INFORMED CONSENT

Protocol Title:

Validate an Easy to Administer Algorithm to Define Penicillin (B-lactam) Allergy Status in STD Outpatients (DMID Protocol #18-0023)

Date of Consent Approval: July 2, 2020

ClinicalTrials.gov: **NCT04620746**

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: Validate an Easy to Administer Algorithm to Define Penicillin (B-lactam) Allergy Status in STD Outpatients (DMID Protocol #18-0023)

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National Institutes of Health (NIH)

**********KEY INFORMATION**********

This is a research study to determine how many patients who report allergy to penicillin-type antibiotics can safely take them in the future.

If you enroll in the study you will answer a questionnaire about your antibiotic allergy history. If the questionnaire shows you have a low-risk of penicillin (PCN) allergy, we will assign you to one of the following testing methods to confirm that you do not have PCN allergy:

1.) a skin test for PCN allergy followed by an oral challenge of amoxicillin, a form of PCN that can be taken by mouth, or
2.) a 2-step oral challenge of amoxicillin.

All study procedures will take place during one or two in-person clinic visits. The length of the study visit will be about 1-3 hours in addition to the clinical appointment. At the end of the study you will be asked for your opinion of the PCN testing procedures and results and given a letter confirming your PCN allergy test results (negative, positive or referral to an allergist for further testing) to share with your medical providers.

There are risks to the PCN allergy testing procedures that are described later in this document. You may or may not benefit from taking part in this study. You may find out whether you have a true allergic reaction to penicillin-type antibiotics. There will be no cost to you to take part in the study.

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Participation is voluntary. We are asking you to take part in a research study. Research studies include only people who choose to take part. The study team members will explain the study to you and will answer any questions you might have. Your regular doctor may be part of this study team. You should take your time to make your decision and discuss with others if needed. You can withdraw from this study at any time.

This is a multi-site study that will take place at several different locations. Because this is a multi-site study, this informed consent form includes two parts. The first part includes information that applies to all study sites. The second part includes information specific to the study site where we are asking you to enroll. This study will enroll about 1000 subjects ages 18 and older, coming for care at outpatient settings where sexually transmitted disease (STD) care is provided in different regions of the United States.

What is the purpose of this research study?
We are asking you to take part in this study because you are here for an appointment and you report a current or past allergy to penicillin-type antibiotics. PCN is one of the most commonly prescribed antibiotics to treat sexually transmitted infections. It is part of a family of antibiotics known as beta-lactams. Many people report allergies to these antibiotics. When patients are tested for allergy with skin testing, only a small number are truly allergic. Patients who report a PCN allergy when they do not have one may not get the best medical treatment for gonorrhea or syphilis. They may receive treatment with a less effective antibiotic.

This study will help investigators determine how many patients who report allergy to penicillin-type antibiotics can safely take them in the future.

What will we ask you to do if you agree to enroll?
This is a one or two-visit study. If you choose to enroll in the study and sign this consent form, the following will happen:

- **Enrollment Visit (Today: length of study visit is about one to three hours in addition to your regular clinical appointment):** We will ask you detailed questions about your antibiotic allergy history and medication use. We will keep your answers confidential. (30 minutes)
- If your antibiotic allergy history shows you to have a higher-risk history of penicillin-type antibiotic allergy, your participation in the study will be complete. We will refer you to an allergist for further testing.
- If your antibiotic allergy history shows you to have a low-risk history of penicillin-type antibiotic allergy, we will assign you to one of two methods of verifying PCN allergy:
  - Method 1 - Skin testing. This is the standard test for PCN allergy. If the skin test shows you are not allergic to PCN, we will offer you an oral challenge of 250 mg of amoxicillin, a form of PCN that can be taken by mouth, to confirm that you do not have PCN allergy.
  - Method 2 - Direct two-step oral challenge with amoxicillin. For low risk persons, many clinics now give a small test dose of amoxicillin, 25 mg, to make sure that there is no reaction. If the first dose of 25 mg of amoxicillin causes no reaction, it is followed by a second dose of 250 mg to confirm that you do not have PCN allergy.
- We will ask you to provide contact information, including your telephone number(s), address, and email.

Method 1 Skin Test Procedures. The skin test involves two steps. Both prick and intradermal tests take about 20 minutes to perform and must both be negative to proceed to the oral challenge. The skin test kit used in this study is approved by the US Food and Drug Administration (FDA) for determining PCN allergy

- **Prick test:** The prick test checks for immediate allergy. This involves pricking the skin of the inner forearm with a drop of 4 different substances. These substances are a very small amount of penicillin at two different concentrations, saline (salt water) which is the negative control, and histamine, which is the positive control. Histamine will cause a small bleb in everyone and we use it to make sure that the test is working correctly. The results of the prick test can be negative, positive or unclear.
  - If the prick test is negative, then intradermal skin testing is done.
- **Intradermal test:** This involves injecting a small amount of 4 different substances just under the skin of the inner forearm. Two different PCN concentrations will be tested twice, and positive histamine control and negative saline controls will be tested once for a total of 6 injections. The results of the intradermal test can be negative, positive or unclear.
  - If the intradermal test results are unclear, the intradermal test may be repeated for a total of 6 injections. The results of the repeat intradermal test can be negative, positive or unclear (20 minutes).
- As part of this research, we are requesting your permission to create and use photographs of your arm to document the results of the skin test. There will be no identifying information included in the photograph except your participant number. The photographs will not be used for advertising or non-study related purposes.
  - You may request that the photographs be stopped at any time.
  - If you agree to allow the photographs and then change your mind, you may ask us to destroy the photographs. If the photographs have had all identifiers removed, we may not be able to do this.
  - We will only use these photographs for the purposes of this research.

  Please indicate your decision below by checking the appropriate statement:

  _____I agree to allow the study team members to make and use photographs of me for the purpose of this study.

  _____I do not agree to allow the study team members to make and use photographs of me for the purpose of this study.

  _____ _____
  Participant Signature Date

- If your prick or intradermal skin test results are positive, we will counsel you that your PCN allergy history is confirmed. Your participation in the study will be complete.
  - We will ask you to complete a short subject acceptability survey to get your opinion of the study procedures and results. (10 minutes).
  - We will give you a letter confirming you do have an allergy to PCN that you can share with your medical providers.
- If your prick or intradermal skin test results are unclear, we will refer you to an allergist for further testing. Your participation in the study will be complete.
  - We will ask you to complete a short subject acceptability survey to get your opinion of the study procedures and results. (10 minutes).
- If your prick and intradermal skin test results are negative, you will undergo an oral challenge of 250 mg of amoxicillin. (60 minutes)

- We will give you a brief physical examination (PE), measure vital signs and test your peak flow (to measure how well air flows in and out of your lungs) before the oral challenge to make sure there are no reasons to withhold the oral dose. Peak flow is measured by blowing into a tube-like device. We will repeat the PE, vital signs and peak flow test after the oral challenge to make sure you did not react to the amoxicillin.
- If you have an unexpected or severe reaction to the oral challenge, we will provide medical treatment and counsel you that your PCN allergy history is confirmed. Your participation in the study will be complete.
  - We will ask you to complete a short subject acceptability survey to get your opinion of the study procedures and results. (10 minutes).
  - We will give you a letter confirming you do have an allergy to PCN that you can share with your medical providers.
- If you have no reaction or a mild expected reaction to the oral challenge, we will counsel you that you do not have an allergy to PCN.
  - We will ask you to complete a short subject acceptability survey to get your opinion of the study procedures and results. (10 minutes).
  - We will give you a letter confirming you do not have an allergy to PCN that you can share with your medical providers.

Method 2 Direct Two-Step Oral Challenge Procedures. The two-step oral challenge begins with a small test oral dose of 25 mg of amoxicillin. Following a 30-minute waiting period with no reaction, a second oral dose of 250 mg is given to verify that there is no allergy to PCN.

- We will give you a brief PE, measure vital signs and test your peak flow (to measure how well air flows in and out of your lungs) before the preliminary oral challenge to make sure there are no reasons to withhold the oral dose. Peak flow is measured by blowing into a tube-like device.
- We will repeat the vital signs after the preliminary dose to make sure you did not react to the amoxicillin before we administer the second dose.
- We will repeat the PE, vital signs and peak flow test after the second oral challenge dose to make sure you did not react to the amoxicillin.
- If you have an unexpected or severe reaction to the oral challenge, we will provide medical treatment and counsel you that your PCN allergy history is confirmed. Your participation in the study will be complete.
  - We will ask you to complete a short subject acceptability survey to get your opinion of the study procedures and results. (10 minutes).
  - We will give you a letter confirming you do have an allergy to PCN that you can share with your medical providers.
- If you have no reaction or a mild expected reaction to the oral challenge, we will counsel you that you do not have an allergy to PCN.
  - We will ask you to complete a short subject acceptability survey to get your opinion of the study procedures and results. (10 minutes).
  - We will give you a letter confirming you do not have an allergy to PCN that you can share with your medical providers.

Pregnant Subjects. Pregnant women will not undergo oral challenge with amoxicillin to verify PCN allergy. If you are pregnant, we will enroll you, administer the questionnaire and perform skin testing. PCN skin testing is safe and is frequently performed during pregnancy. If necessary, we may ask you to return to the clinic at a later date to complete the skin testing.

Follow-up Visits. We may need to follow-up with you by telephone after your visit today to gather additional information. If you cannot stay to complete all the study procedures in one visit, we can schedule you to return to the clinic within 2 weeks to complete the questionnaire, skin test and/or oral challenge.

Overview of Study Procedures: This study will use three different procedures to develop a tool to predict which patients can safely take penicillin-type antibiotics in STD outpatient clinics. The three steps are:

1. Questionnaire (to better understand your antibiotic allergy history)
2. Penicillin Skin Test (if the questionnaire shows you have a low-risk of PCN allergy)
3. Amoxicillin Oral Challenge (if the questionnaire shows you have a low-risk of PCN allergy)

Procedure	Result	Action
PCN allergy history screening questionnaire **(all enrolled subjects)**	Higher-risk for PCN allergy	- Given a letter referring you to an allergist for further evaluation - Study participation completed
	Low-risk for PCN allergy	- Offered skin test for PCN allergy
PCN skin test (prick and intradermal testing) **(subjects with a low-risk of PCN allergy)**	Skin test positive (itchy red bump on skin)	- Counseled that your PCN allergy history is confirmed - Complete subject acceptability survey - Given a letter confirming you do have an allergy to PCN - Study participation completed
	Skin test negative (no reaction on skin)	- Offered an oral challenge of 250mg of amoxicillin - Given brief PE, including measurement of peak flow breathing before and after oral challenge
	Skin test unclear (cannot be interpreted)	- Counseled that your PCN allergy test results are unclear - Complete subject acceptability survey - Given a letter referring you to an allergist for further evaluation - Study participation completed
Amoxicillin oral challenge	Unexpected or severe reaction to oral challenge	- Receive treatment - Counseled that your PCN allergy history is confirmed - Complete subject acceptability survey - Given a letter confirming you do have an allergy to PCN - Study participation completed

Procedure	Result	Action
(subjects with negative PCN skin test*)* **and/or** **(subjects assigned to direct two-step oral challenge)**	No reaction or mild expected reaction to oral challenge	- Counseled that you do not have an allergy to PCN - Complete subject acceptability survey - Given a letter confirming you do not have an allergy to PCN - Study participation completed

Are there any risks to you if you are enrolled in this study?
There are risks associated with participation in any research study. PCN skin tests are generally safe for adults and children of all ages, including infants. The most common risks are listed in the table below.

Study procedure	Risk
Participation in Research	Inconvenience, loss of time, breach of confidentiality
Study forms / questionnaires	Become tired or bored from answering questions. You do not have to answer any question you do not want to answer.
PCN skin test (subjects with a low- risk of PCN allergy)	Slightly swollen, red, itchy bumps (wheals) – most noticeable during the test. Occasionally, an area of swelling, redness and itching may develop a few hours after the test and persist for as long as a couple of days. This can be effectively treated with antihistamines.
Amoxicillin oral challenge (subjects with a low-risk of PCN allergy)	A very small percentage of people (less than 3%) may develop (within 6 hours) a mild allergic reaction which may be itchy skin, rash or hives. This can be effectively treated with antihistamines.

Occasionally, allergy skin tests can produce a severe, immediate allergic reaction. These are largely eliminated by first doing the skin prick test. These can be treated with antihistamines, steroids or both. Infrequently, this can require emergency medical care.

Rarely, an oral challenge in a patient with a low-risk allergy history or who has negative skin test results can produce anaphylaxis, a serious allergic response that often involves swelling, hives, lowered blood pressure and in severe cases, shock requiring emergency care. The risk of this is estimated to be no different than that of an individual who does not have an allergy history. If this occurs, we will initiate treatment and if necessary, provide transport to a facility where you can receive a higher level of care.

Are there any benefits to you if you are enrolled in this study?
You may or may not benefit from being in this study. You may find out whether you have a true allergic reaction to penicillin-type antibiotics.

If you take part in this study, you may help others in the future. The study may help investigators develop rapid screening tools to identify allergy to penicillin-type antibiotics. Correctly labeling PCN allergy may have important impact on treatment for gonorrhea and syphilis to ensure that more patients are treated appropriately. It will provide information that might benefit future patients.

What alternatives do you have if you do not want to be enrolled in this study?
You do not have to participate in this study if you do not want to participate. This will not affect your care at the clinic today and in the future in any way. The staff of this clinic will offer you testing, routine care, and treatment or you can go to the local health department or your private doctor.

How much will it cost you to take part in this study?
We will provide the skin testing that you get as part of this study free of charge. There will be no cost to you to take part in the study. We will not bill your insurance for any of the study procedures.

What happens to data that are collected in the study?
Sharing data is part of research and may increase what we can learn from this study.

Often, data sharing is required as a condition of funding or for publishing study results. It also is needed to allow other researchers to validate study findings and to come up with new ideas.

Your data may be shared:

- directly with research collaborators, other researchers, sponsors, government agencies, publishers of papers and other research partners
- through government or other databases/repositories

Data sharing could change over time, and may continue after the study ends.

We will do our best to protect and maintain your data in a safe way. Generally, if we share your data without identifiers (such as your name, address, date of birth) further review and approval by an Institutional Review Board (IRB) is not needed. However, when we share data, we limit the uses of the information and whether these data can be shared with another research team. If data are shared with identifiers, further IRB review and approval may be needed and the IRB will determine whether additional consent is required.

If you are not comfortable with the use of your data in future research, you may not want to participate in this study.

What about confidentiality?
Participation in research may involve a loss of privacy. We will do our best to make sure that your personal information is kept private. We will keep your records as confidential as is possible under the law. The research records will identify you by a unique study number, not your name. We will not use your individual identity in any reports or publications resulting from this study.

In addition to the efforts of the study team to help keep your personal information private, we have a Certificate of Confidentiality (COC) from the NIH. This certificate means that researchers cannot be forced to tell people who are not connected with this study, including subpoenas from the court system, about your participation. It does not protect information that we have to report by law, such as child abuse or some infectious diseases. The Certificate does not prevent us from disclosing your information if we learn of possible harm to yourself or others, or if you need medical help.

Disclosures that you consent to in this document are not protected. This includes putting research data in the medical record or sharing research data for this study or future research. Having a COC does not prevent you from releasing information about yourself and your participation in the study.

People who may review your records include the Office for Human Research Protections (OHRP) or other government agencies as part of their duties, the FDA, Institutional Review Board (IRB), NIH, study team members, and their designees. An IRB is a committee that watches over the safety and rights of research subjects.

The investigators may use or disclose, for purposes described above, identifiable information (which may include identifiable medical information) related to your being in this study for a minimum of 2 years and for as long (indefinite) as it may take to complete this study.

Because it is important that we can contact you after the study, we will ask for your address, phone number(s), and email. We will also ask for contact information for one other person such as a family member or friend. If we are unable to reach you during the study, we may call your contact to ask for your new contact information. We will not give out your confidential information if we call your contact.

What are my rights as a research subject?
Study participation is completely voluntary. Your participation in this study is completely your choice. You do not have to be a part of this study. Refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled. You can leave this study at any time. If you wish to leave the study, please tell us right away. You will be treated the same no matter what you decide. We will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in the study.

If you decide not to allow the use of your private information, you will be withdrawn from further participation in this study. Any information obtained during your taking part in this study may continue to be used. If you no longer want to be in this study and end your participation, just tell the study team. Your decision will not affect your relationship or the care you are entitled to receive at the clinic.

If I agree to take part in this study, can I be removed from the study without my consent?
The study doctor has the right to take you out of the study if:

- the study (in the opinion of the doctor) would pose a health risk to you,
- you fail to follow the study requirements,
- the study is stopped, or
- you are not eligible for the study.

There may be other reasons to take you out of the study that we do not know at this time. If you are taken out of the study early, we may use or give out your information that has already been collected if the information is needed for this study or any follow-up activities.

What other things should you know about this research study?
A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time. If you would like to review the information for this study, or a summary of the results, ask the study team doctor for the ClinicalTrials.gov study registration number.

What if I have questions?
You can talk to the study team about any questions, concerns, or complaints you have about this study. You may call the lead study investigator, Dr. Jonathan Zenilman at 410-550-9080.

What is the Institutional Review Board (IRB) and how does it protect you?
This study has been reviewed by an IRB, a group of people that reviews human research studies. For this multi-site study, Johns Hopkins has agreed to serve as the single IRB (sIRB) providing oversight for all sites. You may contact the Johns Hopkins IRB by phone at 410-502-2092 or by email at jhmeirb@jhmi.edu if you cannot reach the lead study investigator or wish to talk to someone other than the study team. The IRB can help you if you have questions about your rights as a research participant or if you have other questions, concerns or complaints about this research study.