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Observational Analysis Guidelines

- **OS alone:** If the exposure is also available in the CT, should consider including all or the appropriate subset of the CT to increase sample size and statistical power.

- **CT alone as cohort:** Adjust for CT randomization arms

- **CT+OS combined as cohort**

Consider exclusions to enhance comparability of the two cohorts. For a list of inclusion and exclusion criteria for each study component see Table 1 in "The Women's Health Initiative recruitment methods and results. Ann Epidemiol 2003 Oct;13(9 Suppl):S18-77".

For example in an analysis combining the HT and OS where breast cancer is the outcome of interest, should exclude women in the OS with a history of breast cancer and require them to have had a mammogram within 2 years prior to enrollment (1).

Nutritional analyses based on FFQ data combining the OS and the DM comparison (DM-C) arm

Because all DM trial participants were required to have a diet with at least 32% total calories from fat at baseline as estimated by a baseline FFQ, an analysis combining the OS and DM-C should use the FFQ from year 1 instead of baseline, and start the observation period at year 1, for the DM-C. The baseline FFQ % of energy from fat values that met this 32% criterion tend to be biased upward by this screening process, whereas the year 1 values are expected to be essentially free of this particular bias. Note also that the year 1 % calories from fat in the DM-C has a more normal distribution compared to the baseline distribution in that arm (2).

Comparability of outcomes data between the study components

Since the adjudication process was not the same across study components, consideration needs to be given to the impact of combining different types of outcomes, i.e. self-report, locally adjudicated or centrally adjudicated. From the start of WHI, cancer outcomes have always been adjudicated for all WHI participants; this is not true for other diseases. For example, non-hip fractures were locally adjudicated during WHI in the CT and OS BMD cohort, but only self-reported data is available for the remainder of the OS. Also, with each Extension study, there were changes in which outcomes were adjudicated, and on which participants. Table 1 in the Data Preparation document on our website summarizes the differences between study components and changes in the adjudication process over time.

- **Type of adjustments for study component and CT arms**

Should adjust for study participation (OS vs CT) and individual CT arms. Because the CaD trial randomization started at year 1 of follow-up, should use a time-dependent type of adjustment. In a time-to-event analysis using a Cox model, adjustment using strata is preferred to inclusion in the model as covariates. Cox models are robust to detailed stratification and can handle a large number of strata.

- **Analyses of Hormone Therapy (HT) other than by HT trial randomization arm**

HT as exposure – Any analyses that plan to examine the effect of HT on a particular outcome in a sample of HT plus non-HT participants should follow the methods outlined by Prentice et al (3). For some outcomes, however, combining an HT trial and non-trial sample may not be justified because of an inability in the modeling to adequately align the characteristics of the two samples (4).

If the focus is on a different aspect from the HT trials, such as comparing dose or formulation (pill vs patch) of HT, a non-HT cohort of participants with appropriate exclusions should be used (5).

HT as subgroup or covariate in models – use baseline Form 43 data, or HT arm if randomized in the HT trial

Separate versus combined analyses of E-alone and E+P HT

Because the HT trial results differed for some outcomes, such as breast and colorectal cancer, one cannot assume it is valide to analyze E-alone and E+P HT as one exposure. The two exposures should first be analyzed separately to determine if combining them is justifiable by the data (6-8).

- **Adjustment for participation in the WHISH and COSMOS clinical trials**

For analyses that have overlapping follow-up time with the intervention periods of either of the WHISH or COSMOS trials, sensitivity analyses should be conducted that take into account the intervention arms. The CCC will perform these analyses.

References

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(3) Prentice RL, Langer R, Stefanick ML, et al, Women's Health Initiative Investigators. Combined postmenopausal hormone therapy and cardiovascular disease: Toward resolving the discrepancy between observational studies and the Women's Health Initiative clinical trial. Am J Epidemiol. 2005 Sep 1;162(5):404-14.

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