1. a. Full Title: “Impact of Elective Oophorectomy on Cardiovascular Mortality in Women 45–64 years old: Results of the ARIC Study”
   b. Abbreviated Title: “Oophorectomy and CV Mortality”

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _AA___

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3. Timeline:
   Proposal to ARIC Study: October, 2007
   Approval/Revisions to Study: November – December, 2007
   Data Collection and Analysis: January – February, 2008
   Writing of Manuscript/Editing/Revisions: March – April, 2008
   Submission for Publication: April – May, 2008

4. Rationale:

   In the United States currently, 600,000 hysterectomies are performed annually, 90% of which are for benign disease. Approximately one half million women per year
need to decide whether or not to conserve their ovaries at the time of hysterectomy. Recent CDC data shows that 78% of these women aged 45 – 64 years old are undergoing elective oophorectomy. This decision has been based mostly on traditional practice rather than evidence, and the assumption that a bilateral oophorectomy added minimal surgical risk for menopausal or perimenopausal women, but could confer the benefit of preventing some cases of ovarian cancer. In multiple international studies, the number of cases of cancer prevented was small compared to the number of oophorectomies performed. It was also assumed that the ovaries are basically inert after menopause and have minimal impact on mortality (other than being a potential site for cancer).

In October, 2005 a Markov computer decision analysis model was published, for determining the age at which ovarian conservation at the time of hysterectomy was of benefit rather than harm to a woman’s health (Parker WH, Broder MS, Liu Z, Shoupe D, Farquahar C, Berek JS. Ovarian conservation at the time of hysterectomy for benign disease. Obstet Gynecol 2005; 106:219-26.) This computer model determined that ovarian conservation until age 65 benefits long-term survival for women undergoing benign hysterectomy. This recommendation is a significant departure from current practice, especially for post-menopausal women. A year later, a retrospective cohort study in Olmstead County, Minnesota performed at Mayo Clinic refuted this claim and determined that overall mortality was not increased in women who underwent elective oophorectomy after age 45 (Rocco WA, Grossardt BR, de Andrade M, Malkasian GD, Melton LJ. Survival Patterns after oophorectomy in premenopausal women: a population-based cohort study. Lancet Oncol. 2006 Oct;7(10):821-8).

In reviewing the first article, it is apparent that 85% of the excess mortality attributed to elective oophorectomy was due to an assumed increase in cardiovascular mortality. If this portion of the model is inaccurate, the overall conclusion is likely to be significantly in error. We would therefore like to determine the cardiovascular risk associated with bilateral oophorectomy at the time of benign hysterectomy in women 45 – 64 years old. We propose using the ARIC data to determine the incidence of definite myocardial infarction, cardiovascular mortality and overall mortality in three groups: women with hysterectomy and bilateral oophorectomy, women with hysterectomy and ovarian conservation and a control group of women without hysterectomy.

We are working with the assumption from the Markov computer decision analysis model that bilateral oophorectomy at the time of hysterectomy is a risk factor, to some degree, for cardiovascular events and that the women in this group would have more events than women in the other two groups. We are also estimating the extent to which any excess risk will diminish or resolve over time. This may allow us to estimate at what age (if any) elective oophorectomy can safely be offered to women at the time of hysterectomy without increasing their risk of cardiovascular events.

5. Main hypothesis/Study Questions:

The main study question is to determine: Are cardiovascular events in women with hysterectomy and bilateral oophorectomy increased over those in women with hysterectomy and ovarian conservation, after adjustment for age and other confounding factors? We would like to determine rates of definite myocardial infarction,
cardiovascular mortality and overall mortality in each group. Also, does this risk diminish over time and at what age (if any) are cardiovascular event rates equivalent?

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis and any anticipated methodologic limitations or challenges, if present).

We would like to include women 45 – 64 years old at baseline and study the incidence of CHD for the full length of the ARIC study follow-up. We propose controlling for age, hypertension (blood pressure >140/90), smoking, diabetes, physical activity levels, obesity (BMI >30), LDL cholesterol >160, HDL cholesterol < 45, HRT use > 1 year, previous history of myocardial infarction, family history of cardiovascular mortality (all currently recognized cardiovascular risk factors for women) and race. Exclusion criteria would be: women with breast cancer, known BRCA mutations or gynecologic cancers at the time of hysterectomy.

The analysis will be performed with a proportional hazards model, adjusting for each of the above-mentioned risk factors (except age, which is used as the baseline scale and requires no parametric assumptions) along with group membership as a three-way factor. Coefficients for the many risk factors are all estimable because of the large sample size in the control. Times to definite myocardial infarction, cardiovascular mortality and overall mortality will be used as outcomes in three separate models, with deaths due to intercurrent disease considered censorable losses to follow-up in the first two groups. All subjects will be left-truncated at the age of hysterectomy. Association of group membership with group membership will be estimated in order to answer the first half of the primary study question for the three outcome measures, rephrased quantitatively as: “Are cardiovascular events in women with hysterectomy and bilateral oophorectomy increased over those in women with hysterectomy and ovarian conservation, after adjustment for confounding factors?” An interaction of age and group membership will be examined to answer the remainder of the primary study question: “Also, does this risk diminish over time and at what age (if any) are cardiovascular events equivalent in both groups?” The latter procedure is a standard procedure for nonproportional hazards, performed here because nonproportionality is of intrinsic interest rather than for diagnostic purposes (see, for example, Grant, M.D., Piotrowski, Z.H., and Chappell, R. Self reported health and survival in The Longitudinal Study of Aging, 1984-1986. Journal of Clinical Epidemiology 48 (1995), pp. 375-387). Splus statistical software (Venables, W. and Ripley, B., Modern applied statistics with S, 4th edition. Springer: NY, 2002) will be used to fit the proportional hazards model. This software incorporates the necessary model diagnostics for proportionality and methods for fitting left-truncated outcomes and time dependent covariates.

Approximate sample size calculations can be performed by ignoring effects of age and other covariates (for these purposes only, rendering the resultant power conservative) and examining what magnitude changes in MI rates will be detectable using simple comparisons of two proportions. Starting with 8000 subjects in the ARIC study, and
Subtracting a conservative 10% for ineligibility, we have 7200 subjects to be included in this substudy. Of those, using an expected hysterectomy rate of 13.5/1000 per year x 17 years x 7200 yields 1486 women with hysterectomies, of whom roughly half are expected to have had elective oophorectomies. Thus the sample sizes in the control and two hysterectomy groups are approximately 5714, 743, and 743 respectively after accounting for ineligibility. From published ARIC data we can estimate the annual rate of MI in women ages 45-64 to be approximately .005/year or .082 over 17 years. Then, using a chi-square test of proportions conducted at the two-sided .05 significance level to compare MI rates in women with hysterectomies and oophorectomy vs. rates in women with hysterectomies and no oophorectomies, there is 90% power to detect a difference in proportions of .047 and 80% power to detect a difference of .040. Thus, this substudy will be well-powered to detect moderate to large effects of oophorectomy on MI in women with hysterectomies. The truncated proportional hazards model with age treated as a time-dependent variable should have higher sensitivity, and comparisons of hysterectomy groups with the control will have much higher power.

7. a. Will the data be used for non CVD analysis in this manuscript? No.

8 a. Will the DNA data be used in this manuscript? No.

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. Done – no overlap.

10. What are the most related manuscript proposals in ARIC? There are no proposals studying oophorectomy, ovaries or hysterectomy at this time. There are 14 proposals studying various aspects of natural menopause, but none looking at the impact of surgical menopause.

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? No.