**Consent Form to Participate in a Research Study**
**University of Oklahoma Health Sciences Center (OUHSC)**
**Oklahoma Medical Research Foundation (OMRF)**
**University of Wisconsin-Madison**

**Study Title:** Does insulin sensitivity impact the potential of metformin to slow aging?

**Sponsor:** National Institutes of Health (NIH)

**Principal Investigator:** Benjamin F. Miller, PhD at OUHSC
**Phone Number:** (405) 271-7767

## *KEY INFORMATION ABOUT THE RESEARCH STUDY*

You are being asked to participate in a research study. Research studies are voluntary and include only people who choose to take part. This consent form begins with a 'Key Information' section to provide important information to help you decide whether or not to participate in this study. More detailed information is provided after the key information. Please take your time, discuss this with family and friends, and ask the investigator and study team any questions you may have.

### WHY HAVE I BEEN ASKED TO PARTICIPATE IN THIS STUDY?

You are being asked to participate in this research study because you are an adult age 40-75, free of chronic disease and not currently treated with glucose-lowering drugs.

### WHY IS THIS STUDY BEING DONE AND HOW LONG WILL IT LAST?

The purpose of this study is to investigate the effects that the anti-diabetic medication metformin has on the aging process in individuals who are free of chronic disease, and whether that effect is influenced by your body's sensitivity to insulin. Your participation in the study will take approximately 16 weeks total.

### WHAT WILL I BE ASKED TO DO IN THIS STUDY?

If you decide to participate in this study, the following will be completed as a part of your participation in the study:

- Participate in an initial screening procedure that includes detailed review of the informed consent, and we will ask you questions about your medical history and physical activity. This may occur in person or virtually through Zoom or Microsoft Teams
- Have an ECG to screen for heart disease, a pulmonary test for lung function, and a blood draw to screen markers of health and disease. The blood sample will be15 mL, which is approximately 3 teaspoons of blood.
- Have body weight and composition measured via a dual x-ray absorptiometry (DEXA) scan.
- Perform a hyperinsulinemic-euglycemic clamp where both insulin and glucose are administered intravenously to test your sensitivity to insulin at the beginning and end of study for a total of two tests. During this procedure we will perform a series of blood draws through a plastic tube that add up to approximately 108 ml of blood, which is about 7 tablespoons,
- Consume a standardized meal on the evening before the insulin clamp. You will be asked to come in for the insulin clamp after fasting for 8-12 hours, only consuming water.
- Undergo muscle biopsies for a total of two muscle samples for the entire study.
- Consume a special water that is indistinguishable from normal water, daily during the last 4 weeks of the study.
- Take placebo or metformin twice a day for 12 weeks. A placebo is a pill that looks the same as the metformin but does not have the active medication.

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- A continuous glucose monitor will be placed for 7-10 days
- Complete a 7 day physical activity recall at the beginning and end of the study
- A urine pregnancy test will be administered prior to each DEXA Scan for women of childbearing potential
- Additional blood sampling at visits 3, 7, and 15, each equivalent to approximately 4 teaspoons of blood. You will be asked to not make any changes to your lifestyle through the course of the study
- You will be asked to fast for 24 hours from alcohol and exercise prior to the insulin clamp visits. Through the course of the study, you will have a limit of less than 3 alcoholic drinks per day.
- After the 12-week intervention, repeat the DEXA scan
- Through the course of the study, you are asked not to make any changes to your current lifestyle or physical activity level. It is also important to notify the study team of any changes to your health, current medications, or supplements.

**WHY MIGHT I WANT TO PARTICIPATE IN THIS STUDY?**

If you agree to take part in this study, there is no direct medical benefit to you. These studies will expand scientific understanding of the potential for metformin to slow some aspects of the aging process.

**WHY MIGHT I NOT WANT TO PARTICIPATE IN THIS STUDY?**

- You should not participate if you have had or are planning to have imaging that requires intravenous contrast dye (within 6 weeks) or are on any of the following medications since they are contraindicated with the use of Metformin: Dofetilide, Lamotrigine, Pegvisomant, Somatropin, Trimethoprim, Trospium, Gatifloxacin, Cephalexin, Cimetidine, Dalfampridine.
- Because tobacco is known to affect the factors being investigated, you cannot participate if you use tobacco. There is also a limit of less than 3 alcoholic drinks per day.
- There is a risk of allergic reaction. If you know you are allergic to lidocaine or Metformin you should not participate because these items will be administered during this study.
- The most serious side effect of the metformin is lactic acidosis, which occurs in less than 1% of those who take metformin.
- There is a risk that either the metformin or the insulin could cause low blood sugar. The symptoms of low blood sugar include dizziness, shakiness, sweatiness, weakness, and confusion.
- There is a risk of bruising, bleeding, or infection from the muscle biopsy.

**WHAT OTHER OPTIONS ARE THERE?**

You may choose not to participate in this study.

**HOW WILL PARTICIPATING IN THE STUDY AFFECT ME FINANCIALLY?**

There is no additional cost to you if you participate in this study. You will be compensated up to a total of $500 for your time and travel for participating in this study.

Compensation per visit is as follows:

- Visit 2 $30
- Visit 3 $160
- Visit 4, 5, 7, 9, 11, and 13 $20 per visit
- Visit 14 $30
- Visit 15 $160



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You will be asked to provide your social security number, your residency status (a copy of your green card must be provided if applicable), and whether you are a University of Oklahoma employee for tax reporting purposes. If you are unwilling or unable to provide your social security number, residency status (and green card if applicable), or University of Oklahoma employment status, you will not be eligible to participate in this research study.

## *DETAILED INFORMATION ABOUT THE RESEARCH STUDY*

The following pages of the consent form will provide you with more information about this study. Please take your time in reviewing this information and ask the investigator and study team any questions you may have.

### HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

248 people divided between two sites (University of Oklahoma Health Sciences Center (OUHSC) and University of Wisconsin-Madison (UW-M)) will take part in this study. We expect to recruit 124 of these individuals from each location.

### WHAT IS THE STATUS OF THE DRUG USED IN THIS STUDY?

Metformin is approved by the US Food and Drug Administration for other treatments, but aging is not currently considered a treatable disease, so it is considered investigational in this study.
Insulin and lidocaine which are used in the muscle biopsy and insulin clamp procedure. These are standard procedures and are not research or investigational procedures. Both of these, insulin and lidocaine, are both approved drugs available on the market.

### WHAT IS INVOLVED IN THE STUDY?

You will be randomized to receive either study drug metformin or placebo (inactive substance, which will look like the study drug).

Randomization means that you are put in a group by chance. You will have an equal 50/50 chance, like the flip of a coin, to receive metformin or placebo. A computer program at the study sponsor will make this random assignment. Neither you nor your physician will choose which group you will be in.

If you take part in this study, you will have the following tests and procedures:

1) An in-person or virtual visit to review the informed consent. Following the informed consent, you will complete , screening procedures including questions about your medical history and demographics, resting ECG, pulmonary function, fasting blood draw, and body measurements (height, weight, blood pressure, pulse and body composition) ( 2 hours). A pregnancy test will be administered for women of childbearing potential.
2) Up to 90 days later you will return to the site to be given a 7-day physical activity recall form. You will also complete a DEXA scan which will measure your body composition. Urine pregnancy tests will be performed on women of childbearing potential. You will be notified of positive results. For some participants, a Continuous Glucose Monitor (CGM) will be placed on to your abdomen to monitor your blood sugar. This device will measure your glucose every 5 minutes, and will be placed for 7-10 days, and removed at your next visit. You will be given a standardized evening meal to consume the evening before your next visit. You will then arrive in the lab the next morning after an overnight fast.



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3) At the third visit, we will then obtain a muscle biopsy. The muscle biopsy will be done in your quadriceps, and will involve taking a small tissue sample through an incision after applying lidocaine to the area. You should be able to maintain normal activities following the muscle biopsy. We will also determine insulin sensitivity using a procedure where an IV is placed to infuse glucose, insulin and a non-radioactive isotope that traces where glucose goes. (< 7 hours). Two IV catheters are placed; one to give you a continuous infusion of insulin until a steady state is reached, and the other for blood sampling. You will then maintain this steady state for 30-60 minutes. This may be extended if necessary. Blood sampling on your blood sugar will be done every 5-10 minutes. The infusion will be stopped early if you become nauseous or your blood sugar decreases. Once this is completed, we will remove the CGM.
4) Study visits to pick up drug or placebo at visits 4, 5, 7, 9, 11, 13, and 14. , at visits 11, 13, and 14 this includes picking up the special water (< 1 hour/week).
5) At week 11 (visit 14) of the intervention period, the subjects will pick up monitors to repeat the 7-10 day CGM monitoring period (< 1 hour).
6) One week after your end of treatment visit, we will repeat the evening standardized meal, insulin sensitivity procedure and muscle biopsy (< 7 hours).
7) Blood samples are taken at visits 1,3, 7, and 15.
8) You will have telephone call visits at visit 6, 8, 10, 12, and 16.

**CAN I WITHDRAW FROM THE STUDY?**

You can stop participating in this study at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

There may be circumstances under which your participation may be terminated by the investigator without your consent.

Examples:

- He/She feels that it is in your medical best interest.
- New information becomes available.
- You fail to follow study requirements, including attending your appointments.
- The sponsor stops the study.

**WHAT ARE THE RISKS OF THE STUDY?**

In addition to the risks described in the Key Information section, you may also be at risk for these side effects. You should discuss these with the researcher and/or your regular doctor. Many side effects go away shortly after the metformin is stopped, but in some cases side effects can be serious or long lasting and permanent.

- Metformin has the risk of causing several side effects, however, there are nearly 50 million people in the US who use metformin on a daily basis to treat their diabetes and do not experience any side effects from metformin use. Metformin may cause lactic acidosis. Lactic acidosis can start slowly and get worse over time and is more prevalent in those with liver or kidney disease or heart failure, conditions that are screened out for this study. Less serious side effects of metformin include: headache or muscle pain; weakness; or mild nausea, vomiting, diarrhea, gas, stomach pain. Although very rare metformin may cause low blood sugar, which could be masked if a subject is taking beta-blockers to control blood pressure.

The list of possible side effects of metformin collated into most likely, less likely, rarely, and rare but serious.



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- Most likely (greater than 20%): These symptoms are generally temporary, occur during the start of treatment, and disappear without stopping the drug.
  - Diarrhea
  - Nausea
  - Vomiting
  - Abdominal bloating
  - Flatulence
  - Anorexia (loss of appetite)

- Less likely [occasional] (5 to 20%):
  - Loss of taste or metallic taste (during start of therapy)
  - Minor weight loss (less than 1 kilogram or 2 pounds)
  - Reduced appetite

- Rarely (1 to 4%): These effects will disappear when metformin is stopped.
  - Rash, redness or itchiness
  - Decrease in the level of vitamin B12 that does not cause symptoms
  - Decrease in the red blood cell count
  - Liver function test abnormalities as seen by blood tests or hepatitis (inflammation of the liver)

- Rare but Serious (less than 1%):
  - Lactic acidosis occurs rarely (3 cases per 100,000 years of use) and can cause death. Individuals at risk of this complication include persons with diabetes who have kidney, liver or heart abnormalities. Symptoms of lactic acidosis may include tiredness, muscle aches, difficulty breathing, vomiting or severe abdominal pain.

The treatment or procedure may involve risks that are currently unforeseeable.

<u>RISKS FROM PROCEDURES:</u>
Some of the procedures completed as a part of the study have a low risk associated with them.

- There can be temporary physical discomfort during the blood drawing procedure, the possibility of bruising or fainting, and small risk of infection. Discomfort during the blood sampling is minor and brief (<30s) and bruising does not last more than one week.
- With all infusions there is a risk of infection. To minimize the risk, all IV fluids will be prepared by a pharmacy and we will use sterile technique to administer the infusion.
- Insulin Infusion: There is a risk of low blood sugar during the insulin infusion. Low blood sugar can make you dizzy, sweaty, shaky or weak. We will be checking your blood sugar every 10 minutes during the insulin infusion and giving you sugar in your IV to keep your blood sugar at a normal, healthy level. As with all infusions there is a risk of infection. To minimize the risk, all IV fluids will be prepared by a pharmacy and we will use sterile technique to administer the infusion.
- There is a small risk of infection at the site of the incision for the muscle biopsy, and a small risk of the biopsy incision reopening or bleeding after leaving the lab. The risk of allergic reaction to lidocaine (the anesthetic used for the biopsy incision) is extremely low. There is also a risk of fainting or muscle cramping during the procedure, loss of feeling in the leg, damage to the skin (cutaneous) nerve and a risk of bruising around the biopsy site. The procedure leaves a small scar at the incision site. The rate and degree of healing varies considerably, but it is expected that scars are difficult to see 6-12 months after the procedure.
- Placement of the continuous glucose monitor (CGM) poses a small risk of infection at the site of insertion. There is also a risk of discomfort (skin irritation, redness, rash, or itchiness) from the adhesive patched to secure the device to the skin.



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- In a small number of cases, transient dizziness may result from the initial consumption of heavy water.
- Violation of privacy and loss of confidentiality are both risks to which research participants are exposed. The possibility of these risks increases when protected health information is collected.

For more information about risks and side effects, ask the researcher.

RADIATION RISKS:
In addition to any radiographic procedures that are being done as part of this research, you may also be exposed to radiation from procedures that are part of your normal care. The number and frequency of these procedures are based on standard clinical practices for a person with your condition; however, your doctor may order an additional radiographic test if he/she thinks it is necessary for your care. The risk from radiation exposure increases over your lifetime as you receive additional exposure to radiation.

The risks associated with the DEXA are very low. The maximum radiation dose we provide is less than 1/1000th of the federal and state occupational whole body dose limit allowed to radiation workers (5,000 mrem). Although minimal, the more radiation received over the course of a lifetime, the more the risk increases of developing a fatal cancer or inducing changes in genes. The radiation from our scans is not expected to significantly increase these risks, but the exact increase in such risks is not known. There are no discomforts associated with this procedure.

REPRODUCTIVE RISKS FOR WOMEN:
If you are a female, you must not be and should not become pregnant nor breast-feed an infant while on this study. Taking the study drug(s) or undergoing a particular procedure or treatment involved in this study while you are pregnant or breastfeeding may involve risks to an embryo, fetus, or infant, including birth defects which are currently unforeseeable. In order to reduce your risk of pregnancy, you or your partner should use one or more of the acceptable methods of birth control listed below, regularly and consistently, while you are in this study.

Acceptable methods of birth control An approved oral contraceptive (birth control pill)

- Intra-uterine device (IUD)
- Hormone implants
- Contraceptive injection (Depo-Provera)
- Barrier methods (diaphragm with spermicidal gel or condoms)
- Transdermal contraceptives (birth control patch)
- Vaginal contraception ring (birth control ring)
- Sterilization (tubal ligation, hysterectomy or vasectomy)

If you are already using a method of birth control, you should check with the study doctor to make sure it is considered acceptable for this study. Certain drugs may interact with contraceptive agents and reduce their effectiveness; therefore, you should inform the study doctor of all medications (prescription and over-the-counter) that you are currently taking or begin taking during the study.

REPRODUCTIVE RISKS FOR MEN:


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There is a recent study that indicates that there is a potential increased risk in males taking metformin versus males not taking metformin in the 90 days pre-conception and birth defects (risk 5.2% with metformin versus 3.3% without metformin). There was no increased risk when metformin was taken before or after the 90 days before conception. Men should not conceive during the trial or 90 days after trial participation ends. In order to reduce the risk of pregnancy you or your partner should use one of the acceptable methods of birth control listed above regularly and consistently while you are in this study and 90 days after participation ends.

IN CASE OF PREGNANCY:
If you become pregnant or suspect that you are pregnant, or (for males) if you make someone pregnant during this study, you should immediately inform the study personnel. If you become pregnant or suspect that you are pregnant while on this study, tell the study doctor immediately; the study doctor will perform a pregnancy test. The study drug may be discontinued until the result of the pregnancy test is known. If pregnancy is confirmed, you may be withdrawn from the study. The study doctor will assist you in getting obstetrical care at your cost. The study doctor and the Sponsor will follow the progress of your pregnancy and will request access to your and/or your infant's medical records for least eight weeks after delivery. Payment for all aspects of obstetrical, child, or related care will be your responsibility.

**TO WHAT EXTENT WILL MY INFORMATION BE KEPT CONFIDENTIAL?**
Efforts will be made to keep your personal information confidential. You will not be identifiable by name or description in any reports or publications about this study. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. You will be asked to sign a separate authorization form for use or sharing of your protected health information.

There are organizations outside the OUHSC that may inspect and/or copy your research records for quality assurance and data analysis. These organizations may include the US Food & Drug Administration and other regulatory agencies, University of Wisconsin-Madison, Oklahoma Medical Research Foundation, The University of Kentucky, and the National Institute of Health. The OUHSC Human Research Participant Program office, the OUHSC Institutional Review Board, OUHSC Office of Compliance, and other University administrative offices may also inspect and/or copy your research records for these purposes.

Posting Study on ClinicalTrials.gov:
A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. However, this website will not include information that can identify you. At most, the website will include a summary of the study and results. You can search this website at any time.

Certificate of Confidentiality:
To help protect your privacy, this research is covered by a Certificate of Confidentiality from the National Institutes of Health. This Certificate means that the researchers cannot be forced (for example by court subpoena) to share information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.



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The Certificate cannot be used to resist a demand for information from personnel of the U.S. government that is used for checking or evaluating federally-funded projects or for information that must be disclosed in order to meet the requirements of the US Food and Drug Administration.

The protection offered by the Certificate of Confidentiality does not prevent us from being required by applicable state law to report information about suspected or known sexual, physical, or other abuse of a child or older person, or a subject's threats of violence to self or others. If any member of the research team is given such information, he or she will be required to make a report to the appropriate authorities.

The Certificate, however, does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information. This means that you and your family should actively protect your own privacy.

Identifiable Private Information and Biospecimens:
Your sample may be used for future studies without your additional consent. We will remove direct identifiers from your information and specimen and assign a code. The key to this code will be kept separately and only the researcher for this study will have access to the code. If your information/sample is shared with another investigator for research purposes, they will not have access to the key code and will not be able to re-identify you.

**WHAT ARE THE COSTS?**
The study sponsor will pay for all costs related to your participation in this study.

**WHAT IF I AM INJURED OR BECOME ILL WHILE PARTICIPATING IN THIS STUDY?**
In the case of injury or illness results from this study, emergency medical treatment is available.

You or your insurance may be charged for this treatment.

Complications arising as a result of the natural progression of an underlying or pre-existing condition will be billed to you or your insurance. Please check with the investigator or with your insurance company if you have questions.

No other funds have been set aside by the University of Oklahoma Health Sciences Center, the University of Wisconsin-Madison, or the NIH to compensate you in the event of injury, illness, or for other damages related to your event of injury or illness.

**WHAT ARE MY RIGHTS AS A PARTICIPANT?**
Taking part in this study is voluntary. You may choose not to participate. Refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled.

If you agree to participate and then decide against it, you can withdraw for any reason and leave the study at any time. However, please discuss leaving the study with the principal investigator or your regular doctor. You may discontinue your participation at any time without penalty or loss of benefits to which you are otherwise entitled.

We will provide you with any significant new findings developed during the course of the research that may affect your health, welfare, or willingness to continue your participation in this study.

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You have the right to access the medical information that has been collected about you as a part of this research study. However, you may not have access to this medical information until the entire research study has completely finished. You consent to this temporary restriction.

Results of research testing on your sample may be given to you or your doctor. Copies of your labs may be available upon request.

**WILL I BE CONTACTED AGAIN?**
The researcher would like to contact you again to recruit you into future research or to gather additional information.

_____I give my permission for the researcher to contact me in the future.

_____I do not wish to be contacted by the researcher again.

**WHOM DO I CALL IF I HAVE QUESTIONS, SUGGESTIONS, OR CONCERNS?**
If you have questions, concerns, or complaints about the study or have a research-related injury, contact the Principal Investigator at your study site.

For participants at the University of Oklahoma Health Sciences Center, contact Dr. Benjamin Miller at 405-271-7767 during daytime hours, or 24-hours at 970-217-7906. You may also reach the study coordinator team at 405-271-3480. If you cannot reach the Investigator at OUHSC or wish to speak to someone other than the investigator and for questions about your rights as a research participant, contact the OUHSC Director, Office of Human Research Participant Protection, at 405-271-2045.

**Contact:**

We are requesting your email address so we can communicate about scheduling and obtaining certain study related information or issues. Email is generally not a secure way to communicate about your health as there are many ways for unauthorized users to access email. You should avoid sending sensitive, detailed personal and/or health information by email. Email should not be used to convey information of an urgent nature.

_____ I give my permission for the researcher to communicate via email

_____ I do not wish to be contacted by the researcher via email



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**SIGNATURE:**

By signing this form, you are agreeing to participate in this research study under the conditions described. You have not given up any of your legal rights or released any individual or entity from liability for negligence. You have been given an opportunity to ask questions. You will be given a copy of this consent document.

I agree to participate in this study:

| | | |
|---|---|---|
| **PARTICIPANT SIGNATURE (age ≥18)** | **Printed Name** | **Date** |
| **SIGNATURE OF PERSON OBTAINING CONSENT** | **Printed Name** | **Date** |



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