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?

This research study plans to learn more about the role of female sex hormones on brown adipose tissue (or brown fat). Brown fat is different from regular “white fat” in that it produces heat and burns calories. In rodents and other animals, brown fat helps keep the animals warm when exposed to cold. Although humans have brown fat, its function in humans is not understood. Young adult women have more brown fat than men, but older men and women have similar levels of brown fat. This suggests that the decrease in female sex hormones that occurs at menopause (specifically, estrogen) may play a role. We know that the amount of estrogen a women has affects her resting metabolic rate (i.e. women with low estrogen have low resting metabolic rate). This study plans to learn more about how estrogen affects brown fat and resting metabolic rate.

You are being asked to take part in this research study because you are either a healthy, pre-menopausal woman between 18 and 50 years old with regular menstrual cycles, or a healthy post-menopausal women (no menstrual cycles for at least 12 months).

Other people in this study

Up to 76 women from the Denver area will participate in this study. The investigators will study 38 pre-menopausal and 38 post-menopausal women. 15 of the pre-menopausal women will be asked to participate in an estrogen suppression portion of this study.

How long will I be in this study?

Pre-menopausal women: Your participation in this study could last up to 7 months, if you participate in the estrogen suppression study. If you do not participate in the estrogen suppression study, the duration of the study will be 1-2 months.
Post-menopausal women: Your participation in this study will last 1-2 months.

What happens if I join this study?

If you join this study, you will be asked to perform studies to measure your resting metabolic rate and activity of brown adipose tissue or brown fat. We will measure how active your brown fat is at normal room temperature and after you have been exposed to cold. These tests will be performed on separate days. For the cold exposure part of the study, you will be asked to wear a cooling suit for 3 hrs. Your skin temperature is normally about 90º Fahrenheit. The cooling suit will adjust the water temperature until your skin temperature is about 82º Fahrenheit. The suit will cover your entire body except for your face, hands, and feet. You may feel cold while wearing the suit and you may shiver some, but based on past studies, any shivering should be minor.

On each of the two test days (room temperature and cold exposure), you will be asked to perform body scans that will take images of your body using a procedure called positron emission tomography/computed tomography (PET/CT). Before the PET/CT scans, we will infuse radioactive tracer into an arm. The PET part of the scan does not use radiation and shows us where the tracer is. CT scans are like an x-ray (use radiation) and shows us where fat is in your body. The radiation dose in the CT scan is much higher than the tracers that will be infused into your vein. When the PET/CT scans are combined, we can identify where the brown fat is and how active it is.

15 pre-menopausal women will be asked to volunteer for a follow up study. For 5 months, pre-menopausal women in this study will receive monthly injections that contain a study drug (leuprolide) that reduces estrogen to postmenopausal levels. This drug is approved by the FDA to reduce estrogen for the treatment of uterine fibroids and endometriosis, but is not approved for use in healthy women. In this study, the drug is being used to decrease hormones to determine if this reduces brown fat activity. 6 months after the first injection, these women will be asked to repeat the PET/CT studies.

Summary of testing schedule and procedures

All volunteers in this study will complete the screening visit and Study Visits #1 and #2 (PET/CT study). Pre-menopausal women who participate in the estrogen suppression study will remain in the study for another 6 months. Pre-menopausal women in this part of the study will be asked to return monthly to receive injection of a drug to suppress estrogen. (Visits #3-7). After 6 months, these women will return to repeat the measurements performed in the beginning of the study (Visits #8 and 9).
**Consent and Authorization Form**

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Cross Sectional Study (SA1-2)</th>
<th>Intervention Study (SA3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All volunteers</td>
<td>Only 15 pre-menopausal</td>
</tr>
<tr>
<td>Measurement</td>
<td>Screening (~2 hrs)</td>
<td>Visit #1 Thermenutral (~5 hrs)</td>
</tr>
<tr>
<td>Health history and physical exam</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Blood chemistries</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>DXA (body composition, bone mineral density)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>PET/CT studies</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Monthly Lupron injections</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

**Screening visit (about 2.0 hours):** If you join the study, we will need to find out if you meet the study requirements. You will be asked to schedule an appointment in the Clinical and Translational Research Center (CTRC). During this screening visit you will:

- Review this consent form with a member of the study team.
- Complete a medical history form.
- Have a physical examination.
- Complete questionnaires about feelings of depression and level of physical activity.
- Have about 1 tablespoon of blood drawn from a vein in your arm.
- Dual x-ray absorptiometry (DXA) scan will be performed to determine your bone mineral density and body composition.

You will be invited to take part in this study if you meet the guidelines for entry and agree to join the study. You will then be scheduled for visit 2. If you do not qualify for this study, we will tell you why.

**Visit #1 - PET/CT study at room temperature (~5 hrs):** The table below shows the timeline for this visit.

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>~8:00 AM</td>
<td>Arrive in lab, placement of sensors, put on cooling suit</td>
</tr>
<tr>
<td>0-90 minutes</td>
<td>rest quietly</td>
</tr>
<tr>
<td>90-120 minutes</td>
<td>Resting metabolic rate</td>
</tr>
<tr>
<td>120-150 minutes</td>
<td>Infuse radioactive fat tracer, PET/CT scan</td>
</tr>
</tbody>
</table>

During this visit:
- You will report to the CTRC at 8 am.
- You will be asked to fast (no food or drink other than water) starting at 10 pm the night before.

Combined Biomedical Consent and Compound HIPAA authorization
CF-151.C, Effective 9-29-15

Page 3 of 15

Initials______
You will wear a pair of hospital slippers and socks, long scrub pants, and a short sleeve t-shirt.

We will place skin temperature sensors at up to 9 different locations (e.g. arm, leg, forehead).

You will put on the cooling suit, but it will not be filled with water.

You will rest quietly for 90 minutes. We will then do a test called a resting metabolic rate (RMR) by placing a clear ventilated plastic hood over your head for 20 minutes. This will measure the air you breathe out and allow us to measure how many calories your body burns at rest.

After the RMR test, we will infuse a radioactive fat tracer into a vein in your arm and perform a PET scan. The tracer will let us see where brown fat is in your body and if it is “active”. To do the scan, you will lie on your back and be positioned in the scanner, similar to what is done during a MRI (magnetic resonance imaging) scan. The scan will last 30 minutes.

Visit #2 - PET/CT study during cold exposure (~6 hrs): The table below shows the timeline for this visit.

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>~8:00 AM</td>
<td>Arrive in lab, 1st blood sample (~1 tablespoon) placement of sensors, put on cooling suit</td>
</tr>
<tr>
<td>0-90 minutes</td>
<td>rest quietly</td>
</tr>
<tr>
<td>90-120 minutes</td>
<td>Resting metabolic rate</td>
</tr>
<tr>
<td>120 minutes</td>
<td>2nd blood sample (~1 tablespoon of blood)</td>
</tr>
<tr>
<td>120-150 minutes</td>
<td>Infuse radioactive fat tracer, 1st PET scan</td>
</tr>
<tr>
<td>150-180 minutes</td>
<td>infuse glucose radioactive tracer, 1st PET/CT scan (radiation)</td>
</tr>
<tr>
<td>180 minutes</td>
<td>You will be instructed to void your bladder</td>
</tr>
<tr>
<td>180-210 minutes</td>
<td>2nd PET/CT scan (radiation)</td>
</tr>
<tr>
<td>210 minutes</td>
<td>You will be instructed to void your bladder</td>
</tr>
</tbody>
</table>

During this visit:

- You will report to the CTRC at 8 am. We will ask you to provide a blood sample
- You will be asked to fast (no food or drink other than water) starting at 10 pm the night before.
- You will wear a pair of hospital slippers and socks, long scrub pants, and a short sleeve t-shirt.
- We will place electrodes over eight muscles to measure muscle activity (electromyography, or EMG), and skin temperature sensors at up to 9 different locations (e.g. arm, leg, forehead).
- You will put on the cooling suit.
- You will swallow a pill that will measure your body temperature.
- The cooling suit will be filled with cool water for 3.5 hours.
After 90 minutes your RMR will be measured again using the same procedures described above.

After 120 minutes, we will obtain a 2nd blood sample and then administer a dose of the radioactive fat tracer into a vein in your arm. This will let us see if the brown fat in your body becomes more active after wearing the cooling suit. This scan will last 30 minutes.

We will then administer a second dose of the radioactive glucose tracer into your vein. This is another way to measure how active your brown fat is.

A final PET/CT scan will be performed. The scan will cover the area from your head to hips. This scan will allow us to determine which areas in your body are white fat and which areas are brown fat.

Visits #3-7 – Lupron injections (~30 mins) – Pre-menopausal women in the estrogen suppression study will be asked to report to the outpatient unit of the CTRC for injections of the study drug to stop estrogen. Prior to the injection, a urine pregnancy test will be used to confirm you are not pregnant. We will ask your some questions about any changes in your health and medication use. We will obtain a measurement of your blood pressure. We will also ask you to complete some questionnaires about menopause symptoms, eating behavior, and sleep quality.

Visit #8 and 9 – Repeat PET/CT study (~6 hrs) – After 6 months, pre-menopausal women in the estrogen suppression study will be asked to repeat the DXA scan, blood draw for blood chemistries, and PET/CT studies.

What are the possible discomforts or risks?

Risks of the study drug: Leuprolide will lower your female hormones. In women who are pregnant, use of leuprolide acetate may cause fetal abnormalities. For this reason, you must have a negative pregnancy before being admitted to the study and before each monthly injection.

You may experience the following symptoms of low hormone levels:

Common side effects of the study drug:

- Feel hot or sweaty for short periods of time (“hot flashes”).
- Vaginal dryness or itching.
- Decreased sex drive.
- Headaches.
- Mood changes.
- Fatigue.
- Fluid retention.
- Feeling achy.
- Feeling sick to your stomach.
- Pimples.
- Dizziness.

Combined Biomedical Consent and Compound HIPAA authorization
CF-151.C, Effective 9-29-15

Page 5 of 15

Initials_______
Consent and Authorization Form

- A rash on your skin where you receive the injections.
- A small amount of bone loss, but this usually reverses when the drug is stopped.
- A small weight gain (1-3 pounds) that may reverse when the study is stopped.

Less common side effects of the study drug:
- Vaginal bleeding or spotting.
- Trouble concentrating or sleeping.
- Fluid retention.
- Menstrual cycles may not resume or may be irregular after the completion of the study because you are approaching the age of menopause.
- Numbness or tingling.

Rare side effects of the study drug:
- An allergic reaction to the injection.
- Unwanted hair growth.

Risk of radiation exposure: You will be exposed to radiation during the DXA and PET/CT scans.
- During each DXA you will be exposed to approximately 0.015 mSv of radiation. This amount of radiation is half of the amount of radiation you are exposed to during a cross-country flight.
- During study visit #1 (room temperature), you will be exposed to approximately 1.87 mSv of radiation. This amount of radiation is about half of the amount of radiation you are exposed to during a cross-country flight.
- During study visit #2 (cold exposure), you will be exposed to approximately 7.92 mSv of radiation. This amount of radiation is about 2.6 times the amount of radiation you are exposed to during a cross-country flight.

After allowing for 20% extra exposure from the procedures, women who complete study visits #1 and #2 will be exposed to a total of up to 11 mSv or radiation (~3.6 cross-country flights). Pre-menopausal women who complete study visits #8 and 9 will be exposed to a total of up to 22 mSv of radiation (7.3 cross-country flights). This is below the annual amount of exposure for radiation workers (50 mSv).

A possible health problem seen with radiation exposure is the development of cancer later in life. As shown in the Figure below, the exposure from the PET/CT scan is well below the level that increases risk of cancer. The risks of cancer from radiation are increased when radiation exposure is greater than 100 mSv every year for 40 years. The risk of this procedure is not equal for everyone. The risk is much higher for unborn babies if the mother has this procedure. The risk is also significantly higher for young children and teenagers who have this procedure. The risk is much lower for people over the age of 30.
Other Risks of PET/CT scan: PET/CT is used to diagnose a few diseases like some cancers and diseases of the brain. If you participate in this study, there is a very small risk that diseases like this may be found. You will be contacted and advised if any signs of disease are found.

The other risks/inconveniences associated with the PET/CT scan are related to claustrophobia and intravenous injection. You may feel discomfort lying still in an enclosed space for an extended period of time. For these exams, a sample of your blood is marked with a small amount of radioactive substance (tracer) and is injected into your vein for imaging a part of your body. Most of the tracer will be eliminated from your body within a day. You may have pain, redness, or swelling at the injection site. Allergic reactions to radioactive substance may occur but are extremely rare and are usually mild. You should inform the radiologist of any allergies you may have or other problems that may have occurred during a previous scan using a radioactive substance.

Core temperature pills: There is a small risk of choking when swallowing the capsule (rare). The capsule moves through the intestinal tract just like food does but, very rarely, the capsule may become stuck in the intestines. It usually takes 1-3 days for you to pass the capsule in your stool. You should not have an MRI test while the capsule is in your body. Because the capsule acts as a radio transmitter, you should not travel on commercial airlines while the capsule is in your body.

Consent and Authorization Form

CF-151.C, Effective 9-29-15

Page 7 of 15

Initials______
Risk of blood draws and venipuncture: You may feel pain when the needle is inserted and a day or two later you may have a small bruise. There is a risk of fainting when blood is drawn. During each blood draw, you will be asked to provide ~1 tablespoon of blood (3-6 tablespoons total for the entire study).

Risks of wearing the cooling suit: You may feel cold while wearing the suit and you may shiver some, but any shivering should be minor.

Risk of EMG and skin temperature sensors: You may experience some minor discomfort and/or skin irritation from the paste used to attach the EMG and skin temperature sensors.

Risks of Resting Metabolic Rate (RMR) measurement: There are no known risks to this procedure. You may however feel claustrophobic when the ventilated hood is placed over your head. The hood is clear plexiglass and will be removed immediately if you begin to feel claustrophobic.

Risks of interviews and questionnaires: The interviews, questionnaires, and collection of medical information may cause you to feel embarrassment or a loss of privacy. If we discover you have signs of depression or feelings of suicide, we will refer you to the University of Colorado Depression Center and/or we will get you immediate help.

Risk of Breach of Confidentiality: There is a risk that people outside of the research team will see your research information. We will do all that we can to protect your information, but it cannot be guaranteed.

Unknown risks: The study may include risks that are unknown at this time.

What are the possible benefits of the study?

This study is designed for the researchers to learn more about how the sex hormone estrogen affects metabolism in women. The study is not designed to treat any illness or to improve your health. Also there are risks as mentioned in the Risk Section.

Who is paying for this study?

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

*Pre-menopausal women:* You will be paid up to $925 if you complete all of the visits. You will be paid $25 for the screening visit, $50 for visit 1, $150 for visit 2, $100 for each Lupron injection (up to 5 injections), $50 for visit 8 and $150 for visit 9.

*Post-menopausal women:* You will be paid up to $225 if you complete all of the visits. You will be paid $25 for the screening visit, $50 for visit 1 and $150 for visit 2.

If you leave the study early, or if we have to take you out of the study, you will be paid only for the visits you have completed.

It is important to know that payments for participation in a study are taxable income.

Will I have to pay for anything?

There is no cost to you for taking part in this study other than the costs of transportation to and from the testing facilities. There will be no charge for any tests or drugs required by the study.

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 choose to take part, you have the right to stop at any time. If you refuse or decide to withdraw later, you will not lose any benefits or rights to which you are entitled.

Can I be removed from this study?

The study doctor may decide to stop your participation without your permission if the study doctor thinks that being in the study may cause you 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?

If you have an injury while you are in this study, you should call Edward Melanson immediately. His phone number is (303) 724-0935. You can also contact the study doctor, Rebecca Boxer, M.D., at (303) 724-1922. We will arrange to get you medical care if you have an injury that is caused by this research. However, you or your insurance company will have to pay for that care.
Consent and Authorization Form

Who do I call if I have questions?

The researcher carrying out this study is Edward Melanson, Ph.D. You may ask any questions you have now. If you have questions, concerns, or complaints later, you may call Edward Melanson at (303) 724-0935. You will be given a copy of this form to keep.

You may have questions about your rights as someone in this study. You can call Edward Melanson with questions. You can also call the responsible Institutional Review Board (COMIRB). You can call them at 303-724-1055.

A Research Subject Advocate is also available on the CTRC at (720) 848-6662 to answer questions relating to participation in this study.

Optional Consent for Data and Specimen Banking for Future Research

Dr. Ed Melanson would like to keep some of the data and blood that is taken during the study but is not used for other tests. If you agree, the data and samples will be kept and may be used in future research to learn more about metabolism in postmenopausal women. The research that is done with your data and samples is not designed to specifically help you. It might help women who are postmenopausal in the future. Reports about research done with your data and samples will not be given to you or your doctor. These reports will not be put in your health records. The research using your data and samples will not affect your care.

The choice to let Dr. Ed Melanson keep the data and 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 data and samples can be kept for research, you can change your mind at any time and contact your study doctor to let her know that you do not want Dr. Melanson to use your data or 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. Melanson decides to destroy them.

When your data or samples are given to other researchers in the future, Dr. Melanson will not give them your name, address, phone number or any other information that will let the researchers know who you are.

Sometimes samples are used for genetic research (about diseases that are passed on in families). Even if your 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 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 data and samples include learning more about what causes weight gain after menopause and other diseases, how to prevent them and how to treat them. The greatest risk to you is the release of your private information. Dr. Melanson 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 data or sample collection and storage by Dr. Melanson.

Combined Biomedical Consent and Compound HIPAA authorization
CF-151.C, Effective 9-29-15

Page 10 of 15

Initials_______
Consent and Authorization Form

Please read each sentence below and think about your choice. After reading each sentence, circle “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 samples, you may still take part in the study.

I give my permission for my blood to be stored in a central tissue bank at the University of Colorado, Denver for future use by the study investigators:

1. I give my permissions for my blood to be kept by Dr. Melanson for use in future research to learn more about how to prevent, detect, or treat weight gain after menopause.
   □ Yes    □ No _____Initials

2. I give my permission for my blood to be used for research about other health problems (for example: causes of heart disease, osteoporosis, diabetes).
   □ Yes    □ No _____Initials

3. I give my permission for my study doctor (or someone he or she chooses) to contact me in the future to ask me to take part in more research.
   □ Yes    □ No _____Initials

Who will see my research information?

The University of Colorado Denver (UCD) and its affiliated hospital(s) 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

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 UCD and its affiliate hospitals may not be covered by this obligation.

We will do everything we can to maintain the confidentiality of your personal information but confidentiality cannot be guaranteed.

Combined Biomedical Consent and Compound HIPAA authorization
CF-151.C, Effective 9-29-15
Consent and Authorization Form

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 Principal Investigator (PI), 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.

Edward Melanson, Ph.D.
Division of Endocrinology, Metabolism, and Diabetes
12801 East 17th Ave, RC1 South RM 7103, MS 8106
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, such as:

- Federal offices such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP) that protect research subjects like you.
- People at the Colorado Multiple Institutional Review Board (COMIRB)
- The study doctor and the rest of the study team.
- The National Institutes of Health, who is paying for this research study.
- Officials at the institution where the research is conducted and officials at other institutions involved in this study who are in charge of making sure that we follow all of the rules for research

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.

You have the right to request access to your personal health information from the Investigator.

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 Diagnosis(es), History and Physical, laboratory or tissue studies, radiology studies, procedure results
- Research Visit and Research Test records
- Psychological and mental health tests

Combined Biomedical Consent and Compound HIPAA authorization
CF-151.C, Effective 9-29-15
Consent and Authorization Form

- Tissue samples and the data with the samples.
- Billing or financial information

What happens to Data, 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, tissue, blood, or other specimens given by you to the investigators for this research no longer belong to you.
- Both the investigators and any sponsor of this research may study your data, 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 Institutional Review Board (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.
HIPAA Authorization for Optional Additional Study Procedures

If you are a pre-menopausal women, you have the option to agree to participate in the estrogen suppression study. Participating in the estrogen suppression study is optional. If you wish to be in this optional study, you must also give us your permission, under HIPAA rules, to use and disclose the information collected from these optional procedures, as described above.

If you decline to give us permission to use and disclose your information, you cannot take part in this optional study, but you can still participate in the main study. Please initial next to your choice:

_____ I give permission for my information, from the optional procedures I have agreed to above, to be used and disclosed as described in this section.

_____ I do not give permission for my information for any optional procedures to be used and disclosed; I understand that I will not participate in any optional procedures.

_____ I am post-menopausal and do not qualify for the optional estrogen suppression study.
Agreement to be in this study and use my data

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 understand and authorize the access, use and disclosure of my information as stated in this form. I know that being in this study is voluntary. I choose to be in this study: I will get a signed and dated copy of this consent form.

Signature: ____________________________ Date: __________

Print Name: ____________________________

Consent form explained by: ____________________________ Date: __________

Print Name: ____________________________

Investigator: ____________________________ Date: __________
Investigator must sign within 30 days

Witness Signature: ____________________________ Date: _________
Witness Print Name: ____________________________
Witness of Signature □
Witness of consent process □