committee decided to halt the trial and revise the protocol.

The revised MAP.3 study now compares exemestane to placebo in a 1:1 ratio in 4560 postmenopausal women who are 35 years of age or older and at increased risk for the development of breast cancer. For the purposes of this protocol, "increased risk" is defined as being over the age of 60, or having a Gail score greater than 1.65, or having a prior atypical breast biopsy (atypical ductal hyperplasia, atypical lobular hyperplasia, or lobular carcinoma *in situ*), or having a prior diagnosis of DCIS that was treated with a mastectomy. Women are stratified on their Gail score (≤2 vs. >2) and current low-dose (<100 mg daily) aspirin use (yes vs. no) before being randomly allocated to the treatment or placebo group.

4.2 Rationale for Placebo

Despite the fact that tamoxifen has been approved as a means to reduce breast cancer risk in women who would be eligible for this trial, it was decided that the use of a placebo control arm was justified for several reasons:

- Although tamoxifen is approved for the indication of reducing the short-term incidence of breast cancer, many women whose level of risk would qualify them for the prescription of tamoxifen refuse the drug because of its toxicity profile [52–55]. Raloxifene is another option that women may consider for breast cancer risk reduction, although it is not yet approved for that indication. However, although the risk profile for raloxifene may be better than that for tamoxifen, it is still associated with increased risk of thromboembolic events and decreased sexual function [27]. Therefore, there remains a population of women eligible for this trial who have chosen or will choose, even after appropriate counselling, to avoid taking tamoxifen or raloxifene. These women may well wish to enter a placebo-controlled trial where the agents under study may have more favourable toxicity profiles.
- The ASCO Technology Assessment of Pharmacologic Interventions for Breast Cancer Risk Reduction Including Tamoxifen, Raloxifene and Aromatase Inhibition [56] concluded that "placebo controls are appropriate for breast cancer risk reduction trials since no intervention has been demonstrated to favorably impact net health or survival." Although the MAP.3 trial is not expected to demonstrate an impact on survival, the results may well indicate a more favourable therapeutic ratio for exemestane than for tamoxifen or raloxifene.
- The placebo arm will allow for a true determination of efficacy in reducing invasive breast cancer, of adverse effects, and of impact on overall and menopausal-specific quality of life.

4.3 Study Procedures

Women enrolled in the MAP.3 research study will have a bone-mineral density test and a mammogram before being randomized. Women can be enrolled at centres in Canada, the United States, or Spain. Participants will be asked to return to their local study centre twice during the first year, at 6 and 12 months, and then annually for follow-up visits for the remaining 4 years of the study. At each visit, participants will be given a new supply of the study medications and will be asked to answer questions about their quality of life and about any illnesses or discomfort they may have experienced since their last visit. At each annual visit, participants will undergo a physical and health exam and a mammogram. At three different times during the study, serum samples will also be taken for hormone testing. If additional consent has been given for DNA testing, a blood sample taken at baseline will be stored for future genetic testing.

4.4 Study Goals and Population

The main objective of the MAP.3 trial is to compare the incidence of breast cancer in the two treatment groups. Information will also be recorded and compared between treatment groups on clinical bone fractures, cardiovascular events, quality of life, tolerability and safety, and incidences of other malignancies. A companion study to evaluate the long-term effects of exemestane on bone density and bone biomarkers is planned for a subset of participating sites.

Some of the biggest challenges of conducting a breast cancer prevention trial include recruiting women from the general population and defining the groups at high-risk for the development of breast cancer that are most eligible for chemoprevention. Well established cancer cooperative groups with affiliated clinical research centers in North America, Europe, and Australia are available to help with recruitment of cancer patients into therapeutic trials. However, that model is not so easy to replicate for cancer prevention trials. The clinicians that typically see well women are more likely to be primary care physicians or other internal specialists such as gynecologists. However, primary care physicians in particular do not appear to be comfortable prescribing chemoprevention medication [57–59], and based on results from a recent national survey in the United States, the decision to prescribe tamoxifen was greatly affected by logistics and the ability of the physician to determine eligibility [59].

For the MAP.3 trial to be feasible, the NCIC CTG had to assemble a consortium of clinical researchers in Canada and the United States who were committed to cancer prevention research and who had participated in earlier prevention trials with the Women's Heath Initiative (WHI) or the National Surgical Adjuvant Breast and Bowel Project. Nonetheless, recruit-