amount of weight loss.
WHI Protocol - Appendices

**Pulse; blood pressure; height, weight, hip, waist and physical strength measures; and clinical breast exams:**

There should be no risks with any of these tests.

**Blood draw**

There is a small risk with drawing blood. You may feel a little discomfort as the needle goes through the skin. There may be some bruising of the site where blood is drawn. Pressing hard on the spot for 1 or 2 minutes after the needle is removed will help to prevent a bruise. Very rarely, the arm may become infected.

**Mammogram**

A mammogram involves the use of radiation which may slightly increase the risk of developing breast cancer. Scientists of the WHI and the National Cancer Institute believe, however, that this small risk is outweighed by the benefit of finding breast cancer early, and recommend yearly screening for all women in your age group.

**ECG**

There should be no risk with this procedure.

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**Bone Density Measurement (Osteoporosis Substudy Clinical Centers only)**

The bone density measurement involves a small amount of radiation. Small amounts of radiation may have potential harm, but the risk is difficult to measure and is probably very small. The total radiation dose from the bone density measurements is less than 5% of the natural background radiation a person receives living in a typical American community for one year. It is about the same as the radiation from 3 coast-to-coast airline flights from the east to the west coast.

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**Benefits**

By taking part in this study, you will help to increase scientific knowledge about the prevention of breast cancer, colon and rectum cancer, and coronary heart disease in women. This study will provide stronger scientific evidence than currently exists about whether eating a low-fat, high fiber, high fruit and vegetable diet will change your risk of these diseases.

**Alternative Treatments**

**Prevention of Breast Cancer**

No treatment has been shown to prevent breast cancer. Other treatments, such as Tamoxifen, are being evaluated. At the present time, the standard treatment would be to have routine physical exams, mammograms, and breast self-examination to find cancer early.

**Prevention of Colon and Rectum Cancer**
No treatment has been shown to prevent colon or rectum cancer. At the present time, the standard treatment would be to have routine physical exams and yearly exams of your stool by your doctor for the presence of blood to find cancer early. Other ways of finding cancer early, such as screening with flexible sigmoidoscopy, are being tested in other studies.

Prevention of Heart Disease

Some studies suggest that taking regular aspirin may reduce the risk of heart disease. At the present time, the standard treatment would be routine physical exams, controlling blood cholesterol, blood pressure, and weight, and keeping a healthy lifestyle including regular exercise, a moderate diet, and not smoking cigarettes.

Costs

The nutritional counseling sessions, ECGs, clinic visits, and laboratory tests are provided free of charge by the study. The mammograms will be provided at no cost to you. The mammogram costs will be charged to your insurance. If you do not have insurance or if your insurance will not pay the costs, any remaining costs of the mammogram will be paid for by the study. You will not be paid for being in the study. [Note: Clinical Centers may modify this section based on their contract regarding charging 3rd-party payers.]

It is extremely unlikely that any unfavorable effects will occur as a result of your taking part in the Dietary Change part of the study. However, any problems that might occur during the course of this study would need to be covered by your medical insurance [or clinic inserts their alternate source of medical care for participants without medical insurance]. The Clinical Center will not pay you for any such medical conditions you may develop. You will not be reimbursed for any wages lost from taking part in this study.

Confidentiality

All of your study records will be kept strictly confidential as provided by law. Your personal identity will not be revealed in any publication or release of results. Only WHI staff at the [name] Clinical Center and the Clinical Coordinating Center at the Fred Hutchinson Cancer Research Center in Seattle, Washington will have access to your personal data (i.e. study number, name, social security number and address) for the purpose of study wide mailings as well as maintaining and updating your study records.

Right to Withdraw

Your decision to join in this study is voluntary. You can decide whether or not to join this study. You may drop out at any time, for any reason, without notice. However, we hope you will take part for the entire time of the study because all of the information is needed to be able to draw correct conclusions. If you decide to leave the study, we hope to be able to contact you yearly to see how you are doing. If you decide to leave the study, it will not affect your regular medical care.
Voluntary Consent

If you have any questions about any part of the study or your rights as a volunteer, a WHI staff person will be on hand to answer them before you sign this consent form. Also, if you have any questions about your rights as a participant in this study, please call ___________________ in the Institutional Review Board Office of [Clinical Center] at [phone number]. If you have any questions at any time, you may call: [Clinical Center name and phone number] or any of the investigators listed at the head of this statement. Before you sign this form, please ask any questions on any part of this study that are unclear to you.

Other Information

Your joining is important to the success of this study. Unless many volunteers such as yourself agree to join, this type of study will not be possible. If, as a result, we learn that a low-fat, high fiber, high fruit and vegetable diet reduces the risk of breast cancer, colon or rectum cancer, or heart disease, many women may benefit.

We have tried to make joining the study as easy as possible for you. Please let us know if there are ways you think it would be easier for you and others to join this study.

In order for this study to be valid, you should not join other health studies where you would be placed by chance into a group.

A doctor, nurse, or physician assistant will review your health history and test results to make sure there is no medical reason why you should not join in the Dietary Change part of the WHI. If you agree to join, you will be asked for the name of your doctor or clinic, so that he or she can be told of your joining the WHI.

If any study test suggests that a health problem needs further study, you will be sent back to your doctor or clinic, who will evaluate the need for further study. Any reports and hospital records of your doctor’s follow-up may be requested by the WHI and become part of your study record at the [Clinical Center]. Whether or not you choose to join the Dietary Change Study will not affect your personal medical care or your medical insurance coverage.
An independent committee of experts in medical research will be reviewing study results on a routine basis to consider whether any changes should be made in the study to assure the safety of the treatments and to evaluate the overall risks and benefits of each treatment.

Investigator's Statement

I have provided an explanation of the above research program. The subject was given an opportunity to discuss this procedures, including possible alternatives, and to ask any additional questions. A signed copy of the consent form has been given to the subject.

________________________________________  __________
Signature of Principal Investigator or Designee  Date
PARTICIPANT STATEMENT

I have read the description of the Dietary Change part of the WHI. I voluntarily consent to participate in this study part. I understand that I may drop out from the study at any time. I have had a chance to ask questions about the Dietary Change part of the Study. I understand that I may ask further questions at any time and that I will receive a copy of this signed consent form for my records.

Signature of Participant ___________________________ Date __________

Signature of Witness ___________________________ Date __________
5. CONSENT FORM FOR THE CALCIUM/VITAMIN D PART OF THE WOMEN'S HEALTH INITIATIVE CLINICAL TRIAL

[Clinical Center]

[Principal Investigator]

[24-Hour Contact]

You are already in the Hormone Replacement and/or Dietary Change parts of the Women's Health Initiative (WHI). This form asks you to think about joining in the Calcium/Vitamin D part of the study. We expect thousands of women across the United States to join this part of this study.

Reason for the Calcium/Vitamin D Part of the WHI

There are many questions about the best ways to prevent some of the major diseases that women may have as they get older. The WHI has been set up to study some of these major diseases; namely, heart disease, breast cancer, colon and rectum cancer, and bone fractures (breaks) due to weakened bones (osteoporosis).

Heart disease is the most common cause of death in women aged 50 to 79. Breast cancer is the most common cancer in U.S. women. Cancers of the colon and rectum are the third most common cancer. Hip fractures occur commonly in older women; about 1 out of 6 women aged 50 and over will have a hip fracture in her lifetime.

The goal of the WHI is to study ways to decrease women's chances of getting these diseases, and to improve their quality and length of life.

Part of the reason why women get weakened or brittle bones as they get older may be because they don't get enough calcium or vitamin D in the food they eat. Some short-term studies in the past have shown that taking extra calcium or vitamin D as a pill will reduce bone weakening, and may make bones less likely to break. The WHI will study whether taking calcium and vitamin D pills decreases fractures, especially the more serious ones, such as hip fractures.

Some studies in the past have suggested that taking more calcium in the diet may protect against cancer of the colon and rectum. The calcium/vitamin D part of the study will also study whether taking calcium and vitamin D pills decreases the risk of colon and rectum cancer.

Purpose

The main purpose of this part of the trial is to determine if taking calcium and vitamin D daily reduces the risk of hip fractures (broken hips) and other broken bones, and cancers of the colon and rectum.
Procedures

If you join in this part of the study, you will be placed in one of two groups. The first group will be given 1000 mg. of calcium (active) and 400 international units of vitamin D (active) daily, and the second group will be given an inactive pill (a placebo, like a "sugar pill"). Medications will be taken twice daily by mouth—one pill at breakfast and one at dinner.

Your placement into one of these groups will occur by chance (like a coin toss) and will be done by a computer, not by a WHI staff member.

Neither WHI clinic doctors, staff, nor you will know whether your study medications are active or placebo. While you are in the study, you will be asked not to take any other calcium or vitamin supplements.

Whether or not you choose to join in the Calcium/Vitamin D part will not affect your being in the other parts of the study.

Joining in this group will not increase the amount of time you spend on the WHI study by more than 2 hours a year, and it will not change the number of clinic visits you need to make or the number of years you are followed.

If you join the calcium/vitamin D part of the study, the following additional activities will take place at the 6-month and yearly clinic visits:

- Your remaining study pills will be collected and you will be given new bottles of pills.

Risks

The doses of calcium and vitamin D in study tablets are too small to be toxic when taken as directed. These medications are available over-the-counter and are taken in the same doses by many people without ill effects. In rare cases, you may need to stop taking study pills because of side effects, such as constipation or increased gas production. Even if you have to stop taking study pills, you will still come to clinic visits, and will be followed to the end of the study.

Benefits

By taking part in the calcium/vitamin D part of the WHI, you will help to increase scientific knowledge about the prevention of hip fractures and other fractures and about colon and rectum cancer. This study will provide stronger scientific evidence than currently exists that taking calcium and vitamin D can reduce the risk of these diseases among American women.
Alternate Treatments

Prevention Of Broken Bones Due To Weakened Bones.

Other treatments to prevent broken bones from bone weakening, such as estrogen replacement therapy and Tamoxifen are being tested. At the present time, the standard treatment would be to have routine physical exams, engage in regular physical activity and eat a diet that contains adequate amounts of calcium and vitamin D.

Prevention of Colon Cancer

No treatment has been shown to prevent colon or rectum cancer. At the present time, the standard treatment would be to have routine physical exams and yearly exams of your stool by your doctor for the presence of blood to find cancer early. Other ways of finding cancer early, such as flexibly sigmoidoscopy, are being tested.

Costs

The tests, medications, and visits that are part of this study will cost you nothing other than your time and travel costs. You will not be paid for being in this study.

Whether or not you choose to join the Calcium and Vitamin D Study will not affect your personal medical care or your medical insurance coverage. It is extremely unlikely that any unfavorable effects will occur as a result of your taking part in the Calcium/Vitamin D trial. Any problems that might occur during the course of this study would need to be covered by your medical insurance [or clinic inserts their alternate source of medical care for participants without medical insurance]. The Clinical Center will not pay you for any such medical conditions you may develop. You will not be reimbursed for any wages lost from taking part in this study.

Confidentiality

All of your study records will be kept strictly confidential as provided by law. Your personal identity will not be revealed in any publication or release of results. Only WHI staff at the [name] Clinical Center and the Clinical Coordinating Center at the Fred Hutchinson Cancer Research Center in Seattle, Washington will have access to your personal data (i.e. study number, name, social security number and address) for the purpose of study wide mailings as well as maintaining and updating your study records. The Food and Drug Administration will be allowed to examine your study records for safety reasons. Study records will be kept indefinitely for analysis and follow-up.
Right to Withdraw

Your decision to join in this study is voluntary. You can decide whether or not to join this study. You may drop out at any time, for any reason, without notice. However, we hope you will take part for the entire time of the study because all of the information is needed to be able to draw correct conclusions. If you decide to leave the study, we hope to be able to contact you yearly to see how you are doing.

Voluntary Consent

If you have any questions about any part of the study or your rights as a volunteer, a WHI staff person will be on hand to answer them before you sign this consent form. Additionally, if you have any questions about your rights as a participant in this study, please call ________________ in the Institutional Review Board Office of [Clinical Center] at [phone number]. If you have any questions at any time, you may call: [Clinical Center name and phone number] or any of the investigators listed at the head of this statement. Before you sign this form, please ask any questions on any part of this study that are unclear to you.

Other Information

Your joining is important to the success of this study. Unless many volunteers such as yourself agree to join, this type of study will not be possible. If, for example, we learn that taking daily calcium and vitamin D reduces the risk of hip and other fractures, or colon or rectum cancer, many women may benefit.

We have tried to make joining as easy as possible for you. Please let us know if there are ways you think it would be easier for you and others to join this study.

In order for this study to be valid, you should not join other health studies where you would be placed by chance into a group.

An independent committee of experts in medical research will be reviewing study results on a routine basis to consider whether any changes should be made in the study to assure the safety of the treatments and to evaluate the overall risks and benefits of each treatment.

Investigator's Statement

I have provided an explanation of the above research program. The subject was given an opportunity to discuss this procedures, including possible alternatives, and to ask any additional questions. A signed copy of the consent form has been given to the subject.

Signature of Principal Investigator or Designee

Date
PARTICIPANT STATEMENT

I have read the WHI study description and I voluntarily consent to take part in this study. I understand that I may drop out of the study at any time. I have had a chance to ask questions and have had my questions answered. I understand that I may ask further questions at any time and that I will receive a copy of this signed consent form for my records.

Signature of Participant

Date

Signature of Witness

Date
6. CONSENT FORM FOR THE OBSERVATIONAL STUDY PART OF THE WOMEN'S HEALTH INITIATIVE STUDY

[Clinical Center]

[Principal Investigator]

[24-Hour Contact]

This form asks you to think about joining the Observational Study (OS) part of the Women's Health Initiative (WHI). If you are able, you may choose to join in this part of the study. We expect thousands of women across the U.S. to be part of this study.

Many of the women who come for at least one clinic visit will not be able or willing to join the WHI Clinical Trial. As one of these women, you have an opportunity to join in a very important study to look at the relation between lifestyle factors and health, as well as quality of life. Women can join in this study by completing the study questionnaire, having a brief physical exam (at start of study and 3 years later), and providing a blood sample (also repeated at 3 years). This study will look at the role of several health habits (for example, physical activity and diet) and exam results (such as blood pressure and body weight), as well as factors measured in the blood sample. The study will then look at how these factors affect risks of heart disease, cancer, general health, and quality and length of life.

Purpose

The main purpose of the Observational Study (OS) part of the WHI is to learn more about women's health, and to learn more about the causes of disease in women aged 50 to 79. The WHI Clinic Staff has determined that you are able to join this part of the WHI.

Reason for the OS Part of the WHI

There are many questions about the best ways to prevent some of the major diseases that women may have as they get older. The WHI Observational Study has been set up to study factors associated with these major diseases; namely, heart disease, breast cancer, colon and rectum cancer, and bones fractures (breaks) due to weakened bones (osteoporosis). Identifying such factors is an important step in learning how to prevent these diseases.

Heart disease is the most common cause of death in women aged 50 to 79. About 1 out of every 8 women in the U.S. will get breast cancer in her lifetime. Cancers of the colon and rectum are the third most common major cancer. Hip fractures occur commonly in older women; about 1 out of 6 women aged 50 and over will have a hip fracture in her lifetime.

The goal of the WHI is to find ways to decrease women's chances of getting these diseases, and to improve their quality and length of life.
Procedures

Women in the OS part will be followed for about 8-12 years. During this follow-up period, you will be contacted by mail each year and asked to complete health update questionnaires and mail them back to the Clinic. These questionnaires should take about 30 minutes to complete.

You will also receive a WHI newsletter each year, informing you of news about the study and general information about health for women your age.

You will be invited to return to the clinic in 3 years. Before that visit, you will be mailed questionnaires to complete and bring with you to the clinic visit. At that clinic visit, you will have the following activities and tests:

- The questionnaires you completed before the visit will be reviewed, or you will complete them in the clinic.
- Clinic staff will record the names and dosages of medications you are currently taking.
- Your pulse will be measured.
- Your blood pressure will be measured.
- Your height and weight will be measured.
- The distance around your hips and waist will be measured.
- You will be given some questionnaires about your personal qualities and lifestyle to complete, either in the clinic or at home.
- You will be briefly interviewed about how you are feeling and about female hormones you may have used in the past.
- Physical strength measures will be made twice:
  1) **Grip Strength**: You will be asked to squeeze 2 handles with your hand, which will measure your hand strength.
  2) **Chair Stand**: You will be asked to stand several times from a sitting position on a chair. This will measure the strength of your leg muscles.
  3) **Time to Walk 18 Feet**: You will be asked to walk a distance of 18 feet and a Clinic staff member will measure how long it takes you to walk that far. This will measure your walking strength.
- Approximately 3 tablespoons of blood will be drawn for laboratory tests. You will need to take nothing by mouth except water and your regular medications for 12 hours before the blood test.

**Osteoporosis Substudy Clinical Centers only:**

- You will be asked to provide a urine sample (at least 1 tablespoon) which will be stored for laboratory tests at a later date.
- Your bone density will be measured in your hip, spine and in your whole body. The test is painless and takes about 30 minutes.
All of the activities of this Third-Year Clinic Visit should take no more than 1½ hours to complete.

You will be told if you have abnormal blood pressure, as well as abnormal blood test for anemia done through your Clinical Center, and if you want, your doctor or clinic will also be told. Some of the blood drawn will be stored for tests at a later date. These blood tests will not replace your usual medical care (for example, your cholesterol will not be reported to you or your doctor). [Clinics may change per their procedures.]

You may be asked to return to the clinic for visits after 6 and 9 years of follow-up. The tests and activities of these visits would be the same as for the Third Year Clinic Visit, and will each take about 1½ hours to complete.

Risks

Pulse: blood pressure; urine sample; height, weight, hip, and waist measures; and physical strength measures:

There should be no risks with any of these tests.

Blood draw

There is a small risk with the process of drawing blood. You may feel a little discomfort as the needle goes through the skin. There may be some bruising at the site where blood is drawn. Pressing hard on the spot for 1 or 2 minutes after the needle is removed will help to prevent a bruise. On very rare occasions, the arm may become infected.

<table>
<thead>
<tr>
<th>Bone density measurement (Osteoporosis Substudy Clinical Centers only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>The bone density measurement involves a small amount of radiation. Small amounts of radiation may have potential hard, but the risk is difficult to measure and is probably very small. The total radiation from the bone density measurements is less than 4% of the natural background radiation a person receives living in a typical American community for one year. It is about the same radiation as 3 coast-to-coast airline flights from the east to the west coast.</td>
</tr>
</tbody>
</table>

Benefits

By taking part in this study, you will help to increase scientific knowledge about the causes of breast cancer, colon and rectum cancer, heart disease, and fractures (broken bones) in women, and about women's experiences and lifestyles that effect their health as they get older.

Alternate Treatments

This part of the study does not involve treatment.

Costs
The tests and visits that are part of this study will cost you nothing other than your time and travel costs. You will not be paid for being in the study.

It is extremely unlikely that any unfavorable effects will occur as a result of your taking part in the Observational Study. However, any problems that might occur during the course of this study would need to be covered by your medical insurance [or clinic inserts their alternate source of medical care for participants without medical insurance]. The Clinical Center will not pay you for any such medical conditions you may develop. You will not be reimbursed for any wages lost from taking part in this study.

Confidentiality

All of your study records will be kept strictly confidential as provided by law. Your personal identity will not be revealed in any publication or release of results. Only WHI staff at the [name] Clinical Center and the Clinical Coordinating Center at the Fred Hutchinson Cancer Research Center in Seattle, Washington will have access to your personal data (i.e. study number, name, social security number and address) for the purpose of study wide mailings as well as maintaining and updating your study records.

Study records will be kept indefinitely for analysis and follow-up.

Right to Withdraw

Your decision to join in this study is voluntary. You can decide whether or not to join this study. You may drop out at any time, for any reason, without notice. However, we hope you will take part for the entire time of the study because all of the information is needed to be able to draw correct conclusions. If you decide to leave the study, we hope to be able to contact you yearly to see how you are doing.

Voluntary Consent

If you have any questions about any aspect of the study or your rights as a volunteer, a WHI staff person will be on hand to answer them before you sign this consent form. Additionally, if you have any questions about your rights as a participant in this study, please call _____________ in the Institutional Review Board Office of [Clinical Center] at [phone number]. If you have any questions at any time, you may call: [Clinical Center name and phone number] or any of the investigators listed at the head of his statement. Before you sign this form, please ask any questions on any aspect of this study that are unclear to you.
Other Information

Your joining is important to the success of this study. Unless many volunteers such as yourself agree to join, this type of study will not be possible.

We have tried to make joining the study as easy as possible for you. Please let us know if there are ways you think it would be easier for you and others to join this study.

Investigator’s Statement

I have provided an explanation of the above research program. The subject was given an opportunity to discuss this procedures, including possible alternatives, and to ask any additional questions. A signed copy of the consent form has been given to the subject.

_________________________  __________________________
Signature of Principal Investigator or Designee   Date

PARTICIPANT STATEMENT

I have read the WHI Observational Study description and I voluntarily consent to take part in this study. I understand that I may drop out from the study at any time. I have had a chance to ask questions and have had my questions answered. I understand that I may ask further questions at any time and that I will receive a copy of this signed consent form for my records.

_________________________  __________________________
Signature of Participant   Date

_________________________  __________________________
Signature of Witness   Date
APPENDIX V

Risk Factors for Major Disease Categories to be Studied in the OS

Data on the OS participants will be obtained from questions that they answer and from physical and laboratory examinations. In common with CT participants, women in the OS will complete a self-administered questionnaire prior to Screening Visit 1. At that visit, a ("supplemental") self-administered questionnaire also will be completed.

The content of the supplemental questionnaire is directed to the epidemiology of diseases that are relatively common, serious, and capable of being readily ascertained by means of the planned OS follow-up mechanisms. Questions that are neither cumbersome nor overly time consuming will be included, with priority given to questions that can be answered reliably, and that provide reasonably valid exposure information.

For exposures ascertained on all OS participants (e.g., baseline questionnaires and supplemental questionnaire), analyses of their association with one or more outcome events can be readily done with no additional data collection. For laboratory tests that would not be routinely performed on specimens obtained from all participants, thawed specimens from women who developed a given adverse health outcome can be tested, and the results compared to those obtained on a random sample of the cohort as a whole. It is expected that while many comparisons will be done within the immediate scope (and budget) of the WHI, others ("ancillary" studies) that require additional funding will be done as well. Ancillary studies could also be based on special tests performed on participants at only one or a group of clinical centers.

The following is a list -- lengthy, but nonetheless partial -- for each of the three major disease categories and for total mortality, of the potential risk factors that will be examined in the Observational Study:

1. Cardiovascular diseases
   A. Use of medicinal drugs -- for treatment of diabetes, hyperlipidemia, hypertension, psychotropic agents; antihistamines; anti-inflammatory agents; vitamins, sympathomimetic agents; exogenous hormones (see section 2A below).
   B. Reproductive history, including gynecological surgery.
   C. Family history of heart disease and stroke.
   D. Personal habits -- smoking, alcohol, coffee consumption, exercise (intensity, walking pace), dietary intake (saturated fat, polyunsaturated fat, dietary fiber, calcium, recent weight loss), maximum weight ever, weight fluctuations.
   E. Psychosocial characteristics -- health status, depression, social support, social network, life events, work strain.
   F. Physical characteristics -- height, weight, waist and hip circumferences, blood pressure, resting pulse.
   G. Laboratory measures -- WBC, hematocrit (hemoglobin), fasting glucose, fasting lipids (TC, MDLC, TG, LDLC, HDL, KDL, Lp(a), fibrinogen, motivated factor VII, antioxidants (tocopherol, carotenoids, selenium, vitamin C).

2. Breast Cancer
   A. Exogenous hormones
      1. Oral contraceptives (age at first use, duration of use, time since first or last use).
      2. DMPA.
      3. DES.
4. Noncontraceptive estrogens and progestogens, type of regimen (ERT vs. PERT), duration, dose, route.

B. Reproductive History
   1. Menstrual, pregnancy, and lactation history.
   2. Infertility.

C. Alcohol consumption, with particular attention to alcohol use at different chronologic ages.

D. Cigarette smoking, passive smoking

E. Family history of breast cancer, colon cancer, other cancers

F. Physical activity

G. Anthropometric characteristics

H. Laboratory assays
   1. Serum lipid fractions.

3. Osteoporotic Fractures
   A. Reproductive history, with particular attention to lactation
   B. Exogenous hormones (see section 2.A above)
   C. Dietary intake
      1. Calcium -- amount, sources.
      2. Protein.
      3. Alcohol.
   D. Cigarette smoking, with particular attention to its joint influence with exogenous hormones
   E. Physical activity -- amount, types
   F. Bone density
   G. History of falls

4. Total Mortality
   A. Markers of clinical disease -- history of hospitalization, use of medicinal drugs, prior disease (respiratory, digestive, cardiovascular)
   B. Markers of subclinical disease -- albumin, hematocrit, cholesterol, history of weight loss, functional status
   C. Psychosocial characteristics -- health status, depression, social support, social network, life events, work strain
   D. Physical characteristics -- height, weight, waist and hip circumference
   E. Change in markers of subclinical disease -- albumin, hematocrit, cholesterol, weight, functional status

While some of the questions asked in the supplemental questionnaire are possibly relevant to the occurrence of cardiovascular disease, breast cancer, and osteoporotic fractures, others are intended to advance our knowledge of the causes of other important health problems of middle-aged and older women. Examples are:

   Genital exposure to powders -- ovarian cancer.
   Occupational exposures -- cancer.
   Weight cycling history -- cardiovascular disease, cancer, mortality.
   Residential history (sun exposure) -- colon cancer, osteoporosis, melanoma.
APPENDIX VI

Dietary Intervention Program and Dietary Assessment Methods

A. Dietary Intervention Program

Several psychosocial and behavioral themes have been identified as central in the WHI intervention. These central themes are grouped into six categories: motivation and reinforcements, self-management, skills training, social support, relapse prevention, and self-reliance and self-efficacy.

Reinforcements and Motivators

The process of successful long-term behavior change begins with a guided self-analysis of initial motivations to participate. Each woman is encouraged to understand her own motivations during the first few sessions as a way of strengthening her resolve to change her diet. The most common motivators in the feasibility trial were: helping in a scientific research project; health; having a close relative or friend with breast cancer; fear of cancer; and learning more about nutrition.

The intervention emphasizes different motivations later in the behavior change process. These include improved self-confidence and self-efficacy, a sense of empowerment and self-control, greater or improved social support, and healthier living. The intervention also counters barriers to change at a very early stage. Some barriers include time and financial costs, increased awkwardness in social and eating situations, guilt for non-adherence, and decreased enjoyment of eating preferred foods. The costs of the intervention are discussed periodically with participants throughout the sessions and methods of minimizing cost barriers are continually identified.

Self-Management

Proven behavioral modification and self-control techniques are used throughout. Participants learn these techniques through a series of steps: self-monitoring of targeted behaviors; defining specific behaviors to be changed; setting quantifiable intervention goals; breaking complex behaviors down into smaller steps; specifying an action plan; getting evaluation of behavior changes and feedback from support network; and reinforcing progress and encouraging self-praise.

Skills Training

Most people need new skills to complete the process of behavior change. The feasibility studies identified several skills needed to modify fat in the diet. Each of these skills has been linked with an appropriate nutritional topic and is being deliberately taught and reinforced throughout the first year. These skills are:

- Problem-solving and analysis, to allow participants to handle new situations with knowledge and confidence;

- Assertiveness and communication, to allow participants to actively seek out necessary foods, ingredients, and workable situations;

- Stress-management, to help participants cope with stressful situations and feelings of stress and fatigue by using non-eating strategies; and

- Cognitive, such as cognitive restructuring and imagery, to assist participants to identify potentially dangerous self-talk and replace it with more healthful thoughts and feelings.

Social Support

Social support is critical in the maintenance of behavior change. The intervention provides social support in three ways. First, the group facilitator is a main source of support and encouragement. Group facilitators are
trained in listening and empathy skills, as well as nutritional knowledge and skills. Participants can discuss any aspect of the trial and trial-related events with the group facilitator, who is trained to remain open to participants' problems and concerns. Second, the group itself serves as a supportive environment. The tone of the group, set initially by the facilitator and continued by the participants, has to be open, honest, sharing, and understanding. In the WHI intervention, problem-solving is a group effort. Participants bring their most difficult situations to the group, which affirms the participant and helps to solve the issue.

The third source of support for participants has to be their family and/or other significant persons in their lives. Long-term dietary change is most easily maintained when it "fits" with normative family behavior. Changing a woman's eating habits often modifies the family's eating habits as well. Women are asked to involve significant others in the change process. Problems regarding others' acceptance of the low fat eating plan are addressed as part of the intervention. Most solutions will need a combination of the participant soliciting help, receiving support from significant others, and learning to cook low fat meals that are acceptable to family members.

Relapse Prevention

Maintaining changed behavior requires a series of steps (known as relapse prevention strategies) to avoid the characteristically high relapse rates of appetitive and addictive behaviors (Marlatt, 1985). Relapse prevention techniques are introduced near the end of the first year. High risk situations, such as holidays, parties and eating in restaurants, are identified so that participants can prepare for them. Next, participants learn to label a "high fat" dietary behavior as a momentary lapse. They are taught to substitute low fat dietary behaviors to prevent relapse back to original high-fat consumption. Slipping gradually back to old high fat patterns is perceived as a specific low fat dietary change relapse. Techniques for managing lapse and relapse, tested in other situations, are applied in this intervention near the end of the first year. Relapse prevention is a major focus in years two and beyond.

Self-Reliance and Self-Efficacy

In a long-term intervention like WHI, participants must be able to rely on their own choices instead of relying on strict adherence to a prescribed dietary plan (Mahony et al, 1978). Self-efficacy is the belief that participants can actually change and maintain dietary behaviors leading to a low fat eating plan (Bandura, 1977; Bandura, 1982). The belief that these behaviors will have the desired effect on dietary fat and risk of cancer and heart disease is also important. The intervention provides deliberate opportunities to increase self-reliance and self-efficacy. For example, women are taught skills necessary to feel more competent and assured in uncomfortable situations. They also learn ways to improve social support as a means to promoting confidence with new ways of eating. In the current intervention, nutritionists will encourage participants to discover their own "inner power" by regular reinforcement of personal accomplishments, no matter how small (Janis, 1984). This process of empowerment and emphasis on self-control is necessary to enable women to maintain dietary changes over the long term.

Intervention Session Summary

The schedule for sessions in the first year of intervention is shown in Table 1. Appropriate nutritional and behavioral concepts are integrated into each session. Both the nutritional and the behavioral concepts are carefully ordered to produce maximum effect. The early sessions (Sessions 1-8) cover the major sources of fat in the U.S. diet and critical nutritional skills (shopping, recipe modification, restaurant selection) needed for major fat consumption changes. Later nutritional topics are more specialized and include increasing fish consumption and low fat party foods. Nutritional topics that deal with maintenance (fats and oil, creating long-term guidelines) are included in the last sessions.

The behavioral session topics are organized into groups around strategies and are ordered to facilitate behavior change. The first two behavioral topics are self-management (self monitoring, goal setting, behavior modification, cognitive-restructuring), and motivations for low fat dietary change (e.g. family and personal health, contributing to science, etc.). Self-management steps form the core of necessary behavior skills, and the identification and reinforcement of motivations are included in the first session to develop and maintain participants' interest in changing. Social influences and support are included in the next five sessions because of
the critical nature of social influences on eating and on successful health behavior change. Time management, problem-solving, and coping with stress are introduced after the initial large decreases in fat consumption have occurred to help incorporate the new low fat behaviors into everyday living. Finally, relapse prevention is included in the last sessions to assist with long-term maintenance.

Nutritional and behavioral strategies are integrated into each session for several reasons. The intervention materials consistently focus on dietary behaviors, not nutrients, as a means of changing fat consumption. Therefore, integrating the two types of strategies in each session is important. Participants and nutritionists in the WHT Feasibility Study were initially uncomfortable during sessions with no nutritional (i.e. only behavioral) content, so complementary nutritional and behavioral topics were included in each session. Implementing the philosophy of the WHT as a self-directed, self-controlled eating plan means that each nutritionist and participant must view dietary changes as a series of activities that will ultimately become part of everyday life. Integrating dietary plans with behavioral strategies in each session helps participants integrate them in daily life. The relative focus on nutrition is highest in the early sessions during the time of most intensive dietary change, while the emphasis on behavioral strategies to maintain the early dietary changes increases in later sessions.
### Appendix VI, Table 1
Summary of Intervention Sessions

<table>
<thead>
<tr>
<th>Session No.</th>
<th>Session Objectives</th>
<th>Nutritional Topics</th>
<th>Behavioral Topics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weekly</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Review goals and objectives of the WHI trial. Discuss the benefits and responsibilities of being a participant. Identify the benefits of group intervention and support process. Identify the amount of fat in foods.</td>
<td>Awareness of fat in foods.</td>
<td>Awareness of costs/benefits to trial participants. Social support in group and home setting. Communication skills.</td>
</tr>
<tr>
<td>Session No.</td>
<td>Session Objectives</td>
<td>Nutritional Topics</td>
<td>Behavioral Topics</td>
</tr>
<tr>
<td>------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Bi-Weekly</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Discuss ways sweets are used as a reward. Select low fat dessert alternatives. Identify social support strategies to deal with sweets and desserts.</td>
<td>High-risk food situations. Fruit dessert alternatives.</td>
<td>Asking for social support. Foods as reinforcers.</td>
</tr>
<tr>
<td>9</td>
<td>Share low fat eating experiences with other WHI participants. Identify ways eating partners can support each other.</td>
<td>Low fat recipe exchange. New food preparation ideas.</td>
<td>Promotion of group cohesiveness.</td>
</tr>
<tr>
<td><strong>Monthly</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Review group progress. Identify potential situations that interfere with low fat eating. Learn how to use the skill of problem solving. Learn the skill of fat budgeting.</td>
<td>Areas that interfere with low fat eating. Fat budgeting skills.</td>
<td>Barriers to change. Self-management strategies.</td>
</tr>
<tr>
<td>Session No.</td>
<td>Session Objectives</td>
<td>Nutritional Topics</td>
<td>Behavioral Topics</td>
</tr>
<tr>
<td>------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>13</td>
<td>Identify time spent in meal preparation activities.</td>
<td>Meal planning skills. Fish preparation ideas.</td>
<td>Organizational and planning strategies and skills.</td>
</tr>
<tr>
<td>14</td>
<td>Identify sources of complex carbohydrates. Identify and describe ways to increase complex carbohydrate intake. Discuss techniques for introducing new cuisines to eating partners.</td>
<td>Sources of complex carbohydrates. Tasting meatless recipes.</td>
<td>Communication skills. Social support.</td>
</tr>
<tr>
<td>16</td>
<td>Identify high-risk situations. Explain coping techniques that can be used when lapses occur. Learn new low fat party alternatives. Identify low fat party goods.</td>
<td>High-risk foods. Low fat alternatives for entertainment.</td>
<td>Relapse prevention.</td>
</tr>
</tbody>
</table>

B. Dietary Assessment Methods

The dietary assessment strategies for the WHI will be based on those used in the Women's Health Trial: Feasibility Study in Minority Populations (WHT:FSMP). All procedures for dietary assessment, training, and quality control have been developed in the WHT:FSMP. These dietary assessment protocols will be validated and modified, if necessary, to optimize their use in the WHI. This work is described in detail below.
Four-Day Food Records

The University of Minnesota's Nutrition Coordinating Center's (UM-NCC) Nutrition Data System will be used for analysis of food records. THE UM-NCC Nutrition Data System consists of data entry software, analysis software, and comprehensive food product and nutrient databases. The UM-NCC was developed to support nutrient analyses for randomized intervention trials in 1974, and has since developed into the United States' leading resource for nutrient database and analysis systems for scientific research. The recent addition of data entry software that prompts coders for information in English makes the Nutrition Data System simple to use. Most importantly, the Nutrition Data System obviates the need for a large programming, data entry, and nutritional sciences staff to support diet record analyses. This system has gained rapid and widespread acceptance by many nutrition research groups, including the National Health and Nutrition Examination Survey.

a. Nutrient database

The UM-NCC has pioneered a comprehensive approach to the collection, maintenance and documentation of its food composition database. Details have been published in several peer-reviewed journals, most recently by Sievert et al (1989). Here we review briefly the highlights of the system:

The UM-NCC database contains over 16,000 foods and 5,000 brand name products. The combination of these foods and the analysis software allows over 150,000 food variants, differing in preparation methods and ingredients. The database is purposefully broad, including culturally unique foods such as foods used in the southern U.S., Hispanic foods and American Indian foods. The database is updated at least annually to reflect new analytic data, new foods, and changes in composition of manufactured foods.

The primary sources for nutrient values in the database are the USDA Nutrient Data Base for Standard Reference (1987) and its periodic revisions. Additional sources include other USDA publications, information from food manufacturers, scientific literature and international food tables. A detailed description of sources used for the UM-NCC database has been published (Schakel et al, 1988). Database maintenance is through an extensive and standardized set of procedures designed to minimize many sources of error. Missing values exist only when there is no information on the presence of the nutrient in the given food; otherwise, values are imputed based on a standardized protocol (Schakel et al, 1988).

The database contains values for 93 nutrients, listed in Table 2. The software can output a variety of reports, including a list of foods consumed and their nutrient content. A machine-readable file is also generated, allowing the use to prepare customized reports, manipulate raw data and export nutrient analyses into other datasets.
## Appendix VI, Table 2
Nutrients Calculated from Nutrition Data System Database

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Source</th>
<th>Other Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy</td>
<td>Vitamin D</td>
<td>MFA 14:1</td>
</tr>
<tr>
<td>Protein</td>
<td>Vitamin D</td>
<td>MFA 16:1</td>
</tr>
<tr>
<td>Total fat</td>
<td>Thiamin</td>
<td>MFA 18:1, oleic acid</td>
</tr>
<tr>
<td>Total carbohydrate</td>
<td>Riboflavin</td>
<td>MFA 20:1</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Niacin</td>
<td>MFA 22:1</td>
</tr>
<tr>
<td>% calories from protein</td>
<td>Folacin</td>
<td></td>
</tr>
<tr>
<td>% calories from fat</td>
<td>Pantothenic acid</td>
<td>PFA 18:2, linoleic acid</td>
</tr>
<tr>
<td>% calories from carbohydrate</td>
<td>Vitamin B₆</td>
<td>PFA 18:3, linoleic acid</td>
</tr>
<tr>
<td>% calories from carbohydrate</td>
<td>Vitamin B₁₂</td>
<td>PFA 18:4</td>
</tr>
<tr>
<td>% calories from alcohol</td>
<td>Cholesterol</td>
<td>PFA 20:4</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Total SFA</td>
<td>PFA 20:5, EPA</td>
</tr>
<tr>
<td>Calcium</td>
<td>% calories from SFA</td>
<td></td>
</tr>
<tr>
<td>Iron</td>
<td>% calories from MFA</td>
<td>Polyunsaturated to</td>
</tr>
<tr>
<td>Magnesium</td>
<td>% calories from PFA</td>
<td>Saturated fat ratio (P:S)</td>
</tr>
<tr>
<td>Phosphorous</td>
<td>SFA 4:0</td>
<td>Cholesterol Saturated fat</td>
</tr>
<tr>
<td>Sodium</td>
<td>SFA 6:0</td>
<td>Index (CSI)</td>
</tr>
<tr>
<td>Zinc</td>
<td>SFA 8:0</td>
<td></td>
</tr>
<tr>
<td>Copper</td>
<td>SFA 10:0</td>
<td>Dietary fiber</td>
</tr>
<tr>
<td>Selenium</td>
<td>SFA 12:0, lauric acid</td>
<td>Water soluble dietary fiber</td>
</tr>
<tr>
<td>Total Vitamin A</td>
<td>SFA 14:0</td>
<td></td>
</tr>
<tr>
<td>Beta-carotene</td>
<td>SGA 16:0, palmitic acid</td>
<td>Water insoluble dietary fiber</td>
</tr>
<tr>
<td>Total alpha-tocopherol</td>
<td>SGA 17:0</td>
<td></td>
</tr>
<tr>
<td>equivalents</td>
<td>SFA 18:0, stearic acid</td>
<td>Pectins</td>
</tr>
<tr>
<td>Total alpha-tocopherol</td>
<td>SFA 20:0</td>
<td>Starch</td>
</tr>
<tr>
<td>equivalents</td>
<td>SFA 22:0</td>
<td>Sucrose</td>
</tr>
<tr>
<td>Alpha-tocopherol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-tocopherol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gamma-tocopherol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delta-tocopherol</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### System Modification

The following modifications will be made to the UM-NCC Nutrition Data System to enhance analysis capabilities related to food classifications and serving sizes. For epidemiological analyses, especially of the relationships of vegetable foods with cancer risk, it is useful to analyze diet in terms of servings of certain food
groups. While the UM-NCC system allows analysis of nutrients from types of foods, analyses of number of servings within food groups will require specifications of serving sizes for each type of food and the means to sum over these servings for each individual record. The UM-NCC has developed a food grouping system for the Health and Nutrition Examination Survey based on the USDA classification scheme, but this scheme is used for historic reasons and is relevant more to agricultural economics than health research.

**Food Frequency Questionnaire (FFQ)**

A modified version of the FFQ developed for the WHT:FSMP will be used for WHI. This FFQ and all FFQs used in the Nutritional Epidemiology Shared Resource are modifications of the NCI/Block FFQ. These FFQs are now used in over 30 studies at the FHCRC and in research institutions throughout the county.

The underlying principle of the food-frequency approach is that average long-term diet intake, for example, intake over weeks, months, or years, is the conceptually important exposure rather than intake on a few specific days. The FFQ consists of three basic components: a food list, a frequency response section for subjects to report how often each food was eaten, and portion size information. In addition, this FFQ is designed to be sensitive to sources of fat and modifications in fat-related diet habits that are components of the WHI nutrition intervention. Many "adjustment" questions that allow more refined analysis of estimated nutrients were incorporated. For example, questions about types of cookies, types of popcorn, and types of added fats such as mayonnaise, are used in order to be sensitive to the fat-modified foods that will be used by low fat intervention group women. A secondary emphasis of the FFQ is on nutrient-rich fruits and vegetables to support analyses related to other cancers and cardiovascular disease. Only minor modifications of the FFQ, based on experiences in the WHT:FSMP and other minority populations, and on expert input from Clinical Center scientists, are planned. These modifications would include (1) adding foods that are important but overlooked, (2) improving the instructions or wording to increase clarity, and (3) adding foods used by minority groups. The FFQ will be modified during the study to include new foods, especially those foods with modified fat content. Although updating the FFQ during WHI will complicate analysis, it will be necessary given the duration of the planned research. FFQ results will be adjusted using nutrient intake estimates from four-day food records as criterion measure.

**24-Hour Dietary Recalls**

The UM-NCC NDS system will be used for administration and analysis of 24-hour recalls. All 24-hour recalls will be unannounced (not scheduled) and administered by trained interviewers at the CCC. A stratified sample of one percent will be selected annually. Stratification will be by race/ethnicity and socioeconomic status (education or income). Protocol for administering 24-hour recalls will be based on the WHT:FSMP.

**Nutrient Database**

The nutrient database used by CCC FFQ analysis software is based on the UM-NCC nutrient database. Nutritional scientists at the CCC maintain a self-documenting, spreadsheet-based system for generating each FFQ nutrient database. Each spreadsheet contains the specific food or foods from the UM-NCC database that are included in each FFQ item. A computer program has been developed to use the NDS system to convert these spreadsheets into a matrix of serving size and nutrient values used by the FFQ analysis system. This allows simple periodic updates of FFQ databases based on changes in the FFQ itself or on updates to the UM-NCC nutrient database. Nutrients available from the CCC software are given in Table VII.1 above. However, all nutrients derived from the FFQ will not be considered to be of equal validity. It is recommended that analysis of FFQs be restricted to the following nutrients: Percentage of energy from macronutrients; beta-carotene, Vitamins C, E, A, and fiber.
APPENDIX VII

Women's Health Initiative
Study Units and Principal Investigators

Project Office

National Institutes of Health, Bethesda, MD
Jacques Rossouw, MD - Project Officer
Bill Harlan, MD - Alternate Project Officer
Carrie Hunter, MD - Special Assistant to the Director
Betty Nordan, Contract Officer

Clinical Coordinating Center (CCC)

Fred Hutchinson Cancer Research Center, Seattle, WA
Ross Prentice, PhD - Principal Investigator
Maureen Henderson, MD, DrPH - Co-Principal Investigator
Jeff Probstfield, MD - Project Director and Co-Principal Investigator
Garnet Anderson, PhD - Director, Statistical and Central Study Unit
Anne McTiernan, MD, PhD - Director, Clinical and Nutrition Intervention Unit

Selected CCC Subcontractors:

Regional Coordinating Center
Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, NC
Curt Furbeg, MD, PhD - Principal Investigator and CCC Co-Principal Investigator

Osteoporosis Coordinating Center
University of California at San Francisco, San Francisco, CA
Steve Cummings, MD - Principal Investigator and CCC Co-Principal Investigator

Drug Distribution and Specimen Storage Center
Ogden Bioservices Corporation, Rockville, MD
Harrison Hoppes - President

Central Laboratory
Medical Research Labs, Cincinnati, OH
Evan Stein, MD - Principal Investigator

Central ECG Reading Center
University of Alberta at Edmonton
Penttu Rautaharju, MD - Principal Investigator
Vanguard Clinical Centers:

Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, NC
*Gregory Burke, MD - Principal Investigator*

Brigham & Women's Hospital, Boston, MA
*Joanne Manson, MD - Principal Investigator*

Emory University, Atlanta, GA
*Dallas Hall, MD - Principal Investigator*

Fred Hutchinson Cancer Research Center, Seattle, WA
*Maureen Henderson, MD, DrPH - Principal Investigator*

The Memorial Hospital of Rhode Island, Pawtucket, RI
*Analouise Assaf, PhD - Principal Investigator*

Northwestern University, Evanston, IL
*Phillip Greenland, MD - Principal Investigator*

The State University of New York, Buffalo, NY
*Maurizio Trevisan, MD - Principal Investigator*

The University of Alabama, Birmingham, AL
*Albert Oberman, MD - Principal Investigator*

The University of Arizona, Tucson, AZ
*Thomas Moon, PhD - Principal Investigator*

The University of California, Davis, Sacramento, CA
*John Robbins, MD - Principal Investigator*

The University of California, San Diego, San Diego, CA
*Robert Langer, MD - Principal Investigator*

The University of Iowa, Iowa City, IA
*Robert Wallace, MD - Principal Investigator*

The University of Medicine and Dentistry of New Jersey, Newark, NJ
*Norman Lasser, MD - Principal Investigator*

The University of Minnesota, Minneapolis, MN
*Richard Grimm, MD - Principal Investigator*

The University of Pittsburgh, Pittsburgh, PA
*Lewis Kuller, MD - Principal Investigator*

The University of Tennessee, Memphis, TN
*William Applegate, MD - Principal Investigator*
APPENDIX VIII

Bibliography

HORMONE REPLACEMENT THERAPY, CORONARY HEART DISEASE AND CANCER OF THE BREAST AND UTERUS


LOWFAT DIETARY PATTERN, CANCER OF THE BREAST AND COLON, AND CORONARY HEART DISEASE


CALCIUM, VITAMIN D, OSTEOPOROSIS AND CANCER


WHI Protocol - Appendices


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SECTION 1

PROTOCReceived Message: EOF received before expected end of data. You can try using a different protocol or sending more data. Ol FOR CLINICAL TRIAL AND OBSERVATIONAL STUDY COMPONENTS

1. Summary

1.1 Summary of Clinical Trial

The Clinical Trial (CT) will evaluate the benefits and risks of Hormone Replacement Therapy (HRT), Dietary Modification (DM), and supplementation with calcium/vitamin D (CaD) on the overall health of postmenopausal women. Health will be assessed on the basis of quality of life measurements, cause-specific morbidity and mortality, and total mortality.

Approximately 64,500 women aged 50-79 from 40 centers will be randomized in a partial factorial design and followed for an average of nine years. Women who are eligible and willing to participate in either the HRT or DM components may enter the trial, but eligible participants will be encouraged to enter both components. Women in the HRT component only will be randomized into placebo or estrogen arms if post-hysterectomy, and otherwise to placebo or estrogen plus progestin arms. Women in the DM component only will be randomized into one of two arms (Dietary Change or Usual Diet), and women in both components will be randomized for both. One year after entry, all eligible trial participants will in addition be invited to be randomized further into one of two arms of the CaD component (CaD supplementation or placebo).

It is hypothesized that estrogen replacement therapy (ERT) and combined progestin and estrogen replacement therapy (PERT) will reduce the risk of coronary heart disease (CHD) and of osteoporosis-related fractures. Women who are post-hysterectomy will be randomized to ERT or placebo, while women with a uterus will be randomized to PERT or placebo. Unopposed estrogen is not included as an option for women with a uterus in order to avoid an unacceptable rate of endometrial hyperplasia and consequent change in treatment regimen. The combined regimen (PERT) is not included as an option for hysterectomized women as the progestin is regarded as an unnecessary drug that could diminish some of the hypothesized favorable effects of ERT for such women. The incidence of endometrial cancer and breast cancer will be monitored during and after the trial. The estimated sample size requirement for the primary outcome of (CHD) is 27,500.

Dietary modification in the form of a low-fat eating pattern is hypothesized to reduce the risk of breast cancer, colorectal cancer, and CHD. The estimated sample size requirement for each of the primary outcomes of breast cancer and colorectal cancer is 48,000. The low-fat eating pattern will include reduced intake of total fat and saturated fat, and increased intake of fruits, vegetables and grains.

Calcium/vitamin D supplementation is hypothesized to reduce osteoporosis-related fractures and colorectal cancer. It is estimated that 45,000 women will participate in this part of the trial.

1.2 Summary of Observational Study

The Observational Study (OS) will consist of CT screenees who have participated in at least one visit but are either not eligible or not willing to participate in the trial, and who agree to participate in the OS. It is anticipated that about 100,000 women will be enrolled into the OS, and they will be followed for an average of nine years.

The OS will complement the CT. Data collected at baseline will be related to subsequent clinical events in order to examine the associations of known and putative new risk factors (and protective factors) with disease. Changes in characteristics over the first three years will similarly be related to subsequent clinical events. Serum, plasma, red cell, and buffy coat specimens will be collected and stored for subsequent analysis in cases and controls. The goals of these studies will be to (1) improve risk prediction of CHD, breast cancer, colorectal cancer, fractures, and total mortality in postmenopausal women, (2) create a resource of data and biologic samples which can be used to unearth new risk factors and/or biomarkers for disease, and (3) examine the impact of changes in individual characteristics on disease and total mortality.
2. Background

2.1 General Considerations

The CT/OS is designed to address some of the major causes of morbidity and mortality in postmenopausal women; namely, CHD, breast and colorectal cancers, and osteoporotic fractures. Cardiovascular disease (CVD) is the most common cause of mortality in older U.S. women, accounting for 29-48% of all deaths in the age range 50-79. Coronary heart disease by itself accounts for 13-22% of all deaths in this age range. Both absolute rates and proportional mortalities from these causes increase steeply with age. Among the cancers, breast cancer is the second most common cause of death. It accounts for 4-11% of deaths, and although rates increase with age the proportional mortality from breast cancer is higher at younger ages. Colorectal cancer is the third most common cause of death among the cancers (after breast and lung), and the second most common incident cancer. Rates increase with age and the proportional mortality is steady at about 4%. Death from complications of hip fractures approximate those for breast cancer and colorectal cancer. In addition, fractures account for much morbidity; the annual incidence of fractures increases from 0.5% of women aged 55-64 to 2.3% of women aged 75-84.

Clinical Trial

The goals of the treatments to be tested are to reduce both the morbidity and the mortality associated with the above diseases. Reductions in morbidity from these common diseases should translate into substantial improvements in the quality of life of postmenopausal women and to major societal benefits if the successful treatments are widely adopted by U.S. women. The treatments will also be studied in relation to a range of other diseases and age-related events.

Multiple outcomes will be studied in order to gauge the effect of the proposed interventions, and of the risk factors, on overall health. These include CHD, other cardiovascular diseases, breast and colorectal cancer, other cancers, and osteoporotic fractures. To assess overall benefit and risk for each of the treatments, overall morbidity and mortality, cause-specific morbidity and mortality, and measures of quality of life will be considered. Unresolved issues relating to possible adverse effects such as an increase in breast cancer or endometrial cancer on HRT, and an increase of renal calculi on CaD, will be examined.

Each of the treatments is expected to influence a number of outcomes. Thus, HRT may benefit both CHD and fractures; low-fat dietary pattern may benefit breast and colorectal cancers and also CHD; and CaD supplementation may benefit fractures and also colorectal cancers. The trial has adequate statistical power for each of these outcomes (see Section 1-A3, Protocol Appendix 3). In general, the trial does not have statistical power to test subgroup hypotheses; nevertheless, trends in certain subgroups will be of interest. Some of the treatments may have synergistic effects in the subgroups receiving a combination of treatments (e.g., HRT and low-fat dietary pattern on CHD and low-fat dietary pattern and calcium on colorectal cancer), while others may tend to cancel out each other's effects (e.g., HRT and low-fat dietary pattern on breast cancer). Negative interactions may exist, so that the effect of a combination of treatments may be little different from each treatment on its own (e.g., the combination of CaD and HRT may have no greater effect on fractures than either treatment alone). Other subgroup hypotheses are that benefit (or risk) may relate to some baseline characteristic (e.g., the protective effect of HRT on coronary disease may be greater in women with existing CHD, while the risk of breast cancer may be exaggerated in women with a family history of breast cancer).

Observational Study

The OS will be used to improve risk estimates for CVD, cancer, and bone fracture in women, so that high-risk women requiring possible treatment may be more precisely identified. Currently, risk factors in women are poorly quantified, or are unknown. The general approach to be used in the OS will be to use nested case-control or case-cohort analyses of the OS cohort in a variety of applications: to examine the associations of known or putative risk factors (including biomarkers) to disease status at baseline and during follow-up; to find new risk markers using the stored biologic samples and data as a resource; and to examine the association of change in known or putative risk factors on disease outcome.
The OS will provide information on the relationship of personal characteristics such as lipid levels, blood pressure, smoking habits, hormonal status, and dietary habits to future clinical events. The OS will also be used to identify new risk factors. Some of these can be hypothesized a priori, while others may arise later and can then be tested. Provided appropriate information and/or biological samples have been gathered and stored at baseline, biomarkers of disease in the form of protein polymorphisms and DNA markers are increasingly being identified. The OS will also be used to examine the impact of involuntary change (i.e., change not induced by treatment) in risk factors on disease outcomes. For example, there is great interest currently in the phenomenon of excess mortality from a variety of causes in persons with low levels of blood cholesterol, albumin, and body weight. The OS will provide an opportunity to test the hypothesis that low levels of blood cholesterol are associated with mortality through the presence of underlying debility or disease which caused both a decline in previously higher levels, and subsequent mortality.

2.2 Hormone Replacement Therapy

2.2.1 Hormone Replacement Therapy and Coronary Heart Disease

The Magnitude of the Problem

The incidence of CHD increases substantially in the decades following the menopause. Both the rates and the proportion of all deaths from CHD increase with age. In 1988 the CHD mortality rates/100,000 (and percentage of all deaths) for U.S. women of ages 50-59, 60-69, and 70-79 respectively were 76 (13%), 260 (19%), and 718 (22%). Coronary heart disease is the leading specific cause of death for women and accounts for the deaths of about 250,000 women each year (National Center for Health Statistics, 1990). CHD in women generally occurs 10-12 years later in life than in men, but because rates approach those of men in the older ages, and there are more older women than older men, overall about half of all coronary deaths occur in women. Almost all these deaths occur in postmenopausal women.

The Potential Role of HRT

The decrease in the circulating levels of estrogens following the menopause is thought to contribute to the increased rates of CHD (Barrett-Connor and Bush, 1991; Korenman, 1990; Godsland et al., 1987). In premenopausal women estrogens may retard the development of atherosclerosis and protect against CHD through their favorable effects on lipoprotein metabolism (and possibly on nonlipid factors such as fibrinogen, blood pressure, insulin levels, body fat distribution, and direct effects on the arterial wall). Reduction in estrogen levels may account in part for the observation that low-density lipoprotein (LDL)-cholesterol levels increase during the transition into the menopause, and continue to increase for some 10-15 years thereafter. There is also a modest decrease in HDL-cholesterol levels during the menopause (Matthews et al., 1989). The effects of exogenous estrogens are pronounced: ERT decreases LDL-cholesterol levels by about 15% and increases HDL-cholesterol levels by a similar amount (Miller et al., 1991; Rijpkema et al., 1990; Walsh et al., 1991). The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial found that women aged 45-64 years randomized to ERT and various PERT regimes experienced similar significant decreases in serum total and LDL cholesterol concentrations, and significant increases in serum HDL cholesterol concentrations, compared with women randomized to placebo. The improvement in cholesterol profile was most marked in the ERT arm, and with PERT arms also giving important, but somewhat variable, improvements.

Some 32 studies have examined the relationship between exogenous estrogen use and CHD. A significantly reduced risk of CHD for women taking ERT has been reported in 11 of 15 published cohort studies and in each of three published cross-sectional angiographic studies (summarized in reviews by Bush et al., 1987; Stampfer et al., 1991; Grady et al., 1992). An additional 13 case-control studies reported less consistent results, and the single small clinical trial yielded promising but inconclusive results (Nachitagall et al., 1979). Various meta-analyses of the pooled studies have indicated highly significant average risk reductions for CHD of 35% to 45% (Bush et al., 1987; Stampfer et al., 1991; Grady et al., 1992), while risk reduction for the combined internally controlled prospective (n=12) and cross-sectional angiographic (n=3) studies was even higher at 50% (Stampfer et al., 1991). In some studies, risk reductions were observed for non-fatal as well as fatal CHD and other CVD, and for all-cause mortality. At least three studies have reported that the risk reductions appear to be even more substantial in women with existing vascular disease (Bush et al., 1987; Sullivan et al., 1990; Henderson et al., 1991).
The data on stroke are less consistent than that for CHD; combined fatal and nonfatal strokes appear not to be reduced, though the studies that provided separate data for fatal stroke consistently showed a decrease in ERT users (Grady et al., 1992). The benefits of HRT appear to increase with prolonged use and current use compared to previous use, though the data are scanty. It is not known whether obese women, who tend to have higher levels of endogenous estrogen, will have the same (hypothesized) benefits from HRT as do lean women.

Progestins are thought to counteract some of the physiologic effects of estrogens. However, it is not known whether progestins will also counteract the putative clinical benefits of estrogens. Cross-sectional studies of CHD risk factors (Nabulski, 1993) and clinical trials (Rijpkema, 1990; Miller, 1991; Lobo, 1994; PEPI, 1995) have provided mixed results. The LDL cholesterol lowering effects of ERT and PERT appear to be equivalent, but in the trials PERT induced a lesser increase of HDL cholesterol than ERT. PERT also induced increases in post-challenge blood glucose levels (but not insulin levels) (Lobo, 1994; PEPI, 1995). However, triglyceride and Factor VII levels were lower on PERT than ERT (Nabulski, 1993; Lobo, 1994). Studies in non-human primates suggest that the anti-atherogenic effects of ERT and PERT are similar, and are mediated through direct vascular effects and LDL cholesterol rather than HDL cholesterol (Adams, 1990; Kushwaha, 1991). Epidemiologic studies (Thomson, 1989; Rosenberg, 1993; Psaty, 1994; Falkeborn, 1992) suggest that the risk reduction for CHD will be similar for users of ERT and PERT. These limited data have not been confirmed in clinical outcome trials.

It is also not clear whether the apparent benefits of HRT from these observational data are largely due to a process of self-selection by which healthier individuals are prescribed HRT, or by other selection biases in the inclusion of subjects or reporting of study results. Such biases may not only exaggerate the apparent benefit, but may also underestimate the magnitude of adverse effects. Studies that have attempted to control for confounders have generally concluded that HRT exerts an independent effect (Stampfer et al., 1991; Henderson et al., 1991; Bush et al., 1987); however, it is almost impossible to control adequately for these (and other, possibly unrecognized) sources of bias in observational studies. Therefore, although the observational studies provide a basis for developing a hypothesis that HRT may reduce the risk of CHD, such a hypothesis can only be tested reliably by a large, well-designed randomized trial.

2.2.2 Hormone Replacement Therapy and Fractures

The Magnitude of the Problem

While fractures are not a major overall cause of death, those women who are hospitalized for hip fracture have a mortality rate as high as 30% from complications such as thromboembolism, fat embolism, pneumonia, and surgical deaths. Fractures are common at older ages and are a major cause of morbidity and loss of mobility (Black et al., 1992 a, b). A woman aged 50 has been estimated to have a 15% chance of being hospitalized for hip fracture during her remaining lifetime (Black et al., 1992 a, b). Annual fracture rates increase markedly with age, being negligible at ages below 55, but rising to 0.5%, 1%, and 2.3% in the age groups of 55-64, 65-74, and 75-84, respectively (Melton et al., 1987). For hip fractures the corresponding rates are 0.1%, 0.3%, and 1.2%. At any age the rates in women are about twice as high as those in men (Melton, 1990). Vertebral fractures are more common than hip fractures but are not usually associated with increased mortality. Other fractures which are associated with osteoporosis include fractures of the pelvis, distal forearm, and proximal humerus.

The Potential Role of HRT

In the main, fractures result from the interplay between bone mass and trauma (Grisso et al., 1991; Melton, 1990). Severe trauma may cause fractures irrespective of bone mass, while even daily activities may result in fracture when bone mass has been severely depleted. Bone mineral density is a particularly good predictor of fractures of the hip, spine, and radius (Black et al., 1992 a, b). Bone loss with aging occurs because the rate of bone formation does not keep pace with the rate of bone resorption. Postmenopausal women lose about a third of their cortical bone and one-half of their trabecular bone. Risk factors relating to bone loss include female sex, increasing age, Caucasian race, oophorectomy, chronic use of oral corticosteroids, early menopause, prolonged immobility, and insufficient dietary calcium. Protective factors include ERT, obesity, and physical activity (Melton, 1990).
Estrogen status is a particularly important determinant of bone mass. Women have an accelerated bone loss at a rate of about 3% per annum immediately following the menopause which is thought to be related to decreases in estrogen levels. Thereafter, bone loss with aging continues at a slower rate of about 1% per annum (Bilezekian et al., 1992; Steiger et al., 1992). Estrogens can prevent both these losses through preventing bone resorption but may be unable to actually increase bone mass (Bilezekian et al., 1992; Prince et al., 1991). Progestins may also aid the maintenance of bone mass. The major effect of estrogens on bone mass is in the years immediately following the menopause, while the peak rate of fractures occurs some decades later. Nevertheless, at any age estrogens may have the potential to prevent further loss of bone, suggesting that even at advanced ages women receiving estrogens may benefit compared to those who do not. Observational studies indicate that women taking estrogens do have greater bone mass and a lower fracture rate (Johnston et al., 1991). However, the effectiveness of estrogens in preventing fractures has not been adequately tested in a clinical trial, due to the large numbers of women needed to obtain a definitive result.

2.2.3 Potential Adverse Effects of Hormone Replacement Therapy

The use of estrogen increases the risk of endometrial cancer, and may increase the risk of breast cancer and of thromboembolism (Barrett-Connor, 1989; Colditz et al., 1990; Willett, 1989; Goldman et al., 1991; Whitehead et al., 1990).

Analyses of pooled observational data have yielded conflicting results in regard to the risk of breast cancer. Sources of bias exist in the observational data, and it is difficult to predict what their effect is on the findings. For example, closer monitoring of patients on HRT may result in more cancers being identified than in the control group, leading to an overestimate of the risk. On the other hand, doctors may be reluctant to prescribe HRT to high-risk women, which may lead to an underestimate of the risk. Meta-analyses indicate that the overall risk of breast cancer from estrogen appears to be increased by a nonsignificant 7% among users of estrogen replacement (Dupont et al., 1991). Risk appears to be related to duration of estrogen use (increasing by 20% after 10 years, and 30% after 15 years), timing (higher in premenopausal women), dose (higher at doses of conjugated equine estrogens above 1.25 mg/day), type of estrogen (higher for estradiol than conjugated equine estrogens), and family history of breast cancer (risk twice as high in women with a family history) (Steinberg et al., 1991). Importantly, there is no consistent evidence that conjugated equine estrogens at a dose of 0.625 mg/day is associated with significantly increased risk.

The relative risk for endometrial cancer incidence appears to be about 1.5 overall but may be as large as 4- to 10-fold over six years of estrogen treatment, and may persist for some years following cessation of treatment (Whitehead et al., 1990). However, the risk of death from endometrial cancer apparently is not increased. This may be because the endometrial cancers are identified early in these women who are generally under close surveillance, or because the type of endometrial cancer induced by estrogen therapy is relatively non-invasive. It is not known whether the risk for endometrial cancer is reduced by regular monitoring of the endometrium, or by early treatment of endometrial hyperplasia. The expected high incidence of endometrial hyperplasia with unopposed estrogen (e.g., PEPI, 1995) and the consequent need for treatment with progestin precludes the study of long-term use of unopposed estrogen in women with a uterus.

The addition of a progestin may reduce or eliminate the risk of endometrial cancer (Whitehead et al., 1990), while the effect of progestins on breast cancer risk is uncertain. In practice, physicians are increasingly adding progestins to ERT in women who have an intact uterus. Progestins tend to reduce the increase in HDL-cholesterol engendered by estrogens, but appear not to influence LDL-cholesterol (Kushwaha et al., 1991; Miller et al., 1991; Rijpkema et al., 1990; PEPI, 1995). It is not known whether the addition of a progestin will counteract the potential benefit of ERT on vascular disease. Progestins may increase the incidence of physical side-effects such as breast tenderness, bloating, edema, withdrawal bleeding, and abdominal cramping, and they also may increase the incidence of psychological side effects such as anxiety, irritability, and depression. The side effects appear to be dose-related, and to be less frequent at smaller doses.

Since CHD accounts for a far larger proportion of all deaths in postmenopausal women than cancers of the breast or endometrium combined, a reduction of 25-50% in CHD will outweigh even substantial increases in deaths from these cancers (Goldman et al., 1991). For example, at age 70-79 CHD accounted for 22% of all deaths in 1988, while cancer of the breast accounted for 4% and cancer of the endometrium for 1% (National
Center on Health Statistics, 1990). ERT has also been reported to increase the risk of thromboembolic events. However, thromboembolism accounted for only a small proportion of deaths (1%) in postmenopausal women.

2.2.4 The Need for a Controlled Trial of Hormone Replacement Therapy

The proposed CT has enormous public health importance, because the diseases to be studied (cardiovascular diseases and fractures) are common, and potential risk reductions obtainable are large. Even if the reductions in CVD mortality and fractures are more modest than those suggested by the observational studies, such reductions could still have a major public health impact, provided that they are not offset by substantial increases in deaths from breast cancer, endometrial cancer, or thromboembolic events.

Currently, a large proportion of physicians do not prescribe postmenopausal HRT beyond the few years after the menopause, either because they are not convinced that such therapy is effective, or because they are concerned about adverse effects. The unfavorable experience of men with preexisting coronary disease who were prescribed large doses of estrogens in the Coronary Drug Project (CDP) have raised doubts about the advisability of using estrogens in patients with CHD, even though the doses currently in use are much smaller than those used in the CDP and the effects in women may be quite different from those in men (Canner et al., 1986; Byar et al., 1988).

When they do prescribe estrogens to postmenopausal women for the purpose of reducing CVD risk, physicians are unsure as to whether the estrogens should be accompanied by a progestin. Though progestins are commonly prescribed together with estrogens in women with a uterus (to protect against endometrial cancer), the epidemiologic data for PERT suggesting benefit in regard to CVD is limited. Progestin-estrogen replacement therapy partly reverses the metabolic effects of ERT, and thus may not have the same magnitude of effect on CVD as ERT. Because of these uncertainties, it is likely that large numbers of women who may benefit from HRT are not receiving it.

These doubts are unlikely to be resolved by further observational studies, because observational studies cannot adequately control for confounding due to differences in the characteristics of women who are treated with HRT compared to those who are not. The similarity of the risk reductions for CVD, CHD, and for all-cause mortality suggests that some or all of the apparent benefit associated with estrogen use may be due to confounding. Some of the possible confounding influences arise from the self-selection of women who go onto hormones, selection bias by physicians as to whom they prescribe hormones to, and socioeconomic biases. A clinical trial, in which selection bias is eliminated by random allocation to treatment and control groups, is needed to evaluate the true benefit of estrogen, and of estrogen plus progestin. Such a trial will provide critical guidance as to the indications for HRT for conditions other than the relief of postmenopausal symptoms. In order to provide this guidance, the trial should test both ERT among hysterectomized women and PERT among women with a uterus.

The CT will be able to assess the benefits and risks of HRT, and thereby provide information on the global impact on women's health. The CT will evaluate the benefits and risks of HRT on CHD, cancers of the breast and endometrium, fracture rates (in particular, hip fractures), quality of life, and total mortality. In addition, information on the possible mechanisms (such as plasma lipids, clotting factors, blood pressure, plasma insulin, body fat distribution) through which estrogens mediate their putative protective effect on CHD will be obtained and analyzed during the trial.
2.3 Dietary Modification

2.3.1 Dietary Modification and Breast Cancer

The Magnitude of the Problem

Among U.S. women, breast cancer is the cancer with the greatest incidence and the one with the second greatest mortality after lung cancer (National Cancer Institute, 1989). In 1991, approximately 175,000 cases of breast cancer were diagnosed and about 44,500 deaths occurred. In 1988 the national mortality rates in the age groups 50-59, 60-69, and 70-79 were 64, 96, and 124 per 100,000 (National Center on Health Statistics, 1990). Breast cancer incidence rates have increased about 1% per year since the early 1970's, whereas mortality rates have remained fairly stable over the past 50 years.

The Potential Role of Diet

International breast cancer incidence rates among postmenopausal women show highly significant positive regression on corresponding per capita dietary fat supply (e.g., Armstrong et al., 1975; Prentice et al., 1990a). In fact, such analysis suggest that a 50% reduction from U.S. fat consumption levels could lead to a two and a half-fold reduction (estimated relative risk of 0.39) in postmenopausal breast cancer incidence (Prentice et al., 1990a). Saturated fat, and particularly polyunsaturated fat, supply correlate with breast cancer incidence in these analyses.

Women migrating from low-fat consumption to high fat consumption areas tend to adopt the higher breast cancer rates of their new country (e.g., Kolonel et al., 1991; McMichael et al., 1988; Margetts et al., 1991). In fact the three-fold higher breast cancer incidence among Japanese women in Hawaii, as compared to Japanese women in Japan (Tominaga et al., 1985) appears to be quite consistent with the international regression analysis noted above upon acknowledging per capita fat supply differences between the two countries (Prentice et al., 1990a).

There is extensive literature relating fat consumption in rodents to mammary tumor incidence (e.g., Carroll et al., 1975). Though these data have been variably interpreted, a recent meta-analysis (Freedman et al., 1990) indicates that dietary fat has a specific positive association with mammary tumor incidence, beyond the association that can be attributed to fat as a source of calories.

Analytic epidemiologic studies have tended to yield equivocal results concerning dietary fat and other dietary factors in relation to postmenopausal breast cancer risk (e.g., Greenwald, 1988; Prentice et al., 1988; Hulka, 1989). In large part, this may be due to a limited range of intakes of fat and other nutrients within populations studied, and to the known major random and systematic errors that attend individual estimates of nutrient intakes based on available dietary assessment techniques.

These factors combine to reduce study power and reliability, and to elevate the importance of minor confounding biases (e.g., Goodwin and Boyd, 1987; Prentice et al., 1989; Byar et al., 1989). Nevertheless, a meta-analysis of the raw data from 12 case-control studies, including several thousand cases and controls, yielded a highly significant positive association between estimated fat consumption and postmenopausal breast cancer risk (Howe et al., 1990). Moreover, the estimated risk relationship appears to be quite consistent with the strong international regression analysis noted above. On the other hand, the three existing sizable cohort studies of dietary fat and breast cancer appear to yield conflicting results. The studies of Howe et al., (1991), and Kushi et al., (1992), report non-significant positive associations that appear to be consistent with the international analyses, while that of Willett et al., (1992), is not suggestive of any positive association between fat consumption and breast cancer risk.
Some of the studies alluded to above have suggested that vegetable intake, or related dietary intakes may be associated with reduced breast cancer risk (e.g., Howe et al., 1990). However, results concerning these associations have often been inconsistent or equivocal in individual analytic epidemiologic studies, quite possibly for the reasons mentioned above.

Feasibility studies of a low-fat eating pattern among healthy women in the age range 45-69 (e.g., Insull et al., 1990; Henderson et al., 1990; Gorbach et al., 1990) show that women randomly assigned to dietary intervention are able to reduce the fat content of their diet to about 20% of calories and to retain the dietary change for two years or more. Change in plasma hormone concentrations were also studied in a subset of women assigned to dietary intervention. These women were found to experience a significant, average 17%, reduction in plasma estradiol concentration following a few weeks of dietary intervention (Prentice et al., 1990 b), thereby adding strength to the low-fat eating pattern and breast cancer prevention hypothesis.

2.3.2 Dietary Modification and Colorectal Cancer

The Magnitude of the Problem

Colorectal cancer is the third leading cause of cancer deaths in U.S. women and the incidence is third only to that of breast and lung cancer (National Cancer Institute, 1989). About 78,500 new cases were diagnosed in 1991 and approximately 31,000 deaths from colorectal cancer occurred. In 1988 national mortality rates for colorectal cancer in the age groups 50-59, 60-69, and 70-79, respectively were 21, 53, and 109 per 100,000 (National Center on Health Statistics, 1990).

The Potential Role of Diet

Epidemiologic and animal studies conducted over the last few decades have established a fairly strong link between dietary factors and colorectal cancer (National Research Council, 1989). Various dietary constituents have been implicated, including fat, excess calories, and reduced dietary fiber. International correlation studies show an approximately linear relationship between total dietary fat availability and colorectal cancer risk (Carroll and Khor, 1975). In fact, such analyses suggest that a 50% reduction from U.S. fat consumption levels could lead to a three-fold reduction in colorectal cancer risk (Prentice et al., 1990a). Studies in migrants from areas with diets low in animal fat and protein to areas with a more typical "Western" diet with high fat intakes show an increase in incidence of colorectal cancer among the migrants when compared to incidence in the country of origin (e.g., migration from Japan to Hawaii, Kolonel et al., 1981; and from Italy to Australia, McMichael and Giles, 1988). A National Cancer Institute sponsored clinical trial is currently assessing the ability of a low-fat, high fiber diet to prevent the recurrence of colonic polyps, which are considered to be precursor lesions for colon cancer.

A rather large number of case-control studies have examined the relationship between estimates of dietary fat consumption, and colorectal cancer risk (e.g., Graham et al., 1988; Jain et al., 1980; Kune et al., 1987; Lyon et al., 1987; Potter et al., 1986; Slattery et al., 1988; Loe et al., 1989; Tuyn et al., 1987, Whittemore et al., 1990). The studies have tended to yield mixed and equivocal results (Kolonel et al., 1987), though collectively they seem to be fairly consistent with projections based on the strong international correlational results (Prentice et al., 1990a). Prospective study results have likewise given mixed results with a study of men of Japanese ancestry (Stemmerman et al., 1984) not suggestive of a relationship between saturated fat and colon cancer, while a recent study in U.S. nurses reported a significant positive association (Willett et al., 1990).

Several international correlation and case-control studies have shown inverse relationships between the intake of high fiber foods and colon cancer risk (National Research Council, 1989; Greenland et al., 1987). High intake of fruits and vegetables has been fairly consistently related to lower risk of colon cancer, whereas the consumption of cereal grain products has been either unrelated or negatively associated with risk of colon cancer. Analytic epidemiological studies that have had a reasonable capability to assess dietary fiber have tended to suggest a protective effect for fiber consumption (e.g., Trock et al., 1990), while considerable recent interest focuses on the potential of various sources of fiber (e.g., wheat bran versus oat bran) to reduce colorectal cancer risk.
2.3.3 Dietary Modification and Coronary Heart Disease

The Magnitude of the Problem

See Protocol Section 2.2.1 on Hormone Replacement Therapy.

The Potential Role of Coronary Heart Disease

The etiology of CHD has been linked through international studies to the consumption of high fat diets. Saturated fat intake as a percent of calories correlated strongly ($r = 0.84$) with CHD mortality rates in the Seven Countries Study (Keys, 1980). A lifelong low-fat diet may in fact exert beneficial effects on CHD rates beyond its influence on blood cholesterol. The slope of the line relating dietary percent calories from saturated fat is nearly two and one-half times greater than that which would be expected if saturated fat operated only by raising serum cholesterol. Migrant studies (e.g., Japanese migrants to Hawaii) suggest an important effect of saturated fat consumption on CHD rates (Robertson et al., 1977). As in the case of cancer, and probably for the same methodologic reasons, it has been difficult to demonstrate a consistent effect of saturated fat on CHD in analytic studies of individuals within populations.

Dietary factors other than saturated fat may influence CHD rates either via reducing blood cholesterol (e.g., food fiber), through decreasing levels of oxidized LDL (by increasing the intake of antioxidants such as selenium, vitamin E, ascorbic acid, and beta-carotene), through effects on the platelet function (fish oils), or through indirect or unknown mechanisms.

Role of Serum Cholesterol on CHD Women

Serum total cholesterol levels generally increase from young adulthood through middle age in both men and women, with levels for men generally higher. However, above age 65, cholesterol and LDL values are considerably higher in women than in men. Increasing levels of serum cholesterol correlate with an increasing incidence of CHD among women up to the age of 65 years. Beyond this age, the association is less robust, but fewer studies are available. There is some evidence that serum triglyceride levels may be predictive of CHD in postmenopausal women. Increasing high-density lipoprotein (HDL)-cholesterol levels appears to be protective in women of any age (Manolio et al., 1992).

Cholesterol Lowering and CHD

The major prospective primary and secondary prevention clinical trials that demonstrate a reduction of CHD events by lowering of plasma cholesterol levels by diet and/or drugs have been conducted in middle-aged men (Lipid Research Clinics, 1984; Frick et al., 1987). Studies in men and women have shown that restriction of dietary fat and cholesterol can lower plasma total and LDL-cholesterol, though the results appear to be somewhat less consistent in women (Ernst et al., 1980; Kris-Etherton et al., 1988). No studies have been conducted in postmenopausal women to determine the long-term effect of a low-fat diet on lipid levels. Furthermore, there have been no large randomized trials in women to study the effects of lowering lipids on CHD incidence. Women's Health Trial feasibility studies (Insull et al., 1990; Henderson et al., 1990) demonstrate a modest but highly significant reduction in plasma cholesterol concentration among women assigned to DM.

2.3.4 The Need for a Controlled Trial of a Low-Fat Eating Pattern

Many types of evidence bear upon the hypotheses of interest in the proposed dietary intervention trial, namely that dietary intakes of fat, grains, fruits and vegetables are related to the incidence of breast and colorectal cancers. Considerable differences of opinion continue to exist among scientists on the "diet-cancer" hypothesis, in large part due to numerous limitations and inconsistencies in the available data.

Animal experiments are important for demonstrating plausible biological mechanisms and for confirming or explaining the results of epidemiological studies, but their results cannot on their own be extrapolated to
humans. If a marker for disease exists, then clinical metabolic studies may be performed to test the effect of DM on the marker. No such marker currently exists for breast or colorectal cancer.

Studies correlating international data on incidence of disease with food disappearance data and migrant studies provide useful information in support of these hypotheses but cannot be entirely relied upon because available dietary data are crude and because results may be subject to confounding and aggregation biases.

Case-control studies overcome some of these problems but suffer from possible biases in the selection of cases and controls and differential recall of dietary intake by cases and controls, as well as from non-differential error in the measurement of dietary intake. Prospective cohort studies avoid selection and recall biases but still rely upon food questionnaires which are known to involve substantial measurement error. These problems are compounded by the narrow range of intakes of the populations typically entering a case-control or cohort study.

Definitive studies to test the effectiveness of dietary interventions to reduce cancer incidence and mortality are not available. The proposed randomized trial of a low-fat dietary pattern, defined as an eating pattern that is low in fat and high in fruit, vegetables and grains, will have an appropriate design and will have the power to provide a definitive answer to a question of great public health importance.

The proposed trial will at the same time provide estimates of the effectiveness of a low-fat dietary pattern in preventing CHD, as well as providing information on the effect of such a dietary pattern on serum cholesterol, blood pressure, and body weight. If a low-fat dietary pattern does reduce the incidence of any one of the clinical outcomes of breast cancer, colorectal cancer, or coronary disease, the public health implications will be important since it can be expected to lead to an even greater emphasis on low-fat dietary patterns and in public health recommendations and in clinical practice. Also, as a result of this CT, dietary guidelines (e.g., National Research Council, 1989) may be able to be refined, and the credibility of such recommendations will be much enhanced.

2.4 Calcium and Vitamin D (CaD) Supplementation

2.4.1 Calcium, Vitamin D and Fractures

The Magnitude of the Problem

See Protocol Section 2.2.2 on Hormone Replacement Therapy.

The Potential Role of CaD

Insufficient dietary calcium is one of the possible risk factors for osteoporosis and hence for fractures (e.g., Heaney 1982; Cummings et al., 1985; Cummings, 1990). An inadequate intake of calcium is common in women; the NHANES data show that calcium intake in women is 40-50% below that of men, and 75-80% of women have daily intakes below 800 mg, while 25% have intakes below 300 mg. According to the 1984 National Institutes of Health (NIH) Consensus Development Conference on osteoporosis, dietary calcium intake required to prevent negative calcium balance increases from around 1000 mg/day in perimenopausal women to 1500 mg/day after the menopause (NIH Consensus Development Panel, 1984). Intestinal absorption of calcium declines with advancing age (Gallagher et al., 1979). An age-related intestinal resistance to the action of 1,25(OH)2D has been implicated in this impaired absorption (Heaney, 1982), as have age-related changes in parathyroid hormone and 1,25(OH)2D levels (Riggs et al., 1986). Estrogen is known to enhance intestinal calcium absorption and renal calcium conservation (Heaney, 1990). Thus, both estrogen and calcium supplementation can help reverse the negative calcium balance that accompanies aging. On the other hand, low-fat diets are sometimes accompanied by a reduced intake of dairy products and of calcium and may thus increase the negative calcium balance (Holbrook et al., 1991), though reduced calcium intake has not been found in feasibility studies of the DM program to be used in the Women's Health Initiative (WHI) (Insull et al, 1990).

Even though low dietary calcium intake may be a risk factor for osteoporosis and for fractures, the data on the effectiveness of calcium supplements are conflicting (Reid, 1990; Dawson-Hughes et al., 1990; Riis et al., 1987;
Prince et al., 1991). This variation may reflect differences in hormonal status and diet of the subjects. In a recent study of older postmenopausal women, calcium supplements were effective in preventing bone loss in those women with a dietary calcium intake of less than 400 mg, but not in those with higher dietary calcium intakes (Dawson-Hughes et al., 1990). The addition of vitamin D appears to increase the effect of supplemental calcium on the prevention of bone loss; it is uncertain whether this is because the absorption of calcium is enhanced, or whether vitamin D exerts an independent effect (Dawson-Hughes et al., 1991). Estrogen therapy reduces bone loss in postmenopausal women, and it is not known whether calcium supplementation in women already on estrogen will induce a significant further reduction in bone loss.

2.4.2 Calcium and Colorectal Cancer

Human observational studies (e.g., Garland et al., 1986; 1989; 1991) and animal experiments suggest that calcium may decrease the risk of colorectal cancer, possibly because increased formation of the calcium salt of bile acids decreases promotion of cancer (Lipkin et al., 1991). Data from controlled trials on the effect of calcium supplementation on colorectal cancer are not available, hence this large trial may provide valuable information.

2.4.3 The Need for a Controlled Trial of CaD

Despite the conflicting data regarding efficacy, many women are currently taking supplements of CaD in the hope of reducing bone loss. Only one trial of the effect of calcium and vitamin D₃ supplementation and fracture rates has been reported; hip fracture rates among healthy elderly women were reduced by 43% (P=0.05) among women completing an 18-month course of 1.2 grams of elemental calcium and 800 IU of vitamin D₃ per day (Chapuy et al., 1992). A definitive clinical trial would provide a rational basis for advising women concerning such supplementation. The CaD component will indicate whether supplementation is effective in reducing bone loss and fracture rates, and in reducing colorectal cancer. Subgroup analyses may provide additional information on aspects such as the effect of varying dietary intake of calcium on efficacy of supplementation in reducing bone loss, the effect of supplementation alone or in combination with estrogens on bone loss, and the effect of calcium alone or in combination with a low-fat dietary pattern on colorectal cancer.

A 1994 NIH Consensus Development Conference panel has recommended that postmenopausal women should have a daily calcium intake of 1000 to 1500 mg to reduce fracture risk, and stressed the need for sufficient vitamin D intake to maximize the benefits of calcium on bone health. The panel also advocated more research on the potential of adequate calcium intake to decrease the risk of cardiovascular disease and colon cancer (NIH Consensus Development Panel, 1994).

2.5 Observational Study

2.5.1 Observational Study Potential

Observational studies have made unique and important contributions to medical knowledge. Historically observational studies have not only generated the hypotheses which were later tested in clinical trials, but have also had a more direct impact on medical practice. For example, a valuable contribution of the Multiple Risk Factor Intervention Trial (MRFIT) was not to be found in the trial results but in the observational data on the large cohort of male screenees. The MRFIT cohort provided very stable estimates of relative and absolute risk for CHD in men by level of serum cholesterol, and these estimates have been of critical importance in the formulation of national guidelines for the prevention of CHD by lowering cholesterol. No comparable data exist for women. Cigarette smoking and lung cancer provide another example of the importance of observational data; the association was so strong and consistent that observational data alone were sufficient to convince health authorities that action to curb smoking was desirable.

Randomized controlled trials offer a unique opportunity to evaluate the influence of preventive measures on health outcomes, since randomization eliminates the possibility that individuals otherwise at altered risk of an outcome selectively have been exposed to the measure. Nonetheless, we cannot rely on the results of randomized controlled trials for all of our information on the causes of disease and the effectiveness of health interventions. First, some potential causes of disease simply are not amenable to study via randomization. For
example, in studies of long-term health outcomes it is rarely possible to randomize individuals to occupational or environmental exposures. Second, because of the costs of large randomized controlled trials, only a limited number of preventive interventions are assessable. In addition, in randomized controlled trials it is necessary to employ a relatively small number of intervention arms, e.g., treated vs. placebo, or treatment A vs. treatment B vs. placebo. Often, the range of potential interventions for a particular health problem is wider than can be encompassed in a single trial. For instance, in the randomized trial portion of the WHI, all women assigned to receive estrogen plus progestin will be asked to take a particular daily preparation at a given dose. Thus, the results from the trial will not speak directly to the influence of other types of progestin, or of hormones taken at different doses or for other durations each month, on the occurrence of breast cancer, myocardial infarction, and other diseases.

Given the foregoing, it is not surprising that many of the inferences made regarding the prevention of disease are based on the results of nonrandomized studies. The latter may take the form of: a) cohort (or follow-up) studies, in which persons with or without (or at various levels of) a given characteristic are monitored for the subsequent occurrence of one or more health outcomes; or b) case-control studies, in which ill and well persons are contrasted for one or more prior exposures. The OS is designed as a cohort study. For efficiency purposes, without the risk of introducing bias, many uses of the OS will involve so-called nested case-control or case-cohort subsampling procedures.

A relative advantage of cohort over case-control studies is the ability to ascertain an individual's exposure status prior to the presence of the outcome, thereby minimizing potential bias that can occur via retrospective ascertainment of exposure. To date, a number of cohort studies have been conducted that have been able, in one way or another, to address risk factors for health outcomes in older women. The planned OS has the potential to provide information that goes well beyond that provided by existing studies. It is large (the Study will seek to recruit some 100,000 subjects) and subjects are to be followed for a relatively long time (9 years). Questionnaires and baseline physical and laboratory examinations will be obtained on all cohort members. In addition, specimens (e.g., samples of blood, separated into its various components) will be obtained and stored for later use. Follow-up of the cohort and ascertainment of illnesses of interest will be highly complete. Finally, the range of health events identified in cohort members will be wide and will encompass the large majority of serious illnesses that occur in middle-aged and older women.

A wide variety of important clinical and public health issues will be assessed with the OS. Firstly, the OS will provide stable estimates of the relative and absolute risks for specific diseases posed by known risk factors such as serum cholesterol (and lipoprotein subfractions), blood pressure, smoking, hormone use, exercise, and obesity for CHD, for example. This information will be gathered by relating information obtained on baseline characteristics to subsequent illness events and mortality. Secondly, the study is designed to address the hypothesis that underlying debility and disease is responsible for the excess mortality at low levels of body weight, cholesterol, and blood pressure. This hypothesis will be tested by relating the markers of clinical and subclinical disease, and change in weight, cholesterol, and blood pressure to subsequent mortality. Previous studies have not had the ability to address this hypothesis because of small numbers, lack of repeated measurements, inadequate ascertainment of subclinical disease, or failure to measure appropriate covariables. The third and perhaps most important purpose is the identification and testing of new hypotheses with regard to disease etiology that are not yet satisfactorily addressed in completed or ongoing studies. In addition to questionnaires and physical data, the gathering of biological specimens at baseline for storage and later analysis will allow hypotheses that arise during the course of the WHI. To be examined in nested case-control or case-cohort studies. It is likely that new potential biomarkers of disease, such as protein polymorphisms and DNA markers, will be identified during the course of the WHI. The availability of stored biological material and information on other factors that might confound or modify biomarker-disease relations will facilitate epidemiologic studies of these newly identified potential determinants of disease.

The large size of the overall cohort, combined with the effort that is to be made to include sizable proportions of members of racial/ethnic minorities, will permit for a number of the more common health outcomes the identification of risk factors in individual minority groups. Minority women have not been well represented in most past or present cohort studies of CVD, cancer, or fractures. The proposed OS can be expected to enroll about 20,000 minority women as subjects. With these much greater numbers, it can begin to explore interracial differences in risk factors for conditions that occur with relatively high frequency, e.g., the major cancers, CVD,
hip or forearm fracture, and other age-related outcomes (e.g., diabetes mellitus, glaucoma, urinary incontinence). Similarly it will be possible to explore differences in risk factor impact on other subgroups; for example, those defined by age and socioeconomic characteristics.

For reasons of cost-effectiveness, the OS participants at individual Clinical Centers (CCs) will generally be drawn from a convenient sample rather than a population-based sample. Also, they will be screenees for the CT. The potential loss of "representativeness" will however be mitigated by the wide geographic distribution of the approximately 40 CCs, which will draw on diverse populations, and by the plan to recruit about 20% minority women in the study-wide sample. It is not the intent of the WHI to compare the cohort as a whole with other populations. All the comparisons will be within the cohort itself, e.g., women with and without high blood pressure, and women who do and do not use a progestin to supplement their use of postmenopausal estrogens. Furthermore, many key risk factors for the diseases of interest will be identified in cohort members, so that a relatively unconfounded estimate of the influence of a particular risk factor should be obtainable. Thus, we believe that the generalization of results obtained from the intracohort comparisons will be no less broadly applicable than those of any other epidemiologic study.

The OS capitalizes on the existence of the CT's needs to screen a very large number of potential participants in order to obtain the targeted number of actual participants. Thus, the marginal cost of cohort identification for the OS is exceedingly small - almost all of the screening costs would be incurred even if there were no OS. While the added expense of following a large group of nonrandomized women for health outcomes is substantial, even this expense is considerably smaller than if the human and physical resources were not to be shared with those of the parallel CT.

2.5.2 Need for the Observational Study

There is an urgent need for stable estimates of the magnitude of risk factor impact on health in postmenopausal women; these estimates are not nearly as complete as in men. There is a need for the identification of "new" risk factors, and the cohort design and procedures of the OS allows for exploration of risk factors of uncertain status, or factors which have yet to be identified. There is a need for the elucidation of the mechanisms underlying the excess risk of mortality at low levels of weight, cholesterol, and blood pressure. Finally, there is a need 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. All of this information is important in setting health policy guidelines. It is unlikely that any of this kind of information will be obtained from clinical trials or from other existing observational studies.
3. **Study Objectives**

3.1 **Objectives of the Clinical Trial**

The overall objective of the trial will be to ascertain the benefits and risks of a number of treatments that may improve the health of postmenopausal women ages 50-79. The treatments to be tested are: HRT, low-fat dietary pattern, and supplementation with CaD.

**The specific aims of each of these treatments are:**

For HRT:

1. To test whether ERT and/or PERT reduce the incidence of CHD and of other CVD.
2. To test whether ERT and/or PERT reduce the incidence of all osteoporosis-related fractures and hip fractures separately.
3. To assess whether ERT and/or PERT increase the risk of breast cancer.

For Dietary Modification:

1. To test whether a low-fat dietary pattern reduces the incidence of breast cancer and colorectal cancer, separately.
2. To test whether a low-fat dietary pattern reduces the incidence of CHD.

For CaD:

1. To test whether supplementation with calcium and vitamin D reduces the incidence of hip fractures.
2. To test whether supplementation with calcium and vitamin D reduces the incidence of colorectal cancer.

Sample size estimates have been based on the first aim for each treatment (see *Section 1-A3, Protocol Appendix 3*), and power calculations have been conducted for the remaining aims. Even though the trial will generally not have sufficient power to test subgroup hypotheses unless there are unexpectedly large effects, various additional analyses will be conducted to obtain information as to whether the effects of treatments appear to vary by participant characteristics or by the presence of another treatment. Subgroup analyses that will be performed will examine:

1. The effect of HRT on the incidence of coronary and other CVD in women with, and in women without, CVD at baseline.
3. The effect of supplementation with CaD on fractures and colorectal cancer in women with low, and women with higher, intakes of dietary calcium.
4. The effect of HRT, and of a low-fat dietary pattern, on breast cancer incidence in women at high and at low risk of breast cancer.
5. The effect of HRT plus low-fat dietary pattern on coronary and other CVD and on breast cancer compared to each therapy alone.
6. The effect of HRT plus CaD supplementation on fracture rates, compared to each therapy alone.
7. The effect of HRT on CHD and other CVD among women with a uterus, as compared to hysterectomized women.
8. The effect of HRT, DM and CaD in subgroups of women defined by age and race/ethnicity.
In the HRT, analyses comparing active hormone therapy to placebo, stratified by hysterectomy status, will be conducted to examine the effects of prescribing the hormone preparation most appropriate with regard to a woman's uterine status. This approach also serves to increase power when the effects of ERT and PERT are similar.

The trial will also offer the opportunity to examine certain other questions such as: the effect of each treatment on perceived quality of life, on combined primary and secondary outcomes, and on total mortality; the effects of HRT and DM on lipids, lipoproteins, clotting factors, blood pressure, body mass index, waist-to-hip ratio, and blood glucose; trends in the magnitude of HRT, DM and CaD effects across age categories and across values of other participant characteristics; the relationship to clinical outcomes of (a) baseline biochemical and physical variables, (b) changes in those variables induced by treatment, and (c) adherence. The ability of changes in such intermediate variables to explain an observed relationship between treatment and disease occurrence will also be examined.

The CT will provide valuable information on various other outcomes, even though the study design has not been motivated by considerations of power for such other outcomes. For example, DM will also be studied in relation to other cancers, including ovary and endometrium cancer, and in relation to diabetes mellitus incidence; and CaD supplementation will be studied in relation to cancers other than colorectal, including breast. Importantly, total mortality rates and other summary measures of benefits versus risks will be monitored in relation to each treatment and treatment combination. An important subsidiary aim is to examine the effect of each CT treatment on bone density (see Protocol Section 8).

3.2 Objectives of the Observational Study

The overall objective of the OS is to provide information complementary to that obtained from the CT. Measurement of baseline characteristics, remeasurement after three years, storage of frozen blood specimens, and ascertainment of clinical events in a large cohort of postmenopausal women allow the following specific objectives to be formulated:

1. Prediction of risk of outcome on the basis of:
   - Questionnaires and interview data: Women in the OS will be asked to complete the same self-administered questionnaire as CT participants. In addition, they will be asked to complete a supplemental questionnaire at the end of the screening visit at which a woman joins the OS, usually Screening Visit 1 (SV1) and at selected follow-up visits. This will permit the evaluation of associations that cannot be studied in the CT.
   - Physical exam findings: The anthropometric measurements will be related to the occurrence of selected illnesses and mortality.
   - Laboratory data: Some previously studied markers of risk can be examined in considerably greater detail than before, e.g., levels of specific lipid components, whose role in the occurrence of CHD in women is not as well understood as it is in men. Of particular interest will be analyses of stored specimens for recently-developed (or as-yet-to-be-developed) potential biomarkers, e.g., apoprotein subtypes in relation to CHD incidence, or genetic polymorphisms identifiable in stored leukocyte DNA in relation to cancer incidence.

2. Extension of results obtained in the CT to related exposures or regimens: For example, if estrogen use (or calcium supplementation) is found to be effective in achieving a given outcome as measured in the randomized controlled trial, then one could assess whether in the OS a similar relationship is present for that exact regimen, adjusting for confounding variables and exposure durations as necessary. If a similar relationship is found, a relatively high level of credibility could be given to analyses of related regimens outside those studied directly in the randomized trial. For example, if use of estrogens plus a given progestin regimen is found to have a beneficial effect on the incidence of myocardial infarction, the data from the OS can be used to assess the extent to which different progestins/doses/durations can achieve the same effect.
3. Assessment of temporal relationships between risk factors and disease occurrence: Changes in characteristics such as weight or serum albumin or cholesterol levels, or changes in hormone use, could be assessed for their ability to predict rates of selected clinical outcomes. By measuring and controlling for the presence of subclinical disease prior to the change in risk factor status, the ability to infer a causal relation between change in a risk factor and the subsequent incidence of diagnosed disease will be enhanced.

4. Documentation of variation in the incidence of CVD, cancer, osteoporosis and fracture in postmenopausal women on the basis of geographic region and other demographic characteristics, and an evaluation of the extent to which differences among demographic subgroups in the prevalence of identified risk factors account for such variation.

Section 1-A5, Protocol Appendix 5 - Women's Health Initiative Observational Study Overview of Objectives and Hypotheses provides a partial list of risk factors that will be examined in the OS.
4. **Study Design**

4.1 **Overview**

The trial will be a partially blinded, controlled clinical trial in postmenopausal women age 50-79 years. The trial will evaluate potential preventive treatments for certain clinical conditions which are important causes of morbidity and mortality in postmenopausal women.

The trial will have three main components and four active treatments. The treatments will be tested in a partial factorial design (*Figure 1*). Such a design allows the total number of participants to be considerably less than would be required for separate experiments for each of the three CT components. The first component will test separately the efficacy of ERT vs. placebo among hysterectomized women, and of PERT vs. placebo among women with a uterus*, on CHD; the second will test the efficacy of low-fat dietary pattern vs. usual dietary pattern on breast and colorectal cancers (two arms); and the third will test the efficacy of CaD supplementation vs. placebo on hip fractures (two arms). In regard to safety, clinical outcomes of interest include breast cancer and endometrial cancer (HRT) and renal calculi (CaD supplementation).

Sample size calculations indicate that for the HRT component, 27,500 women, and for the DM component 48,000 women, treated for an average of nine years would provide adequate power for the primary outcomes of interest. Assuming some overlap between the HRT and DM components, it is anticipated that a total of 64,500 women would enter the CT. It is assumed that about 45,000 (70%) of these women will be willing to subsequently enter the CaD component (see *Section 1-A3, Protocol Appendix 3* for statistical power calculations). Post-trial mortality and breast and endometrial cancer incidence surveillance for a further five years is envisaged, so that total follow-up will be for an average of 14 years. The longer follow-up will protect against the possibility of missing adverse effects, such as breast cancer in relation to HRT, which may not have had sufficient time to manifest clinically during the nine year average follow-up period.

Women will be recruited on the basis of their eligibility and willingness to participate in either the HRT or the DM components, or both. It is anticipated that about 40% of women who are enrolled in the HRT component will also be enrolled in the DM component. This 40% rate is the product of 0.60, the fraction of HRT women who are expected to meet DM-specific eligibility criteria (*Protocol Section 4.4*), and 0.67, the fraction of HRT women who are assumed to be willing to be randomized into the DM component. A smaller proportion (23%) of women in the DM component are expected to also be eligible and willing to enter the HRT component. The distribution of women in the dietary component will be 40:60 active treatment:control, and in the HRT 9:11:20 ERT:PERT:placebo as is elaborated in the following paragraph. The unequal distributions are intended to decrease study costs while maintaining statistical power. The randomization in the CaD component, which will take place at a participant's first annual visit, will be 50:50 active treatment:placebo. The total trial cohort size is projected to be 64,500.

Women who are post-hysterectomy will be randomized in the HRT between placebo and ERT in the ratio of 1:1. PERT will not be an option for such women, as the role of the progestin is primarily to protect the uterus. Women with an intact uterus will be randomized to placebo or PERT in the ratio of 1:1. The fraction of women with a hysterectomy at baseline will be restricted to be approximately 45%. This distribution was chosen in order to achieve adequate power for ERT vs. placebo and PERT vs. placebo in respect to CHD. *Figure 1* shows the projected number of women in each cell of the CT defined by the HRT and DM randomizations.

*In the original design, women with a uterus could also be randomized to ERT with annual endometrial monitoring. The PEPI experience (PEPI, 1995) clearly indicated that the unopposed estrogen arm was infeasible because of an unexpectedly high incidence of endometrial hyperplasia. Randomization to ERT among women with a uterus was therefore stopped on December 16, 1994. The 331 women who had previously been randomized to ERT were changed to PERT. They will be followed in the PERT arm for routine analyses. Separate analyses of women randomized before December 16, 1994 or additional stratification to account for this change will be used in key analyses.*
The frequency of women by age group will have the following targets, with acceptable age ranges given in parentheses: 10% (0-15%) for ages 50-54; 20% (15-25%) for ages 55-59; 45% (40-50%) for ages 60-69; and 25% (20-30%) for ages 70-79. These frequencies were motivated by a desire to retain the entire age range 50-79, while paying suitable attention to overall risk versus benefit projections. Power calculations (Section 1-A3, Protocol Appendix 3) have been based on the above age targets. To achieve the designated power, accrual of women into both the HRT and the DM components will be restricted to the given age-specific ranges in each clinic.

Women aged 50-79 who have been screened and found not to be eligible for the trial, or who after screening are not willing to participate in the trial, will be invited to participate in the OS component. Supplemental recruitment to the OS may be required in some CCs. Much of the same baseline information as for women in the trial will be collected, and mortality and morbidity surveillance will be maintained for an average of nine years. A supplemental epidemiologic questionnaire will also be administered to OS women. In addition, women will be invited to attend a second visit three years after baseline, in order to allow examination of the effects of changes in characteristics on disease outcomes. It is anticipated that 100,000 women will be recruited into the OS.

### 4.2 Choice of Treatments

#### 4.2.1 Hormones

As previously mentioned, women participating in the HRT component will be randomized based on the presence or absence of a uterus.

1. Women with a uterus will be randomized to one of two arms:
   - Conjugated equine estrogen (CEE) 0.625 mg per day plus medroxyprogesterone* (MPA) 2.5 mg per day continuously (PERT)

* In each cell, approximately 70% of women are projected to be eligible and willing to be randomized to receive calcium and vitamin D supplementation or placebo (1:1 allocation).
Placebo estrogen plus placebo progestin

2. Women without a uterus will be randomized to one of two arms:
   - Conjugated equine estrogen (CEE) 0.625 mg per day (ERT)
   - Placebo estrogen

The drug manufacturer will provide the single and combined hormones in single tablets, so that all participants will take only one tablet per day, regardless of the arm to which they are randomized. The drugs will be distributed in 6- to 12-month supplies in bottles that women will return for tablet measuring and replacement.

Drug dosages and regimes were chosen to minimize side effects and adverse effects, and provide ease of administration while maintaining clinical effectiveness.

The selected hormones and the rationale for these choices are as follows:

1. Conjugated equine estrogens (CEE) at a dose of 0.625 mg/day:
   - This lower dose and type of estrogen is associated with favorable changes in blood lipids, bone loss, and coronary risk, and may be less likely to increase rates of breast cancer and endometrial cancer. Furthermore, conjugated equine estrogens are the most commonly prescribed estrogen preparation in the United States.

2. Medroxyprogesterone (MPA) at a dose of 2.5 mg/day, continuous:
   - This agent was chosen from among the progestins because at this continuous low dose it appears to cause less reversal of the beneficial effects of estrogen on lipids than the higher dose cyclic MPA, or the 19-nortestosterone derivatives. It is the most widely prescribed progestin in the United States and is also believed to be as protective of the endometrium as higher dose cyclic MPA. Many women are reluctant to have regular menstrual periods that occur in 85% of women on cyclical regimes. In addition, there will be the benefits of ease of administration for the participants, as well as facilitation of blinding, timing of clinic visits, and drug packaging.

4.2.2 Dietary Modification Component Goals

The nutritional goals for the intervention group are to reduce the intake of total dietary fat to 20% of corresponding daily calories, reduce the intake of saturated fats to less than 7% of calories, and to increase servings of vegetables and fruits to five or more daily and servings of grain products to six or more daily. Each participant's fat intake goals will be expressed in grams of fat per day. The fat gram goal will be calculated using an algorithm based on height and a fat gram goal of 15% energy from fat, calculated using expected caloric intake after one year of intervention (Table 1).
### Table 1

<table>
<thead>
<tr>
<th>Height (cm)</th>
<th>Fat Gram Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td>23</td>
</tr>
<tr>
<td>152</td>
<td>23</td>
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<tr>
<td>154</td>
<td>24</td>
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<td>162</td>
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<td>164</td>
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<td>166</td>
<td>25</td>
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<td>168</td>
<td>25</td>
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<td>170</td>
<td>25</td>
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<td>172</td>
<td>26</td>
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<td>174</td>
<td>26</td>
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<tr>
<td>176</td>
<td>26</td>
</tr>
<tr>
<td>178</td>
<td>26</td>
</tr>
<tr>
<td>180</td>
<td>27</td>
</tr>
</tbody>
</table>

### Dietary Control Group

Women in the DM control group will not be offered a nutrition intervention program since the general strategy to be adopted for this group will be minimum interference with customary diets while collecting nutritional data considered appropriate for comparison with the nutrition intervention group. Participants in the control group will be provided a standard packet of health promotion materials including information on basic nutrition principles for maintaining nutritionally adequate diets, and a copy of the USDA/DHHS Dietary Guidelines for Americans.

### Dietary Intervention Procedures

Women randomized to the DM intervention arm will be assigned to a permanent group of 8-15 members led by a designated nutritionist. Each such woman will attend her first group meeting within 12 weeks of randomization. The first meeting for each group will be within four weeks of its formation. The group will meet weekly for six weeks, bi-weekly for six weeks, and monthly for nine months. Each woman will have an individual counseling session with her Group Nutritionist between weeks 12 and 16 from the beginning of intervention sessions. The importance of attendance at scheduled sessions will be emphasized. If a participant misses a group session she will be strongly urged to complete make-up activities. All dietary intervention women will receive a packet of health promotion materials similar to that of control participants but without dietary information.

Self-monitoring tools (Food Diary with Fat Counter and Fat Scan) will be used as educational and monitoring aids during the first year of intervention and a shorter alternative tool will be used during maintenance. For early monitoring of adherence with dietary fat goals, the fat scores calculated from the Food Diary and Fat Scan collected from group sessions 4, 8, 12 and 16, and from the individual counseling visit, will be entered into the CT database. Consumption of fruits, vegetables, and grain products will be self-monitored at these same time points in the first year. The intervention integrates knowledge and skills in both nutritional and behavioral sciences. It uses a small group format and a self-reliant, self-directed approach. Self-monitoring and self-correction have been shown in extensive feasibility testing to produce dietary changes. There is individual flexibility about the exact changes in dietary composition and the rate at which they are made.
information and skills presented during the group sessions build upon the content of previous sessions and provide opportunities for necessary practice, feedback, and reinforcement. All the knowledge and skills required to bring about the dietary change goals are covered during the first year of intervention. Throughout the first year, the intervention will be delivered according to a standardized protocol in all clinics.

Weight reduction and reduction in total calories are not stated goals of the nutrition intervention. Neither body weight nor dietary caloric consumption will be controlled, but reductions in both are expected to accompany successful intervention. Maintenance of dietary change will begin in the second year and will involve about four meetings each year. The meetings will provide opportunities to update nutritional information, and review and practice skills that aid in the maintenance of dietary change. Intervention groups seeking added social support will be encouraged to meet more frequently under the guidance of "peer group leaders." "Peer-led help groups" will be discussed during the last six months of year one. In addition to the planned quarterly meetings, there will be two large group social functions yearly. The emphasis will be to promote social support among group members and between intervention groups.

After the first year, 2 - 4 newsletters will be sent to all CCs for use with their intervention participants. Some variation will be allowed during the maintenance phase in the delivery of the intervention. Vol. 2 - Procedures will define the range of variation allowed.

Section 1-A6, Protocol Appendix 6 provides some further detail on the intervention program and dietary assessment methods.

### 4.2.3 Dose and Preparation of CaD

CT women will be asked at their first annual visit if they are interested in joining the CaD component. Willing and eligible women will be randomized in the ratio of 1:1 to one of two arms:

1. Calcium carbonate containing 1000 mg elemental calcium per day plus vitamin D3, with meals. Women will be given a choice of taking chewable or swallowable pills.
   - Each will contain 1000 mg elemental calcium per day plus vitamin D3, up to a maximum of 400 International Units (IU) per day. This will be dispensed as two tablets.

2. Placebo calcium and placebo vitamin D, with a meal, also dispensed as two tablets. Both a chewable and swallowable placebo will be available to correspond to the chewable and swallowable active tablets.

The manufacturer will provide the active and placebo supplements in single chewable tablets. The supplements will be distributed in 6 - 12 month supplies in bottles. Women will be asked to return all bottles for tablet measuring and replacement.

The dose and preparations of calcium were chosen for ease of administration, satisfactory blood absorption, and low frequency of hypercalciiuria. This type of supplement is available over-the-counter and has been widely used in the United States for many years. Women will be encouraged, but not required, to take the two pills at different mealtimes, each day. The dose of 1000 mg per day aims to yield an average total calcium intake in excess of 1500 mg per day of elemental calcium in the active treatment group.

The dose of 250 to 400 IU of vitamin D3 is large enough to ensure adequacy (RDA is 200 IU daily), without risking toxicity. This is a typical dose for supplementation in multivitamin tablets, and has been found to raise 25-hydroxy vitamin D3 concentrations to acceptable levels (Ohmdahl et al., 1982; Webb et al., 1990), and to slow bone loss (Dawson-Hughes et al., 1991). This dose can be given safely without risking hypercalciiuria.
4.2.4 Exercise Advice

All randomized women will receive advice and a pamphlet encouraging them to follow a program of moderate exercise (e.g., including walking briskly for half an hour per day).

4.3 Outcomes of Interest

4.3.1 Major Clinical Outcomes

Clinical outcomes are divided into primary outcomes for the CT (with sufficient power for detection in a pertinent CT component), subsidiary outcomes of interest (but not necessarily with adequate power), and composite outcomes (combinations of primary and subsidiary outcomes). The primary outcome for the HRT component is fatal and non-fatal CHD; for the DM component, breast cancer and colorectal cancer separately; and for the CaD component, hip fractures.

Three general classifications of morbidity define major clinical outcomes for the CT and OS: CVD, cancer, and fractures. Mortality will also be an important clinical outcome, and will include all-cause and cause-specific mortalities (e.g., CHD, other CVD, and cancer). Clinical outcomes in the CT will be initially identified by semi-annual self-administered questionnaires, and in the OS by annual self-administered mailed questionnaires, with telephone follow-up as needed. After initial identification, clinical outcomes in the OS will be ascertained and classified in the same way as in the CT with some minor differences in the extent to which outcomes are adjudicated. Volume 8 - Outcomes provides further detail on the outcome ascertainment and classification plan. Each outcome category listed below will be ascertained separately.

1. Primary outcomes:
   A. Coronary heart disease:
      - acute myocardial infarction requiring overnight hospitalization
      - coronary death
   B. Cancer
      - Breast
      - Colorectal
   C. Hip fracture

2. Subsidiary outcomes:
   A. Cardiovascular disease
      - Acute (including aborted) myocardial infarction (fatal or non-fatal requiring overnight hospitalization)
      - Coronary death (sudden and non-sudden)
      - Stroke (fatal and non-fatal requiring overnight hospitalization)
      - Congestive heart failure (requiring overnight hospitalization)
      - Angina pectoris (requiring overnight hospitalization)
      - Peripheral vascular disease (requiring overnight hospitalization)
      - Coronary revascularization
   B. Other Cancers
      - Colon
      - Rectum
      - Endometrium
• Ovary

C. All other fractures

D. Venous thromboembolic disease requiring overnight hospitalization
  • Pulmonary embolism
  • Deep venous thrombosis

E. Diabetes mellitus requiring therapy

F. Other age-related outcomes
  • Inflammatory arthritis
  • Glaucoma
  • Urinary incontinence
  • Physical function status
  • Cognitive function and dementia

3. Composite outcomes:

A. Cardiovascular disease
  • Major: CHD, stroke, or congestive heart failure requiring overnight hospitalization, peripheral vascular disease with amputation
  • Any: major CVD plus congestive heart failure, other peripheral vascular disease, coronary revascularization, or angina requiring overnight hospitalization

B. Cancer
  • Diet-related: breast, colorectal, endometrial, ovarian
  • Hormone therapy-related: breast, endometrial
  • Total cancer (exclusive of non-melanoma skin cancer)

C. Any fracture

D. Any hospitalization (except certain elective procedures listed in WHI Manuals Vol. 8: Outcomes Procedures)

E. Total mortality

F. Cause-specific mortality
  • Atherosclerotic cardiac disease
  • Cerebrovascular disease
  • Other CVD
  • Cancer
    • Diet-related: breast, colorectal, endometrial, ovarian
    • Hormone therapy-related: breast, endometrial
    • All cancer

G. Violent/Accidental/Suicide

H. Other deaths

All clinical outcomes will be monitored in all participants in the CT and the OS. Selected outcomes are related to specific program components as shown in Table 2.
Table 2
Outcomes for WHI CT and OS
"1°" indicates primary outcomes; "2°" subsidiary and composite outcomes; "x" ascertained

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HRT</th>
<th>DM</th>
<th>CaD</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CARDIOVASCULAR:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>1°</td>
<td>2°</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Stroke</td>
<td>2°</td>
<td>2°</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>2°</td>
<td>2°</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Angina</td>
<td>2°</td>
<td>2°</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>2°</td>
<td>2°</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>2°</td>
<td>2°</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Total cardiovascular</td>
<td>2°</td>
<td>2°</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td><strong>CANCER:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>2°</td>
<td>1°</td>
<td>2°</td>
<td>x</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>2°</td>
<td>2°</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>x</td>
<td>1°</td>
<td>2°</td>
<td>x</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>2°</td>
<td>2°</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Total cancers</td>
<td>2°</td>
<td>2°</td>
<td>2°</td>
<td>x</td>
</tr>
<tr>
<td><strong>FRACTURES:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip</td>
<td>2°</td>
<td>x</td>
<td>1°</td>
<td>x</td>
</tr>
<tr>
<td>Other fractures</td>
<td>2°</td>
<td>x</td>
<td>2°</td>
<td>x</td>
</tr>
<tr>
<td>Total fractures</td>
<td>2°</td>
<td>x</td>
<td>2°</td>
<td>x</td>
</tr>
<tr>
<td>Venous thromboembolic disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>2°</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>2°</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Diabetes mellitus requiring therapy</td>
<td>x</td>
<td>2°</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>2°</td>
<td>2°</td>
<td>2°</td>
<td>x</td>
</tr>
</tbody>
</table>

4.3.2 Intermediate Outcomes

In addition to clinical outcomes of interest to the WHI, other findings determined by laboratory, radiologic, pathologic or physical examination will serve as intermediate outcomes. A detailed schedule for measurement of intermediate outcomes during the follow-up period is included in Volume 8 - Outcomes. Some of these outcomes will be ascertained in all participants and others in defined subsamples of participants.

Most intermediate outcomes will be measured at baseline and one year of follow-up in CT participants to assess short-term effects of treatment. These outcomes will then be measured in a subsample at three, six, and nine years after randomization. For example, prospective laboratory analyses of a subsample of CT participant blood specimens for fasting glucose, lipids/lipoprotein, fibrinogen, factor VII and antioxidants are planned. Intermediate outcomes related to safety are assessed on a schedule determined to be appropriate for the intervention under test. Intermediate outcomes will be measured at baseline and three years of follow-up in OS participants. Some laboratory outcomes will only be measured in a subsample.

4.4 Study Population

The eligibility and exclusion criteria are as broad as possible in order to increase the generalizability of the results to the population of postmenopausal women. The trial will combine primary and secondary prevention. Thus, women with prevalent CVD, and women with a past history of fractures, will be included.
(with some exclusions noted below). The study population can be drawn from a convenient population (e.g., a clinic-based sample), the general population (population-based sample), or a combination of both. In view of cost considerations and the near-impossible goal of obtaining a truly representative population sample for a clinical trial, it is anticipated that most of the participants in the CT/OS will be drawn from convenient populations. Though this does limit the generalizability of estimates of disease and risk factor prevalence, it is expected to have a minimal impact on the generalizability of treatment effects or relative risk estimates.

To maintain power, some restrictions will be made on accrual for defined subgroups. In all components, as mentioned above, the target fractions for randomized women will be 10%, 20%, 45%, and 25% for ages 50-54, 55-59, 60-69, and 70-79, respectively. In the HRT, hysterectomized women will represent a target 45% of the accrued population. These distributions will be monitored within each CC and enrollment may be temporarily closed to appropriate subgroups to achieve these goals. Social/ethnic minority women will be represented in the overall sample with a target of at least the proportion that they are found in the general population of women age 50-79 (17% according to the 1990 census) with a specific target of 20% minority women in the CT/OS. Efforts will be made to ensure adequate representation of minority women and women of lower socioeconomic status, primarily by including CCs having access to large numbers of women in such population subgroups.

In the planning stage it was anticipated that 45 CCs would participate. Recruitment goals for each CC are therefore defined as 1/45 of the study-wide goal for study component and age. To fulfill the additional recruitment needs created by the funding of only 40 CCs, existing CCs will be asked to apply for funding to extend their recruitment beyond original goals.

**Inclusion Criteria for All Components**

1. Postmenopausal female volunteers of all races and ethnicity, with or without a uterus or ovaries (see Vol. 2 - Procedures for detailed procedures for establishing menopausal status).
2. Ages 50-79 years, inclusive, at first screening contact.
3. Likely to be residing in study area for at least three years after randomization or enrollment.
4. Providing written informed consent.

**Exclusion Criteria**

A. Exclusion Criteria for All Components

1. Competing Risk
   - a. Any medical condition associated with predicted survival of less than three years in the judgment of a Clinic physician (e.g., class IV congestive heart failure, obstructive lung disease requiring long-term ventilation or supplemental oxygen in the past, severe chronic liver disease with jaundice or ascites, kidney failure requiring dialysis, sickle cell anemia)

2. Adherence or Retention Reasons
   - a. Alcoholism
   - b. Other drug dependency
   - c. Mental illness, including severe depression
   - d. Dementia
   - e. Active participant in any other interventional trial where participants are individually randomized to an intervention or control group

*Note: An asterisk (*) in the above listing implies that a woman who is temporarily excluded may be re-evaluated for eligibility as appropriate to the excluding condition. If more than six months have elapsed since the woman's SV1, however, most baseline and screening activities must be repeated.
B. Additional Exclusion Criteria for All CT Components

1. Competing Risk
   a. Invasive cancer of any type in the past 10 years
   b. Breast cancer at any time (in situ or invasive)
   * c. Baseline mammogram or clinical breast examination findings suspicious of breast cancer
      (see Vol. 2 - Procedures for detailed criteria)
   * d. Acute myocardial infarction in past six months
   * e. Stroke or transient ischemic attack (TIA) in the past six months
   f. Known chronic active hepatitis or severe cirrhosis

2. Safety Reasons
   ** a. Severely underweight (recommended limit** of BMI < 18 kg/m² or unintentional loss of 15 or more pounds in previous six months)
   * b. Hematocrit < 32%
   * c. Platelets < 75,000 cells/ml
   * d. Severe hypertension (systolic BP > 200 mmHg or diastolic BP > 105 mmHg)
   e. Current use of oral corticosteroids

3. Adherence or Retention Reasons
   a. Unwilling to participate in baseline or follow-up examination components such as mammograms, clinical breast exams, phlebotomy, electrocardiograms, questionnaires and forms; or unable to complete baseline study requirements

4. (Bone Densitometry Clinics) Femoral neck bone mineral density of more than 3.0 standard deviations below the age specific mean.

C. Additional Exclusion Criteria for Hormone Replacement Component

1. Safety Reasons
   a. Endometrial cancer of any stage at any time
   b. Endometrial hyperplasia at baseline (no recycling)
   c. Malignant melanoma of any stage at any time
   d. History of pulmonary embolism or deep vein thrombosis
   e. Previous osteoporosis-related fracture being treated with HRT
   f. History of bleeding disorder serious enough to require transfusion
   g. Lipemic serum leading to diagnosis of hypertriglyceridemia (>500 mg/dl) on baseline blood draw
   * h. Currently on anticoagulants

*Note: An asterisk (*) in the above listing implies that a woman who is temporarily excluded may be re-evaluated for eligibility as appropriate to the excluding condition. If more than six months have elapsed since the woman's SV1, however, most baseline and screening activities must be repeated.

** Recommended limits are given for aspects where Clinician judgment may be used to evaluate eligibility on a case-by-case basis.
i. Currently on tamoxifen or other selective estrogen receptor modulators
j. Abnormalities in baseline PAP smear, pelvic exam or pelvic ultrasound (if performed)

2. Adherence or Retention Reasons
a. Severe menopausal symptoms that would make placebo therapy intolerable to the participant
* b. Inadequate adherence with placebo run-in (less than 80% of daily pills taken) (only one repeat run-in period is allowed)
c. Unable or unwilling to discontinue use of HRT (women must discontinue current replacement hormone therapy for at least three months prior to baseline measures for HRT enrollment)
d. Unable or unwilling to discontinue use of oral or injectable testosterone (must discontinue current testosterone use for at least three months prior to baseline measures for HRT enrollment)
e. Unwilling to have baseline or follow-up endometrial aspirations (women with a uterus)

D. Additional Exclusion Criteria for Dietary Modification Component
1. Adherence or Retention Reasons
* a. Special dietary requirements incompatible with the intervention diet (such as celiac sprue, other malabsorption syndromes). Women will be eligible if they are following a diabetic diet or a low salt diet.
b. Colorectal cancer at any time
c. Unable to complete Four-Day Food Record adequately
* d. FFQ percent of calories from fat below a cutpoint chosen to exclude about 40% of screened women (may repeat assessment after 1 month). FFQ energy intakes of < 600 kcal or > 5000 kcal at screening.
* e. Number of main meals prepared out of home \( \geq 10 \) per week
f. Type I (insulin-requiring, ketosis-prone) diabetes mellitus
g. Gastrointestinal conditions that contraindicate a high fiber diet
h. Bilateral prophylactic mastectomy

E. Additional Exclusion Criteria for CaD Component
1. Competing Risk: The following "all components" and "all CT components" exclusion criteria will be reassessed just prior to randomization into the CaD component.
   a. Any medical condition associated with predicted survival of less than three years as described above (A.1.)

2. Safety Reasons
   a. History of renal calculi
   b. History of hypercalcemia
   c. Current use of oral corticosteroids
   d. Continuing use of > 600 IU Vitamin D

*Note: An asterisk (*) in the above listing implies that a woman who is temporarily excluded may be re-evaluated for eligibility as appropriate to the excluding condition. If more than six months have elapsed since the woman's SV1, however, most baseline and screening activities must be repeated.
e. Current use of calcitriol

3. Adherence or Retention Reasons
   a. Dementia

4.5 Sample Size and Duration

To have sufficient power to test the primary hypotheses, it is estimated that the CT will need to randomize 27,500 women into the HRT component to be followed for an average of nine years; 48,000 women into the DM component to be followed for an average of nine years. An estimated 45,000 women will be randomized into the CaD component to be followed for an average of eight years. For details of the sample size calculations, see Section 1-A3, Protocol Appendix 3. The total sample size required to achieve the above sample size targets will depend on the proportion of women willing to participate in more than one CT component. Only women who are potentially eligible and interested in the HRT or DM components will be invited for an SV1. The total sample size of 64,500 shown in Figure 1 is based on the assumption that 40% of the women who choose the HRT component will also be eligible and willing to be randomized to the DM. It is further assumed that about 45,000 of these 64,500 women (70%) will be eligible and willing to participate in the CaD component, for which randomization will typically take place at the participant's first annual visit (Figure 1). It is envisaged that CT women will be followed for mortality and for breast and endometrial cancer incidence for an additional five years beyond the end of the nine year average follow-up period mentioned above. This will allow more precise safety evaluations and total mortality comparisons for the CT.

Assuming that approximately one-third of women who attend SV1 will be enrolled into the CT, we anticipate that approximately 100,000 women will be entered in the OS. This sample size will provide adequate power to obtain precise estimates of the strength of risk factors, since substantial numbers of clinical events can be expected to occur (Table 3, see also Section 1-A3, Protocol Appendix 3). It may be necessary to recruit some women directly to the OS in order to meet this 100,000 recruitment goal.

Table 3
OS - Estimates of Cumulative Number of Events For 100,000 Women Age 50-79 at Screening Visit

<table>
<thead>
<tr>
<th>Average Years of Follow-Up</th>
<th>Total Deaths</th>
<th>CHD</th>
<th>CVD</th>
<th>Breast Cancer</th>
<th>Colorectal Cancer</th>
<th>Selected *Fractures</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>5,000</td>
<td>1,900</td>
<td>4,000</td>
<td>1,000</td>
<td>500</td>
<td>3,300</td>
</tr>
<tr>
<td>6</td>
<td>11,100</td>
<td>4,200</td>
<td>8,500</td>
<td>2,000</td>
<td>1,100</td>
<td>7,000</td>
</tr>
<tr>
<td>9</td>
<td>18,200</td>
<td>6,700</td>
<td>13,800</td>
<td>3,100</td>
<td>1,900</td>
<td>11,200</td>
</tr>
</tbody>
</table>

* Indicates hip, pelvis, vertebrae, distal radius and proximal humerus fractures

4.6 Informed Consent

The participant's full understanding of the pertinent study components is important for ethical reasons and for adherence with study protocol. Verbal consent will be obtained from each woman who is contacted by phone and asked screening questions. At the beginning of SV1, each woman will be given general information about the CT components and the OS, and she will be given the opportunity to view a video describing the study. A general limited informed consent will be obtained at this time for the initial screening activities, including processing of questionnaire data, drawing blood, and obtaining medical records. Material written in large print in 6th grade level English or Spanish, that describes the study in general terms will be given. Toward the end of SV1, if the woman is deemed eligible, the components for which she is eligible and interested will be described in detail, and written material describing each pertinent CT component will be provided. After she has had the opportunity to read and discuss this information with the study personnel, she will be given a copy.
of the informed consent form to take home and review. At the beginning of Screening Visit 2 (SV2), each woman continuing to be CT eligible and interested will be given an opportunity to ask additional questions. She will then be asked to make a decision regarding her participation in the HRT and DM components, and if such decision is positive, she will be asked to sign a consent form specific to the components she plans to enter.

Written material on the CaD component will be provided to CT women prior to their first annual visit, along with a copy of a corresponding consent form. At the beginning of the first annual visit, each CT woman will have the opportunity to discuss the CaD component with study personnel, and to ask related questions. Eligible women will then be asked to make a decision concerning participation in the CaD component and if such a decision is positive, will be asked to sign an informed consent form specific to this CT component.

Women who express initial interest but turn out to be ineligible or unwilling to enter the CT at any point in the screening process will be invited to participate in the OS if they meet OS eligibility criteria. In order to meet OS recruitment goals, some women may be invited to be screened for the OS regardless of initial interest in the CT. Interested women will be asked to sign an OS informed consent form. Model informed consent forms are listed in Section 2 - Consent Forms. Clinical Centers are allowed to modify these consent forms only for language and clarification. All consent forms must be submitted to the Project Office for approval.

### 4.7 Randomization Assignment Blinding

#### 4.7.1 Hormone Replacement Therapy**

All clinic personnel and participants will be blinded to individual treatment assignments. All efforts will be made to prevent unblinding of participants for the duration of the trial. However, in some instances of unexpected or abnormal uterine bleeding, or of serious adverse experiences, it may be necessary for a clinic consulting gynecologist or a private physician to be unblinded to ensure maximal patient safety.

Some amount of spotting is expected during the first six months, particularly in the PERT arm of the HRT component, but this may resolve. Each site will identify an individual(s) ("designated clinic contact(s)") who will be trained to give uniform and consistent advice to participants calling to report bleeding during the first six months of therapy. During the first year, a designated clinic contact will be responsible for reviewing the bleeding calendar as well as interacting with participants to follow-up on episodes of bleeding. Because of the likely association between bleeding (and other) symptoms and treatment assignment, this individual should not be involved in ascertainment and adjudication of outcomes. Should a designated clinic contact need to consult with other clinic staff who are following the participants, she/he should make every effort to describe the woman's symptoms without identifying the person.

Depending on the clinical findings, unblinding will be considered under circumstances involving either participant safety or management of side effects. Such conditions are discussed in Protocol Section 5.5 and Vol. 2 - Procedures. Should unblinding become necessary, the Clinic Unblinding Officer will exercise a database algorithm, detailed in Vol. 2 - Procedures, that confirms that unblinding criteria have been met, and that records the unblinding activity in the database. The unblinded information will be restricted to the

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*On July 9, 2002, the intervention for the PERT arm was stopped. After an average follow-up of 5.2 years, the DSMB concluded that the risks of taking active estrogen plus progestin outweighed the benefits (Writing Group for the Women’s Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women’s Health Initiative randomized controlled trial. JAMA. 2002;288:321-33). The Estrogen-Alone trial continues without change.

**The ERT Arm was continued until March 1, 2004, when the NIH announced that they were stopping this arm. After an average of 6.8 years of follow-up, there was a statistically significant increase in stroke, a significant reduction in hip fractures, and no clear effect on CHD (WHI Steering Committee. Effects of Conjugated Equine Estrogen on Postmenopausal Women with Hysterectomy: the Women’s Health Initiative Randomized Trial. JAMA. 2004;291:1701-1712).
Unblinding Officer and the clinic consulting gynecologist. The Unblinding Officer will be a CC staff person without other participant interaction responsibilities (e.g., a data coordinator or support person). As long as the unblinded information is limited to these individuals and these persons are not involved in outcome adjudication, the potential for biasing study outcomes is minimal. Bias can further be minimized by maintaining participant blinding, even when unblinding of the consulting gynecologist becomes necessary. Serious complications such as those requiring surgery may, of course, necessitate unblinding a small number of participants. The same unblinding mechanism will be used in the event of study medication overdose by a participant or other person (see Vol. 2 - Procedures).

4.7.2 Dietary Modification

This trial will, of necessity, be unblinded. However, personnel investigating and classifying laboratory determinations and other intermediate data, as well as clinical outcomes of interest, will be blinded to the participants' randomization group.

4.7.3 Calcium/Vitamin D

All efforts will be made to maintain double-blinding throughout. The same mechanism alluded to above will be used to unblind in the event of overdose.

4.7.4 Coordinating Center Blinding

Access to individual participant's treatment assignment(s) by Clinical Coordinating Center (CCC) personnel will be strictly limited and based on need-to-know criteria. Functions requiring treatment assignment information in the CCC include quality assurance and reporting. For quality assurance of CC unblinding, it will be necessary for CCC medical personnel to review unblinding occurrences at CCs to determine the appropriateness of unblinding and the adequacy of follow-up. For those cases, CCC medical personnel involved in these quality assurance procedures will be prohibited from any subsequent outcome ascertainment or adjudication procedures for those participants whose treatment assignments were revealed to them.

For reporting purposes, access to individual treatment assignment will be limited to analytic and programming staff. The Statistics and Data Management Units of the CCC will produce all routine reports on primary and intermediate outcomes, safety issues, and laboratory determinations by treatment arm for examination by the Data and Safety Monitoring Board (DSMB). Distribution of these reports will be limited to the DSMB members, appropriate NIH staff, the CCC PI, and necessary Statistics and Data Management staff. To reduce further the risk of unauthorized release of information, the following steps will be taken: in preparing the analyses and reports, all CCC staff involved will be reminded of the nature of the data and reports; working versions of all output will be shredded prior to disposal; and CCC personnel not involved in producing reports will not be given access to these documents. After each review the reports will be collected and stored centrally in a secure location. For study management purposes, summary reports accumulated across treatment arms will be presented to display overall study progress.
5. Study Plan

5.1 General

The feasibility of funding and completing a study of this size and duration depends on cost-effective methods of recruitment, intervention, and follow-up. Clinic visits will be kept to a minimum frequency and duration. Only data that are essential to answering the study hypotheses and to the safety of participants will be gathered routinely. Considerable effort will be made to ensure complete and accurate ascertainment of clinical outcomes. However, for many intermediate questionnaire data, physical measurements, and biochemical variables, strategies to contain data proliferation and cost will be developed and implemented, including the freezing of samples to allow retrospective measurement among cases and controls, obtaining data on subsamples of the study population only, and obtaining data at extended intervals rather than annually.

For example, the effects of a particular treatment on an intermediate variable over time will be assessed by making observations at extended intervals or in an appropriate subsample. It is envisaged that repeated measurements on a random sample of about 5% of the total CT population (with oversampling of racial/ethnic minorities and of HRT vs. DM women) will be sufficient to provide information on trends over time for the intermediate outcomes.

Secondly, to allow the relationship of change in intermediate variables to clinical outcomes to be evaluated, various observations will be made in all CT participants at entry and after one year, and of all OS women after three years. However, analyses of most samples will be confined to subsequent cases and appropriate controls.

5.2 Enrollment

5.2.1 General Screening

The major activities and flow for screening are presented in Figure 2 and Figure 3. Recruitment activities will be targeted toward women eligible for and interested in the CT, though some recruitment of women directly into the OS may ultimately be necessary to meet OS recruitment goals. An eligibility screen is planned prior to the first clinic visit in order to minimize clinic burden.

The activities listed in Figure 2 and Figure 3 represent a model screening scenario. Departures from this scenario may be exercised at clinic options as is elaborated in subsequent subsections. In particular, activities may be moved forward in the screening process provided that pertinent participant consent has been obtained. CT women who do not complete all required screening activities within six months of their SV1 will be required to provide updated baseline information prior to randomization. Women may prove to be ineligible or unwilling for CT enrollment at various points in the screening process. Such women will be offered the opportunity to participate in the OS and will be asked to complete certain OS baseline activities prior to leaving the clinic. In the event that a fasting blood sample has not been obtained, such women will need to return to the clinic for a fasting blood draw prior to OS enrollment.

A three-year recruitment period is anticipated for each CC. Section 1-A1, Protocol Appendix 1 provides a more detailed list of the measures to be collected at each clinic visit.

5.2.2 Pre-Screening

Multiple recruitment strategies may be needed at each CC. To meet the high recruitment goals of the program, it is recommended that mass mailings be used to produce a steady flow of interested, potential participants for the initial screening. Addresses for these mass mailings can be obtained from such sources as motor vehicle registration lists, drivers' license lists, HMOs, HCFA, health insurance companies, and commercial mailing lists. These can be supplemented with the following:

1. Media efforts: Use of newspapers, radio, TV, newsletters
2. Mass screening of certain high yielding communities (e.g., senior housing facilities), special social
groups (churches), special occupational groups
3. Blood banks
4. Laboratory lists
5. Medical referrals
6. Mammography screening centers

The model initial contact will involve a letter and/or brochure providing basic information on the WHI and a
postage-paid postcard to be returned indicating interest in participation. Age-eligible women indicating an
interest will be contacted by phone by trained interviewers to identify women ineligible for the CT. Women
interested in HRT who are currently taking hormones will be asked to discontinue hormone use for three
months prior to proceeding with the screening visits. These women will be encouraged to discuss this with
their personal physician and CCs will provide informational materials to these women and physicians as
needed. Women ineligible for both the HRT and DM components will be thanked for their time and interest,
and contact information on such women will be retained for possible later contact in relation to the OS.

Those continuing eligible for the CT will be scheduled for a First Clinic Visit (SV1), and will be instructed
that a packet of materials will be mailed to them for their attention before SV1. The packet will include a
cover letter, directions and information for travel to the clinic, a logo bag for all of their current prescriptions
and regularly used over-the-counter medications and vitamin supplements, a personal information form and
an FFQ. Women should be scheduled for SV1 as soon as possible after their initial interview. Women given
appointments before noon will be asked not to eat or drink anything except water for 12 hours before their
appointment and if possible to refrain from smoking and vigorous exercise for 12 hours prior to the
appointment in preparation for a blood draw. Clinical Centers should schedule as many SV1s as possible in
the morning so that the blood sample can be obtained during this first visit.

There are a number of clinic options that can be exercised between the initial contact and SV1. For example,
clinics wanting to maximize the HRT/DM overlap may choose to selectively invite women continuing eligible
for both the HRT and DM to SV1. Clinics wanting to minimize SV1 visits that do not lead to CT enrollment
could request that the FFQ be returned by mail and scanned in order to avoid visits for women who are
eligible for neither CT component, or for the HRT only. Clinics concerned about the ability of women to
complete an FFQ and Personal Information Form on their own could schedule pre-screening visits (SV0) in
order to provide assistance with these and possibly other forms. The pre-screening visits (SV0) may be
scheduled for other reasons (e.g., to more fully explain the study prior to ascertaining interest in various
program components) as a clinic option. A self-administered version of the eligibility screen will also be
available for clinics that choose to obtain eligibility information by mail or in a pre-screening clinic visit. For
efficiency, pre-screening visits would likely be conducted in a group setting.

Prior to a woman's SV1, she should be classified as continuing eligible for HRT, DM, or both. First
screening visits will not typically be conducted for women known to be ineligible for both the HRT and DM
components unless needed to meet OS recruitment goals.
Figure 2
WHI's Model Enrollment Activities and Flow: Pre-screening Through First Screening Visit

Invitation:
Letter of Invitation and return postcard

Eligibility Screen:
Screening and invitation of eligibles to SV1, followed by mailing of Personal Information Q; Food Frequency Q and other materials

SCREENING VISIT 1 (SV1)
Initial screening consent; review of Personal Information Q, Interviewer Administered Q; Physical measures; Medications and Supplements inventory; Fasting blood draw; FFQ scan and eligibility updates for HRT and DM

CT Eligibility

Yes

CT

Detailed description of pertinent CT components; ascertain willingness

No

OS

OS description and consent; complete Medical, Reproductive, Family History, Personal Habits, Psychosocial, and Supplementary OS Q’s

CT Willingness

Yes

Provide CT consent forms; Medical History, Reproductive History, and Psychosocial Qs; schedule SV2

No
5.2.3 First Screening Visit (SV1)

At SV1, women will first be given a general description of the WHI study, and consent will be obtained to cover SV1 activities. A general medical information release form will be signed at this time. Women who have not completed a Personal Information Form or FFQ will do so at this time. Completed forms and eligibility information will be reviewed and the FFQ will be scanned. Clinic personnel will record each medication and each vitamin or mineral supplement bottle a woman brings; and will conduct a brief in-person exogenous hormone usage interview. Note that women interested in HRT who have recently been on hormones must have discontinued hormone use at least three months prior to this visit. All baseline measures except the Eligibility Screen and FFQ must be completed after the 3-month washout.

Women will then undergo limited screening measurements including pulse, systolic blood pressure, diastolic blood pressure, waist and hip circumference measures, and height and weight measurements. If they are fasting, blood will be drawn. The blood tube to be sent to a local lab will not require processing but must be refrigerated and delivered to the local lab within 12 hours. The blood to be centrally stored will be centrifuged and aliquoted, and frozen to -70°C for forwarding to the specimen repository. Blood pressure should be measured before the blood draw is done. Women at the three selected Osteoporosis CCs will also provide a urine sample and will be referred for bone densitometry.

By this time, the completed FFQ should have been scanned and analyzed and a determination of FFQ eligibility for the DM component made. This, along with physical measurements, will permit an updated assessment of continuing eligibility for the HRT and DM components. Eligible women will then be given an in-depth description of the pertinent CT components and will be asked to indicate which, if any, CT components they are willing to enter. Those indicating willingness for one or both CT components will be provided pertinent consent forms as well as Medical History, Reproductive History, and Psychosocial questionnaires to complete and return at SV2. As a local option, these forms could be filled out in clinic and may be administered any time before randomization.

An SV2 will be scheduled as soon as possible after SV1, allowing sufficient time to obtain local laboratory results. If blood was not drawn at SV1, arrangements for a fasting blood draw will be made on or before SV2.

Women who prove to be ineligible for either the HRT or the DM components at the time of eligibility updating, or women who subsequently decide that they are unwilling to be enrolled in the CT, will be invited to consider OS enrollment. As shown in Figure 2, such women will then be provided an OS description and will be asked to sign an OS consent form. They will be asked to complete Medical History, Family History, Reproductive History, Personal Habits, Psychosocial and Supplementary OS questionnaires in order to complete their baseline OS requirements. As a clinic option, some or all of these forms may be sent home with the participant for completion and return to the clinic within a 2-week period.

The OS participants will be asked to keep the CC abreast of any change in address and will be told to expect to be contacted in three years for a follow-up visit, once yearly by means of a newsletter, and once yearly near the anniversary of their enrollment for completion of some self-administered questionnaires. They will be thanked for their participation and the visit will be closed.

Potential OS participants who have not provided a fasting blood sample (or urine sample, if appropriate) will have a clinic visit scheduled, preferably within the subsequent two weeks, for the provision of such a sample. OS enrollment will not be effected until all baseline information and specimens have been obtained.
5.2.4 Second Screening Visit (SV2)

The SV2 is designed around the medical procedures required for CT participants (see Section 1-A1, Protocol Appendix 1). Attempts should be made to complete and evaluate all SV1 activities prior to a woman's second visit. Women who are found to be ineligible in the interim should be notified and invited to join the OS. Those agreeing will have a clinic visit scheduled to afford completion of OS baseline activities as shown in Figure 3. Alternatively, if specimen collection and physical measures have been completed, OS consent and outstanding questionnaire information may be obtained by mail, followed by OS enrollment.

At the beginning of SV2 each woman will be given an opportunity to ask additional questions about the CT and the informed consent. Women who are still interested will be asked to sign the informed consent for each component to be entered. The Medical History, Reproductive History, and Psychosocial questionnaires will be collected and reviewed if they have not been reviewed previously.

Women with continued eligibility for the CT will have a resting 12-lead electrocardiogram. The electrocardiogram and complete blood count reports will be reviewed by the clinic practitioner (registered nurse, nurse practitioner, physician assistant, or physician), who will also perform a clinical breast exam and provide breast self-examination instruction.
Women who have had a mammogram within 12 months of SV2 will be asked the name of the mammographer and facility so that results can be obtained. If more than 12 months have elapsed since the last mammogram, a mammogram will be scheduled.

During this part of the second visit, all potential participants of the HRT component will receive a pelvic exam and Pap smear. Those women without prior hysterectomy will also have an endometrial aspiration. Women who have had a Pap smear, endometrial biopsy (or diagnostic D&C) within 12 months prior to SV1 may not need to have these tests at baseline. Women for whom an endometrial biopsy was not successful due to cervical stenosis will have a transvaginal uterine ultrasound as their baseline endometrial evaluation.

Women eligible for, and planning to enroll in, the HRT component, will receive the run-in placebo tablets dispensed in a bottle containing 50 tablets. WHI tablet dispensers should also be given at this time. The potential HRT participants will be instructed carefully regarding steps they should take should they experience vaginal bleeding and will be instructed on keeping a HRT Calendar that they will bring with them to Screening Visit 3 (SV3).

For those women wanting to enroll in the DM component, training in completing the Four Day Food Record will be given with the help of an instructional video. Potential DM participants will then be given time to practice recording a meal, and the dates for completion of the four day food record will be assigned.

A third clinic visit will be scheduled for all women interested in and eligible for either or both the HRT and DM components. To ensure mammography and gynecologic pathology results are available, up to six weeks should be allowed between Screening Visits 2 and 3. The minimum interval needed for the HRT run-in is four weeks. These women will be provided with Family History and Personal Habits questionnaires to complete and return at SV3.

Women who do not provide CT consent, or who are found to be ineligible or unwilling during the course of SV2 will be invited to join the OS. As shown in Figure 3, consenting women will be asked to complete the remainder of the OS baseline activities as were detailed in the SV1 description.

5.2.5 Third Screening Visit (SV3)

Final evaluation of CT eligibility and subsequent randomization are the primary activities of SV3. All SV1 and SV2 activities should be completed and evaluated prior to a woman's third visit. Women found to be ineligible between SV2 and SV3 will be notified and invited to join the OS. Those agreeing will have a clinic visit scheduled to allow completion of OS activities. If specimen collection and physical measures have been completed, OS consent and outstanding questionnaire information may be obtained by mail, followed by OS enrollment.

At the beginning of SV3, the Family History and Personal Habits questionnaires will be reviewed. Other SV3 activities are specific to the CT components in which the woman intends to participate. Women planning to enter both the HRT and DM components must complete both sets of activities as described below. The two randomizations for women entering both the HRT and DM components should be conducted on the same day.

1. HRT

Before SV3, the clinic practitioner will review the results of the mammogram, the Pap smear and, for non-hysterectomized women, the endometrial aspiration. The women in the HRT component will be asked to bring their WHI tablet bottles and dispensers with any remaining tablets, to this visit. When the women arrive at the clinic, medication adherence will be assessed and their HRT Calendar will be reviewed. HRT-only women judged ineligible or declaring themselves unwilling to be randomized will be invited to participate in the OS and, if interested, will complete OS activities as shown in Figure 3. Women with any abnormal mammogram, Pap smear, or endometrial biopsy results will be referred back to their primary physician for further evaluation.
Women still eligible for the HRT component will be randomized as described in Protocol Section 5.2.6 and instructed in the use of medications, and their first 6-month supply of tablets will be dispensed. They will be instructed carefully regarding steps to take should they experience vaginal bleeding and will be instructed on keeping the HRT Calendar that they will bring with them for the next two visits. They will also be asked to contact their CC should they see a physician or be hospitalized for any of the relevant potential adverse effects including breast or endometrial cancer, endometrial hyperplasia, or hysterectomy. All HRT participants will be given a randomization packet containing general health information and written material describing their role in the trial.

2. DM

Women interested in the DM component will have completed their Four-Day Food Records and will bring them to this visit for review according to completeness criteria. Their mammogram reports will be reviewed and final eligibility determined. Those still eligible for this component will be randomized at this time. Women assigned to the DM control group will have the importance of their role described and emphasized. Enrollees assigned to the DM intervention will be assigned to a dietary intervention group. All DM participants will receive a randomization packet that includes general health information and written material describing their role in the trial. DM-only women who became ineligible or unwilling to participate in the DM component will be invited to participate in the OS and, if interested, will complete OS activities, as shown in Figure 3.

Cognitive function and functional status measures will be completed on subsamples of CT women (cognitive function 100% of HRT women age 65 and older; functional status 25% of CT women age 65 and older). Clinical Centers may choose to conduct these assessments before randomization.

5.2.6 Study Registration and Randomization

Women who express interest in the DM component, the HRT component, or both will be screened to assess their eligibility for the designated component(s) and all necessary data will be entered into the clinic database during the time between Screening Visits 1 and 3. In each case, informed consent will be obtained according to relevant institutional and legal requirements and recorded in the database. When a woman has completed the necessary screening and provided consent, the data coordinator or designated clinic staff person will execute a database function that will verify eligibility for the designated component(s), assign the woman to a trial arm according to the algorithm described below, determine membership(s) in appropriate subsamples, and produce a confirmation of randomization report. Once a woman has been randomized into a trial arm, she will be followed in that arm regardless of her adherence to her assigned treatment.

To reduce potential contamination in the DM component certain natural groupings of women (particularly those residing in the same household) who are both interested in and eligible for the DM will be randomized as a group to the same trial arm. See Vol. 2 - Procedures for approved group formation and randomization procedures.

Women who participate in the DM component, the HRT component or both will be mailed descriptive information on the CaD trial component prior to their first annual visit*. Those expressing interest will have CaD eligibility assessed at their first annual visit, with randomization to occur within an 8-week window surrounding the anniversary of the woman's baseline randomization date.

CT randomization will use a randomized permuted block algorithm, stratified by clinic, age (50-54, 55-59, 60-69, 70-79), and for the HRT, by hysterectomy status. Treatment assignments for all participants in each CT will be generated in the proportions described in Figure 1. Block size will be allowed to vary randomly to further preclude any exercise in judgment in the assignment of participants to trial arms. Enrollment into certain cells (e.g., younger ages or post-hysterectomy women) may be closed from time to time in order to meet the design criteria for distributions on these key factors.

* (or through the time of their second annual visit in selected cases)
Observational Study

Women attending at least one clinic visit who are not eligible for or willing to participate in either the DM or the HRT components will be offered the opportunity to participate in the OS. Informed consent will be obtained, additional OS data will be collected and all necessary data entered into the clinic database. When this has been completed (including the provision of a blood specimen and, if appropriate, a urine specimen), the data coordinator will execute a database function that will register the woman in the OS, determine membership in appropriate subsamples, and generate a registration confirmation report.

Sampling for Substudies

Some intermediate effects of trial interventions and measures of adherence and secular trends will be assessed in a subsample of study participants. To account for the different sample sizes for CT components, a cohort of 8.6% of HRT participants and 4.3% of DM participants will be selected at the time of randomization. These subsamples will be stratified by clinic, age, race, and hysterectomy status in a manner that achieves equity in CC burden while preserving the ability to address questions of interest, particularly intermediate effects, in minority populations. Laboratory measures, completion and documentation of Four-Day Food Records, collection of 24-Hour Dietary recalls and repeated assessment of quality of life will be performed on these cohorts. All HRT women 65 years of age and older will be selected for cognitive function assessment at baseline and follow-up. Another 25% sample of CT women 65 years of age and older will be selected for baseline and follow-up measures of functional status. Additional subgroups will be randomly selected using repeated cross-sectional sampling for other selected measures (e.g., FFQ, 24 hour dietary recall, endometrial aspirations in PERT and placebo arms). A 1% subsample of OS enrollees will be selected for reliability studies to be conducted at baseline and year 3. Details of sampling schemes for other studies can be found in Vol. 1 - Study Protocol and Policies.

5.3 Follow-Up

5.3.1 Clinical Trial

1. General CT Follow-Up

Clinical Trial participants will be followed through regularly scheduled examinations to collect data on study variables, to monitor the occurrence of possible adverse effects, and to promote adherence to study protocol. Annual visits will be scheduled within the four-week interval surrounding the anniversary of their randomization into the CT. All CT participants will have interim six-month contacts, either by phone, mail or visit, at clinic option, to obtain the participant's updated medical history. Clinic visits will be conducted at six months following enrollment into the HRT component. In the event that the annual or six-month contact cannot be conducted within the target time interval, such a visit will be conducted as close as possible to the time window. All participant data will be entered into the database. The required procedures and data to be collected at each visit are specified in Appendix 1.

Before each annual visit, all CT participants will be mailed the Medical History Update and other questionnaires (including the occurrence of any outcomes of interest) to be completed at home and brought with them to their clinic appointment. At years 1, 3, 6 and 9, they will also be asked to bring in all their medications and vitamin supplements for an updated inventory. At the annual visit, all CT participants will have their questionnaires reviewed for potential outcomes. In addition, CT participants will have a brief physical exam. ECGs will be obtained at years 3, 6 and 9. Additional measures will be obtained at the first annual visit and at years 3, 6, and 9, with some elements restricted to a subsample. If the participant has any concerns or symptoms, she will have an opportunity to discuss them with a clinic practitioner. If any potential outcomes are reported, the clinic will initiate the appropriate ascertainment and classification protocol. An appointment may be made for the participant's next visit.
At least six weeks prior to each HRT participant's anniversary of her most recent mammogram, the CC will request that the woman have a mammogram, thereby ensuring that the results will be available at the annual clinic visit. For DM participants not randomized into HRT, a mammogram will be required every second year using the same procedure.

At the first annual visit all CT participants will have their blood drawn and stored. Blood will be drawn and stored on a subsample of women at the third annual visit and at every subsequent third annual visit. For women randomized at clinics participating in the osteoporosis substudy, bone densitometry studies and urine collection will be done at the first and third annual visit and every three years thereafter.

Certain behavioral questionnaires will be re-applied to all CT participants at their first annual visit and in a subsample at 3, 6, and 9 years.

2. Hormone Replacement Component Specific Follow-Up

At approximately six weeks after randomization, HRT participants will be contacted by phone by CC personnel in order to answer questions the participant may have and to identify any major adverse experiences that have not been self-reported. For safety reasons HRT participants will be scheduled for 6-month interim contacts. The first 6-month interim contact will be a clinic visit. Subsequent interim 6-month contacts may be by either mail, phone, or visit, as determined by the CC.

At both the first 6-month semi-annual and all annual contacts, HRT participants will be asked to return their unused HRT tablets and their adherence will be assessed by measuring remaining tablets. During the first year, their HRT calendars will be reviewed by the designated clinic contact. A brief questionnaire will be administered to each participant to identify potential adverse effects and adherence problems. If there has been any bleeding, or if the participant has had any adverse effects other than minor symptoms, the participant will be seen by the designated clinic contact and the bleeding/adverse effects will be reviewed. The contact may decide at this time that other work-up or referral is necessary. After the participant is cleared, she will be dispensed a new supply of tablets and a new HRT Calendar (first semi-annual visit only).

For HRT participants with a uterus the annual physical exam will include a pelvic exam (performed by the WHI clinic medical staff or the participant's personal physician). Every three years, HRT participants will have a Pap smear, either through the CC or their personal physician. On a 5-6% random subsample, the WHI clinic practitioner or gynecologist will perform endometrial aspirations in years 3, 6, and 9. A transvaginal ultrasound will be performed if an endometrial aspiration proves impractical (see Protocol Section 5.5.2.2).

On July 9, 2002, after an average follow-up of 5.2 years, the intervention phase of the PERT (Estrogen plus Progestin) trial ended and Estrogen plus Progestin participants were told to stop their Estrogen plus Progestin study pills (see Section 4.7.1. – Hormone Replacement Therapy) and asked to complete a current medical history update. During the subsequent three months, these participants were unblinded to their treatment arm. Follow-up of the Estrogen plus Progestin participants continues on a semi-annual basis with the following changes: HRT safety interviews will be completed for the next two semi-annual contacts after stopping study pills. Pelvic exams and Pap smears are no longer required for Estrogen plus Progestin participants, but may be continued for retention purposes at CC option. The 5-6% random subsample endometrial aspirations are no longer required. Follow-up of ERT (Estrogen-Alone) participants continues as before.

3. Dietary Modification Component Specific Follow-Up

An FFQ will be collected at year 1 on all DM participants and in a subsample of DM participants in the remaining years. The subsample of women selected at randomization will be asked to complete a Four-Day Food Record at year 1 and multiple unannounced 24 hour dietary recalls at years, 3, 6 and 9. An additional small independent sample (1%) will be chosen for unannounced 24-hour dietary recalls at selected time points.
4. **Calcium/Vitamin D Trial Component Specific Follow-Up**

At approximately four weeks after randomization, CaD participants will be contacted by phone by CC personnel in order to answer questions the participant may have and to identify any major adverse experiences that have not been self-reported. Any difficulties in taking the pill of choice (either chewable or swallowable) should be addressed and options discussed. Thereafter their follow-up schedules are determined by their involvement in the other CT components. Women participating in the CaD component will be asked to return their unused tablets at follow-up visits. Adherence will be measured by measuring remaining tablets. Unless contraindicated by a report of renal calculi or other adverse experiences as described in Protocol Section 5.5, a new supply of tablets will be dispensed.

5.3.2 **Observational Study**

At the time of enrollment, a 1% sample of OS participants will be selected to have a repeat visit between one and three months of their enrollment visit and again after their 3-year visit. The measures and specimens collected at these visits will be those thought to be subject to noteworthy measurement error (e.g., laboratory measures, physical activity).

Routine follow-up for OS participants consists of mailed newsletters and self-administered questionnaires and limited clinic visits. Additional measures may be incorporated through the ancillary study mechanism.

Before the anniversary of their enrollment in the OS, OS participants will be mailed a self-administered Medical History Update questionnaire, an OS Exposure Update questionnaire and a postage prepaid return envelope. A sequence of contact attempts involving both CCC and CC efforts will be implemented to assure the follow-up goals are met. For the first annual follow-up the goals are: 1) to ascertain vital status on 99% of OS participants; 2) to have completed Medical History Update questionnaires on 95% of participants; and 3) to have OS Exposure Update completed by 90% of participants.

OS participants will also be mailed an annual newsletter prepared by the CCC at about six months following their OS enrollment or their OS enrollment anniversary. The purpose of the newsletter is to further bond participants to the study and to obtain updated addresses.

Three years after enrollment into the study, all OS participants will be invited to a follow-up clinic visit. Before this visit they will be mailed a packet of questionnaires that will include questions on health habits, medical history and outcomes, as well as psychosocial and food frequency questionnaires. They will be asked to bring in their current medications and supplements. Participants will have the option of completing forms at the clinic. At the clinic visit, they will have blood drawn, their medications and supplements will be recorded and the following measurements will be taken: height, weight, waist and hip measurements, and blood pressure. At the three osteoporosis substudy centers, bone densitometry studies and urine samples will be completed for all OS women every three years. If no response is received to the 3-year visit invitation, every effort will be made to contact the participant by phone and to schedule a clinic visit.

5.3.3 **Study Close-out**

Assuming that one or more CT components are not terminated early, planning for close-out will begin four years prior to the actual close-out year. This will begin first with the formation of a close-out committee, consisting of representatives from NIH, the CCC, and the CCs. This committee will consider the issues involved in the scheduled termination of clinical activities, and will present detailed plans to the Steering Committee. During the three years prior to the close-out year, efforts will be intensified to locate lost-to-follow-up participants at the time of their anniversary date and last scheduled follow-up visit.

CT participants who attend the annual visit prior to their final close-out visit will be notified that the study termination is approaching, and efforts to lessen the psychological effects of study termination will be initiated. Six months before their close-out visit, participants will be sent literature about the study close-out, and reminded to expect their close-out visit. The close-out contacts will consist of a visit around the calendar time of the annual visit.
The close-out visit will have many of the same elements as an annual visit, that is, participants will be mailed questionnaires, including the Medical History Update to complete and bring to the visit. They will be asked to bring in their study medications for measurement. All CT women will have a mammogram (unless contraindicated). A detailed personal data form will be completed at this time, so that all contact information can be updated. In addition, all CT women will also be informed as to the schedule and nature of information that they will receive concerning principal results from the trial. Additional close-out procedures for each specific CT component will be as follows:

1. **HRT**

   Both participants and providers will continue to be blinded at the close-out visit. Study medications will be discontinued, and participants will be carefully instructed regarding symptoms they might expect from discontinuation of hormones. A list of common symptoms and suggested steps to alleviate symptoms will be provided. Participants will be advised to call the clinic practitioner if they have any severe symptoms, or any significant vaginal bleeding. It may be necessary for the designated clinic contact to consult with the consulting gynecologist before the next scheduled contact, if it appears that a participant will require ongoing HRT. In this case, the designated clinic contact will contact the participant's primary physician, and make arrangements for the participant to be treated by the primary physician, after speaking with the clinic consulting gynecologist.

   Participants will also fill out a form to record their best guess of what treatment group they were assigned to, to assess the degree of the double-blind. A form will also be completed to ascertain if the participant has a continuing source of medical care and whether all study medications have been returned.

   A close-out telephone contact will take place approximately six weeks after the close-out visit. This may be a clinic visit for participants without phones. Both participants and clinic staff will be unblinded at this time. At this contact, participants will be asked questions regarding symptoms since discontinuing study medications. Questions to be addressed will include:

   - Whether symptoms thought to be associated with study drugs have been relieved once medication was discontinued.
   - Whether new problems have arisen that could be associated with stopping study medications.
   - Whether the participant has been prescribed hormones by an outside physician since her close-out visit.

2. **DM**

   Participants in the DM component will be told that the formal trial will end. The intervention group participants will be told that dietary supervision and meetings arranged by clinic staff will end but they will be given every possible assistance to maintain their low-fat, high fruit and vegetable eating patterns and to arrange their own meetings before their final visits. Women in the control group will be told that official dietary intervention for the other group will end and that control group participants will be offered self-help materials to help them to modify their eating patterns. Any new dietary advice that becomes available during the conduct of the trial will be shared with both groups of women.

3. **CaD**

   Women in the CaD component will be participants in at least one of the two other clinical trials, and the measurements taken during their close-out visit will follow those for the HRT and DM components. At the close-out visit their adherence to study medications will be assessed by tablet measurement, and their drugs will be discontinued. Participants will be asked to provide their best guess of their treatment assignment. It is unlikely that they will experience any significant symptoms from stopping treatment, and they will be informed of this. At this contact, forms will be completed to document participants' continuing source of medical care, and to document that study drugs have been returned. If participants on the active CaD arm choose to continue treatment, drug and dosage information will be provided to them.
4. Training and Trial Documentation

Training will be provided for CC staff to counsel CT participants as they exit from the study. After primary CT papers are published, each participant will be provided with a summary of overall trial results as appropriate. The CCC, in accordance with guidelines developed by the Project Office and the Council, will prepare and document the final database.

5. OS

Two months prior to study close-out, participants in the OS will receive notification by mail that the study is coming to a close. At this time they will be sent a final medical history update questionnaire to complete and return to the CC. They will also be sent literature about the study close-out.

5.4 Adherence and Retention

Retention of study participants and their adherence with the study protocol is a dominant focus after the participant is enrolled. Retention has several components: Adherence (taking study drugs), Performance (maintaining low-fat dietary consumption), and Participation (attending follow-up visits, and accepting telephone calls). The evidence from randomized evaluations and evidence from observational studies of participant accrual and follow-up suggests that personal attention from study staff and specific and reassuring feedback about required follow-up activities are themselves useful retention strategies. Correlational evidence indicates that freedom from worries about health, comfort with the intervention materials, and higher SES are related to retention. Taken together, these studies suggest that a retention protocol that will increase social support and positive interactions while minimizing unnecessary health concerns and worry, will maximize retention in WHI.

The CCC will provide each CC with a package of core study-wide retention enhancements. Personal contacts, visits, and follow-up phone calls will be the cornerstone of CC-specific retention efforts, while making sure to avoid the introduction of any contamination or bias. The CCC will coordinate scripts and provide interviewer and staff training and guidelines for standardized contacts using social support and health-related messages. Each CC will continue to implement its own local additional retention efforts to complement study-wide functions. The following strategies exemplify those that may be included:

- Appointment reminders (postcards and telephone contacts)
- Newsletters
- Methods for involving family members
- Special events
- Local Participant Ombudsman
- Modest incentives (magnet, pins, mugs, calendars, etc.)
- Health-related informational materials
- Weekly tablet dispenser
- Physician letters
5.5   Evaluation and Management of Adverse Experiences in the CT

5.5.1   Adverse Experience Monitoring

When informed consent is obtained, potential adverse effects of study treatments will be explained to each prospective participant. Written material outlining these adverse effects will be provided and the women will be instructed to notify the CC of any adverse experiences, illnesses or hospitalizations. Data on adverse experiences will be entered in the database and reported regularly through the processing of outcomes. The Food and Drug Administration granted a waiver of standard Investigational New Drug Serious Adverse Experiences report. These adverse experiences will be collected and reported under all circumstances and without the assumption that they are related to study treatment. Participants will be appropriately monitored until the end of the trial. Copies of the documentation that led to the identification of an adverse experience will be archived at the CC for at least two years after termination of the study.

The Data and Safety Monitoring Board (Protocol Section 10) will periodically monitor a range of potential side effects and make appropriate recommendations to ensure participant safety.

5.5.2   HRT

5.5.2.1   General

Prior to randomization, HRT participants will be briefed on the possible side effects from the study drugs and the medical significance of these possible side effects. Written material outlining these adverse effects will be provided. During the first year participants will be instructed to record any vaginal bleeding or spotting in their HRT Calendar and to notify the designated clinic contact (see Protocol Section 4.7) at the time vaginal bleeding first occurs. Routine endometrial aspiration biopsies will be performed prior to randomization and in an appropriate subsample of HRT participants, at regularly scheduled intervals during the trial. Diagnostic endometrial evaluation will be performed at the request of the clinic consulting gynecologist.

5.5.2.2   Endometrial Evaluation

Routine endometrial evaluation will be performed in all women with a uterus at baseline, and in a random 5-6% subsample in years 3, 6, and 9. Women with abnormal baseline biopsies will be excluded from HRT.

Diagnostic endometrial evaluation will be performed at the request of the clinic consulting gynecologist, who will maintain a copy of all records concerning vaginal bleeding and baseline, follow-up and diagnostic endometrial evaluations. Appropriate clinic staff will record this information on the study forms. All follow-up endometrial biopsy samplings will be evaluated locally for therapeutic decision-making. A standardized classification system will be used.

All endometrial biopsies (routine or diagnostic) will be performed with a flexible aspirator device. Entry into the uterus, by definition, will indicate a successful procedure, regardless of whether or not adequate tissue is obtained. If the uterus cannot be entered with the flexible aspirator device, a second attempt will be made by a different operator, using cervical block anesthesia. If these two attempts fail at passing the cervical OS, a transvaginal uterine ultrasound will be performed.

Normal endometrium refers to any pathologic finding from tissue biopsy that is compatible with atrophic, proliferative or secretory endometrium. Insufficient tissue obtained for diagnosis also qualifies as normal endometrium. Other biopsy findings require evaluation and management or referral to the primary physician by the clinic gynecologist. Endometrium with a thickness ≤ 5 mm on transvaginal uterine ultrasound is considered normal.

Abnormal endometrial findings refer to:

- Simple hyperplasia

or
• Adenomatous, complex or atypical hyperplasia or endometrial cancer

If the transvaginal uterine ultrasound shows a thickness of the endometrium > 5 mm, the participant will be referred to her primary physician for further evaluation.

5.5.2.3 Management of Vaginal Bleeding

CCs should do an endometrial aspiration on those Estrogen plus Progestin participants who stopped intervention in July 2002 and present with spotting or bleeding more than 8 weeks after stopping study pills. Participants may elect to have this procedure done by their outside provider. Any abnormal endometrial findings (as defined in Section 5.5.2.2. – Endometrial Evaluation) will require follow-up and management by an outside provider.

5.5.2.4 Discontinuation of HRT Treatment*

If a woman develops breast cancer, deep vein thrombosis, pulmonary embolus, malignant melanoma, or triglycerides >1000 mg/dl, her Estrogen-Alone study pills will be permanently discontinued without unblinding.

Study pills will also be discontinued (without unblinding) if the participant’s physician prescribes estrogen, progesterone, testosterone, Tamoxifen, or other selective estrogen receptor modulators.

Refusal of a routine post-randomization mammogram within 18 months of her previous mammogram will result in discontinuation of Estrogen-Alone study pills with continued follow-up of the woman. See Vol. 2, Section 16.4.2.1 – HRT (Minimum Procedures for a CT Participant to Remain on Intervention) for other minimum safety requirements. If the participant later agrees to the procedure, study pills will be resumed.

In addition, Estrogen-Alone study pills will be discontinued temporarily if any of the following experiences occur:

• Myocardial infarction;
• Stroke;
• Surgery involving the use of anesthesia;
• Any fracture or major injury involving hospitalization;
• Any illness that results in immobilization for more than one week; or
• Any severe illness in which HRT is temporarily inappropriate (including newly diagnosed TIAs or other cardiovascular conditions that may increase a participant’s risk of a thrombotic event).

Finally, women who have intolerable symptoms refractory to conservative therapy according to a step-down protocol described in Vol. 2 - Procedures, Section 5.4.1.4 - Step-Down Dose Management for Refractory Symptoms may need to stop their study pills.

5.5.2.5 Changing the HRT Arm

Women who were randomized to the PERT arm but who subsequently had a hysterectomy for reasons other than cancer were eligible to continue on study pills. Since there is no routine clinical indication for women without a uterus to be given progestins, women who had a hysterectomy during the trial follow-up (before the intervention was stopped in July 2002) were changed from PERT to ERT. They will be followed in the PERT arm for outcomes, however.

All changes in hormone use will be documented in the study database.

* The Estrogen plus Progestin intervention was stopped for all PERT participants in July 2002. Discontinuation of HRT Treatment refers only to participants in the Estrogen-Alone (ERT) trial.
5.5.3 Dietary Modification Component

Any experiences that require a special diet may result in the temporary or permanent discontinuation of the dietary intervention, including:

- Newly developed Type I (ketosis prone) insulin-requiring diabetes
- Gastrointestinal disease or surgery, such as malabsorption syndrome, short gut syndrome, etc.
- Acute or chronic pancreatitis

Such discontinuation will be decided by the clinic physician in conjunction with the participant's primary physician and notification will be sent to the CCC. All such women will continue to be followed for outcomes in their assigned randomization group.

5.5.4 Calcium/Vitamin D Component

Women who develop renal calculi or hypercalcemia or those requiring kidney dialysis will have CaD pills permanently discontinued. Women taking Calcitriol or > 1,000 IU of personal vitamin D supplements will have CaD pills discontinued while on these therapies.

The following adverse experiences may result in the temporary discontinuation of the CaD therapy:

- Any hospitalization
- Accidents resulting in immobilization
- Myocardial infarction
- Stroke
- Any severe illness in which the administration of CaD is temporarily inappropriate

5.5.5 Notifications

5.5.5.1 Immediate and Urgent Referrals

The clinic physician or practitioner will need to evaluate the urgent referrals to determine if it is necessary to move a referral from urgent to immediate. Immediate referrals are medical emergencies which require immediate notification of both the participant and her primary physician. Immediate notification of the participant should occur during the clinic visit. Immediate notification of the participant's physician should be accomplished by telephone, to be completed before the participant leaves the CC. A follow-up letter documenting information discussed by phone should also be sent to the participant's physician. Findings requiring immediate referral are as follows (clinics may define additional referral criteria at their discretion):

- Medical History:
  - Severe depression
- Physical Examination:
  - Any problem the CC physician feels requires attention immediately (for example, exacerbation of congestive heart failure, acute asthma episode, BP > 210/120 mmHg, serious arrhythmia, etc.)
- Electrocardiogram (CT only):
  - Acute myocardial ischemia/injury
  - Sustained ventricular tachycardia
Urgent referrals are made for abnormalities detected which require medical attention but not on an emergency basis. Urgent notification of the participant should occur before the participant leaves the CC, or immediately upon receipt of the finding from the local laboratory or central pathologist. Urgent notification of the participant's physician should be sent within the week. Findings requiring urgent referral are as follows:

- Medical History:
  - Severe vaginal bleeding*

- Physical Examination:
  - Resting pulse rate < 40/min or > 130/min
  - DBP > 105 mm Hg
  - Suspicious breast mass
  - Pelvic mass

- Endometrial Evaluation:
  - Cancer or atypia*

- Mammography:
  - Finding suspicious for cancer

- Electrocardiogram (CT only):
  - Atrial flutter or fibrillation (new onset)
  - Mobitz type II AV block

- Hematology
  - Hematocrit < 30% or hemoglobin < 10 gm/dl
  - WBC < 1,000 cells/mm3
  - Platelet count < 50,000 cells/ml

*Note: Asterisks (*) in the above listing imply that the finding is evaluated and referred by the clinic gynecologist.
5.5.5.2 **Routine Referrals**

Physical findings and laboratory values as well as copies of electrocardiograms and Pap smear, endometrial aspiration and mammography reports could be sent routinely to participant's physicians (or given to participant to bring to her physician). Decisions regarding specific reporting should be made at the CC level in the context of community referral practices and participant's preferences. Participants will be asked at the beginning of the study for their permission to send such reports to their physician.

The following findings may be considered for reporting if measures are available:

**Medical History:**
- Unexplained weight loss
- Cognitive decline
- Angina (new or uncontrolled)

**Physical Examination:**
- Blood pressure
- Weight

**Bone Densitometry:**
- Baseline bone mineral density at hip more than 3 standard deviations below mean for age
- Rapid bone loss (>10% per year, or >20% over 3 years)
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6. Centralized Study Operations

6.1 Data Management

All routine data will be collected and entered by the CCs using certified data collection staff and data collection forms or direct entry screens provided by the CCC. For data and clinic management purposes, each CC will be equipped with a local area network (LAN) consisting of a Novell file server, five personal computers (PC), a printer, two barcode readers, and a mark-sense reader (scanner). Each file server will be loaded with software for the following functions: network management graphical user interface (Windows), data management (developed by the CCC in Oracle), word processing (Word for Windows), spreadsheet (Excel for Windows), and electronic mail. Each CC PC will be connected to the file server through the LAN in order to provide shared access to clinic data and software. Each CC LAN will be connected to the CCC by a wide area network (WAN). The WAN will link all WHI file servers over dedicated communications lines and will provide continuous communication abilities. Most equipment will be delivered directly to the CCs. The file server and WAN equipment will be delivered to the CCC for configuration. The CCC will be responsible for daily incremental back-ups of all study-wide data over the WAN. Additional aspects of the data management system will be specified in Vol. 5 - Data System.

6.2 Quality Assurance

The quality of study-wide operations, data, and products will be assured by a variety of methods including clear and complete documentation, centrally and locally managed training and certification, routine reports, quality assurance (QA) site visits and task specific quality assurance measures (e.g., routine observation, chart audits, duplicate data entry) as deemed appropriate by the CCC, the Steering Committee and Project Officer. The training and certification required for each study task is described in Vol. 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 CCs for resolution, and a systematic means of updating the central database based on their responses will be established. To assist in addressing these queries, the CCs will be required to store hard copies of their data collection forms in a readily accessible manner, and to respond to queries in a timely fashion. Standards for performance are proposed by the CCC (see Protocol Section 9), approved by the Steering Committee, and documented in the WHI Manuals. Study units determined to be operating below acceptable performance levels will be required to submit plans for remedial action to the Steering Committee for approval and will be subject to more intensive monitoring.

6.3 Drug Distribution

Study medications will be shipped to the CCs on a regular basis by the CCC drug distribution center located at McKesson BioServices. Study medications will come in several forms: placebos for the run-in period of the HRT; blinded medications for the HRT (Placebos, ERT and PERT); open label conjugated equine estrogen and medroxyprogesterone for management of some adverse and side effects of HRT; and blinded medications for the CaD component. Bottles for the run-in period will contain 50 tablets; for follow-up, HRT bottles will contain 215 tablets. CaD tablets will be dispensed in bottles. All medications will be identified with a unique bottle number for tracking and inventory purposes. CCs will log each incoming shipment and each bottle dispensed or returned into the CC database upon receipt or dispensation. For blinded study medications, the bottle number will be linked to trial arm in the CC database. This link will not be accessible to CC database users. To dispense blinded study medications, the data coordinator or other authorized clinic staff member will execute a database function that will identify an appropriate bottle in the drug inventory at the clinic site. Clinical Centers will be responsible for labeling each bottle with the participant's name, identification number, and CC information.

6.4 Outcome Adjudication

For purposes of attaining high quality outcome data for each CT component, the primary outcome diagnosis will be analyzed by local CC physician representatives. Until strong agreement is assured between local clinical diagnoses and a central determination (≥ 90% agreement on primary diagnosis for CHD and fractures)
the data packets, including discharge summary and respective data reports, will be sent to the CCC for central adjudication. After satisfactory agreement has been demonstrated for a CC in these categories, central adjudication will occur on a sampling basis. For the primary cancer outcomes, all data packets will be submitted to the CCC for coding by a qualified SEER coder. The specifics for each scheme of adjudication within the cardiovascular, cancer and fracture outcomes is detailed in Volume 8 - Outcomes. In general, while central adjudication may be part of outcome assignment for each study component in the CT, the expectation is that the central adjudication and quality assurance measures for the CT will be sufficient to assure the quality of local diagnoses for the OS.
7. Study Monitoring and Data Analysis

7.1 General

Progress in the CT and OS will be monitored in several ways: reports on subject accrual, adherence to follow-up procedures, and on intervention adherence rates in the CT will be provided by the CCC to the Steering Committee, as well as to the DSMB and the NIH on a regular basis. Reports on adverse effects and on clinical outcomes by randomization group will be provided on a regular basis to the DSMB. These reports will provide the basis for considerations of remedial actions or protocol changes, and for considerations of early stoppage of CT components.

7.2 Accrual, Adherence and Accumulated Outcome Events

Developing information on subject accrual, and hence average follow-up duration at planned study termination, on adherence, and on the total number of primary outcome events among women randomized to each CT component will be used to produce updated primary outcome power projections, of the type shown in Section 1-A3, Protocol Appendix 3. The design assumptions concerning intervention effect on primary outcome rates will be retained in these power calculations, the results of which will be provided annually to the DSMB and the NIH. Remedial action may be indicated if powers (about 90% or greater) under CT or OS design assumptions are projected to fall as low as 80%. Reports on accrual, intervention adherence in the CT, completeness of participation in follow-up and outcome ascertainment activities, and on other aspects of quality assurance, will be provided regularly to the Steering Committee and the NIH for each active CC in order to allow early identification of potential problems.

Accrual information by age, racial/ethnic subgroup, and socioeconomic subgroup will also be monitored in the CT and OS, as will be the fraction of women who are post-hysterectomy in the HRT component of the CT. Noteworthy departures from targeted fractions may give rise to specialized recruitment efforts to recover the desired distributions, or to the temporary closure of some enrollment categories. Adherence in the CT will also be monitored by age, racial/ethnic, and socioeconomic subgroups.

7.3 Monitoring of Clinical Events by Randomization Group in the CT

The development of procedures for monitoring the CT for possible early stoppage poses specific challenges, some of which are unique to the WHI. There is the danger of over-interpreting treatment effects for a CT component early in the trial follow-up period, without adequately acknowledging the fact that multiple outcomes are being monitored and hence chance differences are more probable, and without adequately acknowledging that hypothesized (beneficial or adverse) effects for some outcomes have a substantially later time course than others. Along the same lines there is a danger in over-interpreting a beneficial effect of a treatment on a given CT outcome since the CT treatments have hypothesized benefits and risks for a number of important diseases. For example, early stoppage of the HRT component on the basis of evidence of hip fracture prevention, without definitive data on CHD or breast cancer effects would leave unanswered some of the most important public health issues surrounding HRT. Similarly, if a CT treatment is observed to have both beneficial and adverse effects then trial monitoring procedures need to rely on some suitable composite or summary outcomes, in order that the public health implications be as unequivocal as possible, while simultaneously paying all due attention to the safety of participating women.

To address these issues an independent DSMB for the WHI has been appointed by the NIH Director. Information on the occurrence of outcomes of interest (Protocol Section 4.3) by treatment group is presented at regular meetings of the DSMB. Evidence of adverse effects, or of adverse risk to benefit profile, may give rise to recommendations for protocol changes (e.g., concerning dosages or dosage modification procedures in the HRT or CaD components, or concerning dietary goals in the DM component), or in the event of a serious adverse effect or a compelling favorable benefit to risk profile, to a recommendation of early stoppage of a CT component, or of certain treatment arms of a CT component.

The specific procedures for accomplishing such monitoring will be developed in collaboration with the DSMB and detailed in a separate document (see Vol. 1 - Study Protocol and Policies). Elements of the plan are...
expected to include a reliance on incidence from primary and subsidiary disease outcomes, and on mortality from other causes, with due consideration of the likely time course of various clinical events. In order to allow greater sensitivity to evolving morbidity data, consideration will be given to multivariate comparisons, and to the construction of a composite disease indices that would combine incidence and mortality information from several disease categories. Each such outcome analysis will make appropriate provision for the multiple time points of interim analyses, and for the hypothesized time course of treatment effects in a manner that attempts to avoid premature stoppage while ensuring participant safety.

7.4 Data Analysis

CT

The basic test statistic to be used to compare an intervention group to a corresponding control group, both for CT monitoring and for periodic analysis, will be a weighted (2-sided) log rank statistic. Such a statistic can be written

\[ T = \sum w_i (O_i - E_i) \]

where \( w_i \) is the value of the weight function evaluated at the ith 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 \( s^2 \) of \( T \) is estimated by \( s^2 = \sum w_i^2 V_i \) and the test for differences between groups is then made by referring \( T^2/s^2 \) to the 95th percentile of a chi-square distribution on one degree of freedom.

The weighting is intended to enhance test power. Since it is anticipated that intervention versus control disease incidence ratios will vary approximately linearly as a function of time since randomization, the weights \( w_i \) will be 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.

The test statistic will be modified slightly for outcome categories that rely on centralized ECG assessments. Since ECG readings are obtained every three years during follow-up, the test statistic will be replaced by a weighted combination of binomial proportions at three, six, and nine years and at close-out for these outcomes. The weights will be averages of those previously described over the pertinent follow-up period.

In acknowledgment of the partial factorial design the (four) primary outcome tests will be stratified on the categories of the other interventions, baseline age (50-54, 55-59, 60-69, 70-79), and self-reported prevalent disease (if applicable) for that outcome. The primary HRT comparisons will be examined separately based on hysterectomy status. In these and other analyses, the times from randomization to disease occurrence will be censored at the time of death from other disease or loss to follow-up. The primary outcome tests will not be adjusted for multiple testing since each component merits a separate hypothesis test. Corresponding to each of these tests, we will estimate intervention versus control group relative risks as a function of time from randomization using relative risk (Cox) regression methods (Cox, 1972) stratified as just described with suitably defined time-dependent covariates (e.g., Kalbfleisch and Prentice, 1980; Cox and Oakes, 1984). Closely related analyses will also be carried out to estimate a 'full adherence' relative risk function for each intervention in relation to its primary outcome.

The same statistical methods will be used for testing and estimation of the secondary and composite outcomes, as well as the subgroup associations listed in Protocol Section 3.1. The same methods will also be used to compare total mortality rates between intervention and control groups. The manner in which these analyses will acknowledge the sequential monitoring aspect of the CT will be described in a separate document, to be developed in conjunction with the DSMB.

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 for the outcomes of interest reliably 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 will have 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 will provide information of the reproducibility of the measurements taken, 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 will be stratified on age, racial/ethnic group, and socioeconomic group. The size of the OS cohort, and the comprehensive set of measurements to be obtained will 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 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 will provide 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.

Section 1-A3, Protocol Appendix 3 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. As indicated earlier (3.2.) under circumstances in which careful analyses of this type lead to substantial agreement between CT and OS results, it may often be reasonable to extrapolate the relative risk results beyond those examined in the CT, using the OS.
8. Osteoporosis Substudy

In order to ensure standardization of equipment and procedures used in bone mineral density measurements (BMD), such measurements will be restricted to the CT and OS participants at three VCCs. Urine samples will also be collected from these women. Changes in bone densities from baseline to prescribed follow-up times in the CT will be examined in relation to each CT component. The ability of such BMD changes to explain the relation between CT treatments and fracture occurrence will also be examined. In the OS, changes in BMD between baseline and three years will be studied in relation to baseline measurements, and the impact of including BMD measurements and changes in analyses of the relationship between fracture and corresponding risk factors will be examined.
9. Ancillary Studies

Ancillary studies will involve CT or OS participants, and will involve the collection of data or specimens that are not part of the core study materials. Such studies may involve all or as few as one of the WHI CCs. Ancillary studies must not interfere with the basic objectives of the CT and OS. 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 of the WHI Council, and following a favorable recommendation, approved by the NIH Project Office. Upon recommendation of the Design and Analysis Committee, ancillary studies of CT participants may also be submitted to the DSMB for approval. Separate informed consent must be obtained for each ancillary study, as must approval of the institutional review boards of the participating institution(s). External funding will typically be required. A separate policy document has been developed to govern ancillary study development (see Section 3.4 - Ancillary Studies).
10. **Study Organization**

The study organization includes the Program Office within the Office of the NHLBI Director, 40 Clinical Centers (CCs), the Clinical Coordinating Center (CCC) (including Core Laboratories and a Clinical Facilitation Center), and the various WHI study committees. The WHI Committees draw their membership from within the participating investigators and staff, and include a Steering Committee, an Executive Committee, and the various Advisory Committees of the Steering Committee. The CC-based committees are organized by region. Two external committees report directly to the NHLBI: the DSMB and the Special Ad Hoc Working Group on the WHI (SAHWG). An internal advisory committee is formed by the Directors of Consortium Member NIH Institutes. Some aspects of the study organization are shown in *Figure 4*.

**Figure 4**

**Organization of the Study**

---

**Program Office**

The study is being conducted 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.

**Clinical Coordinating Center (CCC)**

The CCC will: develop an initial and final Protocol and WHI Manuals, as well as other study materials in collaboration with other study units; train CC staff; collect and store data and biological specimens; analyze and report on data; monitor CC performance in collaboration with the project office via the Performance Monitoring Committee (PMC); establish and maintain the central laboratories, drug distribution center and specimen storage facility; arrange and coordinate committee meetings; and, develop a data collection,
management, analysis and reporting system, with quality assurance and quality control procedures and develop and maintain the WHI network.

**Clinical Centers (CC)**

Clinical Centers will: recruit women according to protocol inclusion and exclusion criteria toward satisfying the overall sample size requirements of the CT and OS studies. They further will perform baseline and follow-up activities in the CT and OS; provide study medications according to randomization assignment; instruct participants in medication use and procedure follow-up; ascertain clinical outcomes; collect and process biological samples; and perform study procedures according to protocol. WHI clinics will deliver the CCC-trained dietary intervention to participants, and will adhere to the dietary modification component of the CT according to the Protocol and WHI Manuals.

The CCs will collect participant data, 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 local quality assurance measures. The CCC will be responsible for electronic data transmission and consolidation.

The CCs will participate in interim and final reports on all phases and activities of the program.

**Special Ad Hoc Working Group on the WHI (SAHWG)**

This committee is appointed by the Director, NIH to provide liaison with groups having special expertise or interest in women's health, and with the community-at-large. It advises the Office of Research on Women's Health (ORWH) Advisory Committee on Research on Women's Health (ACRWH) on strategies to promote the acceptance of WHI by women, helps identify potential problem areas which might have a negative impact on WHI, and participates in activities which promote the WHI. Its membership is drawn from the original Women's Health Initiative Program Advisory Committee (WHIPAC) which was comprised of public, lay, and scientific leaders. This SAHWG meets twice a year and will precede the ACRWH. A written report will be made to the ACRWH at their bi-annual meetings by the SAHWG representative.

**Data and Safety Monitoring Board**

This is an independent board appointed by the Director, NIH to monitor study progress, outcomes, and participant safety and to make recommendations in regard to protocol changes. The DSMB approves the procedures used to monitor the study for consideration of early stoppage of any of its components, and will make corresponding recommendations, when appropriate, based on the regular review of all pertinent study data, including adverse effects and unblinded outcome data in the CT. The CCC will provide study data for review by the DSMB. The DSMB reports its recommendations to the Director, NIH. The DSMB will normally meet twice a year.

**Steering Committee**

The Steering Committee provides overall scientific direction to the WHI. It is the arbiter of issues referred to it by the Executive Committee. It is empowered to make protocol changes, subject to confirmation by the Project Office. The Steering Committee may refer management and operational issues to the Executive Committee. The Steering Committee Members are WHI PIs (40 CC, 3 CCC) and a representative from the Program Office. The Steering Committee chair will be selected from its members, and will be the current chair of the Executive Committee. The Steering Committee will normally meet twice a year.

**Executive Committee**

The Executive Committee is a subset of the Steering Committee. The members of this committee work with the advisory committees to insure that issues and ideas are developed to a mature form prior to review and action by the Steering Committee. This committee also keeps an eye on the progress of the trials and the OS,
bringing important issues to the attention of the Steering Committee. They will routinely meet monthly by conference call and face-to-face twice a year in conjunction with the Steering Committee meetings.

**Advisory Committees**

There will be 9 standing Advisory Committees of the Steering Committee. They will be the Dietary Modification, the Hormone Trials, the Calcium/Vitamin D and Osteoporosis, the Observational Study, the Special Populations, the Behavioral, the Publications and Presentations, the Design and Analysis, and the Morbidity and Mortality Committees. These committees are charged with advising the Steering and Executive Committees on protocol and policy issues pertaining to their respective areas of expertise. Each Committee will have a membership of 6-8, including the chair.

**Regional Clinical Center Principal Investigator Groups:** There will be 4 Regional CC PI Groups of about 10 members each. The Groups will consider any issues relevant to CC participation in the WHI CT/OS. The 4 regions will be: Northeast, Southeast, Midwest, and West.

**Clinical Center Staff Groups:** Clinical Center staff groups will be comprised of members of the 5 staff groups: Clinic Managers, Clinic Practitioners, Lead Nutritionists, Data Coordinators, and Outcomes Coordinators. Each staff group will consider issues in their respective areas of responsibility which are relevant to CC implementation of the WHI CT/OS, will identify problem areas, and exchange ideas for the solution of problems. Issues that have potential study wide implications or may result in changes to the WHI Manuals will be referred to the relevant regional PI group, which may bring the issues to the attention of the Executive Committee. A liaison member from the CCC will be designated for each of the regional staff groups.
11. **Timetable**

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*Assuming that recruitment is uniform over the designated three-year periods and that closeout visits occur on average three months prior to the end of Phase 2D, the average follow-up period will be 10 years in the VCCs and eight years, seven months in the other CCs for an overall average of 8.9 years, exclusive of the additional five years of follow-up for mortality and for breast and endometrial cancer incidence.
SECTION 1-A8
PROTOCOL APPENDIX 8

BRIEF PROTOCOL HISTORY

1-A8.1 Protocol Version Dated June 28, 1993

The reader is referred to Rossouw et al (1995) for a description of the antecedents to the Women's Health Initiative (WHI), particularly in the hormone replacement therapy (HRT) and dietary modification (DM) areas, and for a description of the specific planning activities leading up to the WHI Clinical Trial (CT) and Observational Study (OS). This process led to the establishment of the WHI Program Office, in the National Institutes of Health (NIH) Director's Office, in late 1991, and to the release of RFP's for a Clinical Coordinating Center (CCC) (March 17, 1992) and for Vanguard Clinical Centers (VCCs) (April 29, 1992). These documents specified a number of key protocol elements, including a CT total sample size of 57,000 and an OS sample size of 100,000, with all participants being postmenopausal women in the age range of 50-79.

The Program Office had produced a draft protocol for the CT/OS by the time the CCC at the Fred Hutchinson Cancer Research Center began its work in September 1992. The CCC and Program Office worked vigorously to further develop and refine the CT/OS protocol during the subsequent few months. An examination of exclusionary criteria for the DM and HRT components of the CT made it clear a lesser HRT/DM overlap could be expected than had previously been assumed, leading to an increase in total CT sample size to 63,000 (48,000 in DM, 25,000 in HRT, including 10,000 in both). Other protocol developments during this time period including delaying a woman's randomization to the calcium and vitamin D (CaD) component of the CT to her one year anniversary from DM/HRT randomization in order to relieve participant burden early in the CT, and the decision to randomize hysterectomized women only to ERT or placebo, but not PERT, in the HRT component. The 16 VCC's were funded in March or April 1993 (see Protocol, Appendix 1-A7 for list) after which a period of further protocol and procedures development took place.

These developments substantially involved the WHI committee structure and led to various improvements, including the setting of specific target fractions for CT women in the age groups 50-54 (10%), 55-59 (20%), 60-69 (45%), and 70-79 (25%) toward ensuring adequate projected study power for designated primary outcomes as well as projected favorable benefits versus risks in each CT component. These activities led to a WHI CT/OS protocol version dated June 28, 1993. Following the development of related procedures and data collection forms, and the securing of all relevant approvals, this protocol version was implemented on schedule in September 1993.
1-A8.2 Protocol Version Dated September 1, 1994

As anticipated with a study as complex and demanding as the WHI, a range of protocol and procedure flexibilities and improvements proved necessary in order that the protocol implemented be consistent with the staffing and budgets for the various WHI units. These improvements were based on the accumulating experience in screening women for CT participation, and experience with the early postrandomization phase of the DM and HRT components of the CT. Specifically, a Screening Task Force functioned in late Fall 1993 to identify opportunities for streamlining and enhancing the flexibilities in the CT/OS screening process. This was followed during the early months of 1994 by a more comprehensive Streamlining Task Force effort that re-examined all elements of the protocol and procedures for opportunities to simplify without appreciable loss of scientific content. These task force efforts led to a series of recommendations, including the reduction of some time consuming CT activities to subsamples (e.g., Four-Day Food Record documentation, cognitive and physical function measurements, etc.); to a reduction in the amount of detail collected at baseline; and to a reduction in the frequency and intensity of follow-up activities in both the CT and OS, whenever practical. A version of such recommendations were adopted by WHI investigators in May 1994, followed by the development of related documentation and the securing of all relevant approvals, leading to a new protocol version dated and implemented September 1, 1994.
1-A8.3 Protocol Version Dated April 3, 1995

Upon learning the key results from the PEPI study (PEPI Trial Writing Group, 1995) WHI investigators and advisors concluded that the unopposed estrogen arm (ERT) should be discontinued among women with a uterus in the HRT component of the CT, on the basis of greater than anticipated occurrence of uterine hyperplasia, including adenomatous hyperplasia. In addition to the related safety concerns, such an elevated hyperplasia incidence made it likely that few such women originally assigned to ERT would remain on unopposed estrogen over the course of the protracted (average 9 year) WHI follow-up period. Dropping the ERT arm among women with a uterus led to a reduction in study power for ERT versus placebo comparisons since ERT versus placebo information now derived only from hysterectomized women, as opposed to all HRT women. In response the target fraction of hysterectomized women in the HRT component was increased from 30% to 45%, a fraction not far from the recruitment experience at that point in time, and the total HRT sample size was increased from 25,000 to 27,500. As a result the total CT sample size increased to 64,500 and the projected DM/HRT overlap (40% of HRT enrollment) to 11,000. These changes, as well as other minor improvements including some further specification of the CaD component of the protocol (initiated in May, 1995) are included in the protocol version dated April 3, 1995.

These revisions outlined below are viewed as an ongoing fine tuning of the WHI Protocol.

This version incorporates numerous protocol changes approved by the Council including a more strictly defined outcomes definition requiring overnight hospitalization of most outcomes; the deletion of hemoglobin < 10.5gm/dl and morbidly obese as exclusions; the ability to administer a second screening FFQ after only 1 month selected women depending on their initial estimate of percent calories from fat; for safety reasons, the use of calcitriol as an exclusion for CaD; administration of cognitive assessment in all HRT women age 65 and over; allowing clinic option for the 6 month interim contact after year 2 (either mail, phone or clinic visit); allowing clinic option for the CBE during annual visits for DM component women (if signed consent has been revised to delete this activity) and participant option (if signed consent indicates CBE); clarifying the need to discontinue HRT medications if a women refuses an unscheduled endometrial biopsy or a routine post-randomization mammogram within 18 months of her previous mammogram; ancillary study approval policy; study organization revisions; revised power calculations; the deletion of Appendix 2 (Outcomes) which will now be addressed in Volume 8 of the WHI Manuals; revisions to Appendix 7 showing current information for participating institutions.
1-A8.5 Protocol Version Dated April 1, 1997

This version of the WHI Protocol reflects an attempt to encourage adherence to study Protocol and continued fine tuning of procedures. Major highlights are:

Currently PERT women may receive short-term labeled progestin along with their assigned study medication for the purpose of controlling bleeding. A maximum dose of 10 mg daily for 12 months is allowed provided that the clinic gynecologist has determined that appropriate evaluation for pathology has been performed and the CC PI has approved. This protocol reflects that thereafter, an additional, 2.5 mg MPA/day (up to 5 mg/day) may be added to PERT indefinitely.

Also provision has been made for the dispensing of open label Conjugated Equine Estrogen (CEE) as a short term treatment (up to 3 months per year) for bleeding after the first 6 months on PERT in HRT women who have atropic endometrium documented by endometrial pathology and who have been unblinded by the consulting gynecologist.

In the DM component a streamlining measure replaces the Four-Day Food Record with multiple 24-hour dietary recalls at years 3, 6 and 9. These 24-hour dietary recalls would be placed by trained staff at the Nutrition Assessment Shared Resource at FHCRC, alleviating considerable effort on CC nutrition staff and CCC dietary assessment training staff.

In the CaD component participants will be given a choice between the current chewable tablet and a swallowable tablet. This decision is an attempt to increase recruitment and encourage adherence in this component of the WHI. Another step we are taking to encourage adherence is a 4 week telephone call after randomization into CaD by CC staff to discuss any problems the woman may be having and to offer some possible solutions and/or provide support.
1-A8.6 Protocol Version Dated April 1, 1998

This version of the Protocol reflects some aspects in the change of program oversight from NIH to NHLBI as well as continued fine tuning of procedures. The most significant changes in procedures are:

- Instituting an exclusion from HRT for women having any history of venous thromboembolism (VTE) or using a selective estrogen receptor modulator (SERM). Women having a VTE or using a SERM post-randomization are required to stop their HRT medications.

- Women already in the CT may be randomized into CaD through the time of their second annual visit. Women taking dietary supplements containing 600 IU of Vitamin D are no longer excluded.

- Women randomized to PERT having persistent bleeding after six months may be offered a cyclic regimen if there are no abnormal histopathologic findings and other methods of managing unscheduled bleeding were not successful.

- Eliminated the central reading of endometrial aspirations.

- Some modest changes in committee formation were incorporated including the introduction of a nominations committee and the expansion of the Steering Committee to include greater Principal Investigator representation.
1-A8.7 Protocol Version Dated April 1, 1999

This version of the Protocol reflects some changes in study organization and minor updates including:

- Replacement of Council by Steering Committee composed of the 40 Clinical Center Principal Investigators and the creation of an Executive Committee.

- Data collection table changed to reflect Personal Information Update collected for OS participants in Years 3, 6, and 9, not annually. Frequency of waist/hip measures was added to the table.

1-A8.8 Protocol Version Dated April 1, 2000

Major highlights of this version of the Protocol include:

- Adverse Experience Monitoring has been changed to reflect an FDA waiver of standard Investigational New Drug Serious Adverse Experiences report. WHI adverse experiences will be reviewed by the DSMB every six months through the processing of outcomes and, if appropriate, recommendations made to the NIH to ensure participant safety.

- Women on anticoagulants is now listed as an exclusion for the HRT component for safety reasons.

- Current use of calcitriol was added as an exclusion for the CaD component for safety reasons.

- The upper limit of continued use of Vitamin D as an exclusion for the CaD component from > 600 IU to > 1000 IU. Also, any CaD participant reporting current use of calcitriol or > 1000 IU of Vitamin D will have CaD pills discontinued while on these therapies.

- The bleeding management and discontinuation of HRT treatment sections have been revised to reflect references to the WHI Procedures Manual 2 for more detail. The revision of Table 6 represents current practice.

- The WHI Frequency of Data Collection Table in Appendix 1 has been updated to show the collection of the Personal Habits Update which was an inadvertent omission. It also shows the deletion of urine specimens and the addition of physical measures at BMD centers at Year 6.

- Since the last review, Jacques Rossouw has assumed the responsibility of the Acting WHI Director and several clinical centers have had a change in principal investigators. These changes are noted in Appendix 7.
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Section 1-A8
Protocol Appendix 8
Brief Protocol History

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Section 1

Current page numbers
Page 1-29
• Added footnote regarding cessation of PERT.
Page 1-40
• Added paragraph regarding the July 9, 2002 cessation of the PERT trail.
Page 1-45
• Deleted “…along with any unblinding action to be taken (without recording actual treatment arm), should this
be necessary” under Section 5.5.2.2 – Endometrial Evaluation.
• Deleted “The woman may be eligible to enter or continue in the HRT if tissue evaluation shows that the
endometrium is normal” under Section 5.5.2.2 – Endometrial Evaluation.
• Added footnote regarding cessation of PERT.
Page 1-46
• Added new procedure under Section 5.5.2.3 – Management of Vaginal Bleeding.
• Deleted the bulleted item “When to Biopsy.”
Page 1-47
• Deleted first paragraph and the two bulleted items below it under Section 5.5.2.4 – Discontinuation of HRT
Treatment.
• Changed “HRT” to “Estrogen-Alone.”
• Changed “medications” to “study pills.”
• Added item in parentheses in the bulleted item regarding “Any severe illness in which HRT is temporarily
inappropriate.”
• Deleted last sentence under Section 5.5.2.4 – Discontinuation of HRT Treatment concerning distribution of ERT
to women with a uterus.
• Added “(before the intervention was stopped in July 2002)” under Section 5.5.2.5 – Changing the HRT Arm.
• Added footnote regarding PERT and ERT.
Page 1-60
• Changed the number of the Steering Committee Members from 1 to 3 from the CCC.
Page 1-61
• Changed “HRT” to “Hormone Trials.”
• Changed “Outcomes Specialists” to “Outcomes Coordinators.”

Section A-1

Current page numbers
Page A-1-2
• Added “Addendum to Medical History Update (Form 40).”
• Added “Addendum to Personal Information (Form 41).”
• Added “145 item” to “FFQ (Form 60).”
• Changed “18 feet” to “6 meters” under “Functional Status (Form 90).”
Page A-1-3
• Added “Observational Study Follow-Up Questionnaire Year 6 (Form 146).”
Page A-1-4
• Added “Observational Study Follow-Up Questionnaire Year 7 (Form 147).”
• Added “Observational Study Follow-Up Questionnaire Year 8 (Form 148).”
Page A-1-5
• Added footnote “3” to “Pelvic”, “Pap”, and “Endometrial Evaluation.”
Page A-1-6
• Added footnote “4” to “Medication Dispensation.”
• Added footnote “5” to “Safety Interview.”
• Added two new footnotes: “3 These tasks are not required for Estrogen plus Progestin (PERT) participants
since study pills were stopped on July 9, 2002” and “5 Safety interviews are only required while HRT or CaD
participants are taking study pills and for two semi-annual contacts (HRT) or one semi-annual contact (CaD)
after stopping.”
• Changed “medications” to “study pills.”
Summary of changes between original data analysis plan\(^1\) and final data analysis plan\(^2\).

- Paragraph 1. Inconsequential notation change between formulae, otherwise the corresponding statistics and tests are identical between plans.

- Paragraph 4. Final plan specifies “primary HRT comparisons” instead of “HRT comparisons.” Final plan states comparisons will be examined “separately” instead of the more technical term “stratify.” Final plan specifies “primary outcome” instead of “primary endpoint.”

- Paragraph 5. Final plan qualifies “Section 3.1” with “Protocol Section 3.1”

\(^1\) Section 7.4 of original protocol.
\(^2\) Section 7.4 of final protocol.
# WHI Extension Study Protocol Outline

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Section 1

Women’s Health Initiative (WHI) Extension Study Protocol
September 9, 2004
Modified May 8, 2006

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 through 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

<table>
<thead>
<tr>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CARDIOVASCULAR:</strong></td>
</tr>
<tr>
<td>Coronary heart disease</td>
</tr>
<tr>
<td>Angina</td>
</tr>
<tr>
<td>Coronary Artery Bypass Surgery (inpatient)</td>
</tr>
<tr>
<td>PTCA</td>
</tr>
<tr>
<td>Stroke</td>
</tr>
<tr>
<td>Transient ischemic attacks</td>
</tr>
<tr>
<td>Carotid artery revascularization (inpatient)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Venous thromboembolic disease</td>
</tr>
<tr>
<td>DVT</td>
</tr>
<tr>
<td>PE (inpatient only)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
</tr>
<tr>
<td><strong>CANCER:</strong></td>
</tr>
<tr>
<td>Breast cancer</td>
</tr>
<tr>
<td>All other cancers except non-melanoma skin cancer</td>
</tr>
<tr>
<td><strong>FRACTURES:</strong></td>
</tr>
<tr>
<td>Hip</td>
</tr>
<tr>
<td>Other fractures</td>
</tr>
<tr>
<td><strong>OTHER AGE-RELATED DISEASES</strong></td>
</tr>
<tr>
<td>Diabetes mellitus requiring therapy</td>
</tr>
<tr>
<td>Hypertension requiring therapy</td>
</tr>
<tr>
<td>Hypercholesterolemia requiring therapy</td>
</tr>
<tr>
<td>Intestinal or colon polyps or adenomas</td>
</tr>
<tr>
<td>Macular degeneration</td>
</tr>
<tr>
<td>Osteoarthritis</td>
</tr>
<tr>
<td>Osteoporosis requiring therapy</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td><strong>SOCIAL/PSYCHOLOGICAL CONDITIONS</strong></td>
</tr>
<tr>
<td>Depression requiring therapy</td>
</tr>
<tr>
<td>Anxiety requiring therapy</td>
</tr>
<tr>
<td><strong>OTHER</strong></td>
</tr>
<tr>
<td>Selected Hospitalizations for 2+ nights</td>
</tr>
<tr>
<td>Death from any cause</td>
</tr>
</tbody>
</table>
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)

<table>
<thead>
<tr>
<th>HRT (CaD)</th>
<th>Intact Uterus</th>
<th>Not Randomized</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>DM (CaD)</td>
<td>Intervention</td>
<td>19,541 (9645)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>29,294 (15,565)</td>
</tr>
<tr>
<td></td>
<td>Not Randomized</td>
<td>19,297 (11,072)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>68,132 (36,282)</td>
</tr>
</tbody>
</table>

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

\[ T = \sum w_i (O_i - E_i) \]

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 \( \sigma^2 \) of \( T \) is estimated by \( \sigma^2 = \sum w_i^2 V_i \) and the test for differences between groups is then made by referring \( T^2/\sigma^2 \) 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 or 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

OSMB-----------NHLBI  
|  
WHI Program Office  
|  
D&A--------P&P--------Study Oversight Committee--------CAC  
|  
Field Centers-----------------Clinical Coordinating Center

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**

<table>
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</tr>
<tr>
<td>OS participant enrollment and consent for Extension</td>
<td>09/04 – 12/05 (16 months)</td>
</tr>
<tr>
<td>CT participant enrollment and consent for Extension</td>
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</tr>
<tr>
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<tr>
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<tr>
<td>CT participants</td>
<td>10/05 – 03/10 (54 months)</td>
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<tr>
<td>WHI database closes</td>
<td>08/15/05</td>
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<tr>
<td>WHI Clinical Centers close, Field Centers open</td>
<td>09/15/05</td>
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<tr>
<td>Close-out Data</td>
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Pepe MS, Self SG, Prentice RL. Further results on covariate measurement errors in cohort studies with time to response data. Statist in Med 1989;8:1167-78.


# WHI Extension Study Protocol Outline

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Section 1
Women’s Health Initiative (WHI) Extension Study Protocol
May 17, 2012

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 thromboembolic 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
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:

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<td>S</td>
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<td>S</td>
</tr>
<tr>
<td>PTCA</td>
<td>A</td>
<td>S</td>
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<tr>
<td>Heart valve problem/repair&lt;sup&gt;1&lt;/sup&gt;</td>
<td>A</td>
<td>S</td>
</tr>
<tr>
<td>Aortic aneurysm&lt;sup&gt;1&lt;/sup&gt;</td>
<td>A</td>
<td>S</td>
</tr>
<tr>
<td>Stroke</td>
<td>A</td>
<td>S</td>
</tr>
<tr>
<td>Transient ischemic attacks</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Carotid artery disease</td>
<td>A</td>
<td>S</td>
</tr>
<tr>
<td>Heart Failure&lt;sup&gt;2&lt;/sup&gt;</td>
<td>A</td>
<td>S</td>
</tr>
<tr>
<td>Atrial Fibrillation&lt;sup&gt;1&lt;/sup&gt;</td>
<td>A</td>
<td>S</td>
</tr>
<tr>
<td>Venous thromboembolic disease 3</td>
<td>A</td>
<td>S</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>A</td>
<td>S</td>
</tr>
<tr>
<td><strong>CANCER:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All sites except non-melanoma skin cancer</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td><strong>FRACTURES:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip</td>
<td>A</td>
<td>S</td>
</tr>
<tr>
<td>Other fractures</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td><strong>OTHER AGE-RELATED DISEASES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease (COPD)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Diabetes mellitus requiring therapy (insulin, pills, diet)</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Hypertension requiring therapy</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Intestinal or colon polyps or adenomas</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Macular degeneration</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Osteoarthritis or arthritis associated with aging</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td><strong>SOCIAL/PSYCHOLOGICAL CONDITIONS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate/severe memory problems</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>(dementia/Alzheimer’s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>OTHER</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selected Hospitalizations for 2+ nights</td>
<td>L</td>
<td>S</td>
</tr>
<tr>
<td>Falls</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>A</td>
<td>S</td>
</tr>
</tbody>
</table>

<sup>1</sup> - Outcome added for 2010-2015 Extension
<sup>2</sup> - Previously by self-report only
<sup>3</sup> - 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](image)

**Figure 1**

**Original and Extension Study Enrollment by Study Component**

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>OS</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original WHI enrollment</td>
<td>68,132</td>
<td>93,676</td>
<td>161,808</td>
</tr>
<tr>
<td>2005-2010 Extension Study enrollment</td>
<td>52,176</td>
<td>63,230</td>
<td>115,406</td>
</tr>
</tbody>
</table>

**WHI CT Partial Factorial Design**

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

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

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

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

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Re-consent and Personal Information Update</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>Medical History Update</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>151</td>
<td>Activities of Daily Life (ADL)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>155</td>
<td>Lifestyle Questionnaire (includes ADL)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>153</td>
<td>Medication and Supplement Inventory</td>
<td>MRC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>In-person visit Consent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>Blood Collection and Processing</td>
<td>IPV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80</td>
<td>Physical Measurements</td>
<td>IPV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90</td>
<td>Functional Status</td>
<td>IPV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 WHI Extension II participants 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 13,000 women over the age of 60 will be selected for inclusion as follows: All WHI Memory Study (WHIMS) participants and the oldest non-WHIMS MRC participants. All eligible participants will have both genome wide study data (GWAS) and 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), has been 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.

Another ancillary study, Evidence for Establishing Optimum Protein Intake in Older Adults (WHI-Food Intake Study, AS340, PI Jeannette Beasley), will begin immediately following the In-person Visit and has the identical eligible population. The In-person Visit post-visit thank you letter packet will introduce participants to AS 340 and provide a Food Frequency Questionnaire (FFQ). (The AS340 cover letter and FFQ, and Waiver of documentation of consent for the AS340 FFQ, were IRB approved as part of the WHI Extension on 9/23/11).

**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 postcard. 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 either telephone consent or a reminder to return their consent form. 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. (Waiver of Documentation of Consent for consent received via phone was IRB approved on 4/26/12.)

**Scheduling:** Once the CCC has received documentation of IPV 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 FHRC-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 (~ 31 ml)
- 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, and should funds be available, the letter will also include $10 as small token of our appreciation. (The mailing and the gift card will be paid for with OPACH80 funds.) 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. The post-visit letter will also include an AS340 cover letter, a FFQ, and a $2 token incentive (should funds be available).

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 stadiometer.
- 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 newly 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 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

\[ T = \sum w_i (O_i - E_i) \]

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 (\( \sigma^2 \)) of \( T \) is estimated by \( \sigma^2 = \sum w_i^2 V_i \).

and the test for differences between groups is then made by referring \( T^2/\sigma^2 \) 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 test 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

OSMB--------NHLBI

WHI Program Office (PO)

Steering Committee--- Advisory Committees

P&P, ASC, OAC, PMC

and ad hoc working groups

Regional Centers (RC)-------------------Clinical Coordinating Center (CCC)

Outcomes Collection ---- Scientific Interest
Satellites (OCS) Groups (SIGs Groups)

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

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<tr>
<th>Activity</th>
<th>Timeline</th>
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<tbody>
<tr>
<td>Protocol Development</td>
<td>11/09 – 12/09 (2 months)</td>
</tr>
<tr>
<td>Participant enrollment and consent for Extension</td>
<td>5/10 – 3/11 (11 months)</td>
</tr>
<tr>
<td>Follow-up data collection</td>
<td>Annual</td>
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<td>In-person Visit</td>
<td>2011-2013</td>
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<td>Close-out</td>
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<tr>
<td>Data Analysis</td>
<td>Ongoing</td>
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</table>
REFERENCES


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