CSP#2001: Investigation of Rifampin to Reduce Pedal Amputations for Osteomyelitis in Diabetics (VA Intrepid)

NCT03012529

IRB Approved on July 11, 2024

Participant Name: _____ Date: _____

Title of Study: CSP #2001 Investigation of Rifampin to Reduce Pedal Amputations for Osteomyelitis in Diabetics (VA INTREPID)

Principal Site Investigator: _____ VA Facility: _____

Principal Investigators for Multisite Study: _____

INTRODUCTION

You are being invited to take part in a research study that is being funded by the Department of Veterans Affairs. Before you decide to take part, it is important for you to know why the research is being done and what it will involve. This includes any potential risks to you, as well as any potential benefits you might receive.

Read the information below closely, and discuss it with family and friends if you wish. Ask one of the study staff if there is anything that is not clear or if you would like more details. Take your time to decide. If you decide to take part in this study, your signature on this consent form will show that you received all of the information below, and that you were able to discuss any questions and concerns you had with a member of the study team.

BACKGROUND AND PURPOSE

What is the purpose of this research study?

The purpose of this research study is to determine if rifampin, an antibiotic (a medicine that treats infections), is effective in treating osteomyelitis (infection of the bone) of the foot in diabetic patients. Despite use of powerful antibiotics prescribed over a long period of time, many diabetic patients remain at a high risk for needing an amputation of part of the foot or lower leg because the osteomyelitis is not cured. Some small research studies have shown that addition of rifampin to other antibiotics is effective in treating osteomyelitis. However, very few diabetics with osteomyelitis have been studied, so there is no proof that it is better than the usual treatments for diabetic patients. If this study finds that adding rifampin to the antibiotics used to treat osteomyelitis reduces the risk for amputations, doctors will be able to more effectively treat Veteran patients with this serious infection.

Why am I being asked to participate in this research study?

We (your research team) are asking you to participate because you are a patient with diabetes who has been diagnosed with osteomyelitis of your foot. We are seeking your consent to test whether adding the antibiotic rifampin to usual treatment will increase your chance for a cure and prevent the need for an amputation.

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What kind of antibiotic treatment would I receive if I wasn't in this research study?

For treatment of your osteomyelitis, your ulcer will be cleaned and any dead bone removed and you will be prescribed antibiotics for about six or more weeks. The specific antibiotics prescribed and how they will be given (IV or oral) will be decided by the doctor(s) responsible for your treatment. They could choose to prescribe rifampin in addition to those antibiotics, but very few doctors in the United States currently use rifampin to treat diabetic foot osteomyelitis. The effectiveness of rifampin in treating diabetic foot osteomyelitis has not been proven.

What are the treatments I will receive as part of this research study and are these treatments approved by the Food and Drug Administration (FDA)?

Rifampin is an antibiotic that is approved by the FDA for the treatment of certain infections in combination with other antibiotics. Although rifampin is occasionally given with other antibiotics for treating osteomyelitis in diabetics, it has not been approved by the FDA for that specific use.

For this research study, you will be assigned by chance (using a process similar to a coin toss) to receive a study drug, which will be either rifampin or a placebo. In this study the placebo is a Vitamin B2 capsule, which looks like rifampin. You will have a 50:50 chance of receiving one or the other. You will take the study drug orally for six weeks along with your prescribed antibiotics, during which time you will be receiving your regular care for osteomyelitis.

Who will be conducting the research study and who is sponsoring this research?

We are conducting this study at <insert VA facility name> as well as at other VA hospitals across the United States. The study is being sponsored and funded by the VA and will be monitored by the VA.

How many people are going to participate in this research study?

This is a large, national study, which will include about 880 men and women Veteran patients from approximately 28 VA Medical Centers. We expect to have up to 75 participants at the <insert VA facility name>.

DURATION OF THE RESEARCH

The total study will take approximately seven years to complete. You will be in the study for up to two years, but your participation may be only between one to two years depending on when you enter the study. You will take the study drug for six weeks while you are taking your regularly prescribed antibiotics. We will follow your progress with study visits, phone calls and reviewing your medical record.

STUDY PROCEDURES

Initial Screening to Determine Eligibility:

- If you consent to the study, a member of the research team will review your medical record and laboratory test results to be certain that you are eligible. We will also talk to your doctor to see if he or she agrees with your participation in the study. You may have already talked to your doctor about being in the study, but we will discuss it with him or her as well, just to be certain that he/she is well informed.

- We will ask you about your medical history, your current health, medicines you are taking (including prescribed and over-the-counter medications, vitamins and herbal treatments), as well any tobacco and alcohol use. If you are taking medications that rifampin may weaken or strengthen when taken together, we will determine with your doctor how to best manage these medications. If you are taking particular medications that interact with rifampin in ways that we cannot manage, you will not be eligible for the study due to safety reasons.

Baseline Tests:

- If you are eligible for continuing in the study, we will perform a brief physical exam including your pulse, blood pressure, weight, and height.

- We will ask you about your ability to walk and get around at the present time and about any falls you may have had. We will also ask you to complete a short questionnaire, called the SF-36, about your physical and emotional health. This questionnaire will take about 10 minutes to complete.

- If not recently done as part of your care, we will draw blood (about 2 tablespoons) to test your blood count, glucose, kidney and liver function, blood clotting, and HbA1C (a test of your diabetes control).

- If you are a woman who is post-menopausal, you will be eligible if you meet other study requirements. If you are pre-menopausal and otherwise able to have children, we will do a pregnancy test on a blood sample. If you are pregnant, you are not eligible for the study. If the test indicates that you are not pregnant and you meet other requirements, you will be eligible to go through the study procedures described below.

Randomization to Rifampin or Placebo:

- After the procedures described above and when no further cleaning of your wound and removal of bone is planned, your study drug will be chosen using randomization by a computer. You will have a 50:50 chance of receiving either rifampin or placebo. The study medication and placebo will appear similar.

- You will only take the study drug during the time period when you are being treated with your regularly prescribed antibiotics. In total, you will take 84 capsules of study drug, taking two capsules each day over a period of six weeks.

- The research team will not know whether you are receiving rifampin or placebo throughout the entire study. If any tests done as part of your regular care or part of the research indicate that the study drug may be affecting your safety, the research team will decide whether it needs to know which study drug you are receiving and whether your participation in the study should end.

Research Visits

- **Research visits at 2, 4 and 6 weeks from when you started the study drug.** At these research visits, we will ask about how you are taking your study medications, about any new medications, about any side effects from medications, about any surgery on your foot that you may have had, and perform a brief physical exam. We will ask you to bring in any unused study drug and at the 6-week visit will count the remaining pills. We will also ask you to bring in your study medication diary to each visit. If not already done as part of your regular care, we will take a blood sample (about two tablespoons) to check your blood count, liver and kidney function, and clotting function.

- **Research visit at 3 months from starting the study drug**. We will ask you about any treatments or side effects that you may have had. We will ask you to again fill out the SF-36 questionnaire, which you did at the beginning of the study. We will ask you about how you are walking or getting around and about any falls. We will also perform a brief physical exam. If not already done as part of your clinical care, we will draw a blood sample (about two tablespoons) to check your blood count, glucose, and your liver and kidney functions. If your cast is off, we will examine your wound to see to what extent it has healed.

- **Research visits at 6-months and 12-months from starting the study drug.** At these visits we will examine your wound to see to what extent it has healed and ask you about any treatments you may have received since the previous research visit. We will again ask you to fill out the SF-36, and ask about your walking and any falls you may have had.

- **Each research visit will take about 30-45 minutes.** ***We will try to arrange each research visit to coincide with your regular clinic appointments so as to minimize any extra travel and inconveniences to you. We will also review your VA medical record daily while you are an inpatient and at regular intervals following hospital discharge for information related to the study. If you are not able to attend a research visit due to being in an extended care facility or because you use a VA outpatient clinic (CBOC) for care, we will attempt to arrange alternate ways to contact you by tele-medicine and to have your research bloods drawn.***

Research Telephone Calls:

- **Several days after your discharge from the hospital**, we will call you to find out if you have any questions about taking your study medication and about new or existing medications you are taking. We will ask you about any side effects you may be having from the medications. We will also arrange for your first research visit.

- **At 8 weeks from your start in the study (about two weeks after stopping the study drug),** we will call you to ask about your current and any new medications, any new treatments for your osteomyelitis and any side effects that you may be having. This phone call should last about 10-15 minutes.

- **At 18 and 24 months after the start of the study**, we will call you to find out about any illnesses or treatments you may have had since we last contacted you.

Review of your medical record:

- During your participation in the study, we will be reviewing your VA medical record periodically to obtain any additional information related to the treatment of your osteomyelitis and any new infections. If you received care for your osteomyelitis at non-VA facilities or are planning to do so, we will request your permission to contact these facilities to find out about the treatment provided. During the study, we may also call you if there are gaps in your VA medical record or if we need to clarify any information.

Summary of Participant Responsibilities

- Your participation in the study will include in-person visits and phone calls. Visits will be scheduled, as best as possible, to coincide with your clinical visits.
- You will regularly take the study medication along with the medication prescribed to treat your infection for up to six weeks from your start in the study.
- If you need to miss a scheduled appointment, please contact the research staff to reschedule as soon as you know you will miss the appointment.
- Please notify the study staff of any hospitalizations or major changes to your health, inform any care providers that you are participating in a study, and contact the research staff with any questions you may have.

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		Visits										
		Baseline Evaluation and Study Start	**Follow-up Phone Call** (within 3 days of discharge from the hospital)	**Week 2 Visit** (±7 days)	**Week 4 Visit** (±7 days)	**Week 6 Visit** (± 7 days)	**Week 8 Phone Call** (± 7 days)	**Month 3 Visit** (± 14 days)	**Month 6 Visit** (± 30 days)	**Month 12 Visit** (± 30 days)	**Month 18 Phone Call** (± 30 days)	**Month 24 Phone Call** (± 30 days)
Study Procedures	Informed Consent	X										
	Your Physician informed of enrollment	X										
	Review of your medications and side effects, if any	X	X	X	X	X	X	X	X	X		
	Review of Medical/Surgical Procedures	X		X	X	X	X	X	X	X	X	X
	Randomization and start of study drug	X										
	Physical exam/Vital Signs	X		X	X	X		X				
	Your foot blood pressure and oxygen level measured	X										
	Examination of your foot by doctor					X		X	X	X		
	Blood tests (as needed)	X		X	X	X		X				
	Pregnancy test (as needed)	X										
	Study drug diary review			X	X	X						
	Return study drug capsules to research staff					X						
	Complete questionnaires	X						X	X	X		

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POSSIBLE RISKS OR DISCOMFORTS

The inconveniences and possible discomforts from participating in the study include the phone calls and extra research visits, the blood tests and wound examinations. Drawing blood may cause pain and bruising at the needle site and very rarely, persons may become light-headed or faint. Examining the wound may cause you some discomfort or pain. The questions asked at the research visits will not typically be ones that would cause discomfort but you are free to choose not to answer any question that you wish.

Any use of a medication or procedure has possible risks and discomforts. We have described below some of the more common and some uncommon risks of rifampin taken either alone or with other medications.

Risks from Study Drug

Both rifampin and the placebo may change your urine and other bodily fluids to a different color. The change can be to either a darker yellowish, orange, or reddish color which may vary with diet, age, medical conditions and other factors.

Risks and side effects related to rifampin are listed below:

- Side effects reported by patients or detected by doctors >10% of the time include:
  - Discolorations of skin, urine, sweat, saliva, tears, and/or stool. This change goes away when the drug is stopped and is not believed to be harmful or damaging to your body.
  - Permanent discoloration of soft contact lenses
  - Increased values of liver function tests which return to their regular values after the study drug is stopped.

- Less frequent side effects reported by patients or detected by doctors 1-10% of the time include heartburn, nausea, vomiting, cramps, diarrhea, mild skin rash, dizziness or drowsiness and decrease in blood cell or platelet counts. These side effects are usually temporary and go away after the study drug is discontinued. Nausea may be controlled by dividing the 600 mg daily dose into a dosage of 300 mg twice daily.

- Some very rare side effects may be more serious than those noted above. These include allergic reactions such as hives or swelling of your hands or throat or blistering of your skin, bloody or decreased urine, numbness or tingling, shortness of breath, general weakness, fever and chills, yellowing of your skin or eyes (jaundice), bleeding and blurred vision. These side effects could be due to an underlying medical problem and you will be asked to report them immediately to your doctor or the research team.

- The placebo will contain riboflavin which is also known as vitamin B2. Riboflavin may cause discoloration of urine which goes away when the placebo is stopped and is not believed to be harmful or damaging to your body. The placebo capsules will contain a total of 25 mg of Vitamin B2 (riboflavin), a much higher dose than the daily recommended adequate intake of vitamin B2. This and higher doses have been used safely in other clinical trials and have not caused any side effects other than discoloring bodily fluids.

Additional Risks Associated with Rifampin:

Rifampin can interact with various medications that you may be currently taking, causing them to be either more or less active. This includes some medications used to treat mental health disorders, such as depression and posttraumatic stress disorder, and could cause the symptoms of a mental health disorder treated with an interacting medication to worsen while taking study medication. We will be closely checking with you and reviewing your medical record to detect any new medications you may be taking. Blood tests that may indicate that the study medication may be interacting with other medications will be monitored. The research team may choose to discontinue your participation for reasons mentioned above.

Drinking alcohol in excess may increase the risk for side effects from rifampin. Although drinking alcohol does not exclude you from the study, the research team will advise you to either not drink or maintain only light drinking while you are taking the study drug.

Risks of the usual care you receive are not risks of the research. Those risks are not included in this consent form. You should talk with your health care providers if you have any questions about the risks of usual care.

POTENTIAL BENEFITS

There are no direct benefits to you from taking part in this research. However, the information from this study will help us treat future patients with diabetes who develop osteomyelitis.

ALTERNATIVES TO PARTICIPATING IN THIS RESEARCH

If you choose not to be in the study, you would receive the antibiotics prescribed by the doctors responsible for the treatment of your osteomyelitis. Rifampin may be added to those antibiotics by the treating doctor, but its effectiveness has not been proven.

CONFIDENTIALITY

Taking part in this study will involve collecting private information about you. We will protect this information in a number of ways. The study team will keep confidential all research records that contain your identifiable health information to the extent allowed by law. All paper copies of study forms with the information we collect from you as part of this study will be stored in locked cabinets to which only approved study staff will have access. We will enter your information on computers protected with passwords to which only approved study staff will have access. Any information shared among the VA Medical Centers conducting the study will not identify you.

The study team will collect your social security number (SSN) for this research study. The study team will use your SSN only as necessary to search your VA medical records or to check your non-VA hospitalizations related to the study. We use a unique code instead of your name or SSN to identify you in our study database. If you choose to withhold your SSN, you will not be able to participate in the study.

We will combine your study data with that from others in the study and will only use combined data in papers or talks about the study. You will not be identified in any of these presentations.

We will not share your records or identify you unless we are required to by law. There are times when we may be required to show your records to other people including representatives from the Department of Health and Human Services, Food and Drug Administration, Office of Human Research Protections, the Government Accountability Office, the Office of the Inspector General, the VA Office of Research Oversight, the VA Central IRB, our local Research and Development Committee, and other study monitors. These agencies may look at or copy portions of records that identify you. These agencies are governed by strict regulations to protect the confidentiality of your study data.

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Information about this study has been or will be submitted to http://www.ClinicalTrials.gov as required by U.S. Law. This website will not include information that can identify you. The website summarizes the study and its results. You can search this website at any time.

We will put a prominent notification in your VA medical record stating that you are participating in this research study. This notice lets doctors who are treating you know about what study medications you may be taking and what tests you may be having.

COSTS TO PARTICIPANTS AND PAYMENT

Costs to Participants

You or your insurance will not be charged for any treatments or procedures that are part of this study. If you usually pay co-payments for VA care and medications, you will still pay these co-payments for VA care and medications that are not part of this study.

Payment Offered for Participation:

You will not be paid for joining this study. You will be compensated for your time and travel to and from all scheduled in-person study visits. You will receive $25.00 for less than a total of 50 miles traveled or $50.00 for greater than a total of 50 miles traveled per study visit to help cover travel expenses. If you are an inpatient at the time of your study visit, you may receive the minimum reimbursement. You must agree to the release of personally identifying information such as your name, address and social security number to the <insert VA facility name> so that you may receive your payment. You will be paid by check or direct deposit within 4 to 6 weeks of your study related visit. Due to limitations in the Financial Management System, payments made to participants through Austin Financial Services Center generate Internal Revenue Service Form 1099 regardless of amount. Your social security number will be used in either of these situations. This payment should not affect (reduce or eliminate) any compensation you are eligible to receive for travel to regularly scheduled clinic visits that may occur on the same day as a research visit.

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MEDICAL TREATMENT AND COMPENSATION FOR INJURY

Every reasonable safety measure will be used to protect your well-being. If you are injured as a result of taking part in this study, the VA will provide necessary medical treatment at no cost to you or your insurance unless your injury was due to your not following study procedures.

If you should have a medical concern or get hurt or sick as a result of taking part in this study, call:

DURING THE DAY:

Dr./Mr./Ms. <insert name of local contact> at <insert phone # of local contact>

AFTER HOURS:

Dr. /Mr./Ms.<insert name of local contact> at <insert phone # of local contact>

Emergency and ongoing medical treatment will be provided as needed.

You do not give up any of your legal rights and you do not release the VA from any liability by signing this form.

PARTICIPATION IS VOLUNTARY

It is your decision to make about whether or not to take part in this study. By signing this consent form, you agree to begin full participation. Please contact the research team immediately if you have any questions or concerns about your ability to continue participation in the study at any time. You have the right to change your mind about participation, and may notify us of your decision either verbally or in writing.

If you decide to leave the study early, we will request your permission to continue reviewing your medical record until the end of your expected study participation date. We will continue to use the protected health information we have already collected about you. We will only collect new information if we have your permission. If at any time during the study period we cannot get in contact with you, we will continue to attempt to reach you and will continue to review your medical record until the end of your expected study participation.

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If you do not wish to be in this study or if you leave the study early, you will not lose any benefits to which you are entitled. If you do not give your consent to take part in the study, you will still receive all usual medical care that is available to you. Your decision not to take part will not affect the relationship you have with your doctor or other staff, and it will not affect the usual care that you receive as a patient.

RIGHT OF INVESTIGATOR TO TERMINATE PARTICIPATION

The investigator(s) may stop your participation in this study without your consent for reasons such as: it will be in your best interest; you do not follow study procedures; or you experience a study-related injury.

PERSONS TO CONTACT ABOUT THIS STUDY

If you have any questions about this study, if any problems arise during the study, or if your medications change during the course of study drug treatment, you can call: *(List local SI)* Dr. _____ at _____ during the day. If any medical problems occur in connection with this project the <site> will provide emergency care.

If you have questions about your rights as a study participant, or you want to make sure this is a valid VA study, you may contact the VA Central Institutional Review Board (CIRB). This Board is responsible for overseeing the safety of human participants in this study. You may call the VA Central IRB toll free at <phone number> if you have questions, complaints or concerns about the study or if you would like to obtain information or offer input.

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SIGNIFICANT NEW FINDINGS

Sometimes during the course of a research study, new information becomes available about rifampin or about the treatment of diabetic foot osteomyelitis that might change a person's decision to stay in the study. If this happens, your research doctor will tell you about it and discuss whether you want to continue in the study. If you decide to withdraw from the study, your research doctor will arrange for your medical care to continue. If you decide to continue in the study, you might be asked to sign an updated informed consent form. Your research doctor could also decide it to be in your best interest to withdraw you from the study. If so, he or she will explain the reasons and arrange for your usual medical care to continue.

FUTURE USE OF DATA AND RE-CONTACT

After this study ends, your study data will be stored indefinitely at the Boston Cooperative Studies Program Coordinating Center, Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC).

Study data will be available for use for VA approved research studies relating to rifampin, diabetes, diabetic foot ulcers and osteomyelitis by investigators associated with this study. Data may also be banked in a data repository. Participation in the data repository is optional and will have no impact on your participation in this study. If you agree to participate in the data repository, any researchers not associated with this study may be able to participate in future VA approved projects using the study data, but will not have access to your identifying information such as name, address, and Social Security Number. Any use of this unidentified research data by other researchers must comply with existing regulations and be approved by appropriate oversight bodies including a VA Institutional Review Board (IRB), a committee that protects the rights of research subjects. The IRB may require that you be contacted for your consent prior to the use of your data in a new study if it decides such consent is required for your protection. Please indicate your decision on whether or not you want to participate in the data repository on the HIPAA Authorization form.

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AGREEMENT TO PARTICIPATE IN THE RESEARCH STUDY

The Local Site Investigator or his/her designee has explained the research study to you. You have been told of the risks or discomforts and possible benefits of the study. You have been told of other choices of treatment available to you. You have been given the chance to ask questions and obtain answers.

By signing this document below, you voluntarily consent to participate in this study. You also confirm that you have read this consent, or it has been read to you. You will receive a copy of this consent after you sign it. *(Include if applicable:* A copy of this signed consent will also be put in your medical record.*)*

I agree to participate in this research study as has been explained in this document.		
_____ Participant's Name	_____ Participant's Signature	_____ Date
_____ Name of person obtaining consent	_____ Signature of person obtaining consent	_____ Date

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