Combined Consent and Authorization to Participate in a Research Study

"Dietary fat, lipoprotein and lipopolysaccharide: role in insulin resistance"

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

You are being invited to take part in a research study about dietary fat, lipoprotein and lipopolysaccharide and their role in insulin resistance and its underlying causes. You are being invited to take part in this research study because you are between the ages of 35 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 40 people to do so.

WHO IS DOING THE STUDY?

The person in charge of this study is Dr. 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?

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 in their blood stream, and the changes in the level of inflammatory chemicals produced by cells in your fat tissues will be studied. One possible source of the inflammation may be the bacteria in your intestine. When you eat fatty foods, some of the bacterial products (endotoxin, or lipopolysaccharide) become attached to the fat in your blood and then get directed to your fat tissue. We wish to determine whether you have an excessive amount of inflammation in your fat tissues, and whether this inflammation comes from the bacteria in your intestines.

To determine this, we wish to treat you with an experimental antibiotic (rifaximin SSD) that reduces the bacteria in your intestines and in your blood, and determine whether this reduces your overall level of inflammation

Rifaximin is an FDA approved antibiotic that is minimally absorbed by the intestine and is used to treat gut bacterial infections and to lower the amount of bacterial products that get into the blood in patients with serious liver disease. You will be receiving rifaximin SSD. This is a new formulation of the same drug which is not yet FDA approved

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/NSAID or any other anticoagulant. If you have a lactose intolerance, inflammatory bowel disease, chronic or frequent diarrhea or other chronic gastrointestinal disturbance, you should not participate.

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 9 research visits; 4 visits for procedures, then you take the antibiotic rifaximin SSD (or a placebo/"sugar pill") and return to the clinic for a compliance visit, and then the procedures are repeated. The study itself lasts for about a 12 week period. Each of these visits will vary in time ranging from 4 hour to 9 hours.

WHAT WILL YOU BE ASKED TO DO?

You will report to the CCTS research unit 4 times over the first 2-3 weeks of the study for baseline testing. After the initial procedures, you will take the study drug, rifaximin SSD or placebo, for 4 weeks and then you will report back to the CCTS research unit for a compliance visit to obtain additional study drug. After 4 more weeks of taking the study drug, you'll return 4 more times over a period of 2-3 weeks to complete the same procedures you did for baseline testing. Your participation will then be completed. Your total participation will be 9 visits over a 12 week period. Each of these visits will vary in time ranging from 4 hours to 9 hours.

<u>CCTS Baseline Visits</u>:

The first visit:

- You will be fasting.
- You will complete the Informed Consent process.
- We will go over your medical history and diet 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.
- You will have a DEXA Scan that measures your bone density and body fat.

The second visit:

- The night before you will have a low fat meal, suggested are: Subway low fat combo meal, Healthy Choice or Smart Ones. You will also abstain from alcohol.
- You will be fasting after 9pm.
- You will drink a high fat shake and have hourly blood draws for up to 8 hours.

The third visit:

- You will be fasting after 9pm the previous night.
- A fat biopsy will be taken from your abdomen under local anesthesia. You will have the sutures removed after 7 days.

The fourth visit:

- You will be fasting after 9pm the previous night.
- You will complete a measurement of insulin sensitivity with a clamp study.
- We will check up on the biopsy site.

Note that scheduling conflicts may change the order of some of the procedures above.

The fifth visit:

After the baseline procedures you will take the study drug, rifaximin SSD for 8 weeks, or a sugar pill/placebo. You will be asked to return after 4 weeks for a compliance visit consisting of having labs drawn and a count of your study drug. After eight weeks you will report back to the CCTS research unit to repeat the same procedures you did for the baseline testing. You will then complete the study.

CCTS Post Visits:

The sixth visit:

- You will be fasting after 9pm.
- Blood taken for labs, measurement of waist and hips.
- You will complete an Oral Glucose Tolerance Test (OGTT) to measure your tendency towards diabetes.
- You will have a DEXA Scan that measures your bone density and body fat.

The seventh visit:

- The night before you will have a low fat meal, suggested are: Subway low fat combo meal, Healthy Choice or Smart Ones. You will also abstain from alcohol.
- You will be fasting after 9pm.
- You will drink a high fat shake and have hourly blood draws for up to 8 hours.

The eighth visit:

- You will be fasting after 9pm.
- A fat biopsy will be taken. You will have the sutures removed after 7 days.

The ninth visit:

- You will be fasting.

- You will complete a measurement of insulin sensitivity with a clamp study.
- We will check up on the biopsy sites. End of Study.

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.

From a fasting blood sample, we will conduct routine blood tests that are a normal part of a physical exam, such as cholesterol, liver enzymes and electrolytes. The amount of blood taken will be about 2 tablespoons. You will be asked to have your weight, height, waist and hip measurements recorded. Measurement of total body fat will be performed to determine your percent body fat using dual energy X-ray absorptiometry (DXA). DXA uses very low levels of X-ray to measure the amount of fat, muscle, and bone in different body areas. You will be asked to lie on a table while wearing light clothing or a gown. The test will take only 5 - 10 minutes, and involves no discomfort.

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.

Lipid tolerance test. You will consume a low fat meal the evening before the test, and then you will be asked to come to the CCTS Outpatient Clinic in the morning after an overnight fast for the lipid tolerance test. You will be asked to drink a high fat shake which will encompass 40% of your daily energy requirements, and will be 50% fat. Blood will be drawn at time points 0, 30 min, 1 hour, and hourly to 8 hours.

Insulin sensitivity and secretion measurements: These procedures will be performed to measure your insulin sensitivity. This procedure is called a Clamp study. For these measurements, you will come to the CCTS after fasting overnight. Two intravenous plastic tubes will be inserted into veins in your arm. You will be given an injection of a small amount of non-radioactive “heavy glucose”, which will be used to measure how much glucose is put out by your liver. You will then be given a constant injection of glucose along with a constant injection of insulin. The glucose and insulin are balanced such that your blood glucose stays constant between 90-100 mg/dl. Blood will then be drawn from the intravenous line frequently (about every 2 to 5 minutes) for measurement of blood glucose and insulin. These blood measurements will continue for 4 hours; the total amount of blood that will be withdrawn will be about 150 cc (about 10 tablespoons), which is about one third as much as would be taken if you were to donate blood, and then the test is over and you will be provided with a meal.

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 from an area of your lower abdomen. The skin at the biopsy site will be anesthetized using the local anesthetic, lidocaine, then a 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.

Study drug. After the initial procedures, you will be assigned to one of two groups: rifaximin SSD 80 mg taken once per day, or placebo (a pill containing no drug). The assignments will be random (by chance, like flipping a coin) and you will not know whether you are on the placebo or rifaximin SSD, but the study coordinator and the PI (Dr. Kern) will be able to determine the drug assignment if it is necessary. You will take your assigned drug for 8 weeks. After you have taken the medication for 8 weeks, all the above studies (blood tests, insulin sensitivity testing, body composition, lipid tolerance, fat biopsies) will be repeated. Your participation in the study will then be concluded, and we will reveal to you the study assignment.

If you qualify for the full study, your total duration of participation in this study, including the time to perform the procedures will be approximately 12 weeks. Your participation is voluntary, and you may withdraw from the study at any time. All of the above procedures are being performed because of the research study, and none are intended to diagnose or treat a medical condition. If you are of child bearing age and not using adequate contraception, a pregnancy test may be performed at the time of initial screening.

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 one to two inches 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, itching or anaphylaxis. If this happens you may be given an antihistamine (Benadryl).

DEXA Scan/Body fat measurement: DXA is a test that is routinely performed for measurement of bone mass, and involves a very small exposure to X-rays.

OGTT/fat tolerance test/clamp measurement of insulin sensitivity. 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. There is a small risk of temporary hypoglycemia (low blood sugar). Although insulin is known to cause a drop in blood sugar if given alone, you will receive insulin along with glucose (sugar), and we will measure your blood sugar repeatedly and feed you or give you glucose if your blood glucose falls.

Study drug (rifaximin SSD). In large studies, people taking rifaximin have reported very few side effects: some subjects have reported mild gastrointestinal disturbances, and in some circumstances there has been mild fluid retention. Other antibiotics can sometimes cause a severe diarrhea called “C. Diff” (*clostridium difficile*), which can even be life threatening. Although this complication has been reported with rifaximin, it has been very rare. You will be receiving rifaximin SSD. Rifaximin SSD is more soluble, which permits the use of a lower

dose. In testing thus far, the side effect profile of rifaximin SSD are not different from that of rifaximin.

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.

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
Radiation from DEXA, CT scan	Common	Minimal	It will be part of your overall environmental exposure
Possible infection from IV	Uncommon	Not serious	Yes, with anti-inflammatory medications and/or antibiotics
Hypoglycemia during insulin test	Uncommon (less than 1:100)	Mild	Temporary; resolved with eating
C. Diff from rifaximin	Very rare. Less than 1:1000	Potentially severe	Stopping drug, other medications

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 University of Kentucky.*

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 and 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. Officials of the Food and Drug Administration, the National Institutes of Health, and the University of Kentucky, 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. If you choose to withdraw from the study early, the data collected until that point will remain in the study database and may not be removed.

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 and glucose tolerance test); $200 after the first set of procedures (insulin sensitivity testing, fat tolerance, and the fat biopsy); $400 after taking the study medication for 8 weeks and completing the final study procedures. Thus, the total compensation for completing the study will be $620 for participants who complete all study procedures and the follow-up procedures. 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 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

Dr. Philip Kern would like to keep some of the blood and fat samples collected during the main study participation but which is not used for other tests for that study. No additional blood or tissue will be taken. If you agree, the blood and fat samples may be used in future research.

Researchers may also need health information about the people who provide specimens. We are also asking for your consent to place information from your medical record and/or research record in a database to be used for research. Your name and other information that could identify you will not be placed in the database. There are no additional risks to you from this banking of specimens.

Please read each sentence below and think about your choice. After reading each sentence, 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, or banking, and future use of your blood and fat samples, you may still take part in the main study. If you answer yes to either choice below you also give your authorization for your accompanying health information to be used and disclosed along with the blood and fat samples.

1. Do you give permission for your blood and fat samples to be kept by *Dr. Philip Kern* 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, 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, for example bowel disorders?

   ☐ 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 *Dr. Philip Kern* regarding your willingness to participate in future research studies about how to prevent, detect, or treat insulin resistance?

☐ Yes ☐ No _____Initials

If you later decide to withdraw your permission for the banking of leftover samples, please contact Dr. Philip Kern, MD; 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 and the maker of rifaximin SSD, Salix pharmaceuticals Inc., a division of Valeant Pharmaceuticals North American, LCC is providing drug and matching placebo.

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 study 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 website 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 (eg. name, address, phone number), medical history, results of routine blood tests, glucose tolerance tests, and the results of research procedures (eg. Results of biopsies)

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 (eg. Lab results, payment of compensation).
- 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.
- Salix Pharmaceuticals Inc., a division of Valeant Pharmaceuticals North America, LLC or their agents, who supplies the drug used for this study

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: *Dr. Philip Kern, MD; 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 or *research subject's legal representative — Date

_____ _____

Printed name of research subject or *research subject's legal representative — Representative's relationship to research subject

*(*If, applicable)* Please explain Representative's relationship to subject and include a description of Representative's authority to act on behalf of subject:

_____

_____

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

_____

Signature of Principal Investigator or Sub/Co-Investigator