You are being asked to be in a research study. This form provides you with information about the study. A member of the research team will describe this study to you and answer all of your questions. Please read the information below and ask questions about anything you don't understand before deciding whether or not to take part.

Why is this study being done?

You are being asked to participate in a research study of women who are either within 6 years of menopause or more than 10 years past menopause. The goal of this study is to see whether the effects of estrogen on insulin metabolism are different in women who are early postmenopausal compared to late postmenopausal.

Other people in this study

You are being asked to participate because you are a healthy postmenopausal woman between the ages of 45-70yr. We will enroll up to 130 women in this study.

What happens if I join this study?

If you agree to take part in this study, we will ask you to do the following things over the course of 2-3 months at the University of Colorado Hospital and Clinical Translational Research Center (CTRC). Your care will include the following visits and procedures.

- **A physical examination and medical history** will be done by a study physician or nurse involved in the study at one of your screening study visits. The physical exam and completion of medical history forms will take about 45 minutes.

- **Standard blood tests** - This will take about 15 minutes and will involve taking approximately 3 Tablespoons of blood. The blood tests measure blood cell count, electrolytes, liver and kidney function, thyroid stimulating hormone (TSH), and follicular stimulating hormone (FSH).

- **Glucose tolerance test** - This test will take about 2.5 hours and determines how quickly your blood sugar (or glucose) levels return to normal after you drink a solution containing sugar. You will need to fast overnight for 12 hours prior to the test. A needle with a plastic sleeve will be inserted in a vein in your arm. The needle will be removed, but the plastic sleeve will remain in place so that multiple blood samples can be obtained without inserting a needle each time. You will drink an 8-ounce solution containing sugar. Blood samples will be obtained immediately before you drink the solution, and 30, 60, 90, and 120 minutes later. Extra blood will be taken in the first sample so that we can also measure your blood cholesterol. Approximately 6 Tablespoons of blood will be collected during this test.
Body composition – We will measure total body fat using a machine called a DEXA and we will measure belly and thigh fat using CT. These tests will require lying still on a table for about 10 minutes for the DEXA scan and 30 minutes for the CT scans. We will also measure your arm, waist, hip, and thigh circumferences using a tape-measure. This will take about 10 minutes.

Physical Activity Questionnaire - We will ask you to answer questions about your physical activity at work and at home. This questionnaire will help us understand how much activity you do daily and how it may relate to your body fat content and metabolism.

Enrollment/ randomization - You will be invited to take part in this study if all of the above screening tests are within normal limits and you meet the guidelines for entry. If you agree, you will be asked to come in for testing on 2 separate occasions, with and without estrogen. You will be randomly (like the flip of a coin) assigned to wear estrogen or placebo (no estrogen) skin patches for 1 week prior to the two insulin metabolism tests.

Insulin metabolism test: For this visit you will either stay in the CTRC overnight or report early in the morning after an overnight fast. Two catheters (hollow plastic tubes for taking blood samples and giving fluids) will be placed in veins in your hand and arm. After we obtain fasting blood samples for 30 minutes, we will raise your blood insulin for the next 3.5 hours and continuously monitor your blood sugar.

The insulin level will be similar to how high your insulin normally goes after eating a meal. Because insulin causes your blood sugar level to go down, we will administer a sugar solution through the catheter in your arm to prevent this from happening. One half of a teaspoon of blood will be drawn through the collection tube in your arm every 5 minutes to sample blood glucose. At 9 timepoints an additional tablespoon of blood will be collected to sample insulin, fats and other hormones. A total of less than 1 cup of blood will be withdrawn during the test.

Muscle and fat Biopsies – On the morning of each insulin metabolism test we need to take a small sample of your muscle tissue and a small sample of your fat tissue. This procedure is called a “biopsy.” Before we collect the biopsy samples, we will give you some medicine (lidocaine) under the skin to numb the area. After the area is numb you may feel pressure but should not feel pain. We will then make a small cut in your skin and take the samples by pressing a hollow needle attached to a syringe into your muscle and fat tissue. When we take the needle out, it will remove a small circle of tissue called a “plug.” After the muscle and fat are removed, the doctor will place thin strips of tape to close the small cuts. This procedure will take approximately 1 hour.

After the insulin metabolism test and the biopsies you will remove the skin patches and be given a meal. We will continue to monitor your blood sugar over this time period. The entire study visit is expected to take about 6 to 7 hours and will be repeated on 2 separate occasions.

Weight maintenance/ 3-day diet period – For the duration of the study we will ask you to maintain your body weight to the best of your ability. We will ask you to record your physical activity (described above) during the baseline screening visit and then maintain your activity for the remainder of the time you are in the study. During the 3 days leading up to the Insulin Metabolism Test you will be given a standard diet prepared by the CTRC metabolic kitchen. You will be asked to eat only the food provided by the dietitians and not to exercise the day before the test meal visit.

Continuous Glucose Monitoring System (CGMS) - In addition to the 3-day diet prior to each Insulin Metabolism Test, we will ask you to wear a continuous glucose monitoring system (CGMS). This is a device that will measure your blood sugar every 5 minutes over 72 hours. A small sensor will be inserted under the skin using a very small needle device. The needle comes out and the sensor (a small flexible tube) stays under your skin. While you are wearing the CGMS, we will ask you not to get it wet. We will teach you how to keep it dry, and will give you special bags to cover it.
while you are in the shower. While you are wearing the CGMS, we will also ask you to check your blood sugar by "finger stick" using a separate monitor 4 times throughout the day and enter the number into the CGMS monitor.

- **Estrogen patches** - For 1 week prior to each of the Insulin Metabolism Tests you will be given patches to wear on your skin. Prior to one test these patches will contain estrogen and prior to one test the patches will contain placebo. The estrogen or placebo will be given in a random order. The placebo skin patch will look like the real estrogen patches, but will have no medical effect on you.

| Schedule-at-a-glance |
|-----------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Test/Visit**        | 1               | 2               | 3               | 4               | 5               | 6               |
| Orientation/Consent and screening blood test (1 hour) | X               |                 |                 |                 |                 |                 |
| Glucose tolerance test and Physical Exam (2.5 hours)   |                 | X               |                 |                 |                 |                 |
| Body composition and activity questionnaire (30 min)   | X               |                 |                 |                 |                 |                 |
| Pick up food for 3-day standard diet (15 min)          |                 |                 | X               |                 |                 | X               |
| CGMS placement and instruction (30 min)                |                 |                 |                 | X               |                 | X               |
| CT scan (30 min)                                         |                 |                 |                 |                 | X               |                 |
| Insulin metabolism test + biopsies (7 hours)            |                 |                 |                 |                 |                 | X               |

**What are the possible discomforts or risks?**

There are certain risks and discomforts that may be associated with this research. They include:

- **Risk of estrogen treatment** - The use of certain types of estrogen therapy in postmenopausal women has been associated with increased risk of blood clots, stroke, heart disease and breast cancer, particularly in women already at risk for these conditions. It is not known whether wearing transdermal (skin) estrogen patches for 1 week carries any risk, but as a precaution we will not enroll women into this study who might be at risk of one or more of these conditions.

- **Risk of DEXA scan** - As part of this study we will perform 1 DEXA scan of your whole body. DEXA is a way of looking inside the body by using X-rays. X-rays are a type of radiation. Your natural environment has some radiation in it. This DEXA will give you about the same amount of radiation that you would get from your environment in 2 days.

- **Risk of CT scan** - As part of this study we will perform a CT scan of your abdomen and thighs. CT is a way of taking detailed pictures inside your body by using X-rays. X-rays are a type of radiation. You get some radiation from your environment. You get radiation from bricks and concrete, from some foods, and from radon gas, which is an invisible gas that seeps out of the ground. The amount of radiation that this CT scan will give your body is about the same as you would get from living in your environment for one and a half months. This is an estimate. The amount of radiation you get could be higher or lower, depending on the machine, the power setting, and your body weight. Exposure to radiation at high levels increases a risk of developing cancer. There is no evidence of such risks for diagnostic procedures.

- **Risk of biopsies** - Small samples of muscle and fat will be removed from the thigh at each visit. It is possible that you could get an infection where the biopsy is taken (it happens about 1 out of 1,000 times). You may also have an allergic reaction to the numbing medicine; it is very rare (less than 1 in 10,000). You may get a small scar from the biopsy. If scars form, they are usually much smaller than the original cut and sometimes almost invisible.

- **Risk of having an IV inserted into your vein** - In this study we will insert a needle, connected
to a plastic tube, into a vein in your arm. We will use the tube to take blood samples or give you fluids. You will feel some pain when we first insert the tube into your vein. You may have some redness, swelling, or bruising where the tube goes under your skin. In some cases, this type of tube can cause an infection where it goes under the skin. In rare cases, it can cause a blood clot in the vein. You will have this tube inserted for about for up to 3 hours during the glucose test and for up to 6 hours during the insulin metabolism test.

- **Risk of insulin infusion** – During the Insulin Metabolism Test we will will administer insulin through the catheter in your arm. Because insulin causes your blood sugar to go down, there is a small chance that your blood sugar will drop very low. To prevent this from happening we will check your blood sugar every 5 minutes. We will administer a sugar solution through the catheter in your arm to keep your blood sugar stable throughout the test. After the test we will give you a meal and will check your blood sugar to make sure it is stable before you leave the research center.

- **Risk of having blood taken** - In this study we will need to get a total of about 2.5 cups (30 Tablespoons) of blood from you. We will get blood by putting a needle into one of your veins and letting the blood flow into a glass tube. You may feel some pain when the needle goes into your vein. A day or two later, you may have a small bruise where the needle went under the skin.

- **Risks of having blood taken by “finger stick”** - In this study we will need you to get a drop of blood from your finger 4 times each day during the glucose monitoring period. To do this, you will make a small prick on your finger and let a drop of blood soak into a test strip attached to a hand held glucose monitor. You will feel a slight pain when the needle pricks your finger. Your fingertips may be sore for a day or two.

- **Risk of Continuous Glucose Monitoring System (CGMS)** - It is possible that you could get an infection where the CGMS sensor is inserted under your skin, but it is very unlikely (less than 1 out of 1,000).

- **Loss of privacy/ confidentiality** - Any time personal health information is collected you are at risk of losing privacy and confidentiality. We will make every effort to protect your information.

- The study may also include risks that are unknown at this time.

**What are the possible benefits of the study?**

This study is designed for the researcher to learn more about the effect of estrogen on insulin metabolism in postmenopausal women. This study is not designed to treat any illness or to improve your health. Also there are risks as mentioned in the Risk Section. There is no guarantee that you will receive any health benefit by taking part in this research study.

**Are there alternative treatments?**

This short-term estrogen study is not intended to treat menopausal symptoms. If you are experiencing menopausal symptoms, there may be other hormonal treatments. You may also choose to get no treatment. You should talk about other treatments with your doctor. Make sure that you understand all of your choices before you decide to take part in the study. You may also quit the study and still have these other treatments available to you.

**Who is paying for this study?**

The sponsor for this study is the National Institutes of Health (NIH).
Will I be paid for being in the study?

All study participants will be compensated $200 for completing each Insulin Metabolism Test and biopsy visit. Total compensation will amount to $400 if all testing is completed.

Will I have to pay for anything?

There are no costs for any of the study-related visits.

Is my participation voluntary?

Taking part in this study is voluntary. You have the right to choose not to take part in this study. If you do not take part in the study, your doctor will still take care of you. You will not lose any benefits or medical care to which you are entitled.

If you chose to take part, you have the right to stop at any time. If there are any new findings during the study that may affect whether you want to continue to take part, you will be told about them.

Can I be removed from this study?

The study doctor may decide to stop your participation without your permission, if he or she thinks that being in the study may cause your harm, or for any other reason. Also, the sponsor may stop the study at any time.

What happens if I am injured or hurt during the study?

You should inform your care provider(s) if you decide to participate in this research study. If you have questions about injury related to the research, you may call Rachael E. Van Pelt, PhD at 303-724-1917 and/or your private physician. Dr. Van Pelt should be informed about any injury you experience while you take part in this study.

If you are hurt by this research, we will give you medical care if you want it, but you will have to pay for the care that is needed.

Who do I call if I have questions?

The researcher carrying out this study is Rachael E. Van Pelt, Ph.D. You may ask any questions you have now. If you have questions later, you may call Dr. Van Pelt at (303) 724-1917. You will be given a copy of this form to keep.

While your primary source of information pertaining to participation in this study is the principal investigator (Rachael Van Pelt, PhD), a Research Subject Advocate is also available on the Clinical Translational Research Center at (720) 848-6662 to answer questions relating to participation in this study.

If you have questions regarding your rights as a research subject, please call the Colorado Multiple Institutional Review Board (COMIRB) office at (303) 724-1055.

Who will see my research information?

The University of Colorado Denver and the hospitals it works with have rules to protect information about you. Federal and state laws including the Health Insurance Portability and Accountability Act (HIPAA) also protect your privacy. This part of the consent form tells you what information about you may be collected in this study and who might see or use it. The institutions involved in this study include:

- University of Colorado Denver
- University of Colorado Hospital

Initials_______
We cannot do this study without your permission to see, use and give out your information. You do not have to give us this permission. If you do not, then you may not join this study.

We will see, use and disclose your information only as described in this form and in our Notice of Privacy Practices; however, people outside the University of Colorado Denver and its affiliate hospitals may not be covered by this promise.

We will do everything we can to keep your records a secret. It cannot be guaranteed.

The use and disclosure of your information has no time limit. You can cancel your permission to use and disclose your information at any time by writing to the study’s Primary Investigator, at the name and address listed below. If you do cancel your permission to use and disclose your information, your part in this study will end and no further information about you will be collected. Your cancellation would not affect information already collected in this study.

Contact: Rachael E. Van Pelt, PhD, UC Denver, 12631 E. 17th Ave., Mail Stop B179, Aurora, CO 80045

Both the research records that identify you and the consent form signed by you may be looked at by others who have a legal right to see that information.

- Federal agencies that oversee human subject research
- Colorado Multiple Institutional Review Board
- The investigator and research team for this study
- The sponsor (NIH) or an agent for the sponsor
- Regulatory officials from the institution where the research is being conducted, to ensure compliance with policies or monitor the safety of the study

We might talk about this research study at meetings. We might also print the results of this research study in relevant journals, but we will always keep the names of the research subjects, like you, private.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site 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.

You have the right to request access to your personal health information from the Investigator. To ensure proper evaluation of test results, your access to some study results may not be allowed until after the study has been completed.

Information about you that will be seen, collected, used and disclosed in this study:
- Name and Demographic information (age, sex, ethnicity, address, phone number, etc.)
- Your social security number
- Portions of your previous and current Medical Records that are relevant to this study, including but not limited to Diagnoses, History and Physical, laboratory or tissue studies, radiology studies, procedure results
- Research Visit and Research Test records
- Radiology Studies (DEXA & CT scans)
- Questionnaire (physical activity)
- Tissue samples and the data with the samples.
- Billing or financial information
Consent Form Approval

What happens to Data, Tissue, Blood and Specimens that are collected in this study?

Scientists at the University of Colorado Denver and the hospitals involved in this study work to find the causes and cures of disease. The data, tissue, blood and specimens collected from you during this study are important to this study and to future research. If you join this study:

- The data, or the tissue, blood, or other specimens is given by you to the investigators for this research and so no longer belongs to you.
- Both the investigators and any sponsor of this research may study your data and tissue, blood, or other specimens collected from you.
- If data, tissue, blood, or other specimens are in a form that identifies you, UCD or the hospitals involved in this study may use them for future research only with your consent or IRB approval.
- Any product or idea created by the researchers working on this study will not belong to you.
- There is no plan for you to receive any financial benefit from the creation, use or sale of such a product or idea.

Agreement to be in this study

I have read this paper about the study or it was read to me. I understand the possible risks and benefits of this study. I know that being in this study is voluntary. I choose to be in this study: I will get a copy of this consent form.

Print Name: ____________________  Signature: ____________________  Date: __________

Consent explained by: ____________________  Date: __________

Investigator: ____________________  Date: __________

Initials _______
Additional Consent and HIPAA Authorization for Blood and Tissue for Research

The Principal Investigator (Rachael E. Van Pelt, Ph.D.) would like to keep some of the blood and tissue that is taken during the study but is not used for other tests. If you agree, the blood and tissue samples will be kept and may be used in future research to learn more about fat metabolism. The research that is done with your blood and tissue samples is not designed to specifically help you. It might help people who have diabetes and other diseases related to insulin metabolism in the future. Reports about research done with your samples will not be given to you or your doctor. These reports will not be put in your health records. The research using your blood and tissue samples will not affect your care.

The choice to let Dr. Van Pelt keep the blood and tissue samples for future research is up to you. No matter what you decide to do, it will not affect the care that you will receive as part of the study. If you decide now that your blood and tissue samples can be kept for research, you can change your mind at any time and contact Dr. Van Pelt to let her know that you do not want her to use your blood and tissue samples any longer, and they will no longer be used for research. Otherwise, they may be kept until they are used up, or until Dr. Van Pelt decides to destroy them.

In the future, people who do research with your blood and tissue samples may need to know more about your health. While Dr. Van Pelt may give the researcher reports about your health, she will not give them your name, address, phone number or any other information that will let them know who you are.

Sometimes blood and tissue samples are used for genetic research (about diseases that are passed on in families). Even if your blood and tissue samples are used for this kind of research, the results will not be told to you and will not be put in your health records. Your blood and tissue samples will only be used for research and will not be sold. The research done with your samples may help to develop new products in the future, but there is no plan for you to be paid.

The possible benefits of research from your blood and tissue include learning more about insulin metabolism and how to prevent and treat diabetes. The greatest risk to you is the release of information from your health records. Dr. Van Pelt will protect your records so that your name, address and phone number will be kept private. The chance that this information will be given to someone else is very small. There will be no cost to you for any blood or tissue collected and stored by Dr. Van Pelt.

The University of Colorado Denver and the University Colorado Hospital have rules to protect information about you. Federal and state laws including the Health Insurance Portability and Accountability Act (HIPAA) also protect your privacy. This part of the consent form tells you what information about you may be collected in this study and who might see or use it.

We will do everything we can to keep your records a secret. It cannot be guaranteed.

The use and disclosure of your information has no time limit. You can cancel your permission to use and disclose your information at any time by writing to the study's Primary Investigator, at the name and address listed below. If you do cancel your permission to use and disclose your information, your part in this study will end and no further information about you will be collected. Your cancellation would not affect information already collected in this study.

Contact: Rachael E. Van Pelt, PhD, UC Denver, 12831 E. 17th Ave., Mall Stop B179, Aurora, CO 80045

Both the research records that identify you and the consent form signed by you may be locked at by others who have a legal right to see that information.

Page 8 of 9

Initials_______
Collected data may be discussed or presented at research meetings. Results of research may be printed in journals but your name will always be kept private.

Please read each sentence below and think about your choice. After reading each sentence, check “yes” or “no.” If you have questions, please talk to your doctor or nurse. Remember, no matter what you decide to do about the storage and future use of your blood and tissue samples, you may still take part in the study.

1. I give my permissions for my blood and tissue samples to be kept by Rachael E. Van Pelt, Ph.D. for use in future research to learn more about how to prevent, detect, or treat diabetes and obesity.
   ______YES  ________NO  _________Initials

2. I give my permissions for my blood and tissue samples to be used for research about other health problems, such as causes of heart disease and diabetes.
   ______YES  ________NO  _________Initials

3. I give my permission for one of the study investigators to contact me in the future to ask me to take part in more research.
   ______YES  ________NO  _________Initials

I give my permission for my blood and tissue to be stored in a central tissue bank at the University of Colorado Denver for future use by the study investigators. I agree to take part in the study having to do with research on blood and tissue as indicated above.

Signature_________________________   Date___________

Initials________