Study Title: Arterial Stiffness, Cognition, and Equol (ACE)

NCT05741060

University of Pittsburgh Informed Consent Form

Wake Forest University Informed Consent Form

Emory University Informed Consent Form

Approval Date: 6-20-2024

University of Pittsburgh

Department of Epidemiology
School of Public Health

CONSENT TO ACT AS A PARTICIPANT IN A RESEARCH STUDY

Title: Arterial Stiffness, Cognition and Equol (ACE)
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SOURCE OF SUPPORT: National Institutes of Health - National Institute on Aging (NIA).

KEY INFORMATION

You are invited to participate in the Arterial Stiffness, Cognition, and Equol Trial (also known as ACE Trial). Equol is a soy-based supplement that has plant estrogen-like compounds in it. The purpose of this study is to learn if taking Equol could slow the progression of:

- stiffening of the arteries
- small blood vessel disease in the brain
- memory decline.

Your participation in this research will involve up to 7 visits to the Health Studies Research Center located at 130 N. Bellefield Avenue, Suite 400, Pittsburgh, PA 15213 at the University of Pittsburgh over two years.

As part of the study, we will complete several non-invasive tests like measuring your blood pressure and heart rate, height and weight, and doing tests of walking and thinking. We will collect a sample of your blood, urine and stool.

We will ask you questions about your health history and medication use, your mood and other topics. To measure stiffening of the arteries, we will do a test called a carotid-femoral pulse wave velocity. It is low risk and without radiation. There is more information on this test on p. 3. To assess the health of small blood vessels in your brain, we will do a Magnetic Resonance Imaging (MRI) scan. We will also do an ultrasound scan of your carotid arteries.

The risks of these tests are not unlike risks with usual medical care, including minor discomfort and breach of confidentiality. If you are assigned to a group that takes Equol, it could give you constipation or bloating. You may benefit from the Equol supplement if the study shows it does have a positive effect on artery or brain health. There is more information on the risks on pp. 8-9.

The remainder of this document contains a more complex description of the ACE Trial. If you are interested, please read through the rest of the document carefully. You can ask any questions if you need help deciding whether to join the study. You can discuss the study with your family or friends if you would like. Your participation is voluntary. You do not need to participate in this study if you do not want to. If you decide not to participate, you will not lose any services, benefits, or rights you normally have.

People with a history of breast cancer should not participate in this study.

INTRODUCTION

You are invited to participate in this research study because you:

1. are between the ages of 65-85
2. do not have dementia
3. are willing to have an MRI scan
4. are willing to take the study supplement/placebo.

How many people will take part in the study? Approximately 400 men and women will be randomized at the three clinical research centers, University of Pittsburgh, Wake Forest University, and Emory University.

What is involved in the study? If you decide to take part in the ACE Trial, we will ask you to complete several examinations within the first month. Then we will ask you to return one time a year for two years with phone calls between visits.

Screening Visit 1 (about 1-2 hours)**:**

At this visit we will ask you to do the following:

1. Complete a questionnaire of your name, address and other information
2. Complete tests of memory and concentration
3. Measure your blood pressure and pulse
4. Collect a urine sample. We will look check to be sure there is no protein in your urine.
5. Draw a blood sample from your vein of about 2-3 tablespoons. This includes such tests as vitamin levels, blood cell count, a test to see be sure you don't have diabetes.

If you are eligible for the study based on the tests completed at the Screening Visit, we will ask you to return for the Baseline Visits. The baseline examination will be divided into two separate days within one month.

Baseline Visit Day 1 (about 5 hours)

At this visit you will be asked to do the following:

1. Complete memory and paper and pencil tasks and on an iPad laptop.
2. Have your blood pressure measured
3. Have your height and weight measured

4. Complete a 400 meter walk at a normal pace
5. Have your grip strength measured.

6. Carotid-femoral Pulse Wave Velocity

We will do a test to measure the hardness and stiffness of your blood vessels. This test uses something called “pulse-wave velocity techniques”. The pulse wave velocity technique measures how fast the waves of movement pushing your blood through your vessels travel from your heart to the different sites measured. For this procedure, you will be required to lay quietly for about one half hour. You will have a blood pressure cuff placed around your right upper thigh, and a small disc-shaped handheld sensor placed on the right side of your neck. The thigh cuff may be placed on a bare thigh or over light clothing. The cuff will inflate several times for various readings. This testing will be performed by trained technologists.

7. Carotid ultrasound

This test will require you to lie down and a cool, jelly-like, hypoallergenic substance will be applied on your neck while a probe is moved up and down the area. Sound waves are bounced off the arteries, creating a picture of what the arteries look like on the inside. This non-invasive painless test takes approximately 40 minutes. The carotid ultrasound images you will have for this study are for specific research purposes and are not being used to evaluate your health or find medical abnormalities. These images will be reviewed by an experienced sonographer. If abnormalities are seen, your test results will be reviewed by a physician with the rest of your health information. The results from this review will be provided to you and your physician. In the event that you do not have a primary physician, we will recommend that you go to a physician.

8. Collect a blood sample of approximately 5 tablespoons from your vein. We will ask that you not eat or drink anything except water for 8 hours before your appointment. After we draw your blood, we will provide a snack before you continue with the rest of your visit procedures. This will be used to measure “biomarkers” - different substances in your blood that test for your body’s response, risk for disease, and a genetic marker for a certain kind of cholesterol in your blood that changes if you develop dementia or cardiovascular disease.

9. Collect a stool sample at home after your Baseline Visit Day 1. We will give you instructions and a container, which is placed on your toilet, so you can collect the stool. You will place a small amount of stool in a special tube. We will remind you to collect the stool sample and provide mailing instructions to send to Indiana University.

10. We will ask you to complete a questionnaire about your diet over a 24 hour time period. A member of the research staff at the University of North Carolina (UNC) Diet and Physical Activity Core in the UNC Nutrition Obesity Research Center will contact you at a prearranged time. This will occur twice within a 2 week time period.

11. So that we can understand how your body processes soy, we will ask you to eat a serving of a soy food product on three consecutive days. This information is important for us to know when we interpret the results of the study since Equol comes from soy. The soy food will be a soy protein shake that the study team will provide you. On the morning of the fourth day, we will ask you to come to clinic to have a urine sample collected as part of your Randomization Visit.

Baseline Visit Day 2 (about 2 hours):

On a separate day, you will have a test called Magnetic Resonance Imaging (MRI).
We will do an MRI scan of your brain. This scan will take up to 1 hour. Once a trained staff member has made sure you have no metal in your body and are safe to have an MRI, the brain scan can proceed. Prior to your scan at the University of Pittsburgh's Biomedical Science Tower Building's 3T scanner, we will ask you questions about the presence of metal in your body that may be attracted to the magnet. In most cases, an MRI is safe for people who have metal implants from surgery. However, you may not participate in the study unless it is determined that you meet the guidelines of the UPMC Health System. The MRI involves lying on a table, which then moves into a hollow machine that contains a powerful magnet. While you are lying in the MRI scanner, you will hear a variety of loud knocking noises. You will be given earplugs, which are required and will provide a barrier to the loud noise. Additionally, a pillow or cushion will be placed under your head and around your ears. These cushions serve two purposes: to stabilize your head to reduce movement and to serve as another barrier to the loud noise. A study team member and/or MR technologist will check in with you periodically throughout each scan (verbally through an intercom), and during these times, you will be able to speak to us as well. At any other times, we ask you to alert us to any problems or concerns using an emergency squeeze ball that will be with you the duration of your scan.

Because this is a research MRI, not a clinical MRI, your scan will not be read by a radiologist. The MR technologists are trained to examine brain images as they are acquired, and if any abnormality is suspected, a radiologist will immediately review the images. If anything previously unknown is found on the MRI that is of clinical significance, the PI will review the findings with you, and you will be given an appropriate referral. A copy of the MRI images along with the clinical notes will be sent to your doctor upon your written request. It is important to note that you may be removed from the study if you are unable to complete this MRI scan. If you are unable to complete this scan for reasons out of your control, such as scanner issues, all attempts to reschedule the scan will be made. If you are unable to complete the scan for reasons such as claustrophobia, discomfort, or personal choice, you may be removed from the study.

Randomization Visit (about 1 hour):

At this visit, we will ask you to provide a urine sample.

You will then be randomly assigned by a computer (by chance, like the flip of a coin) to a group that takes 10 mg Equol daily or to taking a daily placebo.

A placebo is a substance that looks like and is given in the same way as an experimental treatment but contains no medicine or supplement (it is an inactive substance). A placebo is used in research studies to show what effect a treatment has compared with taking nothing at all. If you are assigned to receive the placebo, you will not receive the benefit of taking Equol, if there are any, nor will you be exposed to its risk, which are described later in this consent form. You and the Study Physician and other staff will not know which group you are assigned to, but that information is available.

The study staff will review how and when to take the study pill. It is important to take the study pill exactly as instructed and to return any unused study pill and empty bottles at your next study visit.

We will ask you to not consume greater than 2 servings of soy per week over the course of the study.

Occasionally, because of equipment failure, incorrect positioning or other technical difficulty, the results from measures may give poor quality information or no information at all. In some cases, biological samples may not be usable. If that were to happen to you, we will ask you to have repeat tests or scans performed or provide another biological sample. We may ask you to repeat certain measures for quality assurance purposes. Another in-clinic visit may need to be scheduled. It is your decision whether to have the tests repeated or not. Additionally, you may be asked to volunteer for specific vascular tests twice. This double testing allows the laboratory to verify how well they can repeat a test on the same participant. This will be strictly voluntary; therefore, if you are unable to stay longer for your visits you will be under no obligation to participate in this double testing.

You may also be audiotaped while performing some of the cognitive tests. Recording your responses will enable us to make sure that the examiners are administering the memory tests the same to everyone. You may request that you are not audiotaped. You should understand that you will not be able to inspect, review, or approve the audiotapes before they are used in this study. The recording will not include any personal identifiers and will be securely sent to the University of Pittsburgh Data Coordinating Center. All recordings may be kept and stored indefinitely and may be analyzed for future research.

Follow-up Visits

If you decide to take part in the ACE Trial, we will contact you a month after you begin to take study pills. Then approximately every 3 months we will call by phone to update your information and ask how you are doing with the study pills. We will also ask you to return for an in-person visit at Years 1 and 2.

The Year 1 visit will consist of repeating the pulse wave velocity exam, tests of memory and concentration, questionnaires regarding lifestyle, medical history, physical activity, and sleep habits. We will obtain your height, weight, blood pressure, pulse and fasting blood draw. We will ask that you complete a 400 meter walk and grip strength measurement. We will ask you to collect another stool sample and will be give you mailing instructions. The blood draw will include testing for safety of the study supplement, e.g., your blood count, cholesterol panel, and basic organ function.

At Year 2, we will ask that you complete all of the above procedures in addition to the carotid ultrasound and MRI scan. The MRI will be scheduled on a separate day, just like the baseline exam.

If we are unable to contact you or if you become incapacitated, we will contact your designated proxy to inquire about your status and ask them to answer the same questions we would have asked you.

In the event that an abnormality is found on your MRI or ultrasound scan, with your permission we can send copies of your test results to your physician. Even if you do not wish to have any of your medical information sent to your physician, you can still participate in this research study.

Collection of Medical Information

This research study may involve the recording of past, current and/or future identifiable medical information from your hospital and/or you physician records. The information that will be recorded will be limited to information concerning any metal objects in your body, hospitalizations, medical, and death records. The information will be used for determining safety for MRI and for documenting illnesses, hospital admissions, and cause of death for the research study. All of the medical information listed above will become part of your participant chart and will be kept indefinitely at the locked research office located at the University of Pittsburgh or on computer servers with secure passwords.

Information from hospitalizations, medical records, and death records will be securely sent to the University of Pittsburgh Data Coordinating Center to track occurrences of diseases, hospitalizations, and accurately determine cause of death. Like all your other information, this data will be kept as safe and private as possible.

If you have care in a system outside of UPMC, we will ask you to complete a medical release form so that we may access your medical records.

Access to Research Data & Biological Samples

The information and biological samples, including genetic information, that are obtained during the ACE Trial will be preserved for research uses in the future. We will store your samples and data indefinitely. There is no limit on the time that these can be used for research.

All information collected during your clinic exams, phone interviews or questionnaires as well as the biological samples that you provide will be labelled only with a special code. Anyone using them will not be able to tell to whom they belong. They will not include any identifiable information about you such as your name, address, telephone number, social security number or medical record. The unique code is assigned at the time of the Telephone Screening call by the ACE team at the University of Pittsburgh. Only the Principal Investigator of this site and limited study staff will have access to the code that links the unique identifier to you. Your name, address, social security number, etc., will never be disclosed to future researchers and neither will the code that links your identifiers to the sample.

Your specimens and data may be used for research by scientists who are part of universities, research institutions, and companies. The research may include any disease, symptoms, measurements, including conditions related to aging. Your specimens and data may also be used for the purpose of developing potential medical or preventive treatments or tests, such as tests to predict the risk of conditions or tests of physical or cognitive health. The research using the specimens and data may be conducted by scientists in universities or commercial companies. Your identity and personal information will not be provided to any company, university or research institutions.

Your data and specimens used in this research study may contribute to a new discovery or treatment. In some instances, these discoveries or treatments may be of commercial value and may be sold, patented, or licensed by the investigators and the University of Pittsburgh and for use in other research or the development of new products. You will not retain any property rights nor will you share in any money that the investigators, the medical center, or their agents may realize.

The research that may be performed with your biological samples is not designed to help you specifically. Other than obtaining medical information about yourself, there is no specific benefit to you from taking part in this aspect of the research study. It might help people who have diseases at some point in the future, but it is not known if this will happen. The results of the research performed with your biological samples will not be given to you or your doctor. The results will not be put in your medical record. The research using your biological samples will not affect your current or future care.

Storage of Biological Samples

Collected samples (blood, urine and stool) will be stored at the National Centralized Repository for Alzheimer's Disease and Related Dementias (NCRAD) at Indiana University, Indianapolis, Indiana. NCRAD is a national resource supported by the National Institute on Aging that prepares and stores biological specimens from all over the world and makes them available to approved scientists who would not otherwise be able to access the material.

A portion of your blood sample will be stored at Wake Forest University, a participating site of the ACE Trial.

HOW LONG WILL I BE IN THE STUDY?

You will be in the study for a little over 2 years. We will ask you to complete four study visits over the course of approximately a one-month period to complete the baseline and randomization visits. Thereafter, you will be contacted at month 1, month 3 then every 3 months by phone to complete a brief questionnaire. At year 1 and 2 year, we will ask you to return to the clinic for follow-up in-person examinations.

You can stop participating at any time. If you decide to stop participating in the study, we encourage you to talk to the investigators or study team member first to learn about any potential health or safety consequences.

Social Security Number (SSN) usage

We will ask you to provide your SSN on the patient contacts document if you have not done so already. This information will be transmitted to the study Coordinating Center at the University of Pittsburgh. The collection of your SSN is necessary for research purposes so that we can track your health through national health databases that are available to the public, such as the National Death Index. The collection of your SSN, **for research purposes other than payment**, is strictly optional and is not required for participation in the study.

WHAT ARE THE RISKS OF THE STUDY?

Besides the risks mentioned on page 1, there are some possible discomforts and risks associated with participating in this study. Information regarding the frequency of possible risks has been categorized using the following categories:

Likely – occurs in more than 25% of people (more than 25 out of 100 people);
Common – occurs in 10% to 25% of people (10 to 25 out of 100 people);
Infrequent – occurs in 1 to 10% of people (1 to 10 of 100 people);
Rarely – occurs in less than 1% of people (less than 1 out of 100 people).

Equol supplement - NOTE

The supplement does NOT contain estrogen. However, because it comes from soy which has chemicals similar to estrogen, if you have a history of breast cancer or have breast cancer in your immediate blood relatives, you should not take this supplement. It could increase the chances of the cancer occurring or re-occurring.

Equol supplement

There is an infrequent risk of an allergic reaction that could result in a rash or other symptoms, including mild stomach discomfort. There is a rare risk of a skin rash, blood clot in the lung or a thickening of the lining of your uterus. Tell the study team immediately if you have or experience any side effects while you are taking the study pills.

There are no known risks to the placebo tablet.

To avoid risks, you should tell the research study team about all the medications, vitamins and supplements you take and any medical conditions you have. As with any study, there may be adverse events or side effects that are currently unknown and it is possible that certain of these unknown risks could be permanent, serious or life-threatening.

Questionnaires

There is no physical risk associated with the measures of memory or paper and pencil tasks, questionnaires or clinic interviews. We will also ask you about your mental health status and if you have thoughts of harming yourself. These measures/questions may cause frustration, boredom or fatigue, but you may take breaks as often as you need. You are not required to answer any question that you feel uncomfortable answering.

Clinic Measures

There is an infrequent risk of losing your balance while standing on the scale for weight measurements, although a study technician will be standing beside you. There is an infrequent risk of injury during the physical performance testing, such as muscle strains or pulls, falls or joint injury. In addition, if you report pain, dizziness, feeling faint, lightheadedness, chest pain or shortness of breath or other medical problem (all infrequent) during these tests they will be stopped. It is common to feel fatigued after these performance tests. The risks of all these tests will be minimized by having experienced/trained examiners conduct these assessments.

MRI

The risks involved with the MRI scans are small and limited to the risks present during routine MRI examinations. There is no radiation exposure associated with MRI scans. There are no known dangers of exposure to the magnetic fields used for the MRI brain imaging studies. During an MRI scanning session, there is potential for the powerful magnetic field to attract metal objects towards the magnet. For this reason, you will be carefully screened for previous exposure to metal fragments or clips that may be inside your body. We will ask you to place all metal and magnetic objects in your possession (e.g., keys, bank cards) in a locker outside the magnetic room. Some people feel claustrophobic, meaning uncomfortable in confined areas, in the scanner, and if that is a problem for you, you will be removed from the study. Finally, the MRI machine is noisy, which has the potential to irritate your hearing. You will be given earplugs to minimize this risk. If an x-ray is necessary, this will involve exposure to radiation.

Carotid Ultrasound Scan

There are no known risks involved with the carotid ultrasound scan. The process is noninvasive and painless. Ultrasound imaging does not use radiation technology. In the event that testing reveals disease that is of clinical significance, we will refer you for medical evaluation. This is expected to be a rare event occurring in less than 2% of people. In the event that you do not have a primary physician, we will recommend that you go to a physician or can refer one to you.

Pulse Wave Velocity test

The blood pressure cuff or tonometer used for the Aortic Pulse Wave Velocity test may occasionally cause some skin redness from the pressure. This is an infrequent adverse event occurring in 1-10% of people (1-10 out of 100 people). This redness may last up to 48 hours. Severe pain may be experienced while cuff is inflated. This is a rare adverse event occurring in less than 1% of people (less than 1 out of 100 people). Past participants have rated this test less uncomfortable than a blood draw.

All measures that are part of the ACE Trial are being conducted only for the purpose of research. They are different tests than what are used in the clinical setting to detect or discover medical conditions. The Ultrasound or MRI scans that are collected for the ACE Trial are not a substitute for a clinical Ultrasound or MRI scan. Research personnel will analyze the scans only for the specified research findings. These scans may not be analyzed until the study has ended. However, if we should happen to see an abnormal finding that may be harmful to your health on the Ultrasound and/or MRI scan, we will notify you.

Unexpected findings on the limited research scans will occasionally allow early discovery of a medical condition for which you may need treatment. They may also cause undue worry or result in additional testing, sometimes costly, which may or may not benefit your health.

Blood draw
There are infrequent risks associated with the drawing of a blood sample, including discomfort at the site of needle insertion, bruising (black and blue discoloration) and/or bleeding where the needle is inserted. Occasionally some people become dizzy, lightheaded, or feel faint. Infection may occur on rare occasions. Frequent donation of blood can result in low iron in your blood (iron deficient anemia).
It is common to experience some fatigue at the end of each study visit.

Stool sample collection
There are no known risks related to collecting a stool sample.

Genetic Analysis
The risk of doing genetic studies includes the potential for a breach of confidentiality, which means someone could see your genetic testing results who is not authorized. The information could be used to affect what insurance or jobs you may be able to get. It could cause stress and conflict in your family relationships, as it can confirm the identity of is a child's father, identify a risk for a certain disease, or cause you or other people to have negative feelings if the results show you may be more likely to get certain diseases. The only genetic testing done in the current study is looking at part of a blood protein that can measure risk for dementia and cardiovascular disease.

In addition, there is a federal law, called the Genetic Information Nondiscrimination Act (GINA), that generally makes it illegal for health insurance companies and group health plans to use genetic information in making decisions regarding your eligibility or premiums. GINA also makes it illegal for employers with 15 or more employees to use your genetic information when making decisions regarding hiring, promoting, firing, or setting the terms of employment. This new Federal law does not protect you against genetic discrimination by companies that sell life, disability, or long-term care insurance. GINA does not protect you against discrimination from previously diagnosed genetic conditions.

Future Genetic testing
While we can't predict how biological samples may be used in the future at this time, future research may include studying your genetic information. At some point in the future, we may be required to share genetic data with federal repositories. The National Institutes of Health (NIH) and other central repositories have developed special data (information) banks that collect the results of genetic studies, especially when the research looks at all or large sections of individual's genetic code. This is often called whole genome sequencing. Genomic information relates to the structure and function of all of the genetic material in the body. These central banks will store your genetic information and give them to other qualified and approved researchers to do more studies. The data that we share with federal repositories will be coded in such a way that you would not be able to be identified. We will not share

your name, birth date, or any other information that could directly identify you. The link to the code would be kept securely at the University of Pittsburgh. Even so, there is a possibility that when your genomic information is combined with other information available to researchers, either now or in the future, they may be able to identify a group you belong to (like an ethnic group or a disease population) or, less likely, you personally. NIH prohibits people from trying to identify individuals whose genomic information is in an NIH-designated repository.

Your identifiers will be removed from the private information and/or biospecimens. This de-identified information and/or biospecimens may be used by other researchers for future research studies. If this happens, we will not contact you for additional consent.

We do not think that there will be further risks to your privacy and confidentiality by sharing your genetic information with these banks. However, we cannot predict how genetic information will be used in the future.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you are assigned to the group to receive Equol, you may benefit from its positive effect on your brain health. Therefore, no direct benefit is guaranteed. You will receive results from some of your clinic tests such as your height, weight, blood pressure, and blood labs. In addition, the information we collect in this study will be valuable to further research on physical health and aging. We hope the information learned from this study will benefit other people in the future.

NEW INFORMATION

If we learn any new information that may change your decision to be in this study, we will let you know.

PROTECTING THE CONFIDENTIALITY OF YOUR INFORMATION

Taking part in this research study involves providing information that you may consider confidential or private. We will take efforts such as coding research records, keeping research records secure and allowing only authorized people to have access to research records to keep your information safe.
The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed unless it is authorized by you, required by law, or necessary to protect the safety of yourself or others. There is always some risk that even de-identified information might be re-identified.
This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific

research, as allowed by federal regulations protecting research subjects. The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law of such as child abuse and neglect, or harm to self or others.

You may choose to voluntarily disclose the protected information and this certificate does not prohibit such voluntary disclosure. Furthermore, the parties listed in the Confidentiality / Authorization section of this consent form may review our records under limited circumstances and this certificate does not prohibit such disclosure.

WHAT ABOUT MY HEALTH INFORMATION?

In this research study, any new information we collect from you is called Identifiable Private Information or "IPI." The IPI we will collect for this research study includes your name, birthdate, address and Medicare (Social Security) number.

Any information we collect from your medical records about your health is considered *Protected Health Information* or "PHI."

We will make every effort to keep your IPI and PHI as confidential (private) as possible. We will store records of your information in a cabinet in a locked office or on a password protected computer at the University of Pittsburgh. You will not be identified by name in any publication of the research results unless you sign a separate form giving your permission (release).

Identifiable information about you may be accessed by others during and after the study. These reasons are to carry out the study, to determine the results of the study, to make sure the study is being done correctly, to provide required reports and to get approval for new products.

Some of the people, agencies and businesses that may receive and use your health information are the research sponsor; representatives of the sponsor assisting with the research; investigators at other sites who are assisting with the research; central laboratories, reading centers or analysis centers; representatives of the University of Pittsburgh Office of Research Protection; representatives from government agencies such as the Food and Drug Administration (FDA) or the Office for Human Research Protections (OHRP), the Department of Health and Human Services (DHHS) or similar agencies in other countries.

This study is being conducted at three clinical sites and being overseen by the ACE team at the University of Pittsburgh Coordinating Center. Some of these people, agencies and businesses may further disclose your health information. If disclosed by them, your health information may no longer be covered by federal or state privacy regulations. Your health information may be disclosed if required by law. Your health information may be used to create information that does not directly identify you. This information may be used by other researchers for future studies. You will not be directly identified in any publication or presentation that may result from this study unless there are photographs or recorded media which are identifiable.

Monitors, auditors, Human Research Protection Office or other regulatory agencies will be granted direct access to the participant's original medical record for verification of clinical trial procedures or data, without violating confidentiality of the participant and to the extent permitted by other applicable laws.

Any PHI or IPI collected from you in this study that is maintained in the research records will be kept for an indefinite period of time for research purposes. This authorization does not expire. You will not be able to obtain a copy of your PHI in the research records until all activities in the study are completely finished. Per University of Pittsburgh policy, research records will be maintained for at least 7 years following final reporting of publication of a project.

You can tell Dr. Sekikawa that you want to withdraw your permission to use and share your medical record information at any time by sending a letter to him at this address:
Health Studies Research Center
130 N. Bellefield Avenue, Suite 400
Pittsburgh, PA 15213.

However, if you withdraw permission to use your PHI you will not be able to be in the study any longer. We will stop collecting any more information about you, but any information we have already collected can still be used for the purposes of the research study and will not be able to be retrieved.

Laboratory test results and other medical reports created as a result of your participation in the research study may be entered into the computer systems of the University of Pittsburgh Coordinating Center that combines the data for analyses. These will be kept secure, with access to this information limited to individuals with proper authority, but who may not be directly involved with this research study.

A Data Safety Monitoring Board, an independent group of experts, will be reviewing the procedures and data from this research throughout the study. They may be provided de-identified data to monitor the research.

CLINICAL TRIALS.GOV
A description of this clinical trial may be available on http://www.ClinicalTrials.gov, if required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

WHAT ARE THE COSTS?
All costs of the study, including any of the procedures related directly to the study, will be paid for by the study. Costs for your regular medical care, which are not related to this study, will be your own responsibility.

WILL YOU BE PAID FOR PARTICIPATING?
You will be paid for study participation throughout the course of the study. Payment will be via a reloadable debit card. The payment schedule is as follows:

$25 baseline clinic exam
$25 MRI scan
$100 at randomization visit
$150 at Year 1
$200 at Year 2

If you withdraw for any reason from the study before completion you will be paid for each part of the study that is completed. We will reimburse or validate parking expenses during your clinic visits. At one of your clinic visits, you may be asked if you know family members or friends who would be interested in participating in this study. You will receive a nominal payment for your referral. Payment received as compensation for participation in research is considered taxable income for a research subject. If payments are more than $600 in any one calendar year, University of Pittsburgh is required to report this information to the Internal Revenue Service (IRS). Research subject payments exceeding $600 during any calendar year will result in a 1099 (Miscellaneous Income) form being issued to the research subject and a copy will be sent to the IRS. Participants who do not provide a social security number may still participate in the research, but the IRS requires that 24% of the payment be sent by the institution to the IRS for 'backup withholding;' thus you would only receive 76% of the expected payment.

WHAT HAPPENS IF I EXPERIENCE AN INJURY OR ILLNESS AS A RESULT OF PARTICIPATING IN THE STUDY?
If you believe that the research procedures have resulted in an injury to you, immediately contact the Principal Investigator who is listed on the first page of this form. Emergency medical treatment for injuries solely and directly related to your participation in this research study will be provided to you by the hospitals of UPMC. Your insurance provider may be billed for the costs of this emergency treatment, but none of those costs will be charged directly to you. If your research-related injury requires medical care beyond this emergency treatment, you will be responsible for the costs of this follow-up care. At this time, there is no plan for any additional financial compensation. You do not give up any of your legal rights by signing this form.

For more information on medical treatment for research related illness or adverse event, you should call Dr. Neelesh Nadkarni (MD, PhD) at (412) 692-2360. Dr. Nadkarni is physician and part of our study team. If you have an emergency in the evenings or on a weekend when the study office is closed, you should call (412) 624-3579. This phone number is answered 24 hours a day, seven days a week.

WHAT ARE MY RIGHTS AS A RESEARCH STUDY PARTICIPANT?
Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. Refusing to participate or leaving the study will not result in any penalty or loss of benefits to which you are entitled. If you decide to stop participating in the study, we encourage you to talk to the

investigators or study team first to learn about any potential health or safety consequences. The investigators or the sponsor also have the right to stop your participation in the study at any time. This could be because you had an unexpected reaction or because the entire study ended.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions, concerns, or complaints about the study, or in the event of a research-related injury, contact the study investigator, Dr. Sekikawa. If you have an emergency in the evenings or on a weekend when the study office is closed, you should call (412) 624-3579. This phone number is answered 24 hours a day, seven days a week.

We will send important medical findings to your personal physician that you indicate, unless you tell us otherwise. We will use your social security number as described on page 8 unless you tell us otherwise.

VOLUNTARY CONSENT

The above information has been explained to me and all my current questions have been answered. I understand that I am encouraged to ask questions, voice concerns or complaints about any part of this research study during this study. Any future questions, concerns or complaints will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) given. I understand that I may always request that my questions, concerns or complaints be addressed by a listed investigator.

I understand that I may contact the Human Subjects Protection Advocate of the Human Research Protection office, University of Pittsburgh (1-866-212-2668) to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations that occurred during my participation. By signing this form, I consent to participate in this research study and provide authorization to use and share my medical records. A copy of this consent form will be given to me.

Participant Name (Printed):_____

Signature: _____ Date: _____

Person Obtaining Consent (Printed):_____

Signature: _____ Date: _____

Wake Forest®
School of Medicine

CONSENT TO ACT AS A PARTICIPANT IN A RESEARCH STUDY

Title: Arterial Stiffness, Cognition and Equol (ACE)

Principal Investigator: Timothy Hughes, PhD
Wake Forest University Health Sciences / Wake Forest School of Medicine
Medical Center Blvd.
Winston-Salem, NC 28677

Source of Support: National Institutes of Health – National Institute on Aging (NIA)

KEY INFORMATION

You are invited to participate in the Arterial Stiffness, Cognition, and Equol Trial (also known as ACE Trial). Equol is a soy-based supplement that has plant estrogen-like compounds in it. The purpose of this study is to learn if taking Equol could slow the progression of:

- stiffening of the arteries
- small blood vessel disease in the brain
- memory decline.

Your participation in this research will involve up to 7 visits to the Alzheimer's Disease Research Center (ADRC) located at Atrium Health Wake Forest Baptist Medical Center over two years.

As part of the study, we will complete several non-invasive tests like measuring your blood pressure and heart rate, height and weight, and doing tests of walking and thinking. We will collect a sample of your blood, urine and stool.

We will ask you questions about your health history and medication use, your mood and other topics. To measure stiffening of the arteries, we will do a test called a carotid-femoral pulse wave velocity. It is low risk and without radiation. There is more information on this test on p. 3. To assess the health of small blood vessels in your brain, we will do a Magnetic Resonance Imaging (MRI) scan. We will also do an ultrasound scan of your carotid arteries.

The risks of these tests are not unlike risks with usual medical care, including minor discomfort and breach of confidentiality. If you are assigned to a group that takes Equol, it could give you constipation or bloating. You may benefit from the Equol supplement if the study shows it does have a positive effect on artery or brain health. There is more information on the risks starting on p. 8.

The remainder of this document contains a more complex description of the ACE Trial. If you are interested, please read through the rest of the document carefully. You can ask any questions if you need help deciding whether to join the study. You can discuss the study with your family or friends if you would like. Your participation is voluntary. You do not need to participate in this study if you do not want to. If you decide not to participate, you will not lose any services, benefits, or rights you normally have.

People with a history of breast cancer should not participate in this study.

INTRODUCTION

You are invited to participate in this research study because you:

1. are between the ages of 65-85
2. do not have dementia
3. are willing to have an MRI scan
4. are willing to take the study supplement/placebo.

How many people will take part in the study? Approximately 400 men and women will be randomized at the three clinical research centers, University of Pittsburgh, Wake Forest University, and Emory University.

What is involved in the study? If you decide to take part in the ACE Trial, we will ask you to complete several examinations within the first month. Then we will ask you to return one time a year for two years with phone calls between visits.

Screening Visit 1 (about 1-2 hours)**:**

At this visit we will ask you to do the following:

1. Complete a questionnaire of your name, address and other information
2. Complete tests of memory and concentration
3. Measure your blood pressure and pulse
4. Collect a urine sample. We will look check to be sure there is no protein in your urine.
5. Draw a blood sample from your vein of about 2-3 tablespoons. This includes such tests as vitamin levels, blood cell count, a test to see be sure you don't have diabetes.

If you are eligible for the study based on the tests completed at the Screening Visit, we will ask you to return for the Baseline Visits. The baseline examination will be divided into two separate days within one month.

Baseline Visit Day 1 (about 5 hours)

At this visit you will be asked to do the following:

1. Complete memory and paper and pencil tasks and on an iPad laptop.
2. Have your blood pressure measured
3. Have your height and weight measured
4. Complete a 400 meter walk at a normal pace
5. Have your grip strength measured.
6. Carotid-femoral Pulse Wave Velocity

We will do a test to measure the hardness and stiffness of your blood vessels. This test uses something called "pulse-wave velocity techniques". The pulse wave velocity technique measures how fast the waves of movement pushing your blood through your vessels travel from your heart to the different

sites measured. For this procedure, you will be required to lay quietly for about one half hour. You will have a blood pressure cuff placed around your right upper thigh, and a small disc-shaped handheld sensor placed on the right side of your neck. The thigh cuff may be placed on a bare thigh or over light clothing. The cuff will inflate several times for various readings. This testing will be performed by trained technologists.

7. Carotid ultrasound
This test will require you to lie down and a cool, jelly-like, hypoallergenic substance will be applied on your neck while a probe is moved up and down the area. Sound waves are bounced off the arteries, creating a picture of what the arteries look like on the inside. This non-invasive painless test takes approximately 40 minutes. The carotid ultrasound images you will have for this study are for specific research purposes and are not being used to evaluate your health or find medical abnormalities. These images will be reviewed by an experienced sonographer. If abnormalities are seen, your test results will be reviewed by a physician with the rest of your health information. The results from this review will be provided to you and your physician. In the event that you do not have a primary physician, we will recommend that you go to a physician.

8. Collect a blood sample of approximately 5 tablespoons from your vein. We will ask that you not eat or drink anything except water for 8 hours before your appointment. After we draw your blood, we will provide a snack before you continue with the rest of your visit procedures. This will be used to measure "biomarkers" - different substances in your blood that test for your body's response, risk for disease, and a genetic marker for a certain kind of cholesterol in your blood that changes if you develop dementia or cardiovascular disease.

9. Collect a stool sample at home after your Baseline Visit Day 1. We will give you instructions and a container, which is placed on your toilet, so you can collect the stool. You will place a small amount of stool in a special tube. We will remind you to collect the stool sample and provide mailing instructions to send to Indiana University.

10. We will ask you to complete a questionnaire about your diet over a 24 hour time period. A member of the research staff at the University of North Carolina (UNC) Diet and Physical Activity Core in the UNC Nutrition Obesity Research Center will contact you at a prearranged time. This will occur twice within a 2 week time period.

11. So that we can understand how your body processes soy, we will ask you to eat a serving of a soy food product on three consecutive days. This information is important for us to know when we interpret the results of the study since Equol comes from soy. The soy food will be a soy protein shake that the study team will provide you. On the morning of the fourth day, we will ask you to come to clinic to have a urine sample collected as part of your Randomization Visit.

Baseline Visit Day 2 (about 2 hours):
On a separate day, you will have a test called Magnetic Resonance Imaging (MRI).
We will do an MRI scan of your brain. This scan will take up to 1 hour. Once a trained staff member has made sure you have no metal in your body and are safe to have an MRI, the brain scan can proceed. Prior to your scan at Atrium Health Wake Forest Baptist Medical Center, we will ask you questions about the presence of metal in your body that may be attracted to the magnet. In most cases, an MRI is safe for people who have metal implants from surgery. However, you may not participate in the study unless it is determined that you meet the guidelines of the Atrium Health System.

The MRI involves lying on a table, which then moves into a hollow machine that contains a powerful magnet. While you are lying in the MRI scanner, you will hear a variety of loud knocking noises. You will be given earplugs, which are required and will provide a barrier the loud noise. Additionally, a pillow or cushion will be placed under your head and around your ears. These cushions serve two purposes: to stabilize your head to reduce movement and to serve as another barrier to the loud noise. A study team member and/or MR technologist will check in with you periodically throughout each scan (verbally through an intercom), and during these times, you will be able to speak to us as well. At any other times, we ask you to alert us to any problems or concerns using an emergency squeeze ball that will be with you the duration of your scan.

Because this is a research MRI, not a clinical MRI, your scan will not be read by a radiologist. The MR technologists are trained to examine brain images as they are acquired, and if any abnormality is suspected, a radiologist will immediately review the images. If anything previously unknown is found on the MRI that is of clinical significance, the PI will review the findings with you, and you will be given an appropriate referral. A copy of the MRI images along with the clinical notes will be sent to your doctor upon your written request. It is important to note that you may be removed from the study if you are unable to complete this MRI scan. If you are unable to complete this scan for reasons out of your control, such as scanner issues, all attempts to reschedule the scan will be made. If you are unable to complete the scan for reasons such as claustrophobia, discomfort, or personal choice, you may be removed from the study.

Randomization Visit (about 1 hour):
At this visit, we will ask you to provide a urine sample. You will then be randomly assigned by a computer (by chance, like the flip of a coin) to a group that takes 10 mg Equol daily or to taking a daily placebo.

A placebo is a substance that looks like and is given in the same way as an experimental treatment but contains no medicine or supplement (it is an inactive substance). A placebo is used in research studies to show what effect a treatment has compared with taking nothing at all. If you are assigned to receive the placebo, you will not receive the benefit of taking Equol, if there are any, nor will you be exposed to its risk, which are described later in this consent form. You and the Study Physician and other staff will not know which group you are assigned to, but that information is available.

The study staff will review how and when to take the study pill. It is important to take the study pill exactly as instructed and to return any unused study pill and empty bottles at your next study visit.

We will ask you to not consume greater than 2 servings of soy per week over the course of the study.

Occasionally, because of equipment failure, incorrect positioning or other technical difficulty, the results from measures may give poor quality information or no information at all. In some cases, biological samples may not be usable. If that were to happen to you, we will ask you to have repeat tests or scans performed or provide another biological sample. We may ask you to repeat certain measures for quality assurance purposes. Another in-clinic visit may need to be scheduled. It is your decision whether to have the tests repeated or not. We may want to do an ECG, a measure of the electrical activity of your heart if your pulse is irregular.

Additionally, you may be asked to volunteer for specific vascular tests twice. This double testing allows the laboratory to verify how well they can repeat a test on the same participant. This will be strictly voluntary; therefore, if you are unable to stay longer for your visits you will be under no obligation to participate in this double testing.

You may also be audiotaped while performing some of the cognitive tests. Recording your responses will enable us to make sure that the examiners are administering the memory tests the same to everyone. You may request that you are not audiotaped. You should understand that you will not be able to inspect, review, or approve the audiotapes before they are used in this study. The recording will not include any personal identifiers and will be securely sent to the University of Pittsburgh Data Coordinating Center. All recordings may be kept and stored indefinitely and may be analyzed for future research.

Follow-up Visits

If you decide to take part in the ACE Trial, we will contact you a month after you begin to take study pills. Then approximately every 3 months we will call by phone to update your information and ask how you are doing with the study pills. We will also ask you to return for an in-person visit at Years 1 and 2. The Year 1 visit will consist of repeating the pulse wave velocity exam, tests of memory and concentration, questionnaires regarding lifestyle, medical history, physical activity, and sleep habits. We will obtain your height, weight, blood pressure, pulse and fasting blood draw. We will ask that you complete a 400 meter walk and grip strength measurement. We will ask you to collect another stool sample and will be give you mailing instructions. The blood draw will include testing for safety of the study supplement, e.g., your blood count, cholesterol panel, and basic organ function.

At Year 2, we will ask that you complete all of the above procedures in addition to the carotid ultrasound and MRI scan. The MRI will be scheduled on a separate day, just like the baseline exam.

If we are unable to contact you or if you become incapacitated, we will contact your designated proxy to inquire about your status and ask them to answer the same questions we would have asked you.

In the event that an abnormality is found on your MRI or ultrasound scan, with your permission we can send copies of your test results to your physician. Even if you do not wish to have any of your medical information sent to your physician, you can still participate in this research study.

Collection of Medical Information

This research study may involve the recording of past, current and/or future identifiable medical information from your hospital and/or you physician records. The information that will be recorded will be limited to information concerning any metal objects in your body, hospitalizations, medical, and death records. The information will be used for determining safety for MRI and for documenting illnesses, hospital admissions, and cause of death for the research study. All of the medical information listed above will become part of your research participant chart and will be kept indefinitely in a secured location at Atrium Health Wake Forest Baptist Medical Center or on computer servers with secure passwords.

Information from hospitalizations, medical records, and death records will be securely sent to the University of Pittsburgh Data Coordinating Center to track occurrences of diseases, hospitalizations, and accurately determine cause of death. Like all your other information, this data will be kept as safe and private as possible.

If you have care in a system outside of Atrium Health Wake Forest Baptist Medical Center we will ask you to complete a medical release form so that we may access your medical records.

Access to Research Data & Biological Samples

The information and biological samples, including genetic information, that are obtained during the ACE Trial will be preserved for research uses in the future. We will store your samples and data indefinitely. There is no limit on the time that these can be used for research.

All information collected during your clinic exams, phone interviews or questionnaires as well as the biological samples that you provide will be labelled only with a special code. Anyone using them will not be able to tell to whom they belong. They will not include any identifiable information about you such as your name, address, telephone number, social security number or medical record. The unique code is assigned at the time of the Telephone Screening call by the ACE team at our site. Only the Principal Investigator of this site and limited study staff will have access to the code that links the unique identifier to you. Your name, address, social security number, etc., will never be disclosed to future researchers and neither will the code that links your identifiers to the sample.

Your specimens and data may be used for research by scientists who are part of universities, research institutions, and companies. The research may include any disease, symptoms, measurements, including conditions related to aging. Your specimens and data may also be used for the purpose of developing

potential medical or preventive treatments or tests, such as tests to predict the risk of conditions or tests of physical or cognitive health. The research using the specimens and data may be conducted by scientists in universities or commercial companies. Your identity and personal information will not be provided to any company.

Your data and specimens used in this research study may contribute to a new discovery or treatment. In some instances, these discoveries or treatments may be of commercial value and may be sold, patented, or licensed by the investigators and for use in other research or the development of new products. You will not retain any property rights nor will you share in any money that the investigators, the medical center, or their agents may realize.

The research that may be performed with your biological samples is not designed to help you specifically. Other than obtaining medical information about yourself, there is no specific benefit to you from taking part in this aspect of the research study. It might help people who have diseases at some point in the future, but it is not known if this will happen. The results of the research performed with your biological samples will not be given to you or your doctor. The results will not be put in your medical record. The research using your biological samples will not affect your current or future care.

Storage of Biological Samples
Collected samples (blood, urine, and stool) will be stored at the National Centralized Repository for Alzheimer's Disease and Related Dementias (NCRAD) at Indiana University, Indianapolis, Indiana. NCRAD is a national resource supported by the National Institute on Aging that prepares and stores biological specimens from all over the world and makes them available to approved scientists who would not otherwise be able to access the material.

A portion of your blood sample will be stored at Wake Forest University, a participating site of the ACE Trial.

HOW LONG WILL I BE IN THE STUDY?
You will be in the study for a little over 2 years. We will ask you to complete four study visits over the course of approximately a one-month period to complete the baseline and randomization visits. Thereafter, you will be contacted at month 1, month 3 then every 3 months by phone to complete a brief questionnaire. At year 1 and 2 year, we will ask you to return to the clinic for follow-up in-person examinations.

You can stop participating at any time. If you decide to stop participating in the study, we encourage you to talk to the investigators or study team member first to learn about any potential health or safety consequences.

Social Security Number (SSN) usage
We will ask you to provide your SSN on the patient contacts document if you have not done so already. This information will be transmitted to the study Coordinating Center at the University of Pittsburgh.

The collection of your SSN is necessary for research purposes so that we can track your health through national health databases that are available to the public, such as the National Death Index. The collection of your SSN, **for research purposes other than payment**, is strictly optional and is not required for participation in the study.

WHAT ARE THE RISKS OF THE STUDY?

Besides the risks mentioned on page 1, there are some possible discomforts and risks associated with participating in this study. Information regarding the frequency of possible risks has been categorized using the following categories:

Likely – occurs in more than 25% of people (more than 25 out of 100 people);
Common – occurs in 10% to 25% of people (10 to 25 out of 100 people);
Infrequent – occurs in 1 to 10% of people (1 to 10 of 100 people);
Rarely – occurs in less than 1% of people (less than 1 out of 100 people).

Equol supplement - NOTE

The supplement does NOT contain estrogen. However, because it comes from soy which has chemicals similar to estrogen, if you have a history of breast cancer or have breast cancer in your immediate blood relatives, you should not take this supplement. It could increase the chances of the cancer occurring or re-occurring.

Equol supplement

There is an infrequent risk of an allergic reaction that could result in a rash or other symptoms, including mild stomach discomfort. There is a rare risk of a skin rash, blood clot in the lung or a thickening of the lining of your uterus. Tell the study team immediately if you have or experience any side effects while you are taking the study pills.

There are no known risks to the placebo tablet.

To avoid risks, you should tell the research study team about all the medications, vitamins and supplements you take and any medical conditions you have. As with any study, there may be adverse events or side effects that are currently unknown and it is possible that certain of these unknown risks could be permanent, serious or life-threatening.

Questionnaires

There is no physical risk associated with the measures of memory or paper and pencil tasks, questionnaires or clinic interviews. We will also ask you about your mental health status and if you have thoughts of harming yourself. These measures/questions may cause frustration, boredom or fatigue, but you may take breaks as often as you need. You are not required to answer any question that you feel uncomfortable answering.

Clinic Measures
There is an infrequent risk of losing your balance while standing on the scale for weight measurements, although a study technician will be standing beside you. There is an infrequent risk of injury during the physical performance testing, such as muscle strains or pulls, falls or joint injury. In addition, if you report pain, dizziness, feeling faint, lightheadedness, chest pain or shortness of breath or other medical problem (all infrequent) during these tests they will be stopped. It is common to feel fatigued after these performance tests. The risks of all these tests will be minimized by having experienced/trained examiners conduct these assessments.

MRI
The risks involved with the MRI scans are small and limited to the risks present during routine MRI examinations. There is no radiation exposure associated with MRI scans. There are no known dangers of exposure to the magnetic fields used for the MRI brain imaging studies. During an MRI scanning session, there is potential for the powerful magnetic field to attract metal objects towards the magnet. For this reason, you will be carefully screened for previous exposure to metal fragments or clips that may be inside your body. We will ask you to place all metal and magnetic objects in your possession (e.g., keys, bank cards) in a locker outside the magnetic room. Some people feel claustrophobic, meaning uncomfortable in confined areas, in the scanner, and if that is a problem for you, you will be removed from the study. Finally, the MRI machine is noisy, which has the potential to irritate your hearing. You will be given earplugs to minimize this risk. If an x-ray is necessary, this will involve exposure to radiation.

Carotid Ultrasound Scan
There are no known risks involved with the carotid ultrasound scan. The process is noninvasive and painless. Ultrasound imaging does not use radiation technology. In the event that testing reveals disease that is of clinical significance, we will refer you for medical evaluation. This is expected to be a rare event occurring in less than 2% of people. In the event that you do not have a primary physician, we will recommend that you go to a physician or can refer one to you.

Pulse Wave Velocity test
The blood pressure cuff or tonometer used for the Aortic Pulse Wave Velocity test may occasionally cause some skin redness from the pressure. This is an infrequent adverse event occurring in 1-10% of people (1-10 out of 100 people). This redness may last up to 48 hours. Severe pain may be experienced while cuff is inflated. This is a rare adverse event occurring in less than 1% of people (less than 1 out of 100 people). Past participants have rated this test less uncomfortable than a blood draw.

All measures that are part of the ACE Trial are being conducted only for the purpose of research. They are different tests than what are used in the clinical setting to detect or discover medical conditions. The Ultrasound or MRI scans that are collected for the ACE Trial are not a substitute for a clinical Ultrasound or MRI scan. Research personnel will analyze the scans only for the specified research findings. These scans may not be analyzed until the study has ended. However, if we should happen to see an abnormal finding that may be harmful to your health on the Ultrasound and/or MRI scan, we will notify you.

Unexpected findings on the limited research scans will occasionally allow early discovery of a medical condition for which you may need treatment. They may also cause undue worry or result in additional testing, sometimes costly, which may or may not benefit your health.

Blood draw
There are infrequent risks associated with the drawing of a blood sample, including discomfort at the site of needle insertion, bruising (black and blue discoloration) and/or bleeding where the needle is inserted. Occasionally some people become dizzy, lightheaded, or feel faint. Infection may occur on rare occasions. Frequent donation of blood can result in low iron in your blood (iron deficient anemia).
It is common to experience some fatigue at the end of each study visit.

Stool sample collection
There are no known risks related to collecting a stool sample.

Genetic Analysis
The risk of doing genetic studies includes the potential for a breach of confidentiality, which means someone could see your genetic testing results who is not authorized. The information could be used to affect what insurance or jobs you may be able to get. It could cause stress and conflict in your family relationships, as it can confirm the identity of is a child's father, identify a risk for a certain disease, or cause you or other people to have negative feelings if the results show you may be more likely to get certain diseases. The only genetic testing done in the current study is looking at part of a blood protein that can measure risk for dementia and cardiovascular disease.

In addition, there is a federal law, called the Genetic Information Nondiscrimination Act (GINA), that generally makes it illegal for health insurance companies and group health plans to use genetic information in making decisions regarding your eligibility or premiums. GINA also makes it illegal for employers with 15 or more employees to use your genetic information when making decisions regarding hiring, promoting, firing, or setting the terms of employment. This new Federal law does not protect you against genetic discrimination by companies that sell life, disability, or long-term care insurance. GINA does not protect you against discrimination from previously diagnosed genetic conditions.

Future Genetic testing
While we can't predict how biological samples may be used in the future at this time, future research may include studying your genetic information. At some point in the future, we may be required to share genetic data with federal repositories. The National Institutes of Health (NIH) and other central repositories have developed special data (information) banks that collect the results of genetic studies, especially when the research looks at all or large sections of individual's genetic code. This is often called whole genome sequencing. Genomic information relates to the structure and function of all of the genetic material in the body. These central banks will store your genetic information and give them to other qualified and approved researchers to do more studies. The data that we share with federal repositories will be coded in such a way that you would not be able to be identified. We will not share

your name, birth date, or any other information that could directly identify you. The link to the code would be kept securely at the University of Pittsburgh. Even so, there is a possibility that when your genomic information is combined with other information available to researchers, either now or in the future, they may be able to identify a group you belong to (like an ethnic group or a disease population) or, less likely, you personally. NIH prohibits people from trying to identify individuals whose genomic information is in an NIH-designated repository.

Your identifiers will be removed from the private information and/or biospecimens. This de-identified information and/or biospecimens may be used by other researchers for future research studies. If this happens, we will not contact you for additional consent.

We do not think that there will be further risks to your privacy and confidentiality by sharing your genetic information with these banks. However, we cannot predict how genetic information will be used in the future.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
If you are assigned to the group to receive Equol, you may benefit from its positive effect on your brain health. Therefore, no direct benefit is guaranteed. You will receive results from some of your clinic tests such as your height, weight, blood pressure, and blood labs. In addition, the information we collect in this study will be valuable to further research on physical health and aging. We hope the information learned from this study will benefit other people in the future.

NEW INFORMATION
If we learn any new information that may change your decision to be in this study, we will let you know.

PROTECTING THE CONFIDENTIALITY OF YOUR INFORMATION
Taking part in this research study involves providing information that you may consider confidential or private. We will take efforts such as coding research records, keeping research records secure and allowing only authorized people to have access to research records to keep your information safe.
The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed unless it is authorized by you, required by law, or necessary to protect the safety of yourself or others. There is always some risk that even de-identified information might be re-identified.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you

have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research participants. The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law of such as child abuse and neglect, or harm to self or others.

You may choose to voluntarily disclose the protected information and this certificate does not prohibit such voluntary disclosure. Furthermore, the parties listed in the Confidentiality / Authorization section of this consent form may review our records under limited circumstances and this certificate does not prohibit such disclosure.

WHAT ABOUT MY HEALTH INFORMATION?

In this research study, any new information we collect from you and/or information we get from your medical records or other facilities about your health or behaviors is considered Protected Health Information. The information we will collect for this research study includes name, birthdate, address and Medicare (Social Security) number.

If this research study involves the diagnosis or treatment of a medical condition, then Protected Health Information collected from you during this study will be placed in your medical record, and may be used to help treat you, arrange payment for your care, or assist with the health care operations of Atrium Health, Wake Forest University Health Sciences, and their respective affiliated entities.

We will take steps to keep your Protected Health Information private. We will store records of your Protected Health Information in secured office suite or on a password protected computer.

Your personal health information and information that identifies you ("your health information") may be given to others during and after the study. These reasons are to carry out the study, to determine the results of the study, to make sure the study is being done correctly, to provide required reports and to get approval for new products.

Some of the people, agencies and businesses that may receive and use your health information are the research sponsor; representatives of the sponsor assisting with the research; investigators at other sites who are assisting with the research; central laboratories, reading centers or analysis centers; the Institutional Review Board; representatives of Wake Forest University Health Sciences and Atrium Health Facilities; representatives of the University of Pittsburgh Office of Research Protection; representatives from government agencies such as the Food and Drug Administration (FDA) or the Office of Human Research Protections (OHRP), the Department of Health and Human Services (DHHS) and similar agencies in other countries.

Some of these people, agencies and businesses may further disclose your health information. If disclosed by them, your health information may no longer be covered by federal or state privacy regulations. Your health information may be disclosed if required by law. Your health information may be used to create information that does not directly identify you. This information may be used by other researchers. You will not be directly identified in any publication or presentation that may result from

this study unless there are photographs, videotapes, audiotapes or other recorded media which are identify you unless we you're your written authorization.

Monitors, auditors, IRB or other regulatory agencies will be granted direct access to your medical record for verification of clinical trial procedures or data to the extent permitted by other applicable laws. These monitors, auditors, and other individuals are also required to maintain the confidentiality of your protected health information.

A Data Safety Monitoring Board, an independent group of experts, will be reviewing the procedures and data from this research throughout the study. They may be provided de-identified data to monitor the research.

If required by law or court order, we might also have to share your Protected Health Information with a judge, law enforcement officer, government agencies, or others. If your Protected Health Information is shared with any of these groups it may no longer be protected by federal or state privacy rules.

Any Protected Health Information collected from you in this study that is maintained in the research records will be kept for an indeterminate period of time. This authorization does not expire. Any research information entered into your medical record will be kept for as long as your medical record is kept by the Medical Center. You will not be able to obtain a copy of your Protected Health Information in the research records until all activities in the study are completely finished.

You can tell Timothy Hughes, PhD that you want to take away your permission to use and share your Protected Health Information at any time by sending a letter to this address:

Timothy Hughes, PhD
Wake Forest University Health Sciences /
Wake Forest School of Medicine
Medical Center Boulevard
Winston-Salem, NC 27157

However, if you take away permission to use your Protected Health Information you will not be able to be in the study any longer. We will stop collecting any more information about you, but any information we have already collected can still be used for the purposes of the research study and will not be able to be retrieved.

By signing this form you give us permission to use your Protected Health Information for this study.

If you choose to participate in this study, your medical record at Atrium Health, Wake Forest University Health Sciences, or their respective affiliated entities will indicate that you are enrolled in a clinical trial. Information about the research and any medications or devices you are being given as a participant may also be included in your medical record. Authorization to access this part of the medical record will only be available to people who have a need to know this information in order to perform their job-related duties. If you are not a patient of these health care facilities, a medical record will be created for you anyway to provide access to this important information to providers in case of an emergency.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this Web site at any time.

Laboratory test results and other clinically relevant medical reports created as a result of your participation in the research study may be entered into the computer systems of Atrium Health, Wake Forest University Health Sciences, and/or their respective affiliated entities. These results and reports will be kept secure in compliance with applicable laws, with permission to access this information limited to individuals with proper authority, but who may not be directly involved with this research study.

A medical record will be created for all study participants seen on-site and if a medical record doesn't already exist. Information about your participation in the study will be placed in the medical record, along with any routine medical test results that were obtained as part of this study.

WHAT ARE THE COSTS?

All costs of the study, including any of the procedures related directly to the study, will be paid for by the study. Costs for your regular medical care, which are not related to this study, will be your own responsibility.

WILL YOU BE PAID FOR PARTICIPATING?

You will be paid for study participation throughout the course of the study. Payment will be via a gift card. The payment schedule is as follows:

$25 clinic screening exam
$50 baseline clinic exam
$75 MRI scan
$100 at randomization visit
$150 at Year 1
$200 at Year 2

If you withdraw for any reason from the study before completion you will be paid for each part of the study that is completed. We will reimburse or validate parking expenses during your clinic visits.

Payment received as compensation for participation in research is considered taxable income for a research participant. If payments are more than $600 in any one calendar year, we are required to report this information to the Internal Revenue Service (IRS). Research participant payments exceeding $600 during any calendar year will result in a 1099 (Miscellaneous Income) form being issued to the research participant and a copy will be sent to the IRS. Participants who do not provide a social security number may still participate in the research, but will not be paid.

WHAT HAPPENS IF I EXPERIENCE AN INJURY OR ILLNESS AS A RESULT OF PARTICIPATING IN THE STUDY?

Should you experience a physical injury or illness as a direct result of your participation in this study, Wake Forest University School of Medicine maintains limited research insurance coverage for the usual and customary medical fees for reasonable and necessary treatment of such injuries or illnesses. To the extent research insurance coverage is available under this policy the reasonable costs of these necessary medical services will be paid, up to a maximum of $25,000. Wake Forest University Baptist Medical Center holds the insurance policy for this coverage. It provides a maximum of $25,000 coverage for each claim and is limited to a total of $250,000 for all claims in any one year. The Wake Forest University School of Medicine, and the North Carolina Baptist Hospitals, Incorporated do not assume responsibility to pay for these medical services or to provide any other compensation for such injury or illness. Additional information may be obtained from the Medical Center's Director of Risk and Insurance Management, at (336) 716-3467.

If you are injured, the insurer may require information such as your name, social security number, and date of birth in order to pay for your care. This is because the insurer is required by law to report any payments made to cover the care of any persons who are members of a government insurance plan to the Department of Health and Human Services.

You do not give up any legal rights as a research participant by signing this consent form. For more information on medical treatment for research related injuries or to report a study related illness, adverse event, or injury you should contact the study doctor at the telephone and address listed on the first page of this form.

WHAT ARE MY RIGHTS AS A RESEARCH STUDY PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. Refusing to participate or leaving the study will not result in any penalty or loss of benefits to which you are entitled. If you decide to stop participating in the study, we encourage you to talk to the investigators or study team first to learn about any potential health or safety consequences. The investigators or the sponsor also have the right to stop your participation in the study at any time. This could be because you had an unexpected reaction or because the entire study ended.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions, concerns, or complaints about the study, or in the event of a research-related injury, contact the study investigator, Timothy Hughes, PhD at 336-713-3851. If you have an emergency in the evenings or on a weekend when the study office is closed, you should call our after-hours number at 336-713-8250 and ask for the Geriatrician on call and reference the ACE study. This phone number is answered 24 hours a day, seven days a week.

We will send important medical findings to your personal physician that you indicate, unless you tell us otherwise. We will use your social security number as described on page 7 unless you tell us otherwise.

VOLUNTARY CONSENT

The above information has been explained to me and all my current questions have been answered. I understand that I am encouraged to ask questions, voice concerns or complaints about any part of this research study during this study. Any future questions, concerns or complaints will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) given. I understand that I may always request that my questions, concerns or complaints be addressed by a listed investigator.

I understand that I may contact the Human Subjects Protection Advocate of the Human Research Protection office, University of Pittsburgh (1-866-212-2668), or the Wake Forest University Health Sciences Research Subject Advocate (336-716-7600) to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations that occurred during my participation. By signing this form, I consent to participate in this research study and provide authorization to use and share my medical records. A copy of this consent form will be given to me.

_____

Printed Name of Participant

_____ _____ am pm

Signature of Participant Date and Time

_____

Printed Name of Person Obtaining Consent

_____ _____ am pm

Signature of Person Obtaining Consent Date and Time

CONSENT TO ACT AS A PARTICIPANT IN A RESEARCH STUDY

Title: Arterial Stiffness, Cognition and Equol (ACE)

Principal Investigator: Whitney Wharton, PhD; (404) 712-7359

Study Coordinators: Niveen Kaddoura, (404) 544-9077

SOURCE OF SUPPORT: National Institutes of Health - National Institute on Aging (NIA).

KEY INFORMATION

You are invited to participate in the Arterial Stiffness, Cognition, and Equol Trial (also known as ACE Trial). Equol is a soy-based supplement that has plant estrogen-like compounds in it. The purpose of this study is to learn if taking Equol could slow the progression of:

- stiffening of the arteries
- small blood vessel disease in the brain
- memory decline.

Your participation in this research will involve up to 7 visits to the Health Studies Research Center located at Emory University School of Nursing located at 1520 Clifton Road, Atlanta, GA 30322 over two years.

As part of the study, we will complete several non-invasive tests like measuring your blood pressure and heart rate, height and weight, and doing tests of walking and thinking. We will collect a sample of your blood, urine and stool.

We will ask you questions about your health history and medication use, your mood and other topics. To measure stiffening of the arteries, we will do a test called a carotid-femoral pulse wave velocity. It is low risk and without radiation. There is more information on this test on p. 3. To assess the health of small blood vessels in your brain, we will do a Magnetic Resonance Imaging (MRI) scan. We will also do an ultrasound scan of your carotid arteries.

The risks of these tests are not unlike risks with usual medical care, including minor discomfort and breach of confidentiality. If you are assigned to a group that takes Equol, it could give you constipation or bloating. You may benefit from the Equol supplement if the study shows it does have a positive effect on artery or brain health. There is more information on the risks on pp. 7-8.

The remainder of this document contains a more complex description of the ACE Trial. If you are interested, please read through the rest of the document carefully. You can ask any questions if you need help deciding whether to join the study. You can discuss the study with your family or friends if you would like. Your participation is voluntary. You do not need to participate in this study if you do not

want to. If you decide not to participate, you will not lose any services, benefits, or rights you normally have.

People with a history of breast cancer should not participate in this study.

INTRODUCTION

You are invited to participate in this research study because you:

1. are between the ages of 65-85
2. do not have dementia
3. are willing to have an MRI scan
4. are willing to take the study supplement/placebo.

How many people will take part in the study? Approximately 400 men and women will be randomized at the three clinical research centers, University of Pittsburgh, Wake Forest University, and Emory University.

What is involved in the study? If you decide to take part in the ACE study, we will ask you to complete several examinations within the first month. Then we will ask you to return one time a year for two years with phone calls between visits.

Screening Visit 1 (about 1-2 hours)**:**

At this visit we will ask you to do the following:

1. Complete a questionnaire of your name, address and other information
2. Complete tests of memory and concentration
3. Measure your blood pressure and pulse
4. Collect a urine sample. We will look check to be sure there is no protein in your urine.
5. Draw a blood sample from your vein of about 2-3 tablespoons. This includes such tests as vitamin levels, blood cell count, a test to see be sure you don't have diabetes.

If you are eligible for the study based on the tests completed at the Screening Visit, we will ask you to return for the Baseline Visits. The baseline examination will be divided into two separate days within one month.

Baseline Visit Day 1 (about 5 hours)

At this visit you will be asked to do the following:

1. Complete memory and paper and pencil tasks and on an iPad laptop.
2. Have your blood pressure measured
3. Have your height and weight measured
4. Complete a 400 meter walk at a normal pace
5. Have your grip strength measured.

6. Carotid-femoral Pulse Wave Velocity

We will do a test to measure the hardness and stiffness of your blood vessels. This test uses something called “pulse-wave velocity techniques”. The pulse wave velocity technique measures how fast the waves of movement pushing your blood through your vessels travel from your heart to the different sites measured. For this procedure, you will be required to lay quietly for about one half hour. You will have a blood pressure cuff placed around your right upper thigh, and a small disc-shaped handheld sensor placed on the right side of your neck. The thigh cuff may be placed on a bare thigh or over light clothing. The cuff will inflate several times for various readings. This testing will be performed by trained technologists.

7. Carotid ultrasound

This test will require you to lie down and a cool, jelly-like, hypoallergenic substance will be applied on your neck while a probe is moved up and down the area. Sound waves are bounced off the arteries, creating a picture of what the arteries look like on the inside. This non-invasive painless test takes approximately 40 minutes. The carotid ultrasound images you will have for this study are for specific research purposes and are not being used to evaluate your health or find medical abnormalities. These images will be reviewed by an experienced sonographer. If abnormalities are seen, your test results will be reviewed by a physician with the rest of your health information. The results from this review will be provided to you and your physician. In the event that you do not have a primary physician, we will recommend that you go to a physician.

8. Collect a blood sample of approximately 5 tablespoons from your vein. We will ask that you not eat or drink anything except water for 8 hours before your appointment. After we draw your blood, we will provide a snack before you continue with the rest of your visit procedures. This will be used to measure “biomarkers” - different substances in your blood that test for your body’s response, risk for disease, and a genetic marker for a certain kind of cholesterol in your blood that changes if you develop dementia or cardiovascular disease.

9. Collect a stool sample at home after your Baseline Visit Day 1. We will give you instructions and a container, which is placed on your toilet, so you can collect the stool. You will place a small amount of stool in a special tube. We will remind you to collect the stool sample and provide mailing instructions to send to Indiana University.

10. We will ask you to complete a questionnaire about your diet over a 24 hour time period. A member of the research staff at the University of North Carolina (UNC) Diet and Physical Activity Core in the UNC Nutrition Obesity Research Center will contact you at a prearranged time. This will occur twice within a 2 week time period.

11. So that we can understand how your body processes soy, we will ask you to eat a serving of a soy food product on three consecutive days. This information is important for us to know when we interpret the results of the study since Equol comes from soy. The soy food will be a soy protein shake that the

study team will provide you. On the morning of the fourth day, we will ask you to come to clinic to have a urine sample collected as part of your Randomization Visit.

Baseline Visit Day 2 (about 2 hours):
On a separate day, you will have a test called Magnetic Resonance Imaging (MRI).
We will do an MRI scan of your brain. This scan will take up to 1 hour. Once a trained staff member has made sure you have no metal in your body and are safe to have an MRI, the brain scan can proceed. Prior to your scan at Emory University Health Science Research Building II 3T scanner, we will ask you questions about the presence of metal in your body that may be attracted to the magnet. In most cases, an MRI is safe for people who have metal implants from surgery. However, you may not participate in the study unless it is determined that you meet the guidelines of the Emory Health System.

The MRI involves lying on a table, which then moves into a hollow machine that contains a powerful magnet. While you are lying in the MRI scanner, you will hear a variety of loud knocking noises. You will be given earplugs, which are required and will provide a barrier to the loud noise. Additionally, a pillow or cushion will be placed under your head and around your ears. These cushions serve two purposes: to stabilize your head to reduce movement and to serve as another barrier to the loud noise. A study team member and/or MR technologist will check in with you periodically throughout each scan (verbally through an intercom), and during these times, you will be able to speak to us as well. At any other times, we ask you to alert us to any problems or concerns using an emergency squeeze ball that will be with you the duration of your scan.

Because this is a research MRI, not a clinical MRI, your scan will not be read by a radiologist. The MR technologists are trained to examine brain images as they are acquired, and if any abnormality is suspected, a radiologist will immediately review the images. If anything previously unknown is found on the MRI that is of clinical significance, the PI will review the findings with you, and you will be given an appropriate referral. A copy of the MRI images along with the clinical notes will be sent to your doctor upon your written request. It is important to note that you may be removed from the study if you are unable to complete this MRI scan. If you are unable to complete this scan for reasons out of your control, such as scanner issues, all attempts to reschedule the scan will be made. If you are unable to complete the scan for reasons such as claustrophobia, discomfort, or personal choice, you may be removed from the study.

Randomization Visit (about 1 hour):
At this visit, we will ask you to provide a urine sample.You will then be randomly assigned by a computer (by chance, like the flip of a coin) to a group that takes 10 mg Equol daily or to taking a daily placebo.

A placebo is a substance that looks like and is given in the same way as an experimental treatment but contains no medicine or supplement (it is an inactive substance). A placebo is used in research studies to show what effect a treatment has compared with taking nothing at all. If you are assigned to receive the placebo, you will not receive the benefit of taking Equol, if there are any, nor will you be exposed to its

risk, which are described later in this consent form. You and the Study Physician and other staff will not know which group you are assigned to, but that information is available.

The study staff will review how and when to take the study pill. It is important to take the study pill exactly as instructed and to return any unused study pill and empty bottles at your next study visit.

We will ask you to not consume greater than 2 servings of soy per week over the course of the study.

How will your study drug be provided?

The study drug that you will take will be dispensed by the pharmacy and delivered to the principal investigator or study team member. The principal investigator or health care providers on his/her research team will provide the study drug to you. If you have questions about the study drug, you should ask the principal investigator or study nurse. You may also call the pharmacy if you have questions about the study drug. The number for the pharmacy is included on your study drug package, if given one.

Note: The research team for this study includes non-licensed team members who may obtain your consent or help guide you through the study. There are some kinds of questions only licensed clinicians can answer. For example, detailed questions about drug interactions. If you have questions like these, the non-licensed coordinator will ask a licensed study team member to answer your questions.

Occasionally, because of equipment failure, incorrect positioning or other technical difficulty, the results from measures may give poor quality information or no information at all. In some cases, biological samples may not be usable. If that were to happen to you, we will ask you to have repeat tests or scans performed or provide another biological sample. We may ask you to repeat certain measures for quality assurance purposes. Another in-clinic visit may need to be scheduled. It is your decision whether to have the tests repeated or not.

Additionally, you may be asked to volunteer for specific vascular tests twice. This double testing allows the laboratory to verify how well they can repeat a test on the same participant. This will be strictly voluntary; therefore, if you are unable to stay longer for your visits you will be under no obligation to participate in this double testing.

You may also be audiotaped while performing some of the cognitive tests. Recording your responses will enable us to make sure that the examiners are administering the memory tests the same to everyone. You may request that you are not audiotaped. You should understand that you will not be able to inspect, review, or approve the audiotapes before they are used in this study. The recording will not include any personal identifiers and will be securely sent to the University of Pittsburgh Data Coordinating Center. All recordings may be kept and stored indefinitely and may be analyzed for future research.

Follow-up Visits

If you decide to take part in the ACE Trial, we will contact you a month after you begin to take study pills. Then approximately every 3 months we will call by phone to update your information and ask how you are doing with the study pills. We will also ask you to return for an in-person visit at Years 1 and 2. The Year 1 visit will consist of repeating the pulse wave velocity exam, tests of memory and concentration, questionnaires regarding lifestyle, medical history, physical activity, and sleep habits. We will obtain your height, weight, blood pressure, pulse and fasting blood draw. We will ask that you complete a 400 meter walk and grip strength measurement. We will ask you to collect another stool sample and will be give you mailing instructions. The blood draw will include testing for safety of the study supplement, e.g., your blood count, cholesterol panel, and basic organ function.

At Year 2, we will ask that you complete all of the above procedures in addition to the carotid ultrasound and MRI scan. The MRI will be scheduled on a separate day, just like the baseline exam.

If we are unable to contact you or if you become incapacitated, we will contact your designated proxy to inquire about your status and ask them to answer the same questions we would have asked you.

In the event that an abnormality is found on your MRI or ultrasound scan, with your permission we can send copies of your test results to your physician. Even if you do not wish to have any of your medical information sent to your physician, you can still participate in this research study.

Collection of Medical Information

This research study may involve the recording of past, current and/or future identifiable medical information from your hospital and/or you physician records. The information that will be recorded will be limited to information concerning any metal objects in your body, hospitalizations, medical, and death records. The information will be used for determining safety for MRI and for documenting illnesses, hospital admissions, and cause of death for the research study. All of the medical information listed above will become part of your participant chart and will be kept indefinitely at the locked research office located at the Emory University School of Nursing or on computer servers with secure passwords.

Information from hospitalizations, medical records, and death records will be securely sent to the University of Pittsburgh Data Coordinating Center to track occurrences of diseases, hospitalizations, and accurately determine cause of death. Like all your other information, this data will be kept as safe and private as possible.

If you have care in a system outside of Emory Healthcare, we will ask you to complete a medical release form so that we may access your medical records.

Medical Record

If you have been an Emory patient before, then you already have an Emory medical record. If you have never been an Emory patient, you do not have one. An Emory medical record will be made for you if an

Emory Atlanta provider or facility gives you any services or procedures for this study. Copies of the consent form/HIPAA authorization that you sign will be put in any Emory medical record you have now or any time during the study.

Access to Research Data & Biological Samples

The information and biological samples, including genetic information, that are obtained during the ACE Trial will be preserved for research uses in the future. We will store your samples and data indefinitely. There is no limit on the time that these can be used for research.

All information collected during your clinic exams, phone interviews or questionnaires as well as the biological samples that you provide will be labelled only with a special code. Anyone using them will not be able to tell to whom they belong. They will not include any identifiable information about you such as your name, address, telephone number, social security number or medical record. The unique code is assigned at the time of the Telephone Screening call by the ACE team at the Emory University. Only the Principal Investigator of this site and limited study staff will have access to the code that links the unique identifier to you. Your name, address, social security number, etc., will never be disclosed to future researchers and neither will the code that links your identifiers to the sample.

Your specimens and data may be used for research by scientists who are part of universities, research institutions, and companies. The research may include any disease, symptoms, measurements, including conditions related to aging. Your specimens and data may also be used for the purpose of developing potential medical or preventive treatments or tests, such as tests to predict the risk of conditions or tests of physical or cognitive health. The research using the specimens and data may be conducted by scientists in universities or commercial companies. Your identity and personal information will not be provided to any company.

Your data and specimens used in this research study may contribute to a new discovery or treatment. In some instances, these discoveries or treatments may be of commercial value and may be sold, patented, or licensed by the investigators and the Emory University and for use in other research or the development of new products. You will not retain any property rights nor will you share in any money that the investigators, the medical center, or their agents may realize.

The research that may be performed with your biological samples is not designed to help you specifically. Other than obtaining medical information about yourself, there is no specific benefit to you from taking part in this aspect of the research study. It might help people who have diseases at some point in the future, but it is not known if this will happen. The results of the research performed with your biological samples will not be given to you or your doctor. The results will not be put in your medical record. The research using your biological samples will not affect your current or future care.

Storage of Biological Samples

Collected samples (blood, urine, and stool) will be stored at the National Centralized Repository for Alzheimer's Disease and Related Dementias (NCRAD) at Indiana University, Indianapolis, Indiana. NCRAD

is a national resource supported by the National Institute on Aging that prepares and stores biological specimens from all over the world and makes them available to approved scientists who would not otherwise be able to access the material.

A portion of your blood sample will be stored at Wake Forest University, a participating site of the ACE Trial.

HOW LONG WILL I BE IN THE STUDY?
You will be in the study for a little over 2 years. We will ask you to complete four study visits over the course of approximately a one-month period to complete the baseline and randomization visits. Thereafter, you will be contacted at month 1, month 3 then every 3 months by phone to complete a brief questionnaire. At year 1 and 2 year, we will ask you to return to the clinic for follow-up in-person examinations.

You can stop participating at any time. If you decide to stop participating in the study, we encourage you to talk to the investigators or study team member first to learn about any potential health or safety consequences.

Social Security Number (SSN) usage
We will ask you to provide your SSN on the patient contacts document if you have not done so already. This information will be transmitted to the study Coordinating Center at the University of Pittsburgh. The collection of your SSN is necessary for research purposes so that we can track your health through national health databases that are available to the public, such as the National Death Index. The collection of your SSN, **for research purposes other than payment**, is strictly optional and is not required for participation in the study.

WHAT ARE THE RISKS OF THE STUDY?
Besides the risks mentioned on page 1, there are some possible discomforts and risks associated with participating in this study. Information regarding the frequency of possible risks has been categorized using the following categories:

Likely – occurs in more than 25% of people (more than 25 out of 100 people);
Common – occurs in 10% to 25% of people (10 to 25 out of 100 people);
Infrequent – occurs in 1 to 10% of people (1 to 10 of 100 people);
Rarely – occurs in less than 1% of people (less than 1 out of 100 people).

Equol supplement - NOTE
The supplement does NOT contain estrogen. However, because it comes from soy which has chemicals similar to estrogen, if you have a history of breast cancer or have breast cancer in your immediate blood relatives, you should not take this supplement. It could increase the chances of the cancer occurring or re-occurring.

Equol supplement
There is an infrequent risk of an allergic reaction that could result in a rash or other symptoms, including mild stomach discomfort. There is a rare risk of a skin rash, blood clot in the lung or a thickening of the lining of your uterus. Tell the study team immediately if you have or experience any side effects while you are taking the study pills.

There are no known risks to the placebo tablet.

To avoid risks, you should tell the research study team about all the medications, vitamins and supplements you take and any medical conditions you have. As with any study, there may be adverse events or side effects that are currently unknown and it is possible that certain of these unknown risks could be permanent, serious or life-threatening.

Questionnaires
There is no physical risk associated with the measures of memory or paper and pencil tasks, questionnaires or clinic interviews. We will also ask you about your mental health status and if you have thoughts of harming yourself. These measures/questions may cause frustration, boredom or fatigue, but you may take breaks as often as you need. You are not required to answer any question that you feel uncomfortable answering.

Clinic Measures
There is an infrequent risk of losing your balance while standing on the scale for weight measurements, although a study technician will be standing beside you. There is an infrequent risk of injury during the physical performance testing, such as muscle strains or pulls, falls or joint injury. In addition, if you report pain, dizziness, feeling faint, lightheadedness, chest pain or shortness of breath or other medical problem (all infrequent) during these tests they will be stopped. It is common to feel fatigued after these performance tests. The risks of all these tests will be minimized by having experienced/trained examiners conduct these assessments.

MRI
The risks involved with the MRI scans are small and limited to the risks present during routine MRI examinations. There is no radiation exposure associated with MRI scans. There are no known dangers of exposure to the magnetic fields used for the MRI brain imaging studies. During an MRI scanning session, there is potential for the powerful magnetic field to attract metal objects towards the magnet. For this reason, you will be carefully screened for previous exposure to metal fragments or clips that may be inside your body. We will ask you to place all metal and magnetic objects in your possession (e.g., keys, bank cards) in a locker outside the magnetic room. Some people feel claustrophobic, meaning uncomfortable in confined areas, in the scanner, and if that is a problem for you, you will be removed from the study. Finally, the MRI machine is noisy, which has the potential to irritate your hearing. You will be given earplugs to minimize this risk. If an x-ray is necessary, this will involve exposure to radiation.

Carotid Ultrasound Scan
There are no known risks involved with the carotid ultrasound scan. The process is noninvasive and painless. Ultrasound imaging does not use radiation technology. In the event that testing reveals disease that is of clinical significance, we will refer you for medical evaluation. This is expected to be a rare event occurring in less than 2% of people. In the event that you do not have a primary physician, we will recommend that you go to a physician or can refer one to you.

Pulse Wave Velocity test
The blood pressure cuff or tonometer used for the Aortic Pulse Wave Velocity test may occasionally cause some skin redness from the pressure. This is an infrequent adverse event occurring in 1-10% of people (1-10 out of 100 people). This redness may last up to 48 hours. Severe pain may be experienced while cuff is inflated. This is a rare adverse event occurring in less than 1% of people (less than 1 out of 100 people). Past participants have rated this test less uncomfortable than a blood draw.

All measures that are part of the ACE Trial are being conducted only for the purpose of research. They are different tests than what are used in the clinical setting to detect or discover medical conditions. The Ultrasound or MRI scans that are collected for the ACE Trial are not a substitute for a clinical Ultrasound or MRI scan. Research personnel will analyze the scans only for the specified research findings. These scans may not be analyzed until the study has ended. However, if we should happen to see an abnormal finding that may be harmful to your health on the Ultrasound and/or MRI scan, we will notify you.

Unexpected findings on the limited research scans will occasionally allow early discovery of a medical condition for which you may need treatment. They may also cause undue worry or result in additional testing, sometimes costly, which may or may not benefit your health.

Blood draw
There are infrequent risks associated with the drawing of a blood sample, including discomfort at the site of needle insertion, bruising (black and blue discoloration) and/or bleeding where the needle is inserted. Occasionally some people become dizzy, lightheaded, or feel faint. Infection may occur on rare occasions. Frequent donation of blood can result in low iron in your blood (iron deficient anemia).
It is common to experience some fatigue at the end of each study visit.

Stool sample collection
There are no known risks related to collecting a stool sample.

Genetic Analysis
The risk of doing genetic studies includes the potential for a breach of confidentiality, which means someone could see your genetic testing results who is not authorized. The information could be used to affect what insurance or jobs you may be able to get. It could cause stress and conflict in your family relationships, as it can confirm the identity of is a child's father, identify a risk for a certain disease, or cause you or other people to have negative feelings if the results show you may be more likely to get

certain diseases. The only genetic testing done in the current study is looking at part of a blood protein that can measure risk for dementia and cardiovascular disease.

In addition, there is a federal law, called the Genetic Information Nondiscrimination Act (GINA), that generally makes it illegal for health insurance companies and group health plans to use genetic information in making decisions regarding your eligibility or premiums. GINA also makes it illegal for employers with 15 or more employees to use your genetic information when making decisions regarding hiring, promoting, firing, or setting the terms of employment. This new Federal law does not protect you against genetic discrimination by companies that sell life, disability, or long-term care insurance. GINA does not protect you against discrimination from previously diagnosed genetic conditions.

In addition to GINA, the State of Georgia has laws that prohibit insurers from using genetic testing information for any non-treatment purpose. However, like GINA, this state law protection has exclusions for life insurance and other types of insurance policies.

Future Genetic testing

While we can't predict how biological samples may be used in the future at this time, future research may include studying your genetic information. At some point in the future, we may be required to share genetic data with federal repositories. The National Institutes of Health (NIH) and other central repositories have developed special data (information) banks that collect the results of genetic studies, especially when the research looks at all or large sections of individual's genetic code. This is often called whole genome sequencing. Genomic information relates to the structure and function of all of the genetic material in the body. These central banks will store your genetic information and give them to other qualified and approved researchers to do more studies. The data that we share with federal repositories will be coded in such a way that you would not be able to be identified. We will not share your name, birth date, or any other information that could directly identify you. The link to the code would be kept securely at the University of Pittsburgh. Even so, there is a possibility that when your genomic information is combined with other information available to researchers, either now or in the future, they may be able to identify a group you belong to (like an ethnic group or a disease population) or, less likely, you personally. NIH prohibits people from trying to identify individuals whose genomic information is in an NIH-designated repository.

Your identifiers will be removed from the private information and/or biospecimens. This de-identified information and/or biospecimens may be used by other researchers for future research studies. If this happens, we will not contact you for additional consent.

We do not think that there will be further risks to your privacy and confidentiality by sharing your genetic information with these banks. However, we cannot predict how genetic information will be used in the future.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you are assigned to the group to receive Equol, you may benefit from its positive effect on your brain health. Therefore, no direct benefit is guaranteed. You will receive results from some of your clinic tests such as your height, weight, blood pressure, and blood labs. In addition, the information we collect in this study will be valuable to further research on physical health and aging. We hope the information learned from this study will benefit other people in the future.

NEW INFORMATION

If we learn any new information that may change your decision to be in this study, we will let you know.

PROTECTING THE CONFIDENTIALITY OF YOUR INFORMATION

Taking part in this research study involves providing information that you may consider confidential or private. We will take efforts such as coding research records, keeping research records secure and allowing only authorized people to have access to research records to keep your information safe. The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed unless it is authorized by you, required by law, or necessary to protect the safety of yourself or others. There is always some risk that even de-identified information might be re-identified.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects. The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law of such as child abuse and neglect, or harm to self or others.

You may choose to voluntarily disclose the protected information and this certificate does not prohibit such voluntary disclosure. Furthermore, the parties listed in the Confidentiality / Authorization section of this consent form may review our records under limited circumstances and this certificate does not prohibit such disclosure.

Authorization to Use and Disclose Protected Health Information

The privacy of your health information is important to us. As part of this study, we will be requesting health care entities who are covered by the Health Insurance Portability and Accountability Act and regulations (HIPAA) to provide us with health information that identifies you ("individually identifiable

health information" or "IIHI"). Because the health care entities are covered by HIPAA, we must have your authorization to obtain your IIHI from them. However, the researchers who get your IIHI from the health care entities are not covered by HIPAA. Once they receive your IIHI from the health care entities, they will put it in a separate research record that is not a part of your medical record. IIHI placed in the separate research record is not be covered by HIPAA.

Purpose of this Authorization:

By signing this form, you give us permission to get your IIHI from health care entities and to use and share your IIHI as described in this document. You do not have to sign this form. If you do not sign this form, then you may not participate in the research study.

Research-Related Treatment

This study involved research-related treatment that will not be electronically billed to any insurance company or government benefits program (e.g., Medicare, Medicaid). You may not receive the research-related treatment unless you sign this authorization. You may receive any non-research related treatment whether or not you sign this form.

IIHI that Will be Used/Disclosed:

The IIHI that we will use or share for the research study includes:

- Medical information about you including your medical history and present/past medications.
- Results of exams, procedures and tests you have before and during the study.
- Laboratory test results.

Purposes for Which Your IIHI Will be Used/Disclosed:

We will use and share your IIHI for the conduct and oversight of the research study. Once we have your IIHI we will keep it in a separate research record that will be used for the conduct of the study. If you leave the study, we may use your IIHI to determine your vital status or contact information.

Use and Disclosure of Your IIHI That is Required by Law:

We will use and disclose your IIHI when we are required to do so by law. This includes laws that require us to report child abuse or abuse of elderly or disabled adults

People Who will Use/Disclose Your IIHI:

The following people and groups will use and disclose your IIHI in connection with the research study:

- The Principal Investigator and the research staff will use and disclose your IIHI to conduct the study.
- Emory may use and disclose your IIHI to get payment for conducting the study and to run normal business operations.

- The Principal Investigator and research staff will share your IIHI with other people and groups to help conduct the study or to provide oversight for the study. This includes sharing your IIHI with people and groups at other sites who are helping conduct the study.
- The National Institute on Aging is the Sponsor of the study. The Sponsor may use and disclose your IIHI to make sure the research is done correctly and to collect and analyze the results of the research. The Sponsor may disclose your IIHI to other people and groups like study monitors to help conduct the study or to provide oversight for the study.
- The following people and groups will use your IIHI to make sure the research is done correctly and safely:
    - Emory University and University of Pittsburgh offices that are part of the Human Research Participant Protection Program and those that are involved in study administration. These include the Emory IRB, the Emory University and Healthcare Compliance Offices, and the Emory Office for Clinical Research and University of Pittsburgh Coordinating Center.
    - Government agencies that regulate the research including: [Office for Human Research Protections; Food and Drug Administration.
    - Public health agencies.
    - Research monitors and reviewer.
    - Accreditation agencies.
- Sometimes a Principal Investigator or other researcher moves to a different institution. If this happens, your IIHI may be shared with that new institution and their oversight offices.

Expiration of Your Authorization

Your IIHI will be used until this research study ends.

Revoking Your Authorization

If you sign this form, at any time later you may revoke (take back) your permission to use your IIHI. If you want to do this, you must contact the study team at:

Dr. Whitney Wharton, PhD
1520 Clifton Road
Room 234
Atlanta, GA 30322

At that point, the researchers would not collect any more of your IIHI. But they may use or disclose the information you already gave them as described in this Authorization. If you revoke your authorization you will not be able to stay in the study.

Other Items You Should Know about Your Privacy

Not all people and entities are covered by the Privacy Rules. HIPAA only applies to health care providers, health care payers, and health care clearinghouses. HIPAA does not apply to research that does not include treatment that is billed to insurers or government benefit programs. If we disclose

your information to people who are not covered by the Privacy Rules, including HIPAA, then your information won't be protected by the Privacy Rules. People who do not have to follow the Privacy rules can use or disclose your information with others without your permission if they are allowed to do so by the laws that cover them. The researchers, the Sponsor, and people and companies working with them are not covered by the Privacy Rules. They will only use and disclose your information as described in this Consent and Authorization.

To maintain the integrity of this research study, you generally will not have access to your IIHI related to this research until the study is complete. When the study ends, and at your request, you generally will only have access to your IIHI that we maintain in a designated record set. A designated record set is data that includes medical information or billing records that your health care providers use to make decisions about you. You will not have a right of access to IIHI kept in a separate research record used only for research purposed. If it is necessary for your health care, your health information will be provided to your doctor.

We may remove identifying information from your IIHI. Information without identifiers is not subject to HIPAA and may be used or disclosed with other people or organizations for purposes besides this study.

WHAT ABOUT MY HEALTH INFORMATION?

Laboratory test results and other medical reports created as a result of your participation in the research study may be entered into the computer systems of the University of Pittsburgh Coordinating Center that combines the data for analyses. These will be kept secure, with access to this information limited to individuals with proper authority, but who may not be directly involved with this research study.

A Data Safety Monitoring Board, an independent group of experts, will be reviewing the procedures and data from this research throughout the study. They may be provided de-identified data to monitor the research.

CLINICAL TRIALS.GOV

A description of this clinical trial may be available on http://www.ClinicalTrials.gov, if required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

WHAT ARE THE COSTS?

There will be no costs to you for participating in this study, other than basic expenses like transportation. You will not be charged for any of the research activities. If the study procedures result in any medical complications that would not fall under "injury" as discussed below, the cost of treatment for those complications may be charged to you or your insurance.

WILL YOU BE PAID FOR PARTICIPATING?

You will be paid for study participation throughout the course of the study. Payment will be via a

reloadable debit card. The payment schedule is as follows:

$25 baseline clinic exam
$25 MRI scan
$100 at randomization visit
$150 at Year 1
$200 at Year 2

If you withdraw for any reason from the study before completion you will be paid for each part of the study that is completed. We will reimburse or validate parking expenses during your clinic visits. You may be asked to fill out a tax form, including your Social Security or Taxpayer Identification Number, in order to be reimbursed, depending on the amount and method of payment. Some payment methods involve mail coming to your house, which may be seen by others in your household. You can decline payment if you are concerned about confidentiality, or you can talk to the study team to see if there are other payment options.

WHAT HAPPENS IF I EXPERIENCE AN INJURY OR ILLNESS AS A RESULT OF PARTICIPATING IN THE STUDY?

If you believe you have become ill or injured from this research, you should contact Dr. Whitney Wharton, PhD at telephone number 404-712-7359 or Dr. Lynn Marie Trotti, MD at telephone number 404-712-7240. You should also let any health care provider who treats you know that you are in a research study.

If you get ill or injured from being in the study, Emory will help you to get medical treatment. Neither Emory nor the sponsor have set aside money to pay for this medical treatment. Your insurer will be billed for your treatment costs. If you do not have insurance, or if your insurance does not pay, then you will have to pay these costs.

For Emory, the only exception is if it is proven that your injury or illness is directly caused by the negligence of an Emory employee. “Negligence” is the failure to follow a standard duty of care. You do not give up any legal rights you may have by being in this study, including any right to bring a claim for negligence.

WHAT ARE MY RIGHTS AS A RESEARCH STUDY PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. Refusing to participate or leaving the study will not result in any penalty or loss of benefits to which you are entitled. If you decide to stop participating in the study, we encourage you to talk to the investigators or study team first to learn about any potential health or safety consequences. The investigators or the sponsor also have the right to stop your participation in the study at any time. This could be because you had an unexpected reaction or because the entire study ended.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions, concerns, or complaints about the study, or in the event of a research-related injury, contact the study investigator, Dr. Whitney Wharton. If you have an emergency in the evenings or on a weekend when the study office is closed, you should call Emory Neurology at 404-778-3444 and ask for the on-call neurologist. This phone number is answered 24 hours a day, seven days a week.

We will send important medical findings to your personal physician that you indicate, unless you tell us otherwise. We will use your social security number as described on page 7 unless you tell us otherwise.

VOLUNTARY CONSENT

The above information has been explained to me and all my current questions have been answered. I understand that I am encouraged to ask questions, voice concerns or complaints about any part of this research study during this study. Any future questions, concerns or complaints will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) given. I understand that I may always request that my questions, concerns or complaints be addressed by a listed investigator.

I understand that I may contact the Human Subjects Protection Advocate of the Human Research Protection office, University of Pittsburgh (1-866-212-2668), or Emory Institutional Review Board (404-712-0720 or 877-503-9797 or irb@emory.edu) to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations that occurred during my participation. By signing this form, I consent to participate in this research study and provide authorization to use and share my medical records. A copy of this consent form will be given to me.

Participant Name (Printed):_____

Signature: _____ Date: _____

Person Obtaining Consent (Printed):_____

Signature: _____ Date: _____