Cover Page

NCT Number: NCT05900284

Study Title: Safety and Feasibility of Metformin for Sepsis Induced AKI

Document: CONSENT TO ACT AS A PARTICIPANT IN A RESEARCH STUDY

University of Pittsburgh

Department of Critical Care Medicine

CONSENT TO ACT AS A PARTICIPANT IN A RESEARCH STUDY

TITLE: A Randomized Clinical Trial of the Safety and FeasibiLity of Metformin as a Treatment for sepsis induced AKI (LIMIT-AKI)

INVESTIGATOR: **Hernando Gomez Danies, MD, MPH**
University of Pittsburgh Medical Center
612C Scaife Hall - 3550 Terrace Street
Pittsburgh, PA 15261
(412) 383-4207

SOURCE OF SUPPORT: National Institute of Health

KEY INFORMATION:

You are being invited to consider joining a research study. Participation in a research study is always voluntary. The first part of this form is a summary of the study. Please also read the Detailed Information section that follows before -deciding about participation in this study. Some who are eligible for this study may not be able to give consent because of their medical condition. Instead, we will ask the person's authorized representative to give consent. Throughout the consent form, "you" always refers to the person who takes part in the study.

Why are researchers doing this study?

Can a common diabetes drug used by millions every day also fight sepsis?

This simple question and hope is the heart of this study.

Researchers have found that Metformin, a drug commonly used to treat diabetes, may help patients with sepsis (a serious infection) by reducing their risk of death and kidney injury. However, Metformin has not been used to treat patients with sepsis. Thus, the reason for doing this study is to establish the safety, feasibility, and possible benefit of using Metformin as a treatment for patients with sepsis. Your kidneys, which are organs in your body that clean the blood by filtering out waste products, are one of the most common organs affected by sepsis. Researchers are very interested in seeing if Metformin can help the kidneys.

What is involved in this study?
The study will begin the day of enrollment. You will be randomly assigned to receive treatment with Metformin (Low dose: 500 mg every 12 hours, or high dose: 1000 mg every 12 hours) or

with placebo (inactive ingredient) for 5 days. This means the treatment you receive will be assigned by chance.

Metformin will be provided as a crushed pill given orally, or through existing feeding tubes that have already been placed for your care. If you participate, you will have blood and urine samples taken daily- for the first 7 days and then at discharge or day 30, whichever comes first. This blood and urine would be stored without identifiers.

What are some reasons I might choose to volunteer?
Researchers are conducting this study because they do not know if Metformin might be helpful to patients with sepsis. Their goal is to determine if metformin can be helpful to treat patients with sepsis to decrease their risk of kidney failure and death.

What risks are involved in the study?
For people assigned to take Metformin, some may experience mild stomach and digestive system side effects as outlined in the 'Potential Risks and Discomforts' section below. These are usually temporary and resolve with continued use of Metformin. Other potential risks are very rare like increasing the levels of lactate, a waste product that accumulates in sick patients especially with sepsis and kidney injury. In patients with diabetes taking Metformin, increased lactate occurs in 1 out of 11,000 patients.

Other minor risks are noted in the 'Potential Risks and Discomforts' section.

What other things should I consider?
You will not be charged for costs associated with the study drug or for any procedures required by the study. Costs associated with your routine medical care and hospital stay will still be your responsibility or that of your insurance provider.

Will being in this study help me?
For those assigned to the placebo group, no direct benefit is expected. For those taking Metformin, it is not known if there will be any direct benefit to you.

What are my choices if I decide not to be in this study?
If you decide not to join the study, this will have no effect on the provision of your medical care while in the hospital and beyond.

DETAILED INFORMATION

INTRODUCTION

This study is being conducted to determine if people taking Metformin have better outcomes and fewer complications after being admitted to the ICU with sepsis. Metformin is a medication commonly given by doctors to reduce blood sugar in people with diabetes (a disease where you have higher than normal blood sugar). The use of Metformin in this research study is investigational. "Investigational" means that the use of Metformin for the purpose of improving

outcome in patients with sepsis is not approved by the United States Food and Drug Administration.

In this consent form, "you" and "your" always refers to the subject and "we" always refers to the study team.

You are being asked to participate in this research study because you are over the age 18 and have been admitted to the ICU with sepsis or septic shock – which is a severe infection that causes the body to stop working properly.

DESCRIPTION OF THE RESEARCH

Up to 80 people may be enrolled in this research study over the next 3.5 years at the University of Pittsburgh/UPMC.

Your study participation will begin after signing the informed consent. As part of this study, you will take a study drug twice a day for 5 days after the date of your enrollment in the study. Medical record information will be collected during the duration of your hospital course until hospital discharge or up to 30 days, whichever comes first.

WHEN THE INVESTIGATOR IS ALSO THE CARE-PROVIDER:

For some of you, your physician is 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.

STUDY PROCEDURES:

If you decide to take part in this research study, certain research procedures may occur.

First, patients will be randomly assigned to receive one of the following study treatments:

- Placebo: every 12 hours for 5 days
- Metformin low dose: 500mg every 12 hours for 5 days
- Metformin high dose: 1000mg every 12 hours for 5 days

The intervention begins the day of enrollment and doses will be administered every 12 hours for a total of 5 days. Study drugs will be given as a crushed pill to take by mouth or through an existing feeding tube placed in your nose or abdomen.

During the study intervention, the research team and the clinical team managing your care will closely monitor you for any development of side effects associated with Metformin. This monitoring will occur by reviewing your daily blood test results and watching your body's response (nausea, vomiting, diarrhea). You will not be told your assigned study drug group.

Blood and Urine Collections

Blood samples will be obtained from your existing IVs and other lines already in place for other clinical reasons. Urine will be obtained from the collection bag at the end of your existing urinary catheter (tube). Where possible, blood samples will be drawn at the time of your routine clinical blood draws and taken from existing lines to minimize discomfort. When possible, we will use lab values obtained as standard of care at any of the scheduled timepoints.

All patients will have a maximum of 30 milliliters of blood (approximately 2 tablespoons) and 20 milliliters of urine (approximately 1.5 tablespoons) collected before the first dose of study drug and every day for the first 7 days of enrollment, and the day of your hospital discharge or day 30, whichever comes first.

The blood will be drawn at the following timepoints:

- 25 milliliters of blood (approximately 5 teaspoons) will be collected before the first dose and once a day for 7 days.
- 1 milliliter of blood (less than 1 teaspoon) will be collected every 12 hours after the first dose for the first 7 days.
- 20 milliliters of urine (approximately 4 teaspoons) will be collected before the first dose and once a day for 7 days.
- 10 milliliters (approximately 2 teaspoons) of blood and urine will be collected on the day of your hospital discharge or day 30, whichever comes first.
- 5 milliliter of blood (approximately 1 teaspoon) will be collected on Days 1 and 5 at the intervals of Time 0 (when drug is administered), 1hr, 2hrs, 4hrs, 8hrs, and 12hrs after the drug has been administered and once a day, on days 2, 3, 4, 6, and 7.

During your hospital ICU stay:

You will continue to receive the study drug during your ICU stay for 5 days.

We may stop the study drug if you have certain side effects. We will reduce the dose in patients who experience gastrointestinal discomfort determined to be associated with Metformin. If gastrointestinal discomfort persists for more than 24 hours, the dose of Metformin will be decreased as follows: Patients allocated to a high dose will shift to the low dose regimen. Patients allocated to the low dose, will decrease to 250 mg twice a day. After 24h of close monitoring, study drug will be withheld if signs and symptoms of gastrointestinal discomfort continue. If symptoms decrease, the intervention will be continued at this reduced dose to complete 5 days.

Study drug administration may be suspended at the direction of the treating clinician based on their assessment of the clinical situation of the patient.

CONTINUED ACCESS TO MEDICAL RECORD INFORMATION

We also would like to have permission to check on how you are doing by collecting medical record information until you are discharged from the hospital (or when you have reached 30 days from study enrollment, whichever comes first). We would collect information related to your

general health and hospital course such as diagnostic laboratory, test results, treatments, vitals and imaging data and physiologic monitoring data, and doctor's notes.

DATA RETENTION and BLOOD SAMPLES

All samples collected during this study will be placed in a specimen bank. Your samples will be kept forever. Some of these samples will be used for genetic analysis. Your past, current, and future medical record information stored at UPMC will be available to be matched with your biological samples. This data will be stored in a controlled-access database. Your data, which may include your health information and your biological samples will be stored with a unique ID number but will not be stored with your name. At some point, your identifiers will be removed from the private information and/or biospecimens. This de-identified information and/or biospecimens may be used by other researchers for future research studies or shared with federal repositories. If this happens, we will not contact you for additional consent.

Research data will be maintained for at least 7 years following closure of this research study.

No clinically relevant results will be returned to you. None of the results of your tests will be placed in your medical record

Your samples and research data collected in this study 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.

POTENTIAL RISKS AND DISCOMFORTS

Metformin: The known risks are effects on your stomach and digestive system such as gas, loss of appetite, nausea, vomiting, diarrhea, and decreased levels of vitamin B12. Low levels of B12 could cause pale skin, weakness, fatigue, and mood changes. These side effects are usually temporary and resolve with continued use of metformin.

There is a rare risk of something called lactic acidosis. This is the build-up of lactate in your blood. Early signs of this are changes in your breathing, such as shallow, rapid breaths, and belly pain. In patients with diabetes taking Metformin, increased lactate occurs in 1 out of 11,000 patients.

You should not participate in this study if you know you have an allergy to metformin.

Blood sampling: You may experience temporary discomfort, bruising, pain at the blood draw site, and fainting (rare risk).

Collection and Storage of Private Health Information: It is possible that someone could find out that you were in this study and could find out information about you. Every effort will be made to prevent this from happening. To protect your confidentiality, we will remove your

name and other personal identifiers from the samples and from the medical record information we obtain. This information will be identified by a code.

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.

Genetic testing: The risk of doing genetic studies includes the potential for a breach of confidentiality, which means someone could see your genetic testing results who is not authorized. The information could be used to affect what insurance or jobs you may be able to get. Or it could affect your decision to have children. It could also cause stress and conflict in your family relationships, as it can confirm who is a child's father, identify a risk for a certain disease, or cause you or other people to have negative feelings if the results show you may be more likely to get certain diseases.

A federal law, called the Genetic Information Nondiscrimination Act (GINA), helps to reduce the risk of discrimination by health insurers and most employers based on your genetic information. This law will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information that we get from this research when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information from this research when deciding to hire, promote, or fire you or when setting the terms of your employment.

Be aware that this federal law does not protect you against genetic discrimination by companies that sell life insurance disability insurance, or long-term care insurance, nor does it protect you against genetic discrimination by all employers. GINA also does not protect you against discrimination based on an already-diagnosed genetic condition or disease.

ANTICIPATED BENEFITS TO SUBJECTS
There is no direct benefit to you from being in this research study.

NEW INFORMATION
If new information, either good or bad, about this treatment develops during the course of this study, which may cause you to change your mind about continuing in this study, it will be promptly provided to you or your representative.

COSTS
Neither you nor their insurance company will be responsible for the costs of any of the procedures required for the study. You or your insurance company will be responsible for the costs that occur as part of your hospitalization.

PAYMENTS
You will not be paid for your participation in this study.

COMPENSATION FOR INJURY
University of Pittsburgh investigators and their associates who provide services at the UPMC Health System (UPMC HS) recognize the importance of your voluntary participation to their research studies. These individuals and their staff will make reasonable efforts to minimize, control, and treat any injuries that may arise as a result of this research.

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 waive any rights by signing this form.

CONFIDENTIALITY
Any information about you obtained from or for this research study will be kept as confidential (private) as possible. A record of your progress while on the study will be kept in a confidential form at the University of Pittsburgh. All records pertaining to your involvement in this research study will be stored in a locked cabinet. A case number will indicate your identity on these records. You will not be identified by name in any publication of the research results unless you sign a separate form giving your permission. All electronic study information is password protected and deidentified for secure storage.

A copy of the consent form and a note stating your involvement in the study will be placed in your medical record.

AUTHORIZATION TO USE PRIVATE HEALTH INFORMATION
We are also requesting your authorization or permission to review your medical records. This research study will involve the recording of current and/or future identifiable medical information from your hospital and/or other health care provider (e.g., physician office) records. This information will be used for the purpose of recording and identifying the measurements obtained following your ICU stay. As part of this study, some research results from testing we do with you will be placed into your medical records held at UPMC. These include lab results for lactate, blood gas, glucose, and creatinine. .

To conduct this study properly and carefully monitor your health, the information that may be recorded will include information concerning your medical history, results of lab tests, diagnostic procedures, reason for your ICU admission, and medical record information related to your hospital stay.

In addition to the investigator listed on the first page of this authorization and consent form and the research study staff, the following individuals will or may have access to identifiable 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 for the purpose of monitoring the appropriate conduct of this research study.
- Authorized representatives of the U.S. Food and Drug Administration may review and/or obtain identifiable information related to your participation in this research study for the purpose of monitoring the accuracy of the research data. While the U.S. Food and Drug Administration understands the importance of maintaining the confidentiality of your identifiable research and medical record information, the University of Pittsburgh and UPMC Health System cannot guarantee the confidentiality of this information after it has been obtained by the U.S. Food and Drug Administration.
- Authorized representatives of the National Institute of Health, the study sponsor.
- In unusual cases, the investigators may be required to release identifiable 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.

In addition, coded data about your participation in this study will be shared with an external Data Safety and Monitoring Board (DSMB). The DSMB will review this coded data for the purpose of overseeing study progress and evaluating the potential risks to subjects associated with study participation.

The investigators may continue to use and disclose, for the purposes described above, identifiable information related to your participation in this research study indefinitely. It is a university policy that all research records must be maintained for at least 7 years following study completion.

Authorized representatives of the 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).

RIGHT TO REFUSE / WITHDRAW

Your participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above, is completely voluntary. (Note, however, that if you do not provide your consent for the use and disclosure of your identifiable information for the purposes described above, you will not be allowed, in general, to participate in the research study.) Whether or not you provide your consent for participation in this research study will have no effect on your current or future relationship with the University of Pittsburgh. 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 Health System hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

Your doctor is involved as an investigator in this research study. As both your doctor and a research investigator, they are interested both in your medical care and the conduct of this research study. Before agreeing to participate in this research study, 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 doctor.

It is possible that you may be removed from the research study by the researchers if, for example, study drug administration may be suspended at the direction of the treating clinician based on that physician's assessment of the clinical situation of the patient.

You may withdraw, at any time, your consent for participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above. (Note, however, that if you withdraw your consent for the use and disclosure of your identifiable information for the purposes described above, you will also be withdrawn, in general, from further participation in this research study). If there is any time you no longer wish to participate in this study while you are in the ICU, please tell your doctor. Once your doctor is notified of your choice to withdraw from the study the device will be removed, and you will be done. Any identifiable research resulting from your participation in this research study prior to the date that you formally withdrew your consent may continue to be used and disclosed by the investigators for the purposes described above. All data collected up until the point of the study will remain in the study database.

To withdraw your consent for participation after you have left the ICU, please call or send a letter to the principal investigator, whose contact information is listed on the first page of this form.

The decision to withdraw your consent for participation in this research study will have no effect on your current or future relationship with the University of Pittsburgh. 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 Health System hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

CLINICAL TRIALS
A description of this clinical trial will be 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.

CERTIFICATE OF CONFIDENTIALITY
This research is covered by a Certificate of Confidentiality from the National Institutes of Health. This means that the researchers cannot release or use information, documents, or samples that may identify you in any action or suit unless you say it is okay. They also cannot provide them as evidence unless you have agreed. This protection includes federal, state, or local civil, criminal, administrative, legislative, or other proceedings. An example would be a court subpoena.

There are some important things that you need to know. The Certificate DOES NOT stop reporting that federal, state or local laws require. Some examples are laws that require reporting of child or elder abuse, some communicable diseases, and threats to harm yourself or others. The Certificate CANNOT BE USED to stop a sponsoring United States federal or state government agency from checking records or evaluating programs. The Certificate DOES NOT stop disclosures required by the federal Food and Drug Administration (FDA). The Certificate also DOES NOT prevent your information from being used for other research if allowed by federal regulations.

Researchers may release information about you when you say it is okay. For example, you may give them permission to release information to insurers, medical providers or any other persons not connected with the research. The Certificate of Confidentiality does not stop you from willingly releasing information about your involvement in this research. It also does not prevent you from having access to your own information.

CONSENT TO PARTICIPATE

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 agree to participate in this research study; and authorize Dr. Gomez and his research team to use and share my medical records for the purposes described in this form. A copy of this consent form will be given to me.

Printed Name of Participant	Signature of Participant	Date and Time

□ The person named above lacks decision making capacity resulting from their acute illness and/or its treatments. Therefore, by signing this form I consent for his/her participation in this study; and authorize this research team's access to his or her medical records.

Representative's Name (Print)	Relationship to Participant
Representative's Signature	Date and Time

INVESTIGATOR CERTIFICATION

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

Printed Name	Signature	Date and Time

Role in Research Study

CONSENT FOR CONTINUED RESEARCH PARTICIPATION

This section is to be used in the event that the participant regains decision-making capacity.

I understand that I am currently participating in a research study. I further understand that consent for my participation in this research study was initially obtained from my authorized representative because of my inability to provide direct consent at the time that this initial consent was requested. I have now recovered to the point where it is felt that I am able to provide direct consent for continued participation in this research study.

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 about any aspect of this research study during this study and that such future questions 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.

_____	_____	_____
Printed Name of Participant	Signature of Participant	Date and Time

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.

_____	_____
Printed Name of Person obtaining consent	Role in Research Study
_____	_____
Signature of Person obtaining Consent	Date and Time