UPMC

Strategies to Promote ResiliencY (SPRY)-An Adaptive Randomized Clinical Trial of Metformin in High Risk Surgical Patients

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CONSENT TO ACT AS A PARTICIPANT IN A RESEARCH STUDY

STUDY TITLE: Strategies to Promote ResiliencY (SPRY)-An Adaptive Randomized Clinical Trial of Metformin in High Risk Surgical Patients

PRINCIPAL INVESTIGATOR:
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SOURCE OF SUPPORT: UPMC Internal Funds

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 making a decision about participation in this study.

Why are researchers doing this study?
Increasing age is a risk factor for having complications after surgery. There are some studies suggesting metformin, a medication often used for diabetes, may be able to reduce inflammation as well as have other effects which may help with complications.

In this study, we want to look at whether or not metformin is able to improve your outcome and reduce complications after elective surgery.

What is involved in this study?
You will be randomly assigned to receive one of 3 doses of metformin (500 mg, 1000 mg, or 1500 mg) or one of three doses of placebo (sugar pills). You will take this study drug starting tomorrow and continue to take this study drug for 90 days after your surgery.
If you participate in this study, you may have blood samples taken at up to 5 timepoints while you take the study drug. This blood would be stored without identifiers.

You may also complete questionnaires during this study.

What are some reasons I might choose to volunteer?
Researchers are conducting this study because they do not know if metformin might be helpful. Their goal is to determine what might help future patients.

What risks are involved in the study?
For those people who are assigned to take metformin, some people may experience mild stomach and digestive system side effects as outlined in the 'Potential Risks and Discomforts' section which follows. These are usually temporary and resolve with continued use of metformin.

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, including your elective surgery 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 who will be 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 your elective surgery.

DETAILED INFORMATION

INTRODUCTION:

This study is being conducted to determine if people taking metformin have better outcomes and fewer complications after having elective surgery compared to people not taking metformin. 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 after surgery 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 as you are scheduled for an elective surgical procedure in a UPMC facility as part of your routine care. You may be eligible for participation in this research study if you are at least 60 years of age and do not have diabetes. You may also be eligible if you are younger than 60 years of age and have certain chronic medical conditions. Women enrolled into this study must be post-menopausal, which means that you have not had a menstrual period within the last 12 months.

DESCRIPTION OF THE RESEARCH

A total of up to 2,000 men and women may be enrolled into this research study over the next two years at the University of Pittsburgh/UPMC.

Your study participation will begin on the day you are seen in the clinic for the pre-operative evaluation prior to your surgery. As part of this study, you will take a study drug prior to your operation and then for ninety (90) days after the date of your surgery. Medical record information may be collected for approximately a year after your completion of the study drug.

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.

Clinic Visit Before Your Surgery:

- You may answer questions regarding your demographic details (date of birth, race, etc.)
- You may answer a few general questions about your medical history, allergies, and your use of alcohol to verify that you are eligible to participate in this study.
- You may be asked to provide contact information (name, phone number, mailing address, e-mail address) for you, your spouse/partner, and maybe for another friend/relative. This contact information is collected as the study team may need to contact you throughout the study. If the study team cannot reach you, they would then try to reach one of the other individuals you have identified for the study team.

- You may have a blood sample drawn. Blood will be drawn to store some blood for future testing to be able to compare how aspects of your blood change as you progress through the study. The blood would likely be drawn by putting a needle into a vein in your arm. About four (4) tablespoons of blood may be taken for this study at the same time as blood is drawn for testing required for your surgery if needed. Your blood would be drawn by a nurse or another skilled medical professional. The blood draw should take about ten minutes. Other blood samples may be taken at other times during the study. When possible, these blood samples would be drawn at the same time as standard of care blood is drawn.
- You will be randomly assigned by chance to receive one of the following study drugs to take one time daily by mouth:
    - 500 mg (1 pill) metformin extended release (ER)
    - 1000 mg (2 pills) metformin extended release (ER)
    - 1500 mg (3 pills) metformin extended release (ER)
    - Placebo (1 pill)
    - Placebo (2 pills)
    - Placebo (3 pills)

A placebo is a sugar pill that looks like a metformin pill but does not contain any active drug. At the beginning of the study, an individual has a 37% (37 in 100) chance of receiving placebo and a 63% (63 in 100) chance of receiving one of the three metformin doses. Once an individual is assigned to receive placebo or metformin, the individual takes this study drug for the duration of the study.

As this study is designed to enroll people over 2 years, the likelihood that those who participate at a later time will receive metformin or placebo will change based on the number of individuals who have participated in the study up to that point.

If you are assigned to either the 1500 mg metformin extended release dose or the 3 pill placebo option, you will take 2 pills for the first 7 days. Starting on day eight, you will then take 3 pills. The reason to begin with the lower dose is that this will help to reduce possible side effects if you are taking metformin.

Both you and the study team will not know if you are taking metformin or placebo during the study. In the event of an emergency, it is possible for the study team to learn what study drug you are taking.

You should start to take the study drug the morning after your pre-operative clinic visit. You should take the study drug every day. You should take the study drug with food to minimize GI effects. You should bring your current study drug pill bottle with you on the date of your surgery. Depending upon when your surgery is scheduled, the UPMC Investigational Drug Service may need to send you additional study drug by mail. It is important that you take all the study drug in the current study drug pill bottle before starting to take study drug from a new study drug pill bottle received in the mail.

You should continue to take the study drug through the day of your elective surgical

procedure and for 90 days following the date of your surgery. The study drug will only be available to you during the study.

- You will be given a wallet card that indicates that you are participating in this study. This card lists that you may be taking metformin. You should carry this wallet card with you and show this wallet card to any health care professional you see while you are taking the study drug.
- We may contact your PCP and other members of your health care team to let them know of your involvement in this study. These communications could occur at various times throughout your study participation.
- As part of the process for you to decide to participate in this study, you will speak with one of the investigators involved with this study. If the investigator cannot promptly come to your clinic location, this interaction may occur via phone or via remote video conference. The purpose of your conversation with the investigator is for the investigator to ensure that you understand what is involved in study participation and to ensure all your questions have been answered. Following the conversation with the investigator, either in person or by telephone/video conference, this informed consent will be signed by you and by the investigator. A copy of the informed consent will be given to you.

These research procedures will likely take place in the clinic where you are having your office visit before surgery. The research procedures may add approximately 45 minutes to your visit.

<u>Prior to the day of surgery, ideally within 48 hours of study enrollment</u>:

- You may receive a phone call from a member of the Long-Term Outcomes Core team. The purpose of this phone call is to remind you of the importance of bringing your study drug pill bottle with you when you come to the hospital for your elective surgery.
- During this phone call, a member of the Long-Term Outcomes Core may ask you some questions about your general health and to assess your thinking and memory. This phone call should take about 15 minutes.

<u>Day of surgery</u>:

- You should give your study drug pill bottle to hospital staff personnel when you arrive at the hospital for your surgery. Your study drug pill bottle will be kept by hospital personnel while you are in the hospital. You will continue to take the study drug while you are in the hospital.
- You may have a blood sample drawn from the intravenous (IV) line that is inserted in your arm for your surgery or directly from a vein. About four (4) tablespoons of blood may be taken. Your blood would be drawn by a nurse or another skilled medical professional. The blood draw should take less than ten minutes.
- We may review your medical records and collect information related to your surgery and the medications you receive for your surgery as well as your general

health. We may continue to review and collect this kind of information while you are in the hospital.

These research activities should take about 25 minutes.

After surgery:

- You may have blood drawn from the intravenous (IV) line that was inserted in your arm for your surgery or directly from a vein. About three and a half (3.5) tablespoons of blood may be taken at this time. Your blood would be drawn by a nurse or another skilled medical professional. The blood draw should take less than ten minutes and should occur in your hospital room.

During your hospital stay:

- You will continue to receive the study drug during your hospital stay. We may decide to suspend giving you the study drug if you have certain types of difficulties as a result of your surgery.

Day 3 after surgery or immediately prior to hospital discharge if earlier than Day 3:

- You may have blood drawn from the intravenous (IV) line inserted in your arm for your medical care or directly from a vein. About three and a half (3.5) tablespoons of blood may be taken at this time. Your blood would be drawn by a nurse or another skilled medical professional. The blood draw should take less than ten minutes.

Day of hospital discharge:

- You should be given another pill bottle containing the same study drug as before your surgery. You should continue to take the study drug for a total of 90 days since the date of your surgery.

These research procedures should take about 15 minutes and would take place in your room at the hospital before you leave the hospital to go home.

Follow-up visit approximately 2-3 weeks after surgery (Usual Care):

- You may have blood drawn from a vein in your arm. About three and a half (3.5) tablespoons of blood may be taken for this study. Your blood would be drawn by a skilled medical professional. The blood draw should take about ten minutes and would take place in the clinic where you see your doctor or in a nearby UPMC location.

Phone call 30 days (+/- 7 days) after surgery:

All subjects participating in this study may receive a phone call from the Long Term Outcomes Core who may ask you questions about your general health, your taking of the study drug, your general level of physical activity, and about whether you have seen

any doctors/been to the hospital since your surgery. This phone call should take about 10-15 minutes.

Phone call 90 days (+ 28 days) after surgery:

The Long-Term Outcomes Core may contact you via telephone to ask you the same kinds of questions as asked during the 30-day call. You may also be asked some questions to assess your memory, attention, and thinking skills.

This phone call should take about 30-35 minutes.

For those subjects who completed their 90-day questionnaires via phone call with the Long-Term Outcomes Core, you will be reminded to discard the wallet card.

CONTINUED ACCESS TO MEDICAL RECORD INFORMATION

We also would like to have permission to collect medical record information for over one year from the time you stop taking the study drug. We would collect information related to your general health such as test results, treatments, and doctor's notes as well as information about any hospital admissions and emergency department visits. In order to collect this medical record information from non-UPMC facilities, you may be asked to sign a separate authorization which would permit the sharing of your non-UPMC protected health information with the study team.

DATA RETENTION and BLOOD SAMPLES

All of the samples collected during this study will be placed in a specimen bank. The purpose of the specimen bank is to collect and store these samples for future research studies related to aging as well as to study various types of diseases and conditions. Your samples will be kept forever. 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, your biological samples, and genetic data generated from your samples will be stored with a unique ID number but will not be stored with your name. Your samples may be used by other investigators here at the University of Pittsburgh and UPMC and may be shared with other researchers, industry, or with a federal repository without additional consent from you.

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

Analysis of these samples may include genetic analysis as previously described.

Any genetic information obtained from these studies will not be entered into your medical records. No clinically relevant results will be returned to you.

As the research questions to be asked are unknown and as the meaning and

significance of the results of any future unspecified testing of the biospecimens collected under this research study is unknown, personal results will not be disclosed to research subjects.

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 B12 (cobalamin).

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 something called lactate in your blood. Lactate in your blood normally is harmful if there too much. Early signs of this are changes in your breathing and belly pain. Always call the study team if you have any concern.

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

As with all medications, in very rare cases, the use of metformin may result in an allergic reaction. Some symptoms of allergic reactions include rash, difficulty breathing, wheezing, sudden drop in blood pressure, swelling around the mouth, throat or eyes, a fast pulse, sweating. Please seek emergency treatment immediately if you experience these kinds of symptoms and then alert the study doctor and study staff if you have these symptoms as a very serious allergic reaction may be life-threatening.

The study drug could interact with other drugs such as carbonic anhydrase inhibitors, gliptins, and cimetidine.

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

Surveys/questionnaires: Individuals completing questionnaires/surveys may experience mild frustration or boredom in completing these assessments.

Breach of confidentiality: 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.

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. Text messages are not encrypted or secure during their transmission, and could be intercepted.

Risks associated with gene studies: 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.

To facilitate communication during the study, this study will use e-mails to update the study team of your progress in the study. This may include the use of your name and other personal identifiers to ensure accurate information. 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.

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.

ANTICIPATED BENEFITS TO SUBJECTS

For those subjects assigned to the placebo group (no metformin will be taken), no direct benefit from study participation is expected. For those subjects who will be taking metformin, it is not known if there will be any direct benefit to you from being in the research study.

ALTERATIVE TREATMENTS

There are no alternative procedures which may be of benefit to you if you choose not to participate in this research study.

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.

COSTS AND PAYMENTS

If you agree to take part in this research study, you and/or your insurance will not have to pay for the study drug or any tests that are being done only for the research study. However, you are still responsible for paying for elective surgery and hospital admission as well as other care you would normally receive. This includes treatments and tests you would need even if you were not in this study. These costs will be billed to you and/or your insurance.

If you complete the entire study, you may be paid up to $200 in return for your time and effort associated with research study involvement. These funds will be provided to you as $50 payments 4 times throughout the study:

$50 following the clinic visit before surgery
$50 following the hospital stay
$50 following the phone call at roughly 30 days after surgery
$50 following the phone call/visit at roughly 90 days after surgery

In addition, if you participate in the Microbiome Sub-study, you will be paid $20 for each of the stool samples and rectal swab collected for this study for a total of $80 over the course of the study.

You will receive this compensation via a reloadable debit card. The debit card is not loaded with funds until you coordinate with the study team to load the card with funds. Since you are being compensated for your participation in this study, your name, address, and social security number will be released to the Accounting Office. If you are not comfortable with providing your social security number for use by the Accounting Office, taxes will automatically be removed from the payment.

USE AND DISCLOSURE OF PROTECTED HEALTH INFORMATION

We are also requesting your authorization or permission to review your medical records. This research study may involve the recording of past, current and/or future identifiable medical information from your hospital and/or other (e.g. physician office) records to determine whether you meet the conditions for participation in this study. The information that may be recorded will include information concerning your medical history, results of lab tests, diagnostic procedures, the reason for your elective surgical procedure, and the type of medical insurance you have. In addition, medical record information related to your hospital stay for your elective surgery and any follow-up visits may be recorded to assess the effects of the study drug. As part of this research

study, some information that we obtain from you may be placed into your medical records held at UPMC, including the results of any testing performed specifically for this research study. This authorization to provide identifiable information available to members of the study team is valid for an indefinite period of time.

In addition to the Principal Investigator listed on the first page of this consent form and the other investigators involved in this study and the study team, 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 for the purpose of monitoring the appropriate conduct of this research study.
- Authorized representatives of UPMC or other affiliated health care providers for the purpose of (1) fulfilling orders made by the investigators for hospital and health care services (e.g., 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 (e.g., quality assurance).
- Authorized representatives of the U.S. Food and Drug Administration (FDA) and other regulatory agencies 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.

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.

In addition, coded data about your participation in this study will be shared with Berry Consultants, LLC, a collaborator, and 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.

We may send your de-identified muscle biopsy samples for analysis to investigators at the University of Pittsburgh and/or to other collaborators such as the University of Utah for analysis. The linkage document containing your name and your study ID will not be shared with these research teams. Descriptors such as your age and gender may be shared but no identifiable information.

We may share your responses from the EQ-5D questionnaires with your health care providers.

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.

MEDICAL CARE FOR RESEARCH RELATED INJURY

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. Currently, there is no plan for any additional financial compensation. You do not, however, waive any legal rights by signing this form.

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 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 hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

As both your doctor and a research investigator, s/he is 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.

To formally withdraw your consent for participation in this research study, you should provide a written and dated letter of this decision to the principal investigator of this research study at the address listed on the first page of this form.

RIGHT TO WITHDRAW

It is possible that you may be removed from the research study by the researchers if, for example,

- You do not or cannot take the study drug properly.
- The researcher feels it is in your best interest not to continue in the study.
- The funding for the study is not continued.
- There may be other reasons to remove you from the study not identified at present.

In the event of study withdrawal, you will be asked to return the study drug pill bottle to the study team using a pre-paid mailing envelope.

Upon your withdrawal from this study, you should participate in additional monitoring follow-up procedures that are being conducted to measure the safety of the study drug.

All information obtained from you up until the date of your withdrawal from the study will be maintained in a coded fashion. No further data will be collected following your withdrawal from the study. Your blood and stool samples which have been placed into storage may continue to be used for analysis, but no further samples will be collected from you for this study.

VOLUNTARY 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 listed on the first page of this consent document at the telephone number 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 provide my authorization to share my medical records with the study team. A copy of this consent form will be given to me.

_____

Printed Name of Participant

_____ _____ _____

Signature of Participant Date Time

INVESTIGATOR CERTIFICATION:

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, 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 of Person Obtaining Consent	Role in Research Study

_____	_____	_____
Signature of Person Obtaining Consent	Date	Time