14. APPENDIX A - SAMPLE INFORMED CONSENT FORM

INFORMED CONSENT FORM - RESEARCH STUDY

Women's Angiographic Vitamin & Estrogen Trial (WAVE)

Principal Investigator -
Telephone -

Introduction
You are being asked to take part in a research study. Before you decide to take part, you need to understand the risks and benefits so that you can make an informed decision. This is known as informed consent. This consent form provides information about the research study which has been explained to you. Once you understand the study and the activities it requires, you will be asked to sign this form if you want to take part. You are free to choose if you take part.

Purpose
The purpose of the WAVE research study is to find out if two treatments, hormone replacement therapy and antioxidant vitamins, reduce the risk of narrowing or closing off in the blood vessels supplying the heart. This research study is being carried out at 5 centers around the country; a total of about 450 women will participate. Participation will last about 3-4 years.

Description of Procedures
Dr. _____ and his/her staff are inviting postmenopausal women (those who have gone through the change of life) to participate in this study if they either have had recent heart catheterization or are scheduled for upcoming heart catheterization. If you agree, you will have your heart catheterization as scheduled. Careful records will be kept of the camera views used and several extra views, taking a few seconds each, may be filmed to be sure that pictures of any narrowings in your blood vessels are clear. If you have any narrowings which meet study requirements (15-75% narrowed), you may be eligible to join the study. If not, you will be so informed by a study staff member.

Ultrasound pictures of the blood vessels in your heart may be recorded during your heart catheterization by placing a small ultrasound device in your blood vessels through the same tubes used for the rest of the heart catheterization. (You cannot feel the ultrasound device.) You may join the research study without having the ultrasound pictures. You will be notified if these ultrasound pictures are planned.

If your heart catheterization results are suitable, you will be scheduled for a screening visit to ensure that you can safely join the study. At that visit you will be asked about your medical

background, have a brief physical examination including breast and pelvic exams (including Pap smear if you have not had one within the past year), and give a blood sample (_____ tablespoons).You will need to have a mammogram if you have not had one within the past year. You will not be charged for the examinations or tests.

You may also be asked to have two additional tests, a dipyridamole SPECT and a brachial reactivity study. The dipyridamole SPECT is a common type of stress test in which a medication called dipyridamole and a small amount of radioactivity are given to you through a vein. A special camera takes pictures of the radioactivity to measure the blood flow to your heart. The brachial reactivity study measures the ability of the artery in your arm to dilate in response to nitroglycerin and after temporarily blocking blood flow in your arm. A blood pressure cuff will be placed around your arm and ultrasound pictures of your artery recorded. You may join the WAVE research study without having the dipyridamole SPECT or the brachial reactivity study.

If the results are satisfactory and you wish to join the study, you will be be enrolled and given study medication. The hormone replacement will be either Premarin 0.625 mg each day (for women with a hysterectomy) or Premarin 0.625 mg + medroxyprogesterone 2.5 mg each day (for women with a uterus). The antioxidants will be vitamins C (500 mg) + vitamin E (400 IU), both taken twice daily. These drugs are approved for sale in the United States; they are not experimental. You will take one tablet of hormone study medication and two capsules of antioxidant study medication in the morning and two capsules of antioxidant study medication in the evening for the duration of the study; the doses of study medication can be adjusted if you should develop a side effect. Whether you are given active medication or inactive medication (placebo) will be determined by chance. You will have an equal chance of receiving each of the following drug combinations.

Active hormone replacement + active antioxidant vitamins
Active hormone replacement + inactive antioxidant vitamins
Inactive hormone replacement + active antioxidant vitamins
Inactive hormone replacement + inactive antioxidant vitamins

Neither you nor the research staff will know which treatment you are receiving. You will be asked not to take other hormone replacement therapy, vitamin C or vitamin E while participating in the study. If you wish, you will be given a multivitamin tablet (Centrum) to take daily.

You will be asked to return for a clinic visit one month and 3 months later to be sure you are not having any problems with the study medication. Every 6 months you will be asked to return to clinic to be given a new supply of study medication and to tell the study staff about any changes in your health. Annual mammograms, breast and pelvic exams will be performed, and a blood sample collected at 3, 18, 24 and 36 months. The dipyridamole SPECT may be repeated at 3 months and 3 years; the brachial reactivity study may be repeated at 3 months.

At the end of 3 years you will have a heart catheterization for comparison with your original study. This catheterization may be performed for research purposes, not necessarily because of medical need. If ultrasound pictures of your heart arteries were recorded during your entry heart catheterization, they may be repeated.

Benefits and Risks

Possible benefits to you include a 3 out of 4 chance that you will be receiving active hormone replacement and/or antioxidant vitamins for free. You will receive free physical examinations, mammograms and Pap smears for the study. Benefit to others includes contributing to the understanding of ways to prevent heart disease in women. Although heart disease is the leading cause of death in women, they have often been excluded from past studies of heart disease.

Risks associated with coronary angiography - Some additional views may be filmed during your angiogram, increasing the amount of radiation you receive. For example, instead of having 6 views of your coronaries filmed, you may have 8 or 9. You will be having a second angiogram performed as part of the study, with associated risks which include bleeding (1%, that is, 1 out of 100) , stroke (0.1%, that is, 1 out of 1000) and death (0.05%, that is, 1 out of 2000) . The amount of radiation during heart catheterization is about 20 rads, which is about 67 times the amount of natural environmental radiation the average person receives in the United States each year.

If you have ultrasound pictures taken of your heart arteries, there is a small risk (0.3%, that is 3 out of 1000) that a coronary artery may be damaged by the ultrasound device.

Adverse effects of the study drugs - Estrogen (Premarin) may cause bloating, nausea, vomiting, abdominal cramps, rash, headache, dizziness, depression, breast tenderness and enlargement, and changes in thyroid activity. Vaginal spotting or bleeding is common, occurring in as many as 1/3 of women, but usually resolves within several months. In some women it may persist. For your safety, if you have persistent or severe bleeding you may be asked to have an endometrial aspiration, in which a few cells from the lining of the uterus are sucked into the thin tube (about the width of a pencil lead) during pelvic exam. Endometrial aspiration may cause abdominal cramps. Fibroids (non-cancerous tumors of the uterus may increase in size while taking estrogen. Estrogen use has been associated with a 2-fold increased risk of gallstones. Among 50-62 year old women not taking estrogen, 10-15% are thought to have gall bladder disease, thus the expected frequency among estrogen users would be 20-30%. Estrogen, when given alone, is also associated with increased of endometrial cancer (cancer of the lining of the uterus). Medroxyprogesterone is given with estrogen in this study to protect against development of endometrial cancer. Prolonged use of estrogen may be associated with a slightly increased risk of breast cancer. This is the reason for the annual mammograms and breast exams performed as part of this study. Women with known breast cancer or endometrial cancer may not participate in this study.

Medroxyprogesterone may cause rash, vaginal bleeding, depression or nausea. Hormone replacement has been associated with a 3-fold increased risk of blood clots in the legs and lungs. If you have had blood clots in your legs within the past 10 years or have ever had blood clots in your lungs, you should not participate in this research study.

Vitamins C and E are thought to be safe in the doses used in this study.

Mammography, blood drawing and endometrial aspiration may be associated with temporary discomfort. Breast compression is required during mammography, which may be uncomfortable. Blood drawing involves a needle stick and may result in bruising at the site. If you have the dipyridamole SPECT pictures, the amount of radiation is about 0.4 rad, equivalent to 1.3 times the amount of natural environmental radiation the average person receives in the United States each year. There is no risk with the brachial reactivity study, although the blood pressure cuff may be uncomfortable while inflated.

Alternate Treatments

An alternative to joining this study is to take hormone replacement and/or antioxidant vitamins prescribed by your physician.

Costs
Participation will cost only your time and travel. Transportation or parking expenses associated with study visits may be reimbursed. Study medication will be provided to you without charge. If your heart catheterizations are done because you and your physician believe them to be important to your health care, they will be billed under normal financial arrangements. If, on the other hand, one or both of your heart catheterizations are being done only for research purposes, the research study will pay for that catheterization. Any charges associated with mammograms, Pap smears and endometrial biopsies will be paid by the study. You will not be paid for your participation.

Taking part in this research study is unlikely to result in injury or harm to you. If you require immediate medical care, you should go to an emergency room. Otherwise the doctor in charge of this study will take care of you or help you get the care you need. You will be sent a bill for whatever medical care you receive. All or part of your bill may be paid by your health insurance. The National Heart, Lung and Blood Institute will not pay for the care. You should not expect anyone to pay you for pain, worry, lost income, or non-medical care costs that may occur from taking part in the study. This position does not prevent you from pursuing whatever appeals may be available under the law.

Confidentiality
The results of this research study will be given to the Study Coordinating Center for this research study at the George Washington University, and to the National Heart, Lung and Blood Institute. Your medical and research records may be also be provided to the Food and Drug Administration and the United States Department of Health and Human Services. Except for these entities, medical and research study records will be kept confidential unless you authorize their release, or the records are required by law (i.e., court subpoena). You will not be identified by name in any reports or publications of this study.

Right to Withdraw
You may decide to stop this study at any time. Your care and relations with the doctors and nurses working on this research study will not be changed in any way if you decide not to participate in the study or to stop the study.

Voluntary Consent
Your participation in this research study is voluntary. If you have any questions about the study, you should contact Dr._____. Also, if you have any questions about your rights as a participant in this study, please call_____, who is your representative and is not affiliated with this research study.

Signatures
By signing this consent form you are agreeing that you understand this consent form, have had an opportunity to ask questions, have had your questions answered to your satisfaction, and agree to take part. You will be given a copy of this consent form.

_____	_____	_____
Signature of participant	Print name	Date

_____	_____	_____
Signature of person obtaining consent	Print name	Date
_____	_____	_____
Signature of principal investigator or designee	Print name	Date