Combined Consent and Authorization to Participate in a Research Study

"Cold Induced Changes in Human Subcutaneous White Adipose"

CONSENT FORM 1: FAT BIOPSY ONLY

WHY ARE YOU BEING INVITED TO TAKE PART IN THIS RESEARCH?

You are being invited to take part in a research study about the effect of cold temperatures on fat tissue. You are being invited to take part in this research study because you are between the ages of 21 and 65, overweight or lean, have a slightly abnormal blood sugar, evidence of metabolic syndrome, or are in good overall health. If you volunteer to take part in this study, you will be one of about 90 people to do so.

WHO IS DOING THE STUDY?

The person in charge of this study is Philip Kern M.D. of University of Kentucky, Department of Medicine, and Division of Endocrinology. There may be other people on the research team assisting at different times during the study.

WHAT IS THE PURPOSE OF THIS STUDY?

An adaptation to a cold environment is a tendency to generate heat within our body. Some of this heat comes from our fat tissue. Although most fat tissue is "white fat", there are pockets deep within the body that are called "brown fat", which are specially adapted to burning fat and making heat. We believe that our white fat, just underneath the surface of our skin, also has this property to burn fat and make heat, although not at the high level of brown fat. This study is to examine this fat-burning property of the white fat under the skin in response to seasons and to cold temperatures. Many such studies have been done in mice, but little has been done in humans.

Metabolic syndrome is a condition involving elevated levels of fat in the blood, a tendency towards diabetes, hypertension, and too much fat around the abdomen (an increased waistline). Individuals with metabolic syndrome often have impaired glucose tolerance, which is a condition where your blood sugar is normal when fasting (before you eat), but is too high after drinking a sugary drink. This is due to an abnormality in your body's sensitivity to insulin (insulin resistance), which is due in part to an inability of your muscle to take up glucose. People with metabolic syndrome have inflammation in their fat tissue and this inflammation in the fat tissue may impair the ability of the white fat to burn fat and continue to promote obesity.

There are a number of factors, including your age, weight, and medical history, that may make you eligible or ineligible to participate in this study. Certain medications that you may be taking could make you ineligible, but if these medications can be safely altered, you may become eligible. Any such changes will be discussed with you and your primary care provider.

ARE THERE REASONS WHY YOU SHOULD NOT TAKE PART IN THIS STUDY?

You should not participate in this study if you are pregnant or breastfeeding, if you have a bleeding disorder, or if you have an allergy to the local anesthetic lidocaine. If you are of childbearing potential, you must be using adequate contraception. You should not participate in this study if you have a history of coronary disease or stroke, chronically use aspirin or any other anticoagulant.

WHERE IS THE STUDY GOING TO TAKE PLACE AND HOW LONG WILL IT LAST?

The research procedures will be conducted at the UK Medical Center at the Center for Clinical Translational Sciences research unit (CCTS). You will need to come to the CCTS Unit for approximately 22-30 visits, as outlined below. Most of these visits will be less than 1 hr, but 6 visits will involve procedures and will vary in time ranging from 4 hour to 6 hours. Thus, your total participation will be approximately 22-30 visits over 6-7 months.

Should you experience an adverse event it may be necessary to schedule an unscheduled visit to address any health issues that you may be experiencing at that time.

WHAT WILL YOU BE ASKED TO DO?

You will report to the CCTS research unit for baseline testing and repeated procedures. You will then be asked to have the same procedures done approximately 6 months later.

Baseline Visits:

- You will be fasting (nothing to eat after 9 pm the night before you are scheduled to have lab work performed).
- You will complete the Informed Consent process.
- We will go over your medical history and make measurements of your waist and hips.
- You will have blood taken for labs.
- You will complete an Oral Glucose Tolerance Test (OGTT) to measure your tendency towards diabetes.
- Pregnancy Testing (if relevant)
- If a recent OGTT or blood work have been done, then it will not be necessary to repeat these tests during this visit.

Initial Biopsies (optional):

- You will be fasting after 9 pm the previous night.
- Two fat biopsies will be taken from your abdomen and thigh under local anesthesia. During the biopsies the study doctor will make a small 1.0 to 1.5-inch incision into your abdomen and thigh and remove a small amount of fat tissue. The incision will be about ½ inch deep
- An ice pack will be applied to your abdomen and thigh on the side opposite the biopsies for 30 min.
- Four hours after removal of the ice pack, two fat biopsies will be taken from your abdomen and thigh at the site of the icing.
- Your skin will been sutured (sewn) back together and the sutures will be removed after 7 days.
- Contacted by study coordinator 48 hours following biopsy

Intermediate Visits:

- You will come to the CCTS every day, for the next 8-12 days, and have an ice pack placed on your thigh and abdomen, on the same side as before, 30 minutes. You may then go home. We will ask you to do this on your own on weekends and holidays. When you apply the ice pack at home, be sure to not supercool the wet ice with dry ice or other cooling methods and do not exceed the 30 minute time period.

Final Biopsies (optional):

- This will be 9-13 days after the second visit
- You will be fasting after 9pm the previous night.
- An ice pack will be applied to your abdomen and thigh on the side opposite the biopsies for 30 min.
- Two fat biopsies will be taken from your abdomen and thigh under local anesthesia from the non-iced side.
- Four hours after removal of the ice pack, two fat biopsies will be taken from your abdomen and thigh at the site of the icing.

- You will have the sutures removed after 7 days.
- Contacted by study coordinator 48 hours following biopsy

End of Treatment Visit:

- You will be fasting (nothing to eat after 9 pm the night before you are scheduled to have lab work performed).
- You will complete an Oral Glucose Tolerance Test (OGTT) to measure your tendency towards diabetes.
- You will have blood taken for labs

Repeat next season. We would like to perform the identical procedures, described above, during the opposite season. For example, if the above procedures (visits 1-11 to 15) were performed in the summer, we will want to repeat them in the winter (approximately Nov 15 through March 15). If they were originally performed in the winter, we will want to repeat them in the summer (approximately June 15 through Sept 15).

Unscheduled Visits: During the study if you or the study staff believes you should be seen for an extra visit the study staff will arrange for this visit. This visit should take no more than 30 minutes. During this visit we will:

- Review your current medication use, including over the counter medications and herbals
- Ask questions about your health or any problems you may have had since your last visit
- If necessary, take a blood sample (about 1 tablespoon) and urine sample (about 6 teaspoons) to monitor your general health.
- If necessary, perform a ECG and measure your blood pressure and pulse
- If necessary, ask questions about how you've been taking of your study medication

Glucose tolerance test, and body composition measurements: To determine whether you qualify for this study, we will first ask you some questions about your medical history, obtain vital signs, and determine whether you have impaired glucose tolerance. You will be expected to come to the CCTS at the UK Medical Center in the morning after an overnight fast for an oral glucose tolerance test (OGTT). A blood sample will be drawn. You will be asked to drink a sweet liquid (sugar water), which contains 75 grams of glucose, followed by blood draws at 30 minute intervals for 2 hours. The total amount of blood drawn will be about 1 tablespoon. This test will determine whether you have impaired glucose tolerance, diabetes, or are normal. We will also draw approximately 2 tablespoons of blood for labs. This fasting blood sample will be used to conduct routine blood tests that are a normal part of a physical exam, such as cholesterol, liver enzymes and electrolytes. If a recent OGTT and labs have been recorded, it will not be necessary to perform these tests.

You will be asked to have your weight, height, waist and hip measurements recorded.

Based on the blood tests, the OGTT, and other measurements, we will determine whether you have impaired glucose tolerance or a normal glucose level, and whether you fit the other criteria of the study. If you meet the criteria of the study, you will be invited to participate in the rest of the study.

Fat biopsies: After an overnight fast, the biopsy procedures will be performed as follows: A sample of your fat (called a fat biopsy) will be removed by Dr. Kern or one of his associates from an area of your lower abdomen and from your thigh. The skin at the biopsy site will be anesthetized using the local anesthetic, lidocaine, then a 1.0 to 1.5-inch incision will be made through the skin and a small amount of fat tissue will be removed. The incision will be about ½ inch deep and will be closed using stitches. This procedure normally takes about 30-45 minutes. After the procedure, you will be provided with a snack.

We will then put a plastic bag of ice on the opposite side of the abdomen and thigh from the first biopsies for 30 minutes. Four hours after removing the ice pack, biopsies from your thigh and abdomen will be performed as described above.

We will then ask you to come back to the CCTS daily on weekdays for a 30 min ice pack on your thigh and abdomen for 8-12 days. On weekends, we will expect you to do the icing on your own. About 9 to 13 days after the initial biopsies, you will come back to the CCTS fasting and we will perform icing on your abdomen and thigh, and again perform fat biopsies from both the iced side and the non-iced side.

Thus, you will have a total of up to 8 fat biopsies: 4 on the first day (abdomen and thigh, iced and non-iced) and again 4 biopsies after 14 days of icing.

It is possible that not all 8 biopsies will be performed in everyone, depending on the discretion of the investigative team.

We would like to repeat all of the above procedures approximately 6 months later, during the opposite season.

Not all 8 biopsies will be performed in both the summer and winter. As stated, the biopsies performed will be at the discretion of the investigative team. The total number of biopsies you will have during your participation in the study will be no more than 12**.**

Urine Collection: If you are female and you are able to get pregnant, you will also be asked to give a sample of urine to see if you are pregnant. If the test results from your urine say that you are pregnant you will not be able to participate in the study.

Pregnancy: If you are capable of becoming pregnant, you must use adequate birth control for the entire study. Check with the study doctor about methods of birth control to use and how long to use them.

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?

Fat biopsy: During the biopsy, there will be some discomfort (a burning sensation) while the anesthetic (lidocaine) is being injected. Following completion of the procedure, the site of the biopsy will be mildly tender for a period of 3-4 days. There is also a small chance (less than 1 in 100) that a problem with excessive bleeding or infection of the biopsy site may occur. In case of bleeding, you might need to have the incision site opened to evacuate the blood clot or you might need antibiotics to control the infection. The biopsy could result in a small area of numbness on the skin around the site of the incision. There will be a permanent scar; the scar from the fat biopsy will be approximately 1 inch in length. You should avoid heavy lifting and strenuous physical activity for two weeks after the biopsy. After this time, you can participate in any activity according to your tolerance. You may take acetaminophen (Tylenol®) after the biopsy. If necessary, the investigators will prescribe other medications for pain.

There is a slight risk that you may have an allergic reaction to local anesthetic lidocaine and experience a rash or itching. If this happens you may be given an antihistamine (Benadryl).

You may experience anaphylaxis. Anaphylaxis is a severe, potentially life-threatening allergic reaction. It can occur within seconds or minutes of exposure to something you are allergic to. Symptoms of an anaphylactic reaction are: drop in blood pressure, difficulty breathing, rapid heartbeat, skin rash, nausea and vomiting, unconsciousness or even death. If you experience any of these symptoms after you leave the clinic, call 911 immediate.

OGTT. Some discomfort may be present at the sites of needle insertion and catheter location, and there could be some soreness, bruising, pain, bleeding, or fainting. There is a small chance of infection or inflammation around the site of needle insertion. Some people get a mild upset stomach from drinking the sugar water.

Possible Risk/Side Effect	How often has it occurred? (percentage/likelihood)	How serious is it?	Can it be corrected?
Pain, bruising, following biopsies	Pain and bruising, common	Pain: mild-moderate	Yes; pain medications; bruising resolves in 3-10 days
Infection from biopsy	Rare (less than 1:100)	Mild-moderate	Yes, antibiotics
Scar from biopsies	Always	small	It will be permanent
Possible infection from IV	Uncommon	Not serious	Yes, with anti-inflammatory medications and/or antibiotics
Upset stomach from sugar water	Uncommon	Not serious	It will get better on its own

Venipuncture. There may be some slight bleeding or bruising at the venipuncture site which may last for a short duration. You may feel faint which will last for a short duration. You may experience some soreness or pain at the site for a few days as well. There is also the slight possibility of infection at the venipuncture site.
There is always a chance that any medical treatment can harm you, and the investigational treatment in this study is no different. In addition to the risks listed above, you may experience a previously unknown risk or side effect.

WILL YOU BENEFIT FROM TAKING PART IN THIS STUDY?

There is no guarantee that you will get any personal benefit from taking part in this study. Your willingness to take part may, in the future, help doctors better understand and/or treat others who have your condition.

DO YOU HAVE TO TAKE PART IN THE STUDY?

If you decide to take part in the study, it should be because you want to volunteer. You will not lose any benefits or rights you would normally have if you choose not to volunteer. You can stop at any time during the study and still keep the benefits and rights you had before volunteering. If you decide not to take part in this study, your decision will have no effect on the quality of medical care you receive.

IF YOU DON'T WANT TO TAKE PART IN THE STUDY, ARE THERE OTHER CHOICES?

If you do not want to be in the study, there are no other choices except not to take part in the study.

WHAT WILL IT COST YOU TO PARTICIPATE?

All of the procedures that are part of this research will be provided at no cost to you, and The University of Kentucky may not be allowed to bill your insurance company, Medicare or Medicaid for the medical procedures done strictly for research. Therefore, these costs will be paid by the research study.

WHO WILL SEE THE INFORMATION THAT YOU GIVE?

We will make every effort to keep private all research records that identify you to the extent allowed by law. Your information will be combined with information from other people taking part in the study. When we write about the study to share it with other researchers, we will write about the combined information we have gathered. You will not be personally identified in these written materials. We may

publish the results of this study; however, we will keep your name and other identifying information private. You will be asked to provide your social security number. This is necessary to provide you with payment for participation in the study and is not being collected for actual research purposes. Your social security number will be kept on a separate form and will be destroyed after you receive your payment. If you would rather not provide your social security number you may still take part in the research study but will not be eligible for payment.

We will make every effort to prevent anyone who is not on the research team from knowing that you gave us information, or what that information is. Your personal information (name, address, phone number) will be kept in a paper chart that is stored in a locked filing cabinet. A unique number will be assigned to you, your data, and any data in electronic records will only contain your unique number, and will not contain information that could identify you.

You should know, however, that there are some circumstances in which we may have to show your information to other people. For example, the law may require us to show your information to a court or to tell authorities if you report information about a child being abused or if you pose a danger to yourself or someone else. Officials of the Food and Drug Administration, the National Institutes of Health, and the University of Kentucky, Center for Clinical and Translational Science may look at or copy pertinent portions of records that identify you.

CAN YOUR TAKING PART IN THE STUDY END EARLY?

If you decide to take part in the study you still have the right to decide at any time that you no longer want to continue. You will not be treated differently if you decide to stop taking part in the study. The individuals conducting the study may need to withdraw you from the study. This may occur if you are not able to follow the directions they give you, if they find that the procedures or drug are technically difficult or result in medically unacceptable side effects, or if the agency funding the study decides to stop the study early for a variety of scientific reasons.

ARE YOU PARTICIPATING OR CAN YOU PARTICIPATE IN ANOTHER RESEARCH STUDY AT THE SAME TIME AS PARTICIPATING IN THIS ONE?

You may take part in this study if you are currently involved in another research study, but this depends on the nature of the other study. It is important to let the investigator/your doctor know if you are in another research study. You should also discuss with the investigator before you agree to participate in another research study while you are enrolled in this study.

WHAT HAPPENS IF YOU GET HURT OR SICK DURING THE STUDY?

If you believe you are hurt or if you get sick because of something that is due to the study, you should call Dr. Kern at (859) 323-4933 during regular working hours. During evenings or weekends, you should call the University of Kentucky page operator at 859-323-5321 and ask for Dr. Philip Kern, or for the Endocrinology fellow on call. If you are experiencing an emergency, you should call 911.

It is important for you to understand that the University of Kentucky does not have funds set aside to pay for the cost of any care or treatment that might be necessary because you get hurt or sick while taking part in this study. Also, the University of Kentucky will not pay for any wages you may lose if you are harmed by this study.

The medical costs related to your care and treatment because of research related harm will be your responsibility or may be paid by your insurer if you are insured by a health insurance company. Please contact your insurer to determine if they will pay for a research related injury.
You do not give up your legal rights by signing this form.

WILL YOU RECEIVE ANY REWARDS FOR TAKING PART IN THIS STUDY?

You will receive a payment for participating in this study as follows:

- $20 for the screening procedures (medical history, glucose tolerance test)
- $60 for icing 8-12 days
- $20 for end of treatment glucose tolerance test
- $50 for each fat biopsy. You may have up to 12 biopsies **(between the summer and winter).** You will receive payment for the biopsies at the end of your seasonal participation:
  For example, if 8 biopsies are performed, you will receive $400
  If the maximum 12 biopsies are performed, you will receive $600.

Dr. Kern will decide how many biopsies you are to receive. There is a chance that you may not receive all they biopsies noted here and your study payment would then be less. A member of the study team will discuss this with you at the start of the study.

Therefore, if you participate in both seasons you could receive up to $700 for being in the study. If you only participate in one season you could receive up to $400 for taking part in the study.

If you receive $600 or above by participating in research it is potentially reportable for tax purposes.

WHAT IF YOU HAVE QUESTIONS, SUGGESTIONS, CONCERNS, OR COMPLAINTS?

Before you decide whether to accept this invitation to take part in the study, please ask any questions that might come to mind now. Later, if you have questions, suggestions, concerns, or complaints about the study, you can contact the investigator, Dr. Kern at 859-323-4933. If you have any questions about your rights as a volunteer in this research, contact the staff in the Office of Research Integrity at the University of Kentucky between the business hours of 8 am and 5 pm EST, Mon-Fri at 859-257-9428 or toll free at 1-866-400-9428. We will give you a signed copy of this consent form to take with you.

WHAT IF NEW INFORMATION IS LEARNED DURING THE STUDY THAT MIGHT AFFECT YOUR DECISION TO PARTICIPATE?

If the researcher learns of new information in regards to this study, and it might change your willingness to stay in this study, the information will be provided to you. You may be asked to sign a new informed consent form if the information is provided to you after you have joined the study.

POTENTIAL FUTURE USE

Banking of tissue and blood specimens
The investigators (Philip Kern, M.D.) would like to keep some of the unused or leftover blood and muscle samples collected during this study. No additional blood or tissue will be taken. If you agree, the blood and muscle samples will be stored for an indefinite amount of time and may be used in future research related to muscle health and disease. **No genetic testing will be performed on your stored samples.** Your stored samples/information will not be shared with anyone outside the bank. There is no benefit to you for allowing us to bank your samples/information. There is no risk to you allowing us to bank your samples/information. This is because your name, and other information that could identify, will not be placed on the stored samples/information. There is no cost to you for participating in the bank and there is no benefit to you for allowing Dr. Kern to store your samples.

Please read the information below and think about your choice. After reading, mark "yes" or "no." If you have questions, please talk to the investigator or staff. Remember, no matter what you decide to do about the storage, and future use of your blood and muscle samples, you may still take part in this study. If you answer yes to either choice below you also give your authorization for your accompanying health information acquired during this study to be used and disclosed along with the blood and muscle samples. Your protected health information such as your name will be de-identified or coded so that others will not know your identity.

1. Do you give permission for your blood and fat samples to be kept by *Philip Kern, M.D.* in a central location/specimen bank at University of Kentucky, indefinitely or until they are used up for use in future research to learn more about how to prevent, detect, or treat insulin resistance, obesity, metabolic syndrome or diabetes?

   ☐ Yes ☐ No _____Initials

2. Do you give permission for your blood and fat samples to be used for future research about other health problems, not necessarily related to obesity or diabetes?

   ☐ Yes ☐ No _____Initials

The blood and fat samples that you are giving will no longer belong to you and might be used in studies that lead to new products for research, diagnosis or treatment. There is no plan to keep you informed of findings from these studies. These products might have some commercial value. There are no plans to provide financial compensation to you should this occur.

Contacting Research Subjects for Future Studies

Do you give your permission to be contacted in the future by *Philip Kern, M.D.* regarding your willingness to participate in future research studies about how to prevent, detect, or treat insulin resistance, or other studies that may be relevant to you?

☐ Yes ☐ No _____Initials

If you later decide to withdraw your permission for the banking of leftover samples, please contact Philip Kern, M.D.; Wethington 521; 900 S. Limestone St, Lexington KY 40536 and request that your leftover samples be discarded after this protocol is completed.

WHAT ELSE DO YOU NEED TO KNOW?

The National Institute of Diabetes and Digestive and Kidney Diseases (a branch of the National Institutes of Health) is providing funding for this study.

The sample(s) (blood, tissue or fluids) that you are giving might be used in studies that lead to new products for research, diagnosis or treatment. These products might have some commercial value. There are no plans to provide financial compensation to you should this occur.

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 web site will include a summary of the test results. You can search this web site at any time.

AUTHORIZATION TO USE OR DISCLOSE YOUR IDENTIFIABLE HEALTH INFORMATION

The privacy law, HIPAA (Health Insurance Portability and Accountability Act), requires researchers to protect your health information. The following sections of the form describe how researchers may use your health information.

Your health information that may be accessed, used and/or released includes:

- Demographic information (e.g. name, address, phone number, study number, social security number)
- Dates including date of birth, hospital admissions/discharges, dates of medical events, study visits
- Medical history and medication history as it relates to this study
- Results of blood tests, glucose tolerance tests, muscle biopsy, DEXA Scans)

The Researchers may use and share your health information with:

- The University of Kentucky's Institutional Review Board/Office of Research Integrity.
- Law enforcement agencies when required by law.
- UK Hospital or University of Kentucky representatives, for purposes of administration of the study (e.g. Lab results, payment of compensation).
- UK Investigational Drug Services
- Officials at the funding agency, the National Institutes of Health, if necessary.
- The Food and Drug Administration (FDA), if necessary
- Center for Clinical and Translational Science (CCTS)
- Collaborating physicians and staff, as required for safety purposes.
- If necessary, my primary physician will be contacted if the researcher in the course of the project learns of a medical condition that needs immediate attention.

The researchers agree to only share your health information with the people listed in this document. Should your health information be released to anyone that is not regulated by the privacy law, your health information may be shared with others without your permission; however, the use of your health information would still be regulated by applicable federal and state laws.

You will not be allowed to participate in the research study if you do not sign this form. If you decide not to sign the form, it will not affect your:

- Current or future healthcare at the University of Kentucky
- Current or future payments to the University of Kentucky
- Ability to enroll in any health plans (if applicable)
- Eligibility for benefits (if applicable)

After signing the form, you can change your mind and NOT let the researcher(s) release or use your health information (revoke the Authorization). If you revoke the authorization:

- You will send a written letter to: *Philip Kern, M.D.; Wethington 521; 900 S. Limestone St, Lexington KY 40536* of your decision.
- Researchers may use and release your health information **already** collected for this research study.
- Your protected health information may still be used and released should you have a bad reaction (adverse event).
- You may not be allowed to participate in the study.

The use and sharing of your information has no time limit.

If you have not already received a copy of the Privacy Notice, you may request one. If you have any questions about your privacy rights, you should contact the University of Kentucky's Privacy Officer between the business hours of 8am and 5pm EST, Mon-Fri at: (859) 323-1184.

You are the subject or are authorized to act on behalf of the subject. You have read this information, and you will receive a copy of this form after it is signed.

_____ _____

Signature of research subject Date

_____

Printed name of research subject

_____ _____

Name of [authorized] person obtaining informed consent/HIPAA authorization Date

_____

Signature of Principal Investigator or Sub/Co-Investigator