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TITLE: A Population-Based Randomized Trial to Assess the Effects of Short-Term Cessation of HRT on Mammography Assessments and Breast Density

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INTRODUCTION:

This randomized controlled trial is designed to test whether short-term (1-2 months) HRT cessation will sufficiently lower breast density to decrease the proportion of women who receive a recommendation for additional evaluation following a screening mammogram, and to examine whether there is a trend by duration of cessation. The study will be conducted at Group Health Cooperative, a managed health care organization with an organized breast cancer screening program. WE will use automated to identify HRT users who are due for screening mammograms. Women will be recruited through mailed correspondence and telephone contact. A total of 1500 women will be recruited and randomized to one of three HRT arms: 1) cessation two months before the screening mammogram, 2) cessation one month before, and 3) continued HRT use. Breast density will be measured using a computer assisted method and recall rates will be determined from an expert radiologist review of the mammograms, blinded to HRT status. We will test whether: 1) HRT cessation 1 or 2 months before a screening mammogram reduces the likelihood of receiving a recommendation for additional evaluation compared to women who continue using HRT; 2) HRT cessation for 1 versus 2 months affects the likelihood of receiving a recommendation for additional evaluation; and 3) there is a greater change in breast density (to lower breast density) among women who stop HRT 1 or 2 months before a screening mammogram to those who do not stop HRT. Change in breast density will be measured as the difference between breast density on the screening mammogram before the trial (while on HRT) and during the trial. As part of this trial we will also evaluate: 1) women's tolerance (defined as continued cessation) for short-term (1-2 months) HRT cessation, 2) the rate of HRT re-initiation after participation in the trial, 3) rates of reported adverse events (return of hot flashes, thromboembolic events within the first 6-months after re-initiation, and return of bleeding with re-initiation among previously amenorrheic women) across randomization groups.

BODY:

Over the past year, members of the study team have developed the protocol, detailed operational procedures and all study materials, including: questionnaires and other data collection forms; informational materials for health care providers; recruitment and participant information materials; consent form; and Data Safety and Monitoring Board (DSMB) reports (see appendix for list of study materials). We worked closely with all study team members including the study nurse and study physician, as well as with members of the lay advisory committee and the DSMB. After an intensive process, the protocol and study materials received full approval from the local IRB in November of 2003.

The IRB-approved materials and other required elements were submitted to the DOD HSRRB on December 4, 2003. The HSRRB provided us with a Memorandum for Record (MFR) on March 16, 2004, which we responded to, making changes to the protocol and study materials as required or recommended. We received a second MFR on May 14, 2004, which we are currently in the process of responding to. The study received a full review by the HSRRB on May 26, 2004. We were notified that we were approved with stipulations, but have not yet received the official minutes from the review with specific items requiring a response or modifications. We have, however, begun revising the protocol and materials based on the MFR received on May 16 and on the feedback received during the review and in subsequent communications with the HSRRB. All revised materials will be

submitted to the HSRRB for final approval and subsequently submitted to the local IRB for approval of all modifications.

A computerized database has been developed to track all operational aspects of study participation. We have been working with key individuals in the delivery/clinical system to ensure that aspects of the study that impact the clinical system will run smoothly and with as little impact on the clinical system and as little inconvenience for the study participant as possible.

Unanticipated delays in starting recruitment:

At this point, we are substantially behind our schedule for starting to recruit women. This has been in large part because of delays in human use approval by the Department of Defense. We submitted our final application to the HSRRB December 4, 2003 and at this point (June 29, 2004) we have not yet received our final minutes from our HSRRB review. However, we have incurred significant costs associated with developing study materials and responding to our local IRB and the HSRRB. Thus, we anticipate that we may have difficulty recruiting 1500 women by the end of the study period (May 31, 2006).

Below we outline our progress on the scope of work outlined in our original proposal.

Task A. Recruit 1500 women to participate in the trial

We have detailed our recruitment plan, developed a tracking database, and written computer programs to link eligible women for recruitment (tasks 1-3). The remaining tasks will be worked once we start recruitment.

Task B. Develop Study Materials

We have developed all study materials including baseline and follow-up questionnaires, instructions on HRT cessation and re-initiation, procedures of operation, and have developed and met with our advocacy board (they have reviewed and provided feedback for all study materials). All items in Task B have been completed.

Task C. Monitor the safety of HRT cessation and initiation

We have formed our DSMB, developed a prototype for our DSMB report, held our first study meeting with the DSMB and have had all study materials reviewed and approved by our DSMB. We will generate our DSMB reports once our study is underway.

Task D. Study staff read all films for clinical interpretation and breast density measurements for the screening mammograms, blinded with respect to HRT status. Validate HRT cessation/use. & Task E. Data quality and control & Task F. Final analyses and report writing

We have not completed any portion of tasks D, E and F, since all elements from these tasks require women to be recruited into the study.

KEY RESEARCH ACCOMPLISHMENTS:

As of June 24, 2004, we have:

- Developed all recruitment and data collection materials (see Attached List)

- Established and met with and had all study materials reviewed our Data Safety and Monitoring Board
- Established, met with and had all study materials reviewed by our Advocacy Board
- Received local human subjects approval for all study materials
- Received approval with stipulations from the HSRRB

REPORTABLE OUTCOMES:

The research portion of this study has not begun. We expect to begin enrollment for the study in August 2004, provided we are able to receive all necessary human subjects approvals by that time.

CONCLUSIONS:

We do not have any results to report at this time since we have not yet started recruitment.

REFERENCES:

N/A

Appendix: List Of Study Materials Developed and Submitted for HSRRB Review

1. Informational Letter to all Primary Care Physicians
2. Letter to Primary Care Physicians Requesting Approval of Patients
3. Initial Recruitment Letter to Subject
4. Study Brochure
5. Telephone Screening Script
6. Consent Form
7. Thank You Letter
8. Long Term Risks of HRT Use Fact Sheet
9. Consent Form Cover Letter to Subject
10. Follow-Up Letter To Physicians Informing of Patient Participation
11. Cover Letter to Subject: Group 1
12. Cover Letter to Subject: Group 2
13. Cover Letter to Subject: Group 3
14. Baseline Questionnaire
15. Study Instructions Group 1
16. Study Instructions Group 2
17. Study Instructions Group 3
18. Cover Letter to Subject: Follow-Up Questionnaire
19. Follow-up Questionnaire Groups 1&2
20. Follow-up Questionnaire Group 3
21. Adverse Events Report
22. DSMB Open Report
23. DSMB Closed Report
24. Adverse Events Flow Chart
25. HSRRB Application/protocol