Consent for Participation in a Clinical Research Study

TITLE: A Multi-Center, Randomized, Open-Label, Comparative Study to Assess the Safety and Efficacy of a Treatment Algorithm to Reduce the Use of Vancomycin in Adult Patients with Blood Stream Infections due to Staphylococci

PROTOCOL NO: **09-0080**

SPONSOR: NIH

INTRODUCTION

This research study is funded through a contract with the National Institutes of Health. Portions of **[Principal Investigator]** and **[his/her research team's]** salaries may be paid using these funds. The study will be conducted at approximately 13 sites across the United States, and 1 site in Spain. The study plans to enroll approximately 500 patients with blood stream infection with staphylococci.

It is important that you read and understand the following information. This study is entirely voluntary. Please read this consent form carefully and take your time making your decision. As your study doctor or study staff discusses this consent form with you, please ask him/her to explain any words or information that you do not clearly understand. We encourage you to talk with your family and friends before you decide to take part in this research study. The nature of the study, risks, inconveniences, discomforts, and other important information about the study are listed below.

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.

PURPOSE OF THE STUDY

You are being asked to participate in this research study because you have a blood infection. The infection is caused by bacteria (a germ) called *Staphylococcus aureus* bacteria (*S. aureus*) or *coagulase negative staphylococci* (CoNS). Both can cause serious health problems and in some people, can even lead to death. In some instances, CoNS can be present in a culture but will not make you ill at all and antibiotic treatment is not needed. Although there are several medicines (antibiotics) used to treat *S. aureus* and CoNS, some of the antibiotics do not work because *S. aureus* and CoNS have developed resistance to them.

You may be given the drug vancomycin to help kill the bacteria in your blood. If you have an allergy or intolerance to vancomycin, and you are selected to be in the planned treatment group of the study, your physician may give you one of the following alternate equivalent antibiotic drugs to treat your infection; either an anti-staphylococcal penicillin

(e.g. Nafcillin and oxacillin in the U.S., or cloxacillin in Spain), a first generation cephalosporin, Cefazolin (to be used only for *S. aureus* bloodstream infections in U.S., not CoNS, but can be used for either *S. aureus* or CoNS bloodstream infections in Spain), or daptomycin in the U.S and Spain. Vancomycin and these alternate equivalent antibiotics are not experimental, and all are approved for use by the U.S. Food and Drug Administration, **or European Medicines Agency (EMA)**. If you are selected to be in the standard of care (SOC) group, your physician will use whichever treatments are normally used at your study site to treat your type of infection. These treatments may prevent *S. aureus* and CoNS from spreading in your body. You might not need any antibiotic treatment.

The purpose of this study is to accurately determine the length of appropriate drug treatment for staphylococcal blood stream infection. The study seeks to address important information about the management of staphylococcal blood stream infections.

BACKGROUND

Blood stream infections, some of which may be intravenous catheter associated, are a common problem that often occurs during hospitalization. These infections are caused primarily by the bacteria *S. aureus* and CoNS and can often be treated with a short course of drugs (antibiotics), or need no antibiotic treatment at all. Severe and life-threatening problems occur in some cases.

Vancomycin has been the primary drug used to treat serious infections due to resistant staphylococci for many years. The overuse of vancomycin has made it less effective in treating staphylococci infections leading to the need to develop new ways to manage and monitor the use of the drug.

STUDY PROCEDURES

If you qualify and agree to participate in the study by signing this informed consent form, you will be randomized (like flipping a coin) to one of two different treatment groups. Each patient will be randomized to either a planned treatment group or a standard of care (SOC) treatment group. The type of bacteria in your blood stream will be identified as either S. aureus or coagulase negative staphylococcus (CoNS) organism. S. aureus has 2 classifications (uncomplicated or complicated) and CoNS has 3 categories (simple, uncomplicated, or complicated), which will determine the how long you are treated. You may not be treated with antibiotics at all if your doctor determines the blood culture contained a bacterial growth that will not make you ill. Patients with complicated infection are not allowed into the study, but if you develop complicated infection after being enrolled in the study and while taking study treatment, you may continue in the trial.

The planned treatment arm's goal is to reduce the length of time you will receive antibiotic. The entire duration of your treatment and participation will vary based on the infection category you have. In the planned treatment arm, patients with *S. aureus* will be treated for about 12 to 44 days and have follow-up for up to 52 days after treatment ends. If you have a CoNS blood infection, you will be treated for about 1 to 30 days, or your doctor may decide you do not need any antibiotic treatment if the no treatment

group has not been capped. Subjects who receive no antibiotic treatment based on the physician's decision may be capped at 80 subjects. For a CoNS blood infection you will have follow-up after treatment ends, or after the day your doctor decides you don't need antibiotic treatment, for up to 38 days.

The entire duration of treatment and participation for patients in the SOC arm will be determined by the patient's primary medical provider according to their usual length of treatment for the type of infection you have, including no treatment at all.

If you receive antibiotic treatment, vancomycin is the preferred drug to be given in both treatment groups. Vancomycin will be given through an IV "intravenous" (needle) in your vein and the infusion will last about 60 minutes.

When you have given your consent, the following will be done as part of the study:

Enrollment Phase

- Collect Medical History
- Collect Antibiotic and other Medication History
- Assess Vital Signs (height, weight, blood pressure, heart rate, temperature)
- Perform Physical Exam
- Perform Blood Tests
- Perform urine or serum pregnancy test if you are female
- Collect Electrocardiogram data (if performed)
- Randomization

Treatment Phase for Patients in the Hospital

- Study Drug Administration daily, if treated
- Assess Vital Signs daily (blood pressure, heart rate, temperature)
- Perform Physical Exam weekly, if you are on antibiotic treatment more than a week
- Perform Clinical Assessment daily
- Perform Blood Tests weekly, if you are on antibiotic treatment more than a week
- Collect information about Concomitant (supplemental) Antibiotics and other supplemental medications daily
- Collect information about SAEs/AEs (Serious Adverse Events/ Adverse Events) daily
- Collect Electrocardiogram data (if performed)
- Perform Transesophageal or Transthoracic Echocardiogram (TEE or TTE) (depending on assigned treatment group). An echocardiogram is an ultrasound of the heart.

End of Treatment or Day of Discharge (whichever occurs first) for Patients in the Hospital;

- Assess Vital Signs (blood pressure, heart rate, temperature)
- Perform Physical Exam

- Perform Clinical Assessment
- Perform Blood Tests
- Collect information about Concomitant (supplemental) Antibiotics and other supplemental medications.
- Collect information about SAEs/AEs
- If treatment continues after discharge and/or for patients who are treated without being admitted to the hospital, study staff will call you 2 times per week and ask about study medication administration, other medications, and adverse events. For patients who are treated without being admitted to the hospital, tests done in person at a clinic visit as standard treatment may be used in the study

Follow-up Phase: Clinic visit or phone call

- You will have approximately 2 follow-up visits in the clinic (preferred) or by phone.
- Perform physical exam, if a clinic visit
- Collect information about Concomitant (supplemental) Antibiotics
- Collect information about SAEs/AEs

TESTING and STORAGE OF Your Staphylococcal Bacteria

Baseline staphylococcal bacteria (germs) will be taken from your first blood culture sample. Your staphylococcal bacteria will be identified only by your study number, isolate identification, and the date it was collected. It will be saved, frozen, and shipped to Dr. Vance Fowler's laboratory at Duke University. Duke University will test your staphylococcal bacteria to determine the lowest amount of vancomycin required to kill the bacteria. Your staphylococcal bacteria may also be stored for future studies to determine the genetic makeup of bacteria and how disease develops.

Your staphylococcal bacteria may also be shipped from Duke University to any of the investigational sites participating in this study to perform additional unspecified testing. Future testing is not part of the current study. No human genetic testing will be performed as part of the current study or future studies/testing.

Please initial the appropriate line to indicate whether or not you agree to allow your blood culture staphylococcal bacteria to be stored for future study testing as described above.

_____ Yes, I agree to have my blood culture staphylococcal bacteria to be stored for future study testing at Duke University and the study sites.

_____ No, I do not agree to have my blood culture staphylococcal bacteria to be stored for future study testing at Duke University and the study sites.

RISKS of STUDY MEDICATION

As a result of your staphylococcal blood stream infection you may be treated with vancomycin, or your doctor may decide you don't need antibiotic treatment. This study seeks to evaluate if doctors can safely shorten the duration of vancomycin therapy for these infections. If the course of antibiotics is too short, possible consequences include

failure to eradicate the staphylococcal infection, progression of infection to other sites, or subsequent relapse of staphylococcal infection. You should discuss this and the following risks with the study doctor and your regular health care provider.

Vancomycin

The bad effects that are rarely reported with the use of vancomycin infusion include kidney failure, elevated serum creatinine and blood urea nitrogen levels (indicators of abnormal kidney function), hearing loss, dizziness, ringing in the ears, low white blood cell (cells that fight infections) count, low platelet (material in blood that helps with clotting) count. A few dozen cases of hearing loss have been reported.

The bad effects that are infrequently reported with the use of vancomycin infusion include inflammation (redness swelling and pain) at the IV site, allergic reactions, fever, nausea, chills, and severe rashes.

ALTERNATIVE TREATMENTS

In appropriate clinical settings, vancomycin alternative drugs that are commercially available and FDA approved for US sites and/or EMA-approved for the site in Spain will also be acceptable for use in the planned treatment group. In the standard of care group, your physician will use any antibiotic that is normally used at your study site for treating your type of infection.

In the planned treatment group, vancomycin can be replaced with an intravenous anti-staphylococcal penicillin (e.g. nafcillin, oxacillin, or cloxacillin) for patients with methicillin susceptible staphylococcal infections (*S. aureus* or CoNS) or a first generation cephalosporin, Cefazolin for patients with methicillin susceptible *S. Aureus* in U.S. or methicillin susceptible *S. Aureus* or CoNS in Spain, or daptomycin for methicillin resistant *S. aureus* infections.

Your study doctor determines whether your treatment should be switched to an alternative drug and which one will be used. If tests show that the alternative drugs are not fighting your infection, other drugs may be available to you that are outside this study if you are in the planned treatment group.

Antistaphylococcal Penicillins

The most common minor bad effects reported with the use of antistaphylococcal penicillins include mild diarrhea, nausea, pain, swelling and redness at the injection site, and vomiting.

The severe bad effects reported with the use of antistaphylococcal penicillins include severe allergic reactions occurring 0.7 to 10% of the time (rash; hives; itching; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips, or tongue); bloody urine or stools; chills; fever; sore throat; joint or muscle pain; pain, redness, or swelling at the injection site; severe diarrhea; stomach pain or cramps; vaginal irritation or discharge; seizures and yellowing of the eyes.

Daptomycin

The most common minor bad effects reported with the use of the antibiotic daptomycin (occurring in 5-11% of patients) include constipation; diarrhea; dizziness; headache; nausea; pain; swelling or redness at the injection site; sore throat; trouble sleeping; vomiting.

The severe bad effects reported with the use of the antibiotic daptomycin (occurring in 3-6 % of patients) include severe allergic reactions (rash; hives; itching; difficulty breathing; chest pain; tightness in the chest; swelling of the mouth, face, lips, or tongue); bloody or watery stools; change in the amount of urine produced – It has been observed that daptomycin is less effective in patients with moderate baseline kidney failure; fever, muscle pain or weakness; numbness or tingling; severe or persistent diarrhea; stomach cramps/pain; swelling (e.g. of the hands, ankles, feet); unusual tiredness or weakness.

Another condition associated with daptomycin (Cubicin) is eosinophilic pneumonia (a disease in which a certain type of white blood cell called an eosinophil fills the lungs). Symptoms include fever, cough, shortness of breath, and difficulty breathing. In general, patients developed eosinophilic pneumonia 2 to 4 weeks after starting daptomycin and they improved when daptomycin was discontinued and steroid therapy was initiated**.** Patients who develop these signs and symptoms while receiving daptomycin should undergo prompt medical evaluation and daptomycin should be discontinued immediately. Treatment with systemic steroids is recommended.

Cefazolin

Cefazolin for Injection should not be taken by patients with known allergy to the cephalosporin group of antibiotics and should be taken with caution in patients with a history of penicillin allergy. The severe bad effects include severe allergic reactions (rash; hives; itching; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips, or tongue);

Increases or decreases in different types of white blood cells, platelets, decreased blood clotting, and increases in liver and kidney enzymes have been reported. Cefazolin should be used with caution when patients have kidney disease and the dose of Cefazolin should be adjusted when the patient has severe kidney disease.

The most common side effects include diarrhea, oral candidiasis (oral thrush), stomach cramps, loss of appetite, inflammation of the colon. Nausea and vomiting have been reported rarely. Pain at the injection site has also been reported.

All Antibacterial Drugs

Clostridium difficile (C. *difficile*) (type of bacteria) associated diarrhea has been reported with the use of nearly all antibacterial drugs including vancomycin and may range in severity from mild diarrhea to fatal inflammation of the colon. Treatment with antibacterial drugs alters the normal bacteria of the colon leading to overgrowth of C. *difficile*.

Risks from Additional Tests

Electrocardiogram (ECG)

You may have an ECG, where small sticky electrodes are applied to your chest, arms, shoulders and legs and the wires are connected to an ECG machine. You will be asked to remain very still. The nurse or technician will record the electrical activity that is created by your heart and processed by the ECG machine and then printed on a special graph paper. You will not experience any pain or discomfort during this test. It takes a few minutes to apply the ECG electrodes, and one minute to make the actual recording. In rare cases, some people may develop skin irritation from the electrode adhesive, but no serious allergic reactions have been reported.

Transesophageal Echocardiogram (TEE)

You may have a TEE (transesophageal echocardiogram), where a tube is placed in your food pipe that connects your mouth to your stomach. You will be given a drug in your IV catheter to help you relax and your throat will be sprayed with a numbing drug. The small tube is passed down your food pipe a short distance as you swallow to allow a view of your heart. Oxygen is given as a preventive measure during the test.

The actual test usually lasts 10 to 30 minutes and requires preparation and observation. TEE is a relatively common test and considered to be safe. You may experience breathing problems, abnormal or slow heart rhythm, allergic or other reactions associated with the drug given for relaxation, and minor bleeding from the tube being in your food pipe. In extremely rare cases (1 in 10,000), TEE may cause tearing of your food pipe resulting in death.

Transthoracic Echocardiogram (TTE)

You may have a transthoracic echocardiogram (TTE) in which ultrasound is used to examine your heart. A colorless gel is applied to your chest and the echocardiogram tube is placed on top of it to look at images of your heart. The echocardiogram technologist will record different parts of your chest to have several views of your heart. This test takes 15 to 20 minutes. There are no known risks from the clinical use of ultrasound during this type of testing.

If you choose not to participate in this study, you will receive the same medical care, including antibiotics (drugs) to treat your bloodstream infection. You should discuss these possibilities with your doctor

Women of Childbearing Age

Being a part of this study while pregnant may expose the unborn child to significant risks. Therefore, pregnant women and women who are nursing their babies will be excluded from the study. If you are a woman of childbearing potential, a pregnancy test will be done (urine or blood will be collected) and it must be negative before you can enter this study. If sexually active, you must agree to use appropriate contraceptive measures for the duration of the study. Medically acceptable contraceptives include: (1) surgical sterilization, (2) approved hormonal contraceptives (such as birth control pills, Depo-

Provera, or Lupron Depot), (3) two barrier methods (such as a condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). The effects of vancomycin on a fetus or unborn child are not fully known and exposure to the drug may involve unforeseeable risks to the fetus. If you do become pregnant during this study, you must inform your study physician immediately.

BENEFITS

You may or may not receive any medical benefit from your participation in this study. In the future, other people with a similar condition may benefit from the knowledge obtained from this study.

One potential benefit of this study depending on your assigned treatment group is that you may receive a shortened antibiotic course, or receive no antibiotic at all, thereby limiting the cost and risk associated with antibiotics.

RIGHT TO WITHDRAW

You may choose not to be in the study, or, if you agree to be in the study, you may withdraw from the study at any time. If you withdraw from the study, no new data about you will be collected for study purposes unless the data concerns an adverse event (a bad effect) related to the study. If such an adverse event occurs, we may need to review your entire medical record. All data that have already been collected for study purposes, and any new information about an adverse event related to the study, will be sent to the study sponsor.

Your decision not to participate or to withdraw from the study will not involve any penalty or loss of benefits to which you are entitled, and will not affect your access to health care at **[Institution/health care provider]**. If you do decide to withdraw, we ask that you contact Dr. **[PI]** in writing and let **[him/her]** know that you are withdrawing from the study. **[His/her]** mailing address is **[address]**.

If you end the study early for any reason, you will have a final visit for follow-up assessment.

You or your legally authorized representative will be informed in a timely manner if new information becomes available that may affect your willingness to continue participation in this study.

Withdrawal of Samples

If you agree to allow your staphylococcal bacteria to be kept for research, you are free to change your mind at any time. We ask that you contact Dr. **[PI]** in writing and let **[him/her]** know you are withdrawing your permission for your staphylococcal bacteria to be used for research. **[His/her]** mailing address is **[address]**. At that time, we will ask you to indicate in writing that you want your staphylococcal bacteria sample destroyed.

INVOLUNTARY WITHDRAWAL

You may be discontinued from participation in the study if:

- Any clinical bad effect, laboratory abnormality, intercurrent illness, or other medical condition or situation occurs such that continued participation in the study would not be in your best interest.
- You have an insufficient response to the study treatment
- NIH, Duke, or IRB terminates the study for any reason
- Another reason occurs (such as administrative reasons or pregnancy)

You are free to withdraw from participating in the study at any time upon request.

COSTS

Any procedures, or tests, such as lab tests, TEE, and TTE, specifically required by the study will be performed or provided to you free of charge. However, routine medical care, including drugs, tests, and procedures that are usually done for your condition (care you would have received whether or not you were in this study) will be charged to you or your insurance company. You may wish to contact your insurance company to discuss this further.

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

CONFIDENTIALITY

Study records that identify you will be kept confidential as required by law. Federal Privacy Regulations provide safeguards for privacy, security, and authorized access. Except when required by law you will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records disclosed outside of **[Institution/health care provider]**. For records disclosed outside of **[Institution/health care provider**], you will be assigned a unique code number. The key to the code will be kept at **[Institution to identify where code will be kept]**.

Every effort will be made to maintain the confidentiality of your study records. Your medical and study records may be reviewed and copied in order to meet federal and state regulations. Reviewers may include:

- Representatives from Spanish regulatory authorities, for patients enrolled at the Spanish site
- The National Institute of Allergy and Infectious Disease (a division of the National Institute of Health) or designee
- Duke Clinical Research Institute
    - The Data Coordinating Center
    - Designated associates
- Institutional Ethics Committee Review Board at (Institution/healthcare provider)

Your study records will not be used for any purpose other than as described in this consent document and will not be disclosed to anyone not described in this document without your permission. While the information and data resulting from this study may

be presented at scientific meetings or published in a scientific journal, your identity will not be revealed.

Authorization for Use and Disclosure of Protected Health Information

If you sign this consent form, you are giving your permission for the following people or groups to give the researchers certain information about you:

- Any health care providers, professionals or agencies who have provided you health services or treatment, such as physicians, clinics, hospitals, home health agencies, diagnostics centers, laboratories, treatment or surgical centers, or government health agencies
- Any agencies that provide payment for health care, such as insurers, or government agencies

If you sign this form, this is the health information about you that the people or groups listed above may give to the researchers to use in this research study**:**

- Laboratory results such as tests that measure blood counts and tests to measure the function of your liver, kidneys and heart
- Radiology tests such as images of your heart
- Electrical activity of your heart
- Medications you have taken prior to and during the study
- Physical assessments by care providers
- Information about your medical history
- Reactions you may have to treatments
- Other treatments or assessment performed prior to and during the study

This information may be shared with, used by, or seen by collaborating researchers, the sponsor of the research study, the sponsor's representatives, and government agencies if needed to oversee the research study. Anybody who receives your information from us could share it with others without your permission and it would no longer be protected by federal privacy laws. We can use or share your information in a way that nobody can tell it is your information.

If you want to participate in this study, you have to sign this authorization to allow access to your medical records. If you choose to not sign it, you are still able to receive your medical treatment that is not related to the study. If you do sign it, you can change your mind later by writing a letter that states you are taking back your permission. Mail the letter to *[Address]* or you can send us an email at *[List email address]* Stopping your authorization will prevent sharing of information in the future, but will not affect any information that has already been shared.

There is no expiration date for the use of this information as stated in this authorization.

You will be given a copy of this authorization. If the results of this study are made public, information that identifies you will not be used.

The purpose of collecting and sharing information is to learn about how vancomycin affects your blood stream infection and any bad effects you may experience as a result of receiving vancomycin and/or any alternative drug.
Dr. Fowler's Laboratory, is being used for the blood culture staphylococcal bacteria analysis and will only receive samples identified with a subject number, isolate identification and collection date/time.

STUDY RECORDS RETENTION

This consent/authorization will be retained along with your study records at **[Institution/Health care provider].** When your doctor receives notification from the sponsor to dispose of the study records, the research information not already in your medical record will be destroyed or information identifying you will be removed from study results at {**Institution/Health care provider}** Any information in your medical record will be kept indefinitely

Compensation in Case of Injury

Immediate necessary medical care is available at **[Institute name]** in the event that you are injured as a result of your participation in this research study. However, there is no commitment by **[Institute name]**, or your **[Institute name]** physicians to provide monetary compensation to you or free medical care to you in the event of a study-related injury. For questions about the study or a research-related injury, contact **[Name]** at **[Phone number]** during regular business hours and at **[Phone number]** after hours and on weekends and holidays.

QUESTIONS

If you have any questions about this study you may contact **[Insert PI name and phone number]**

If you have questions regarding your rights as a participant in this study, you may contact **[Insert name and phone number]** at the **[Institutional Review Board or Office of Risk Management]**.

THIS SPACE INTENTIONALLY LEFT BLANK

STATEMENT OF CONSENT

"The purpose of this study, procedures to be followed, risks and benefits have been explained to me. I have been allowed to ask the questions I have, and my questions have been answered to my satisfaction. I have been told whom to contact if I have additional questions. I have read this consent form and agree to be in this study, with the understanding that I may withdraw at any time without affecting my future medical care. I have been told that I will be given a signed copy of this consent form."

"By signing this form, I have not waived any of the legal rights I otherwise would have as a patient."

_____
Printed Name of Subject

_____ _____
Signature of Subject Date

_____
Printed Name of Legally Authorized Representative (if applicable)

_____ _____
Signature of Legally Authorized Representative (if applicable) Date

_____
Relationship of Legally AuthorizedRepresentative to Subject (if applicable)

_____
Printed Name of Person Obtaining Consent

_____ _____
Signature of Person Obtaining Consent Date

_____
Printed Name of Witness (if applicable)

_____ _____
Signature of Witness (if applicable) Date