Official Title: Effects of Metformin on Low Back Pain

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University of Pittsburgh

School of Medicine / Department of Physical Medicine & Rehabilitation

Metformin and Beyond: Individualizing Care for Low Back Pain

This summary provides basic information to help you decide whether to consent or not to participate in this study. More detailed information is provided in the following pages of this document. If you have any questions, please be sure to ask the research team.

The purpose of this *voluntary* research is to determine if Metformin improves low back pain and to examine what characteristics are associated with response to the study product.

Study Procedures will take place during study visits. You may have up to 6 study visits. The procedures include:

- Taking Metformin or placebo for 6 months
- Providing blood, stool, & saliva samples
- Completing questionnaires and an interview
- Completing a 10-meter walking speed test

How long is my participation? You may be enrolled in the study for up to 15 months.

The risks of this study include the possibility of:

1. Potential breach of confidentiality
2. Side effects from Metformin including gastrointestinal side effects.

For more details about risks, please see page 8 of the consent document.

Benefit: Should Metformin have a positive effect on back pain, it is possible that you may receive some benefit from the study product, however, such a benefit cannot be guaranteed.

Compensation: You may receive up to $250 for participating in this study

For more information continue reading this document or contact the research team. Contact information is provided on the following page.

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CONSENT TO ACT AS A PARTICIPANT IN A RESEARCH STUDY

TITLE: **Metformin and Beyond: Individualizing Care for Low Back Pain**

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SOURCE OF SUPPORT: UPMC Immune Transplant and Therapy Center

You may be eligible to take part in a research study. This form gives you important information about the study. It describes the purpose of the study, and the risks and possible benefits of participating in the study.

Please take time to review this information carefully. After you have finished, you should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others (for example, your friends, family, or other doctors) about your participation in this study. If you decide to take part in the study, you will be asked to sign this form. Before you sign this form, be sure you understand what the study is about, including the risks and possible benefits to you.

Your physician may be involved as an investigator in this research study. Before agreeing to participate, or at any time during your study participation, you may discuss your care with

another doctor who is not associated with this research study. You are not under any obligation to participate in any research study offered by your physician.

Description:
Low back pain is one of the most common musculoskeletal conditions requiring medical care and contributing to patient impairment and disability, with over 25% of the general population reporting low back pain at any given time and a lifetime incidence exceeding 80%. However, the care of low back pain represents one of the greatest challenges facing musculoskeletal care today. With increasing interest in the beneficial effects of metformin, the favorable side effect profile and low cost make metformin an attractive therapeutic candidate for the treatment of low back pain.

You are being asked to participate in a research study in which we will investigate if Metformin improves low back pain. Currently, Metformin is not approved by the FDA for treatment of low back pain. However, Metformin is an FDA approved medication for type 2 diabetes mellitus. For this double blind, wait-list controlled and placebo-controlled study, we will compare results from individuals who are randomized to take metformin for 6 months to those who take a placebo. We will also compare those results to individuals who wait 3 months to be randomized (wait-list control group). The purpose of the placebo is to see if there is a difference between metformin and placebo. To account for the placebo effect, we have introduced the wait list control group. You will not be eligible if you refuse randomization to the wait list control group.

Who can take part in this study?
Patients who have been diagnosed with low back pain are being invited to participate in this study. Individuals invited to participate in this study must be over the age of 18 and if female, cannot be pregnant.

How many people (subjects) are expected to take part in this study?
Approximately 400 people are expected to participate in this trial.

What procedures will be performed for research purposes?
If you decide to take part in this research study, you will undergo the following procedures. The following 'screening procedures' will determine if you are eligible to take part in this research study.

Visit 1 – Screening and Baseline Procedures (Day 0)

- After you sign the informed consent, you will undergo the screening process. You will meet with a clinical research coordinator who will ask about your demographics, medical history and medications that you are taking. You will also be asked questions about your current living situation and functional status. Some additional questions may be asked about alcohol, drug, and tobacco use.
- Blood will be drawn (approximately 55.5ml or 3.7 tablespoons) from a vein in your arm.

If you are a woman capable of bearing a child, an extra 5ml of blood will also be collected to test for pregnancy. This is done prior to starting the study product to avoid risk to a fetus. A portion of the blood collected will be sent to a UPMC laboratory to make sure that it's safe for you to enter the study. If these lab values clinically significant, we will inform you and will recommend following-up with your primary care doctor. The remaining blood will be used as part of this research study will be examined for research purposes.

- If you have taken NSAIDS (nonsteroidal anti-inflammatory drugs such as Aspirin or Ibuprofen, or Naproxen) within 7 days of screening visit, some blood samples will be collected after you have been off of NSAIDS for at least 7 days. This could result in an extra visit and an additional 6.5 ml of blood being collected.
- You will be asked to provide a saliva sample for genetic analysis and a second saliva sample for microbiome analysis (looking at the organisms in your mouth). You will also be asked to provide a stool sample for microbiome analysis (looking at the organisms in your gut). If saliva is not collected for genetic analysis during the baseline visit, it may be collected at a follow-up visit.
- You will be asked to complete a series of questionnaires that look at things such as pain, disability, anxiety, and general health. You will also be asked to complete a 10-meter walking speed test.
- To confirm eligibility, it is possible that a study physician will need to complete a brief exam. If you meet all the inclusion and exclusion criteria, you will be assigned randomly (by chance) to one of the following groups:

Metformin/Placebo Group	3 Month Wait List Group
You will be instructed to take either a placebo or metformin as prescribed. The study product will be one of the following: -Metformin (1,500mg) -Metformin (500mg) -Placebo: at either a high dose (3 tabs) or low dose (1 tab)	You will not be prescribed a study product until your month 3 visit. At your month 3 visit, you will be randomized to receive one of the following: -Metformin (1,500mg) -Metformin (500mg) -Placebo: at either a high dose (3 tabs) or low dose (1 tab)
75% chance of being randomized to this group at the baseline visit. The ratio of subjects randomized to metformin and placebo is 2:1.	25% chance of being randomized to this group at the baseline visit.
Complete the following follow-up visits: • Month 3 • Month 6 • Month 12	Complete the following follow-up visits: • Month 3 • Month 6 • Month 9 • Month 15

- Subjects have a 1:1:1 ratio or 33.3% chance of being randomized into each study group.
- The placebo looks just like Metformin but contains no active medication. Neither you, nor the physicians taking care of you, or the research investigators, will know which study product you are receiving.

    - You will be instructed to take the tablets as described above for a total of 6 months.
    - Study product will be provided to you in pre-packaged blister packs containing one of the following:
        - High Dose Metformin Group: 3 metformin tabs
        - Low Dose Metformin Group: 1 metformin tab
        - High Dose Placebo Group: 3 placebo tabs
        - Low Dose Placebo Group: 1 placebo tab
        - Note: For the high dose groups, you will take 2 tabs per day for the first week and then increase to 3 tabs per day for the remainder of the 6 months.
- Depending on the availability of the results from the blood tests, you may not be randomized during this visit.
- The study product will be given to you free of charge during your participation.
- This visit is approximately 2 hours in length. It will take place at a UPMC Facility.
- If it is determined that you do not meet the eligibility criteria, biosamples collected during this visit will be retained for analysis.

Follow-Up Visits for Metformin and Placebo Groups Only

Study Product Distribution

- As soon as your eligibility is confirmed, your study product will be mailed to your house. You will be instructed to take the study product as prescribed.
- If you had taken NSAIDS within 7 days of the screening visit, you will be asked to come back into the study center to collect blood samples that could not be collected during your screening visit.

Month 3 visit – Follow-Up Visit1 1 for Metformin and Placebo Groups

- You will meet with a clinical research coordinator who will ask about your health, any medication changes, and if you've experienced any side effects.
- Blood will be drawn (approximately 3.7 tablespoons) from a vein in your arm. A portion of the blood collected will be sent to a UPMC laboratory to collect labs examining your response to the study product. The remaining blood will be used as part of this research study and will be examined for research purposes.
- Stool sample for microbiome analysis.
- Saliva sample for microbiome analysis
- Series of questionnaires that look at things such as pain, disability, anxiety, general health, and medication compliance.
- You will be asked to complete a 10-meter walking speed test.
- This visit is approximately 2 hours in length.

Month 6 visit – Follow-Up Visit 2 for Metformin and Placebo Groups

- Study product will be discontinued at this time. You will be asked to return any unused study product.
- You will meet with a clinical research coordinator who will ask about your health, any medication changes, and if you've experienced any side effects.

- Blood will be drawn (approximately 3.7 tablespoons) from a vein in your arm. A portion of the blood collected will be sent to a UPMC laboratory to collect labs examining your response to the study product. The remaining blood will be used as part of this research study and will be examined for research purposes.
- Stool sample for microbiome analysis.
- Saliva sample for microbiome analysis
- Series of questionnaires that look at things such as pain, disability, anxiety, general health, and medication compliance.
- You will be asked to complete a 10-meter walking speed test.
- This visit is approximately 2 hours in length.

Month 12 visit – Follow-Up Visit 3 for Metformin and Placebo Groups

- You will meet with a clinical research coordinator who will ask about your health, any medication changes, and if you've experienced any side effects.
- Blood will be drawn (approximately 2.7 tablespoons) from a vein in your arm. The blood will be used as part of this research study and will be examined for research purposes.
- Stool sample for microbiome analysis.
- Saliva sample for microbiome analysis
- Series of questionnaires that look at things such as pain, disability, anxiety, and general health.
- You will be asked to complete a 10-meter walking speed test.
- This visit is approximately 2 hours in length.

Follow-Up Visits for 3 Month Wait List Group Only

If you had taken NSAIDS within 7 days of the screening visit, it is possible that you will have to come in for an additional visit to collect some of the blood samples once you've been off NSAIDS for at least 7 days.

Month 3 visit – Follow-Up Visit 1 for Control Group

- You will meet with a clinical research coordinator who will ask about your health, any medication changes.
- Blood will be drawn (approximately 3.7 tablespoons) from a vein in your arm. A portion of the blood collected will be sent to a UPMC laboratory to collect labs confirming it is safe for you to take the study product. If you are a woman capable of bearing a child, an extra 5ml of blood may also be collected for a pregnancy test. The remaining blood will be used as part of this research study and will be examined for research purposes.
- Stool sample for microbiome analysis.
- Saliva sample for microbiome analysis.
- Series of questionnaires that look at things such as pain, disability, anxiety, and general health.
- You will be asked to complete a 10-meter walking speed test.
- Once your eligibility has been confirmed, you will be randomized to receive either Metformin or Placebo. Neither you, the investigators, or the study staff will know what you are taking. You will be instructed to take the study product as prescribed.
- This visit is approximately 2 hours in length.

Study Product Distribution

- As soon as your eligibility is confirmed, your study product will be mailed to your house. You will be instructed to take the study product as prescribed.

Month 6 visit – Follow-Up Visit 2 for Control Group

- You will meet with a clinical research coordinator who will ask about your health, any medication changes, and if you've experienced any side effects.
- Blood will be drawn (approximately 3.7 tablespoons) from a vein in your arm. A portion of the blood collected will be sent to a UPMC laboratory to collect labs examining your response to the study product. The remaining blood will be used as part of this research study and will be examined for research purposes.
- Stool sample for microbiome analysis.
- Saliva sample for microbiome analysis
- Series of questionnaires that look at things such as pain, disability, anxiety, general health, and medication compliance.
- You will be asked to complete a 10-meter walking speed test.
- This visit is approximately 2 hours in length.

Month 9 visit – Follow-Up Visit 3 for Control Group

- Study product will be discontinued at this time. You will be asked to return any unused study product.
- You will meet with a clinical research coordinator who will ask about your health, any medication changes, and if you've experienced any side effects.
- Blood will be drawn (approximately 3.7 tablespoons) from a vein in your arm. A portion of the blood collected will be sent to a UPMC laboratory to collect labs examining your response to the study product. The remaining blood will be used as part of this research study and will be examined for research purposes.
- Stool sample for microbiome analysis.
- Saliva sample for microbiome analysis
- Series of questionnaires that look at things such as pain, disability, anxiety, general health, and medication compliance.
- You will be asked to complete a 10-meter walking speed test.
- This visit is approximately 2 hours in length.

Month 15 visit – Follow-Up Visit 4 for Control Group

- You will meet with a clinical research coordinator who will ask about your health, any medication changes, and if you've experienced any side effects.
- Blood will be drawn (approximately 2.7 tablespoons) from a vein in your arm. The blood will be used as part of this research study and will be examined for research purposes.
- Stool sample for microbiome analysis.
- Saliva sample for microbiome analysis
- Series of questionnaires that look at things such as pain, disability, anxiety, and general health.
- You will be asked to complete a 10-meter walking speed test.
- This visit is approximately 2 hours in length.

It is possible that some study activities may be conducted remotely. For example, you may complete some of the questionnaires via the internet on your personal device or a device of your choosing.

Blood Collection: The blood collected during this study for research purposes will be used as part of this research study and will be examined for serum biomarkers (molecules found in biological fluids) and may be used by the investigators to help them to have a better understanding of a relationship between low back pain and metformin. Genetic analysis, including whole genome sequencing, will also be conducted to analyze genes associated with low back pain. The remainder of these samples will be stored indefinitely within the jurisdiction of UPMC and the University of Pittsburgh under the direction of the Principal Investigator of this research, Dr. Gwendolyn Sowa. These samples may be used in future research related to back pain. It is possible that these samples may be shared with other investigators at some point in the future, but samples would be shared without your identifiable information. The results of any analysis of these samples will not be given to you as they are being drawn for research purposes only and will have no impact on your clinical care.

Blood collected and sent to the UPMC Clinical Laboratory will be reported back to you if medically necessary. These values may also be put into your medical records. This includes results of pregnancy tests.

Saliva Collection: A saliva sample will be collected for genetic analysis of genes related to pain (collected once) and an additional saliva sample will be completed for microbiome analysis (collected at each visit). The microbiome is the bacterial make-up of your mouth. You will be provided with saliva collection kits. You will be asked to spit into the clear plastic tube until the saliva sample reaches the "fill line." This should take no more than 10 minutes for each kit.

Stool Collection: A stool sample will be collected for microbiome analysis. The microbiome is the bacterial make-up of your stool. You will be instructed on how to collect a stool specimen at home. You will receive instructions and a container, which is placed on your toilet, so that you can collect the stool and place a small amount of stool in a special tube. You will be given a pre-paid envelope and supplies to collect and mail the sample back to our center.

Information regarding your health may be collected from your medical records. Information collected from your medical records may be matched to your biosamples. Information collected as part of this study may also be compared to results from other studies conducted by the investigators.

Restricted Medications

The following medications are restricted during your participation in this study:

- Oral or injected steroids
- Nonsteroidal anti-inflammatory drugs (NSAIDS) such as aspirin, ibuprofen, naproxen
- Diabetic medications such as sitagliptin, saxagliptin, linagliptin, alogliptin, sitagliptin with metformin
- Carbonic anhydrase inhibitor such as topiramate, zonisamide, acetazolamide, dichlorphenamide, methazolamide
- Cimetidine

Follow-Up Phone Calls
A member of the study team will call you on the phone **after you start taking the study product.** You will receive a phone call week 1, week 2, and week 4 after you start the study product. You will be asked if you are experiencing any side effects and how you are feeling.

Study Risks
Metformin – It is possible that you may be randomized to receive metformin. Common side effects include diarrhea, nausea/vomiting, flatulence, asthenia (lack of energy), indigestion, abdominal discomfort, anorexia, headache, or metallic taste in your mouth. Serious reactions include lactic acidosis (buildup of lactate in the body), anemia, megaloblastic anemia (abnormal red blood cells), and hepatotoxicity (damage to the liver). These risks will be evaluated by blood tests.

As is possible with any drug, you may have an unexpected allergic reaction, including severe immediate reactions. Early symptoms of allergic reaction are often related to the skin, with flushing (warmth and redness of the skin), itching (often in the groin or armpits), and hives as common initial findings. These symptoms are often accompanied by anxiety, and sometimes a rapid irregular pulse. If the throat and tongue swell, this will result in hoarseness, difficulty swallowing, and difficulty breathing. Symptoms of rhinitis or asthma may occur causing a runny nose, sneezing, and wheezing, which may worsen the breathing difficulty. Vomiting, diarrhea, and stomach cramps may develop. About 25% of the time, subjects with an allergic reaction may experience a drop in blood pressure, lightheadedness, or even loss of consciousness. If you experience symptoms of an allergic reaction while participating in the study, go to the emergency room or seek other immediate medical attention and contact study team when safe to do so.

There is a risk of hypoglycemia (low blood sugar). Symptoms of hypoglycemia may include shakiness, dizziness, sweating, hunger, irritability, nervousness, and headache. If you report symptoms of hypoglycemia, extra safety labs may be obtained. Safety labs are collected at every visit while you are taking the study product. If you develop diabetes while on the study product, you will be referred to your Primary Care Physician (PCP) to manage the diabetes. If you develop diabetes during the course of the study, you may not be removed from the study unless your treating physician requests discontinuation of the study product based on their treatment plan.

While taking Metformin, radiologic studies with dye can increase the risk of lactic acidosis. Symptoms of lactic acidosis may be nonspecific (eg, abdominal pain, malaise, muscle ache, respiratory distress, somnolence); severe cases may also present with hypothermia, hypotension and resistant bradyarrhythmias (disturbance in the heart rhythm in which the heart rate is abnormally slowed.) If you are to undergo a procedure involving the administration of contrast dye, the study drug should be discontinued for 48 hours.

You should avoid excessive alcohol while taking the study product.

Blood Draw - Likely risks of drawing blood from your arm may cause pain and/or bruising. On rare occasions infection or lightheadedness can occur.

Saliva Sample – There are no anticipated risks associated with collection of the saliva sample.

Stool Sample – There are no anticipated risks associated with collection of the stool sample.

Questionnaires - It is possible that you may become frustrated or experience anxiety during the screening interview and/or completion of questionnaires. To minimize the discomfort associated with the screening tests/interview, we will be using standard questionnaires that are widely used in clinical practice. We are having trained staff members conduct our sessions, and breaks will be allowed as necessary.

Risks of Genetic Testing - The purpose of genetic testing for this study is to find unknown genes, learn how genes work, and advance our understanding of the relationship between genetics and low back pain. The goal is not to determine a person's susceptibility to any inherited disorder. Therefore, genetic test results will not be given to your doctor and will not be placed in your medical records. You will not receive your own test results because right now, no one knows whether the results provide useful information about your health or treatment. In this study, all genetic samples are stored without personal identification information and all specimens are labeled with a unique non-identifying number. However, it is possible that if the results of your genetic testing were to become known, that could affect your future plans for children, family relationships, or ability to be insured or employed.

The risks associated with gene studies include the potential for a breach of confidentiality which could affect future insurability, employability, or reproduction plans, or have a negative impact on family relationships and/or result in paternity suits or stigmatization.

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

Your research data/samples may be shared with investigators conducting other research; this information will be shared without identifiable information. These research data/samples may contribute to a new discovery or treatment. In some instances, these discoveries or treatments may be of commercial value and may be sold, patented, or licensed by the investigators and the University of Pittsburgh for use in other research or the development of new products. You will not retain any property rights, nor will you share in any money that the investigators, the University of Pittsburgh, or their agents may realize.

The data, samples, and genetic data generated from samples may be shared with other researchers and with federal repositories, in a de-identified manner (without identifiers). The data, samples, and genetic data obtained from this study may also be combined with other databases in which the PI of this study is listed as an investigator or PI.

Risk related to placebo - Risks of placebo include allergy to component that makes up the placebo.

Risk related to pregnancy- Metformin is considered a pregnancy category B medication. However, there is no current data regarding metformin and pregnancy, so the risks are unknown. To avoid risk to the fetus, it is important that you (for female participants), or your female sexual partner (for male participants), not become pregnant while you are participating in this research study. Please use an effective preventative measure (for example, birth control pills, condoms, other barrier methods, etc) while taking the study product. However, please be advised that avoiding sexual activity while taking the study product is the only certain method to prevent pregnancy. If you or your partner become pregnant while being enrolled in this study, please let the study staff know immediately.

Breach of confidentiality is a possible risk of data collection and collection of biosamples. The information gathered will be stored on secure online servers and in locked filing cabinets/offices in order to prevent breach of confidentiality. Biosamples will be stored without identifiers and with subject ID only. Every precaution will be taken to maintain confidentiality, but total confidentiality cannot be guaranteed.

As with any experimental procedure, there may be adverse events or side effects that are currently unknown and certain of these unknown risks could be permanent, severe or life-threatening.

Risk of data collection via the internet - Although every reasonable effort has been taken, confidentiality during Internet communication activities cannot be guaranteed and it is possible that additional information beyond that collected for research purposes may be captured and used by others not associated with this study.

Possible Benefits
Should Metformin have a positive effect on back pain, it is possible that you may receive some benefit from the study product, however, such a benefit cannot be guaranteed. Individuals assigned to the placebo group are expected to receive no direct benefit from study participation. However, due to the placebo effect, it is possible that subject's randomized to receive placebo may also see some improvement. Your participation in this study may help us to improve our care of those who experience low back pain in the future. Such improvements in care would benefit the individual and society at large.

New Information
You will be promptly notified if any new information we learn during this research study may cause you to change your mind about continuing to participate in the study.

Privacy & Confidentiality
Any information about you obtained from this research will be kept as confidential (private) as possible. All paper records related to your involvement in this research study will be stored in a locked file cabinet in a locked office of the department of Physical Medicine and Rehabilitation. Your identity will be included in these research records. Your biosamples will be stored with a

subject ID number. The linkage code linking the ID to your name will be kept in a separate, locked database on a restricted network drive. The results from the "safety lab" analysis and pregnancy test results (if applicable) will be placed in your medical record. You will not be identified by name in any publication of the research results unless you sign a separate consent form giving your permission (release).

The investigators may continue to use and disclose your information for an indefinite period of time. Samples collected for research purposes will be stored indefinitely.

It is possible that we may use the information obtained from this study (including your biological specimens) in other research studies examining outcomes after back pain. This research information, including genetic information and biological specimens, may also be shared with other researchers here and at other research centers, but those researchers will never be provided with any personal identifiers that would allow them to learn your identity. Information collected as part of this study may also be compared to results from other studies conducted by the investigators.

Who will have access to identifiable information related to my participation in this research study?

In addition to the investigators listed on the first page of this authorization (consent) form and their research staff, the following individuals will or may have access to identifiable information (which may include your identifiable medical information) related to your participation in this research study:

Authorized representatives of the University of Pittsburgh Office of Research Protections may review your identifiable research information (which may include your identifiable medical information) for the purpose of monitoring the appropriate conduct of this research study.

Authorized representative of the University of Pittsburgh Clinical and Translational Science Institute may review your identifiable research information (which may include your identifiable medical information) for the purpose of performing data analysis.

In unusual cases, the investigators may be required to release identifiable information (which may include your identifiable medical information) related to your participation in this research study in response to an order from a court of law. If the investigators learn that you or someone with whom you are involved is in serious danger or potential harm, they will need to inform, as required by Pennsylvania law, the appropriate agencies.

Authorized representatives of the sponsor of this research study, UPMC Office of the Medical and Scientific Officer, may review and/or obtain identifiable information (which may include your identifiable medical information) related to your participation in this research study for the purpose of monitoring the accuracy and completeness of the research data and for performing required scientific analyses of the research data. Authorized representatives of the study sponsor may also be present during your participation in this research study. The investigators involved in the conduct of this research study may receive funding from the sponsor to perform the research procedures and to provide the sponsor with identifiable research and medical information related to your participation in the study.

Authorized representatives of UPMC hospitals or other affiliated health care providers may have access to identifiable information (which may include your identifiable medical information) related to your participation in this research study for the purpose of (1) fulfilling orders, made by the investigators, for hospital and health care services (e.g., laboratory tests, diagnostic procedures) associated with research study participation; (2) addressing correct payment for tests and procedures ordered by the investigators; and/or (3) for internal hospital operations (i.e. quality assurance).

Authorized representative of US and foreign government regulatory agencies such as the U.S. Food and Drug Administration (FDA) may review and/or obtain your identifiable information (which may include your identifiable medical record information) related to your participation in this research study for the purpose of monitoring the accuracy of the research data. While these agencies understand the importance of maintaining the confidentiality of your identifiable research and medical record information, UPMC and the University of Pittsburgh cannot guarantee the confidentiality of this information after it has been obtained by them.

Per University of Pittsburgh policy all research records must be maintained for at least 7 years following final reporting or publication of a project.

Will this research study involve the use or disclosure of my identifiable medical information?
This research study may involve the recording of past and/or current identifiable medical information from your hospital and/or other (e.g., physician office) records. The information that will be recorded will be limited to information concerning your eligibility to participate in this research study as well as collection of information necessary to address the study goals.

May I have access to my medical information that results from my participation in this research study?
In accordance with UPMC Notices of Privacy Practices document that you have been provided, you are permitted access to information; however, your access to the study specific information will not be available for review until the end of the study. At that time, you have the right to see and copy the medical information collected during the study for as long as that information is contained within your medical records and/or filed with your health care provider.

FDA Clinical Trial Registry
A description of this clinical trial is available on http://www.clinicaltrials.gov, as required by US 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.

Withdrawal from Study Participation
You can, at any time withdraw from this research study; you can also withdraw your authorization for us to use your identifiable medical information for the purposes described above. This means that you will also be withdrawn from further participation in this research study. Any identifiable research or medical information obtained as part of this study prior to the date that you withdrew your consent will continue to be used and disclosed by the investigators for the purposes described above.

To formally withdraw from this research study, you should provide a written and dated notice of this decision to the principal investigator of this research study at the address listed on the first page of this form. Your decision to withdraw your consent for participation in this research study will have no effect on your current or future medical care at a UPMC hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

If you decide to withdraw from study participation after you have received the study drug, you should participate in additional monitoring follow-up procedures that are being conducted to measure the safety of the study drug.

All biosamples collected will be retained unless requested in writing that they be destroyed.

Could I be removed from the study?
It is possible that you may be removed from the research study by the researchers if, for example, the investigator feels that it isn't in your best interest to continue, for safety reasons, or if you are no longer eligible to participate. We may request follow-up for safety reasons.

Will I be paid if I take part in this research study?
Yes, you will be compensated a total of $50 ($40 for completing the visit and $10 after stool sample is received) for completing the questionnaires, assessments, and sample collection during each visit.

Individuals randomized to the placebo/metformin groups may receive up to $200 for completion of all study visits. Individuals randomized to the 3 month wait list group may receive up to $250 for completion of all study visits. If needed, parking will be validated. You will be paid on a reloadable debit card. Your name, address, and social security number will be released to the Accounting Office. All compensation is taxable income to the participant. If you receive $600 or more in a calendar year from one organization, that organization is required by law to file a Form 1099 – Miscellaneous with the IRS and provide a copy to the taxpayer. Individuals who do not provide a social security number may still participate in the research, but the IRS requires that 24% of the payment be sent by the institution to the IRS for 'backup withholding;' thus you would only receive 76% of the expected payment.

Your biological samples may lead, in the future, to new inventions or products. If the investigators are able to develop new products from the research use of your biological sample, there are currently no plans to share with you any money or other rewards that may result from the development of these new products.

Is there a cost to participate in this study?
No, there is no cost to participate in this study. All tests and procedures outlined in this consent form will be paid for by the study. All study medications, tests and procedures are covered by the research study. However, your insurance will be billed for your normal, standard clinical care.

Who will pay if I am injured as a result of taking part in this study?
If you believe that the research procedures have resulted in an injury to you, immediately contact the Principal Investigator who is listed on the first page of this form. Emergency medical

treatment for injuries solely and directly related to your participation in this research study will be provided to you by the hospitals of UPMC. Your insurance provider may be billed for the costs of this emergency treatment, but none of those costs will be charged directly to you. If your research-related injury requires medical care beyond this emergency treatment, you will be responsible for the costs of this follow-up care. At this time, there is no plan for any additional financial compensation. You do not, however, waive any legal rights by signing this form.

CONFIDENTIALITY AND AUTHORIZATION TO RELEASE YOUR PROTECTED HEALTH INFORMAITON:

We are also requesting your authorization or permission to review your medical records to determine whether you meet the conditions for participation in this study, to compare your earlier test results to the findings from this study, and if possible, to use your previous exam results in place of, or in addition to, some of the exams needed for this study. We will obtain the following information: your diagnosis, age, past medical history, diagnostic procedures such as x-rays and MRIs, and results of any blood tests, including results of genetic tests, current medications, information related to your back pain and diagnosis.

As part of this research study, some information that we obtain from you will be placed into your medical records held at UPMC, including the results of safety lab values and other medical tests.

This identifiable medical record information will be made available to members of the research team for an indefinite period of time.

Your medical information, as well as information obtained during this research study, may be shared with other groups, possibly including authorized officials from the Food and Drug Administration, , and the University of Pittsburgh Office of Research Protections, for the purpose of monitoring this study. Authorized representatives of UPMC or affiliated health care providers may also have access to this information to provide service and addressing billing and operational issues.

We will protect your privacy and the confidentiality of your records, as described in this document, but cannot guarantee the confidentiality of your research records, including information obtained from your medical records, once your personal information is disclosed to others outside UPMC or the University.

This authorization is valid for an indefinite period of time. However, you can always withdraw your authorization to allow the research team to review your medical records by contacting the investigator listed on the first page and making the request in writing. If you do so, you will no longer be permitted to participate in this study. Any information obtained from you up to that point will continue to be used by the research team.

By signing this form, I consent to participate in this research study and provide my authorization to share my medical records

VOLUNTARY PARTICIPATION:

Your participation in this research study is entirely voluntary. You may want to discuss this study with your family and friends and your personal physician before agreeing to participate. If there are any words you do not understand, feel free to ask us. The investigators will be available to answer your current and future questions.

Whether or not you provide your consent for participation in this research study will have no effect on your current or future medical care at a UPMC hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

VOLUNTARY CONSENT:

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

I understand that I may always request that my questions, concerns or complaints be addressed by a listed investigator. I understand that I may contact the Human Subjects Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668) to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations that occurred during my participation.

By signing this form I consent to participate in this research study and provide my authorization to share my medical records with the research team. A copy of this consent form will be given to me.

Participant's Signature	Printed Name of Participant	Date

CERTIFICATION of INFORMED CONSENT

I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions as they arise. I further certify that no research component of this protocol was begun until after this consent form was signed.

Printed Name of Person Obtaining Consent	Role in Research Study

Signature of Person Obtaining Consent	Date