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.

1-A8.4 Protocol Version Dated March 15, 1996

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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