
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

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STATEMENT OF COMPLIANCE

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

- United States (US) code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, and 21 CFR Part 56)
- ICH E6; 62 Federal Register 25691 (1997)
- Requirements for the conduct of clinical trials, including GCP, as implemented in the Clinical Trial Directive (Directive 2001/20/EC) and the GCP Directive (2005/28/EC)

All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Subjects Protection Training.

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The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ANOVA	Analysis Of Variance
AST	Aspartate Aminotransferase
BAL	Bronchoalveolar Lavage
BCX	Blood Culture
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CD	Compact Disc
CDC	Center for Disease Control and Prevention
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
cfu	Colony-forming Units
CIOMS	Council for International Organizations of Medical Sciences
CMH	Cochran-Mantel Haenszel
CoNS	Coagulase Negative Staphylococcus
CONSORT	Consolidated Standards of Reporting Trials
CQMP	Clinical Quality Management Plan
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CVC	Central Venous Catheter
DCRI	Duke Clinical Research Institute
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH, DHHS
DSMB	Data and Safety Monitoring Board
DV	Discharge Visit
EC	Executive Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capturing
FDA	Food and Drug Administration
FWA	Federalwide Assurance
GCP	Good Clinical Practice
HACEK	<i>Haemophilus</i> species, <i>Actinobacillus actinomycetemcomitans</i> , <i>Cardiobacterium hominis</i> , <i>Eikenella corrodens</i> , and <i>Kingella</i> species

HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDSA	Infectious Diseases Society of America
IE	Infective Endocarditis
IEC	Independent or Institutional Ethics Committee
IEOT	Inpatient End of Treatment
IRB	Institutional Review Board
ITT	Intent- to -Treat
JAMA	<i>Journal of the American Medical Association</i>
LAR	Legally Authorized Representative
MDRD	Modification of Diet in Renal Disease study
MedDRA [®]	Medical Dictionary for Regulatory Activities
MIC	Minimum Inhibitory Concentrations
MOP	Manual of Operating Procedures
N	Number (typically refers to patients)
NEJM	<i>New England Journal of Medicine</i>
NIAID	National Institute of Allergy and Infectious Diseases, NIH, DHHS
NIH	National Institutes of Health
OCRA	Office of Clinical Research Affairs, DMID, NIAID, NIH, DHHS
OHRP	Office for Human Research Protections
OHSR	Office for Human Subjects Research
ORA	Office of Regulatory Affairs, DMID, NIAID, NIH, DHHS
PB	Privacy Board
PDF	Portable Document Format
PENS	Potentially Effective Non-study Antibiotic
PHI	Protected Health Information
PI	Principal Investigator
PP	Per Protocol Population
PSB	Protected Specimen Brush
RBC	Red Blood Cell
SAE	Serious Adverse Event/Serious Adverse Experience
SBP	Systolic Blood Pressure
SGOT	Serum Glutamic-Oxalocetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase

SI	Sub-Investigator
SOC	Standard of Care
TEE	Transesophageal Echocardiogram
TOC	Test of Cure
TTE	Transthoracic Echocardiogram
US	United States
WBC	White Blood Cell
WHO	World Health Organization

PROTOCOL SUMMARY

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
Phase:	II
Population:	Approximately 500 patients at least 18 years of age who have a blood stream infection with staphylococci
Number of Sites:	Thirteen sites in the United States (US) and one site in Europe
Study Duration:	Six years
Patient Participation Duration:	Duration of treatment varies based on algorithm or standard of care (SOC) and organism identified (<i>S. aureus</i> vs coagulase negative staphylococcus). In the algorithm arm, patients will be treated for 14 (-/+2) days for uncomplicated <i>S. aureus</i> , or 28-42 (-/+2) days if complicated <i>S. aureus</i> develops within the treatment period after randomization. In the algorithm arm, simple CoNS will be treated for 0 – 3 (+1) days, uncomplicated CoNS will be treated for 5 (-/+1) days, or 7-28 (-/+2) days if complicated CoNS develops within the treatment period after randomization. Duration in the SOC arm will be determined by the patient's primary medical provider.
Description of Agent or Intervention:	Vancomycin or protocol-approved alternate antibiotic, with duration determined by clinical treatment algorithm vs SOC
Objectives:	<p>Primary:</p> <ul style="list-style-type: none">• To demonstrate that the clinical efficacy of algorithm-based treatment of patients with staphylococcal blood stream infection is noninferior to current standard of care.• To evaluate the safety of algorithm-based treatment as an alternative to current standard of care. <p>Secondary:</p> <ul style="list-style-type: none">• To demonstrate that algorithm-based treatment of patients with staphylococcal blood stream infection can decrease

antimicrobial usage when compared to current standard of care (SOC).

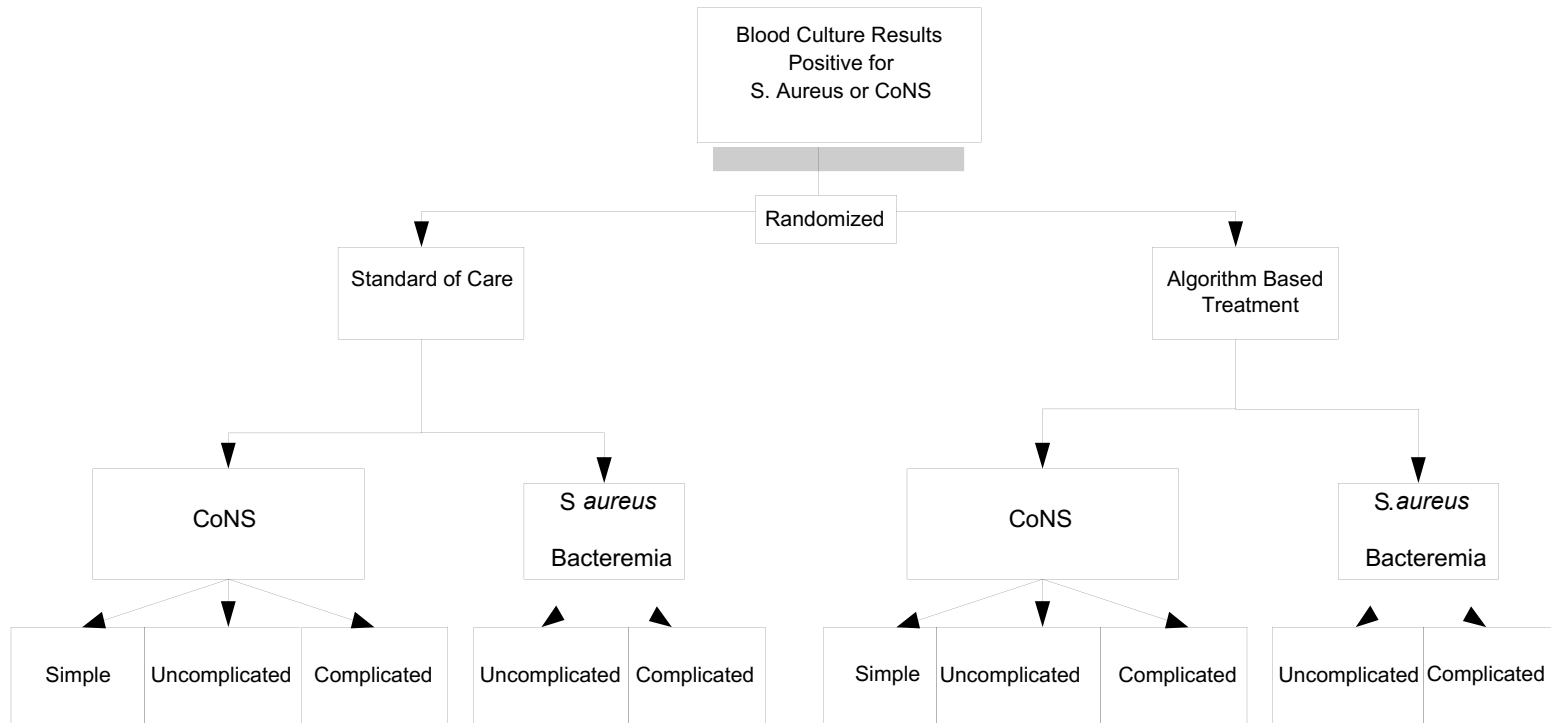
Description of Study Design:

Multi-center randomized open label algorithm-based clinical trial.

Estimated Time to Complete Enrollment:

It is estimated that sites will enroll 2 patients per month per site and that enrollment will be completed within four years.

Figure 1: Schematic of Study Design



*** Complicated infection is one of the protocol exclusions however, it is not reason to withdraw patient when diagnosed following randomization.**

Algorithm Based Treatment

Table 1: Algorithm Based Treatment; Definition of Clinical Classification

<i>Staphylococcus aureus</i> Blood Stream Infection	
<p>Uncomplicated</p> <p>14 (-/+2) calendar days of treatment - All of the following:</p> <ul style="list-style-type: none"> Intravascular catheter source of infection (if present) removed within 5 days of initial blood culture draw. Negative follow up blood culture (drawn 24 - 72 hours following initial blood culture collection ^b) Defervesce (Oral temperature < 38.0C) within 72 hours of initial positive blood culture draw. Normal echocardiogram^a No symptoms or signs of metastatic infection such as vertebral osteomyelitis, endocarditis, septic thrombophlebitis (superficial septic thrombophlebitis is permitted) No indwelling intravascular prosthetic devices (e.g., prosthetic cardiac valve, intravascular permanent pacemaker/ defibrillator) ^c 	<p>Complicated (all other) ^a</p> <p>28-42 (-/+2) calendar days of treatment - Any of the following:</p> <ul style="list-style-type: none"> Positive follow-up blood culture for <i>S. aureus</i> Persistent fever (Oral temperature ≥ 38.0 C) for > 72 hours following initial positive blood culture collection Echocardiography reveals evidence of endocarditis Symptoms or signs of metastatic infection, such as vertebral osteomyelitis, endocarditis, septic thrombophlebitis (superficial septic thrombophlebitis is permitted) <p>Reminder: Complicated infection is one of the protocol exclusions. However, it is not reason to withdraw patient when diagnosed after randomization but before the completion of the treatment period for uncomplicated <i>S. aureus</i>.</p>

Coagulase negative staphylococcal Blood Stream Infection		
<p>Simple</p> <p>0-3 (+1) calendar days of treatment - All of the following:</p> <ul style="list-style-type: none"> Single blood culture positive for coagulase negative staphylococci No signs or symptoms of local infection Negative follow up blood culture (drawn 24 -168 hours following initial blood culture collection) No symptoms or signs of metastatic infection, such as vertebral osteomyelitis, endocarditis, septic thrombophlebitis (superficial septic thrombophlebitis is permitted) No indwelling intravascular prosthetic devices (see above) 	<p>Uncomplicated</p> <p>5 (-/+1) calendar days of treatment</p> <p><u>EITHER:</u></p> <ul style="list-style-type: none"> ≥ 2 sets blood cultures positive for coagulase negative staphylococci from samples drawn ≤ 24 hours apart (e.g. 23:50 hours Tues. night and 14:00 Wed. afternoon). <p>Or</p> <ul style="list-style-type: none"> Single set of blood cultures positive for coagulase negative staphylococci PLUS signs/ symptoms of infection at catheter site (e.g., focal pain, induration, erythema, drainage, etc). <p>PLUS ALL of the following</p> <ul style="list-style-type: none"> Removable focus (intravascular catheter) removed, if present, within 5 days of initial blood culture draw. Negative follow up blood culture (drawn 24 - 168 hours following initial blood culture collection) No symptoms or signs of metastatic infection, such as vertebral osteomyelitis, endocarditis, septic thrombophlebitis (superficial septic thrombophlebitis is permitted) No indwelling intravascular prosthetic devices (see above). 	<p>Complicated</p> <p>7 - 28 (-/+2) calendar days of treatment – Any of the following:</p> <ul style="list-style-type: none"> ≥ 2 sets blood cultures positive for CoNS from samples drawn > 24 hours apart. Symptoms or signs of metastatic infection, such as vertebral osteomyelitis, endocarditis, septic thrombophlebitis (superficial septic thrombophlebitis is permitted). <p>Reminder: Complicated infection is one of the protocol exclusions. However, it is not reason to withdraw patient when diagnosed after randomization but before completion of the treatment period for the baseline clinical classification of bacteremia (i.e. simple or uncomplicated CoNS).</p>

- Echocardiography (TEE preferred) mandated for algorithm *S. aureus* patients
- Follow-up blood cultures should be drawn 24-72 hours after the index culture; however, if this is not feasible, for example because the index cultures did not turn positive until >72 hours has elapsed, then follow-up cultures should be obtained within 24 hours of randomization
- Coronary artery stents, inferior vena cava (IVC) filters, non-hemodialysis grafts > 90 days following implantation, hemodialysis grafts not used within past 12 months and not previously infected, synthetic hernia repair mesh, and non-arthroplasty orthopedic prostheses including pins or plates permitted

1 KEY ROLES

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2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

2.1.1 Vancomycin Overuse and Resistance

Antimicrobial resistance represents an urgent unmet global medical need. Although sepsis (blood stream infection) is a leading cause of death in the United States (US), the number of treatment options for infected patients is decreasing. This decrease is driven in part by rising rates of antimicrobial resistance among many pathogenic bacteria. Simultaneously, the pipeline of new antibiotics is dwindling just as the clinical need for these novel treatments is expanding.^{1,2} This dual threat of increasing antimicrobial resistance and decreasing numbers of anti-infectives under development underscores the need to identify new strategies to maximize the clinical utility of existing antibiotics through more rational utilization of this precious national resource.

For more than three decades, vancomycin has been the mainstay antibiotic for the treatment of serious infections due to resistant staphylococci. This reliance on vancomycin has led to significant overuse. For example, in 1995, over 14,000 kilograms of vancomycin were used in the US and Western Europe alone.³ This overuse of vancomycin has ultimately contributed to a diminished clinical utility of the antibiotic in staphylococci. Several reports have documented increasing resistance to vancomycin in clinical isolates of *S. aureus*^{4,5,6,7} and coagulase negative staphylococci^{8,9,10,11,12,13} as well as rising vancomycin minimum inhibitory concentrations (“MIC creep”) among large surveys of clinical strains of staphylococci⁸.

Nowhere is the challenge of vancomycin overuse more pervasive than among hospitalized patients with suspected or confirmed blood stream infection. Sepsis is a leading cause of nosocomial mortality and staphylococci are the leading cause of sepsis in the US.^{14,15}

Mortality among patients with untreated blood stream infection exceeds 80%.¹⁶ As a result, many patients with staphylococcal blood stream infection require antibiotic therapy, often with vancomycin. However, every patient with staphylococci isolated from blood cultures may not require prolonged treatment with vancomycin.

2.1.2 Management of Intravenous Catheter-associated Infections

Intravenous catheter-associated blood stream infection is a frequent nosocomial complication. Caused primarily by staphylococci (*S. aureus* and coagulase negative staphylococcus [CoNS]), these infections can often be treated with a short course of antibiotics. However, in a minority of cases severe, even life-threatening complications occur, including but not limited to: infective endocarditis, septic arthritis, deep tissue abscess, vertebral osteomyelitis, epidural abscess, septic thrombophlebitis, psoas abscess, and meningitis.^{17,18,19}

Catheter removal is a critical component in the treatment of catheter-related infections.²⁰ However, there are clinical situations—such as patients with limited vascular access options—

where the intravenous catheter needs to be left in place. Therefore, treatment of catheter-associated infections becomes complicated in terms of the decision to remove the catheter as well as in determining the drug of choice and the duration of treatment.

In 2001, the Infectious Diseases Society of America (IDSA) published guidelines for the management of catheter-associated infections.²⁰ Guidelines were revised in 2009.²¹ Catheter removal was recommended in most cases of non-tunneled catheter-associated infections following completion of blood cultures and other appropriate diagnostic tests. It was also recommended that intravenous therapy be initiated on the basis of clinical clues, the patient's condition, and the potential pathogen involved. Unfortunately, these clinical clues are far from perfect in establishing a diagnosis of catheter-associated infection because of their poor specificity and sensitivity.²¹ For example, in a recent prospective cohort study of patients with central venous catheter-associated *S. aureus* blood stream infection, we demonstrated that the sensitivity of physical examination findings for ultrasonogram-confirmed catheter-associated thrombosis was only 24%.¹⁹ Blood cultures that yield CoNS or *S. aureus* increase the suspicion for catheter-associated infections, but do not exclude additional sites of infection, such as endocarditis, septic thrombophlebitis, or septic arthritis.

Additionally, management of staphylococcal bloodstream infection may differ according to whether the infection is nosocomial, health care-associated, or community acquired. This trial will enroll patients with staphylococcal infections from these various settings, to better delineate appropriate management of staphylococcal bacteremia across all settings encountered in clinical practice.

2.2 Rationale

Accurately differentiating patients with severe staphylococcal blood stream infection requiring extended courses of vancomycin from those patients whose condition could safely receive brief durations of therapy could allow clinicians to treat patients appropriately while simultaneously limiting unnecessary vancomycin use. In this clinical trial, we will describe treatment algorithms based upon clinical, echocardiographic, and laboratory features to identify which patients may safely and successfully undergo shortened antibiotic therapy.

The purpose of this clinical trial is to accurately determine the complication potential and thus the length of appropriate therapy for staphylococcal blood stream infection, allowing careful stewardship of our remaining antibiotic resources. In addition, the current protocol seeks to address important aspects of the management of staphylococcal blood stream infections.

This study is particularly important since there are no clearly defined universally accepted guidelines for the treatment duration of patients with blood stream staphylococcal infections.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

This clinical trial compares the efficacy and safety of algorithm-based antibiotic therapy to standard therapy for the treatment of staphylococcal bacteremia. The primary potential risk of the study is that the duration of antibiotic therapy is inappropriately short. For example, patients randomized to algorithm-based therapy may receive shorter courses of antibiotic therapy than required, while patients in the standard treatment arm may receive longer courses of antibiotic therapy than necessary. 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.

All antibiotics used in this trial are commercially available; however, a second risk is that antibiotic therapy will lead to adverse events (AEs) related to the antimicrobial therapy. The package insert should be consulted prior to prescription and dosing of any of the protocol-approved, commercially-available antibiotics to be provided to patients as part of this clinical study. A summary of major AEs associated with these antibiotics is provided below. Please consult the relevant package insert for a more detailed description of these AEs.

All Antibacterial Agents:

- *Clostridium Difficile Associated Diarrhea (CDAD)* - CDAD has been reported with use of nearly all antibacterial agents and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Vancomycin:

- *Contraindications* – Vancomycin hydrochloride is contraindicated in patients with known hypersensitivity to this antibiotic
- *Nephrotoxicity* – Rarely, renal failure, principally manifested by increased serum creatinine or blood urea nitrogen (BUN) concentrations, especially in patients given large doses, has been reported.
- *Ototoxicity* – A few dozen cases of hearing loss associated with vancomycin hydrochloride have been reported. Most of these patients had kidney dysfunction or a pre-existing hearing loss, or were receiving concomitant treatment with an ototoxic drug. Vertigo, dizziness, and tinnitus have been reported rarely.
- *Hematopoietic* – Reversible neutropenia, usually starting one week or more after onset of therapy with vancomycin hydrochloride or after a total dosage of more than 25 g, has been reported for several dozen patients. Neutropenia appears to be promptly

reversible when vancomycin hydrochloride is discontinued. Thrombocytopenia has rarely been reported.

- *Phlebitis* – Inflammation at the injection site has been reported
- *Gastrointestinal* – Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment
- *Miscellaneous* – Infrequently, patients have been reported to have had anaphylaxis, drug fever, nausea, chills, eosinophilia, rashes (including exfoliative dermatitis), Stevens-Johnson syndrome, toxic epidermal necrolysis, and rare cases of vasculitis in association with the administration of vancomycin.

Anti-Staphylococcal Penicillins (e.g. penicillin, nafcillin, oxacillin, cloxacillin):

- *Contraindications* – A history of a hypersensitivity (anaphylactic) reaction to any penicillin is a contraindication.
- *Nervous System Reactions* – Neurotoxic reactions similar to those observed with penicillin G may occur with large intravenous doses of anti-staphylococcal penicillins, especially with patients with renal insufficiency.
- *Urogenital Reactions* – Renal tubular damage and interstitial nephritis have been associated infrequently with administration of anti-staphylococcal penicillins. Manifestations of this reaction may include rash, fever, eosinophilia, hematuria, proteinuria, and renal insufficiency.
- *Gastrointestinal Reactions* – Pseudomembranous colitis has been reported with the use of anti-staphylococcal penicillins. The onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment.
- *Metabolic Reactions* – Hepatotoxicity, characterized by fever, nausea, and vomiting associated with abnormal liver function tests, mainly elevated SGOT levels, has been associated with the use of anti-staphylococcal penicillins.

Cubicin® (daptomycin)

- *Contraindications* - CUBICIN® is contraindicated in patients with known hypersensitivity to daptomycin.
- *Eosinophilic Pneumonia* – Eosinophilic pneumonia has been reported in patients receiving CUBICIN®. In reported cases associated with CUBICIN®, patients developed fever, dyspnea with hypoxic respiratory insufficiency, and diffuse pulmonary infiltrates. In general, patients developed eosinophilic pneumonia 2 to 4 weeks after starting CUBICIN® and improved when CUBICIN® was discontinued and steroid therapy was initiated. Recurrence of eosinophilic pneumonia upon re-exposure has been reported. Patients who develop these signs and symptoms while receiving CUBICIN® should be discontinued immediately. Treatment with systemic steroids is recommended.
- *Severe Adverse Events* – Those 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; 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.

- *Miscellaneous* – The most common minor adverse 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.

Cefazolin

- *Contraindications* – Cefazolin for Injection is contra-indicated in patients with known allergy to the cephalosporin group of antibiotics.
- *Warnings* - Before therapy with Cefazolin is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefazolin, cephalosporins, penicillins, or other drugs. If this product is given to penicillin-sensitive patients, caution should be exercised because cross-hypersensitivity among beta-lactam antibiotics has been clearly documented and may occur in up to 10% of patients with a history of penicillin allergy.
- *Gastrointestinal* - Diarrhea, oral candidiasis (oral thrush), vomiting, nausea, stomach cramps, and anorexia. Nausea and vomiting have been reported rarely.
- *Allergic* - Anaphylaxis, eosinophilia, itching, drug fever, skin rash, Stevens-Johnson Syndrome.
- *Hematologic* - Neutropenia, leukopenia, thrombocytopenia, thrombocytopenia
- *Hepatic and Renal* - Transient rise in SGOT, SGPT, and alkaline phosphatase levels has been observed without clinical evidence of renal or hepatic impairment.
- *Local Reactions* - Rare instances of phlebitis have been reported at the site of injection.
- *Other Reactions* - Genital and anal pruritus (including vulvar pruritus, genital moniliasis, and vaginitis)

2.3.2 Known Potential Benefits

One potential benefit is for improved overall patient care in the algorithm-based treatment arm. By making use of a careful, systematic approach to a common clinical problem, infection severity may be accurately identified. In this way, patients with complicated staphylococcal bacteremia may appropriately receive extended courses of antibiotic treatment, while those with simple or uncomplicated staphylococcal bacteremia may safely receive abbreviated antibiotic courses, thereby limiting the cost and risk associated with parenteral antibiotics. That is, an individual patient in the study may safely receive a shorter course of treatment than s/he would have otherwise, thereby reducing risk of treatment-related adverse effects and decrease resistance. Additionally, there is potential benefit in that the information gained from this study will support future studies leading to improved care for patients requiring antibiotic treatment.

3 OBJECTIVES

3.1 Study Objectives

3.1.1 Primary Objectives

To demonstrate that the clinical efficacy of algorithm-based treatment of patients with staphylococcal blood stream infection is noninferior to current standard of care (SOC).

To evaluate the safety of algorithm-based treatment as an alternative to current SOC.

3.1.2 Secondary Objective

To demonstrate that algorithm-based treatment of patients with staphylococcal blood stream infection can decrease antimicrobial usage when compared to current SOC.

3.1.3 Exploratory Analyses

The exploratory analyses include comparisons of the treatment effects for the endpoints, cure rate, days of antibiotic use and days to discontinuation using survival analysis methods for the following diagnostics subgroups in the ITT and PP populations, respectively:

1. Cohort of Coagulase Negative Staphylococcus
2. Sub-cohort within Coagulase Negative Staphylococcus and simple case
3. Sub-cohort within Coagulase Negative Staphylococcus and uncomplicated case
4. Cohort of *S. aureus* Bacteremia
5. Sub-Cohort within *S. aureus* Bacteremia and uncomplicated case

In addition, potential associations between vancomycin MIC values and clinical outcomes (e.g., cure rates, duration of bacteremia on treatment, and incidence of development of new complicated staphylococcal infection) will be assessed as part of exploratory efficacy analyses.

3.2 Study Outcome Measures

The primary analyses are 1) to compare cure rate at Final Test of Cure (TOC) evaluation, between the proposed treatment algorithm and the SOC treatment and 2) to evaluate the safety of algorithm-based treatment as an alternative to current SOC. Final TOC evaluation will occur at different time points for *S. aureus* and CoNS to reflect the different clinical characteristics of infections with each organism. Final TOC for CoNS infections will be evaluated at 28 ± 4 days following last dose of antibiotic. Final TOC evaluation for *S. aureus* infections will be evaluated at 42 ± 4 days following last dose of antibiotic. The secondary analysis is to compare the days of antibiotic use between the proposed treatment algorithm and the SOC treatment.

Primary efficacy endpoint is the outcome at final TOC evaluation by treatment group.

Primary safety and efficacy analysis will be conducted in the Intent-to-Treat (ITT) population by evaluating the difference in cure rates at final TOC by treatment group and calculating 95% confidence intervals around the difference in cure rates among study patients randomized to algorithm-based treatment vs cure rates among study patients randomized to standard treatment. Safety analysis will include analysis of all AEs leading to study drug withdrawal and all SAEs. In addition, if patient changes from vancomycin or a protocol-approved study antibiotic to another protocol-approved study antibiotic due to AE associated with study drug, incidence rates will be calculated from these data.

3.2.1 Secondary Outcome Measures

The secondary outcome measure is antibiotic days by treatment group.

Secondary outcome analysis will be conducted in the PP population by evaluating the difference in antibiotic days (vancomycin or approved vancomycin alternative) by treatment group and calculating 95% confidence intervals around the difference in antibiotic days among study patients randomized to algorithm-based treatment vs among study patients randomized to standard treatment. The patients identified with a complicated staphylococcal infection after randomization but prior to the completion of study treatment for their baseline clinical classification of bacteremia (i.e. Simple CoNS, Uncomplicated CoNS, Uncomplicated *S. aureus*) will be excluded in the duration of treatment analysis as the duration of treatment for both Algorithm-based and Standard treatment groups will be identical. Antibiotic days will also be compared by treatment group for the various diagnostic subgroups in the ITT and PP populations as described in the exploratory outcome measures below.

3.2.2 Exploratory Outcome Measures

The exploratory outcome measures include:

- a. cure rate, days of antibiotic use and days to discontinuation using survival analysis methods for the following diagnostics subgroups in the ITT and PP populations, respectively:
 1. Cohort of Coagulase Negative Staphylococcus
 2. Sub-cohort within Coagulase Negative Staphylococcus and simple case
 3. Sub-cohort within Coagulase Negative Staphylococcus and uncomplicated case
 4. Cohort of *S. aureus* Bacteremia
 5. Sub-Cohort within *S. aureus* Bacteremia and uncomplicated case;
- b.) vancomycin MIC values to investigate potential associations to clinical outcomes (e.g., cure rates, duration of bacteremia on treatment, and incidence of development of new complicated staphylococcal infection).

3.2.3 Definitions

3.2.3.1 Definition of primary efficacy endpoint

Outcome at early and final TOC will be assessed as either “Success”, “Failure”, or “Non-Evaluable”.

Success:

Patients will be classified as “Success” at the respective TOC visit if they meet all of the following Criteria:

- Were judged “Cure” by the Site Principal Investigator (PI) or designated Sub-Investigator (SI) at the respective TOC visit (see Section 3.2.3.8 below for definition of “Cure”).
- Exhibited none of the criteria for “Failure” or “Non-Evaluable” outcomes.

Failure:

Patients will be classified as “Failure” at or before final TOC if they meet any of the following Criteria*:

- Were judged “Failure” at early or final TOC by the Site PI or designated SI
- Treatment was changed due to Unsatisfactory Clinical Response defined as failure to resolve clinical manifestations of infection (e.g. fever, elevated WBC count).
- Had persisting or relapsing infection (Section 3.2.3.2 and Section 3.2.3.3, respectively).
- Identification of a New Complicated Staphylococcal Infection (Section 3.2.3.5) defined as not known to be present at both randomization and at the completion of study treatment for their baseline clinical classification of bacteremia but is discovered at any time after the completion of the study treatment up to the final TOC. These patients will be retained in their original group and counted as treatment failures.
- Died prior to early or final TOC evaluation.

** if patients fail prior to the final TOC visit, final TOC assessments can be conducted at the time of failure and the patient can be classified as completing the study at that time.*

Non-Evaluable:

Patients will be classified as “Non-evaluable” at or before final TOC if they meet the following Criteria*:

- Failure for Administrative Reasons (e.g., patient withdraws consent for study participation; patient discontinues medical treatment against medical advice; patient withdrawn from the study; patient lost to follow-up) in patients who do not fail for other reasons.

All non-evaluable patients will be considered failures for the ITT analysis, will be considered missing for the sensitivity analysis and will be excluded from the PP population.

** if patients are determined non-evaluable prior to the final TOC visit, safety and outcome data will be collected at the time that the patient is determined non-evaluable and the patient can be classified as terminating the study at that time.*

ITT Population: All patients randomized into the study will be analyzed in the ITT population analysis.

PP Population: Patients meeting any of the following criteria will be EXCLUDED from PP analysis:

- Received a PENS antibiotic
- Did not undergo removal of intravascular catheter suspected to be infected. Note that patients with simple CoNS bacteremia may retain the catheter; all other patients should have their catheter(s) removed.
- Had blood stream infection with a vancomycin-resistant staphylococcus; or a staphylococcus resistant to protocol-identified alternative drugs if these were used
- Discontinued study medication prematurely for reasons other than clinical failure
- Did not undergo final TOC assessment
- Did not comply with all Patient Inclusion Criteria as listed in 5.1.
- Violated any Patient Exclusion Criteria as listed in 5.2.
- Died within 3 days of randomization
- Were classified as non-evaluable per the definition above

PPE Population: Patients from the PP population who did not have complicated staphylococcal infection.

3.2.3.2 Persisting infection

Persisting infection is defined as a staphylococcus that represents the same bacterial strain as the Baseline Infecting Pathogen (based on bacterial speciation, antibiotic susceptibility testing, and/or genotyping tests, as appropriate) **plus** either a) or b).

- a) is repeatedly isolated from the bloodstream or other sterile body site for ≥ 7 days despite appropriate surgical debridement as necessary, and appropriate antibiotic treatment as documented by culture susceptibility data; or

- b) patient exhibits ongoing signs and symptoms of acute infection without significant clinical response for ≥ 7 days.

Workup for persisting infection will consist of the follow-up blood cultures per protocol, along with symptom- and sign-based evaluation (eg. MRI of spine for new back pain, arthrocentesis for concern of septic arthritis, etc).

3.2.3.3 Relapsing infection

Relapsing infection is defined as a staphylococcus that:

- represents the same bacterial strain as the Baseline Infecting Pathogen (based on bacterial speciation, antibiotic susceptibility testing, and/or genotyping tests, as appropriate);
- is documented by a culture yielding staphylococcus obtained 3 days or more after the most recent documented positive cultures, is separated by at least 1 set of negative blood cultures drawn on a separate calendar day and is accompanied by resolution of clinical signs and symptoms of staphylococcal infection for at least 3 days.
- is judged by the Site PI not to represent a Contaminant.

For the purposes of defining a relapsing infection, a contaminant will include CoNS isolated from the bloodstream after the collection of the index blood culture if:

- only a single blood culture per day is positive for CoNS;
- it is judged by the site PI to represent a contaminant; *and*
- patient treatment is not altered by the identification of the culture result

The following organisms will be considered contaminants if grown from only one blood culture (either alone or in addition to a clinically significant staphylococcus isolated from the same blood culture): *Propionibacterium* species, Micrococcus species, viridans-group streptococcus, *Corynebacterium* species, *Bacillus* species other than *B. anthracis*²², or enterococcus species²³. All isolates of Staphylococcus will be considered clinically significant.

3.2.3.4 Polymicrobial Bacteremia

Polymicrobial bacteremia. Polymicrobial bacteremia is defined as a blood culture that grows an organism in addition to the baseline infection pathogen.

3.2.3.5 New Complicated Staphylococcal Infection

A complicated staphylococcal infection will be defined as “New” if it is not known to be present at both randomization and at completion of treatment for the baseline clinical classification of bacteremia but is discovered at any time after the completion of the study treatment up to the

final TOC. These patients will be retained in their original group and counted as treatment failures.

3.2.3.6 Complicated Staphylococcal Infection

The presence of any one of the following conditions will be defined, by category (e.g., endocarditis), as a complicated staphylococcal infection.

Positive Follow-up Blood Cultures- Either of the following:

- Follow-up blood culture positive for *S. aureus* (follow up blood culture drawn 24 - 72 hours following initial blood culture collection showing *S. aureus*).
- ≥ 2 sets blood cultures positive for CoNS from samples drawn > 24 hours apart

Persistent fever

- Oral temperature ≥ 38.0 C for > 72 hours following initial positive blood culture draw for staphylococcus

Meningitis - Either of the following:

- Positive Cerebrospinal Fluid (CSF) culture for Staphylococcus
- CSF yields either pleocytosis (> 10 neutrophils/mm³) or Gram positive cocci on CSF Gram Stain in a patient with documented staphylococcal blood stream infection

Brain abscess - Either of the following:

- Culture of abscess contents yields Staphylococcus; or
- Abscess visualized by radiographic imaging.

Epidural abscess - Either of the following:

- Culture of abscess contents yields Staphylococcus; or
- Abscess visualized by radiographic imaging.

Intracranial hemorrhage secondary to mycotic aneurysm

- Abnormalities visualized by radiographic imaging or direct operative inspection.

Endocarditis (Modified Duke Criteria)

Definite Infective Endocarditis:

Pathologic Criteria

- Microorganisms demonstrated by culture or histologic examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or
- Pathologic lesions; vegetation or intracardiac abscess confirmed by histologic examination showing active endocarditis

Clinical Criteria

- 2 major criteria; or
- 1 major criterion and 3 minor criteria; or
- 5 minor criteria

Possible Infective Endocarditis:

- 1 major criterion and 1 minor criterion; or
- 3 minor criteria

Modified Duke Criteria for the Diagnosis of Infective Endocarditis:

Major Criteria

- Blood culture positive for IE
 - Typical microorganism consistent with IE from 2 separate blood cultures:
 - Viridans streptococci, *Streptococcus bovis*, HACEK¹ group, *S. aureus*; or
 - Community-acquired enterococci, in the absence of a primary focus; or
 - Microorganisms consistent with IE from persistently positive blood cultures, defined as follows:
 - At least 2 positive blood culture samples drawn > 12 hours apart; or
 - All of 3 or a majority of > 4 separate cultures of blood (with first and last sample drawn at least 1 hour apart)
 - Single positive blood culture for *Coxiella burnetii* or antiphase titer of > 1:800
- Evidence of endocardial involvement

¹ Haemophilus species, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and Kingella species

- Echocardiogram positive for IE (TEE recommended in patients with prosthetic valves), rated at least “possible IE” by clinical criteria, or complicated IE [paravalvular abscess, echocardiogram (TEE preferred) is mandated in algorithm patients with uncomplicated *S. aureus* bacteremia]; TTE as first test in other patients), defined as follows:
 - Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative explanation; or
 - Abscess; or
 - New partial dehiscence of prosthetic valve
- New valvular regurgitation (worsening or changing of pre-existing murmur not sufficient)

Minor Criteria

- Predisposition, predisposing heart condition or injection drug use
- Fever, temperature >38°C
- Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway’s lesions
- Immunologic phenomena, glomerulonephritis, Osler’s nodes, Roth’s spots, and rheumatoid factor

Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE.

Visceral Abscess (eg. Liver, spleen, kidney, etc.) - *Either of the following:*

- Abscess visualized on radiographic exam or
- Isolation of Staphylococcus from culture of abscess contents.

Pneumonia – *All of the following:*

- Pulmonary infiltrate consistent with pneumonia in patients *with S. aureus* bacteremia and
- *S. aureus* in pleural fluid, needle aspirate biopsy, or growth from bronchoalveolar lavage (BAL)/protected specimen brush (PSB) **and**
- Clinical evidence of pneumonia (eg. Increased O₂, increased respiratory rate, cough, mechanical ventilation, purulent sputum, etc)

Osteomyelitis - *Either of the following:*

- Radiographic evidence of bone lesion consistent with osteomyelitis; **or**

- Culture of bone yields staphylococcus.

Pyomyositis – *Either of the following:*

- Radiographic evidence consistent with pyomyositis; **or**
- Culture of abscess contents yields staphylococcus.

Septic Arthritis – *Either of the following:*

- Staphylococcus in culture of synovial fluid; **or**
- Positive Gram stain of synovial fluid for Gram positive cocci AND synovial fluid cell count $\geq 20,000$ WBC/mL without alternate explanation

Septic Thrombophlebitis:

- Positive follow-up blood cultures, **and either of the following:**
- Palpable venous cord; **or**
- Evidence of thrombosis on radiologic exam

3.2.3.7 Potentially Effective Non-Study (PENS) Antibiotics

PENS antibiotic is defined as any antibiotic course not indicated by the study protocol with potential efficacy against a patient's infecting staphylococcal bloodstream pathogen, that is received by the patient **from the time of collection of the baseline blood culture until final TOC evaluation, and that may have influenced patient outcome**. Please see the caveat below regarding empiric administration of more than one agent. A PENS antibiotic may be either an antibiotic not specifically indicated by the protocol (e.g., linezolid for patients in the algorithm arm) or a protocol-approved antibiotic received outside of the protocol indications (e.g., a one-week course of I.V. vancomycin received 2 weeks after completion of protocol-approved antibiotic regimen). For patients in the SOC arm, in which the primary provider has unrestricted choice of antibiotics, any antibiotic given expressly as initial treatment for the patient's staphylococcal infection will not be considered a PENS antibiotic. As an example of a potential PENS antibiotic, a patient who completed his/her study treatment for the baseline staphylococcal bacteremia, but received a clinically significant course of doxycycline prior to final TOC evaluation for an episode of bronchitis would be judged to have received a PENS antibiotic if his/her initial staphylococcal isolate(s) were susceptible to doxycycline. Potential episodes of PENS will primarily be identified by Site Investigators and will be triggered for blinded adjudication. Designation of PENS will be established by blinded review of study documents by the Clinical Events Committee (CEC).

The following will **not** be considered to represent PENS antibiotics:

1. Protocol-approved alternative antibiotics (Table 2) administered according to study designation (e.g., per algorithm or per Standard Treatment).

2. For patients in the SOC arm, in which the primary provider has unrestricted choice of antibiotics, any antibiotic given expressly as initial treatment for the patient's staphylococcal bloodstream infection.
3. In the instance of **empiric** administration simultaneously of more than one antibiotic with potential antistaphylococcal efficacy (e.g., vancomycin and piperacillin/tazobactam), the nonstudy agent will not be considered a PENS antibiotic from the time of collection of the baseline blood culture until randomization. . The rationale for this accommodation is to ensure that the study protocol remains consistent with Guidelines for empiric treatment of sepsis suspected to be due to Multi-Drug Resistant Pathogens.²⁴ Even though the nonstudy agent will not be considered a PENS, it may be counted towards antibiotic days per Section 6.2.
4. Patients who developed their index bacteremia after at least 7 days of prophylaxis with oral antibiotics have by definition failed prophylaxis and the oral antibiotic regimen can be deemed non-effective for the index bacteremia. Oral antibiotics that have failed as prophylaxis in this manner will not be considered a PENS or count towards antibiotic days unless continuing or re-starting after randomization.

3.2.3.8 Assessment of Cure by Site PI or designated SI

“Cure” as defined by Site PI or designated SI is one criterion for Establishing Primary Efficacy Endpoint (see Section 3.2.3.1). Assessments of cure will occur at the early and final TOC for both algorithm-treated and Standard Care-treated patients. Patients will be defined by Site PI as “Cure” at the respective TOC visit if all of the following criteria are met:

Simple CoNS bacteremia

- Resolution of bacteremia as demonstrated by negative follow-up blood culture
- Clinical resolution of signs and symptoms of staphylococcal blood stream infection; and
- No development of a) persisting infection; b) relapsing infection; or c) New Complicated Staphylococcal Infection, up to the respective TOC evaluation

Uncomplicated CoNS bacteremia

- Resolution of bacteremia as demonstrated by negative follow-up blood culture
- Clinical resolution of signs and symptoms of staphylococcal blood stream infection; and
- No development of a) persisting infection; b) relapsing infection; or c) New Complicated Staphylococcal Infection, up to the respective TOC evaluation

Complicated CoNS bacteremia

New Complicated Staphylococcal Infection is reason for Failure when identified after the completion of study treatment for the baseline clinical classification of bacteremia for patients with Simple and Uncomplicated CoNS bacteremia. We anticipate that complicated CoNS bacteremia will be relatively uncommon in the trial. However, some patients with CoNS bacteremia with no apparent complications at randomization will be found to have complicated infection after randomization but before the completion of study treatment for their baseline clinical classification of bacteremia. These patients will remain in the trial, be categorized as Complicated CoNS bacteremia, and will be treated per Protocol. For such patients, "Cure" will be defined as -

- Resolution of bacteremia as demonstrated by negative follow-up blood culture
- Clinical resolution of signs and symptoms of staphylococcal blood stream infection; and
- No development of a) persisting infection; b) relapsing infection; or c) additional sites of complicated staphylococcal infection, up to the respective TOC evaluation

Uncomplicated *S. aureus* bacteremia

- Resolution of bacteremia as demonstrated by negative follow-up blood culture
- Clinical resolution of signs and symptoms of staphylococcal blood stream infection; and
- No development of a) persisting infection; b) relapsing infection; or c) New Complicated Staphylococcal Infection, up to the respective TOC evaluation

Complicated *S. aureus* bacteremia

New Complicated Staphylococcal Infection is reason for Failure when identified after completion of all diagnostic tests and completion of the study treatment period for patients with uncomplicated *S. aureus* bacteremia. We anticipate that complicated *S. aureus* bacteremia will be relatively uncommon in the trial. However, some patients with *S. aureus* bacteremia with no apparent complications at randomization will be identified by the study evaluation (blood cultures, echocardiography) after randomization but on or before completion of the treatment period for the baseline clinical classification of bacteremia. These patients will remain in the trial, will be categorized as Complicated *S. aureus* bacteremia, and will be treated per Protocol. For such patients, "Cure" will be defined as -

- Resolution of bacteremia as demonstrated by negative follow-up blood culture
- Clinical resolution of signs and symptoms of staphylococcal blood stream infection; and
- No development of a) persisting infection; b) relapsing infection; or c) additional sites of complicated staphylococcal infection, up to the respective TOC evaluation

3.2.4 Committees and Helplines

There are 3 committees and 2 help lines. The responsibilities for each committee/helpline are listed below and will be referenced throughout the protocol.

3.2.4.1 Clinical Event Committee (CEC)

The CEC will consist of 3 physicians with expertise in infectious diseases who are not involved in study conduct. The CEC will develop a charter and will adjudicate events on at least a yearly basis. All CEC members will be blinded to randomization and treatment category.

The CEC Review Committee will be responsible for defining the presence and significance of potentially effective nonstudy (PENS) antibiotics received from the time of collection of the baseline blood culture until final TOC based upon review of all available culture, susceptibility, and antibiotic administration data. In addition, the CEC will evaluate clinical outcomes and antibiotic days in at least 10% of randomly selected patients. The DSMB will review CEC adjudication decisions.

3.2.4.2 Executive Committee (EC)

The Executive Committee is comprised of study leadership in NIAID and DCRI. This committee is responsible for protocol development and oversight of study progress. The Executive Committee will meet monthly or more frequently during study start up. As study progresses, committee meeting schedule will be reassessed based on need.

3.2.4.3 Data Safety Monitoring Board (DSMB)

The DSMB is an independent body appointed and managed by DMID. The DSMB is charged with monitoring patient safety throughout the trial according to their charter. Refer to Section 9.5 for details regarding DSMB responsibilities and meeting frequency.

3.2.4.4 Coordinating Center Physician Helpline

The physician help line was developed to help sites with inclusion/exclusion questions or patients treatment on a medical level. You may reach the DCRI infectious disease physician on call by paging 919-970-1232.

3.2.4.5 Safety Surveillance Helpline

The Safety Surveillance helpline is to help answer site questions regarding SAE reporting. DCRI Safety Surveillance helpline is 919-668-8624, or at 866-668-7799 (within the US only).

4 STUDY DESIGN

Study patients will be identified by the site staff through daily review of the positive blood culture results in the clinical microbiology laboratory of each participating site followed by reviewing each potential patient's medical chart. If the patient has a documented blood stream infection (defined in Section 5.3) and appears to meet enrollment criteria, then the patient (or his/her legally authorized representative [LAR]) will be asked to sign an informed consent form (ICF). The study will be explained to the patients or their LAR and then they will be asked to sign the informed consent document after they have had all their questions answered and have been given adequate time to consider consenting. Once consented and speciation and clinical classification are confirmed, the patient will be randomized to algorithm-determined treatment or SOC treatment.

During their treatment, patients will be evaluated every day while they are inpatients until the Inpatient End of Treatment (IEOT) \pm 2 days. Patients discharged while still on study treatment will have a Discharge Visit (DV) up to 2 days prior to or on the day of discharge. Some CoNS patients may be treated solely as outpatients. These patients will only have IEOT/DV visit procedures performed if they have an in-person clinic visit as part of their treatment plan between the enrollment visit and the end of treatment. Subjects on treatment as outpatients, or continuing treatment after discharge, will be monitored for compliance with study antibiotics by twice-weekly telephone calls from site study personnel during study treatment; and then by a telephone call on the day study treatment is scheduled to end (\pm 2 days). All subjects will undergo an early TOC assessment by telephone call or clinic visit at 14 - 4 + 10 days for CoNS or 21 - 4 + 10 days for *S. aureus* after completion of study antibiotic treatment. In-clinic evaluation is preferred but not mandatory for the TOC assessments.

All subjects will undergo a final TOC assessment by telephone call or clinic visit at 28 - 4 + 10 days for CoNS or 42 - 4 + 10 days for *S. aureus* after completion of study antibiotic treatment. Subjects who, at the time of the phone call(s) or clinic visit(s), state that they have any signs or symptoms of potentially continuing infection will be referred to their primary care physicians for further evaluation as needed, with a subsequent follow-up call made to the patient to establish the results of that evaluation.

4.1 Number of Sites

A total of Fourteen sites will participate in the clinical trial; thirteen in the US and one in Spain.

4.2 Number of Patients

It is anticipated that 500 patients will need to be enrolled in the study based on the sample size calculations described in Section 11.2.

Simple CoNS subjects who do not receive any study drug (i.e. the “zero days” subjects), may be capped at approximately 80 subjects to allow for enrollment of additional uncomplicated CoNS and *S. aureus* subjects.

A blinded sample-size re-estimation was performed after 250 patients were enrolled in the study and was assessed by the DSMB per Section 11.2.

DSMB’s recommendation for sample size increase was made based on a conservative sensitivity analysis approach to account for variability associated with the observed difference in cure rates at interim. This recommendation will be confirmed at the next blinded sample size re-estimation at 350 subjects enrolled.

Total patient target may be adjusted if the DSMB determines that the study will be sufficiently powered at that patient number.

4.3 Timeline for Patient Enrollment

It is estimated that each site will enroll 2 patients or more per month, and enrollment will be completed within four years. This estimate is based upon the extensive experience of the investigators in conducting similar randomized, controlled multicenter trials in staphylococcal blood stream infection.^{25, 26} The difficulty of enrolling patients into staphylococcal blood stream infection trials is well known.²²⁷ The primary challenge for such trials is the high numbers of patients screened. For example, over 2000 patients were screened in more than 44 sites in four countries for three years to enroll 235 patients for the daptomycin *S. aureus* blood stream infection and endocarditis trial, and more than 2639 patients were screened to enroll 73 patients in the dalbavancin vs standard therapy catheter-associated blood stream infection trial.²²⁸ Enrollment is further challenged by the need to exclude hemodialysis-dependent patients from the trial due to difficulty in calculating vancomycin days in this patient population.

5 STUDY ENROLLMENT AND WITHDRAWAL

The study population will consist of patients at least 18 years of age, who have a positive blood culture for *S. Aureus* or CoNS. Patients who fulfill all of the inclusion criteria and none of the exclusion criteria listed below will be eligible for randomization.

5.1 Patient Inclusion Criteria

A patient must fulfill all of the following criteria prior to randomization:

1. Provide signed and dated informed consent (the patient's LAR can provide a signed informed consent for the patient if allowed by local IRB/IEC policy).
2. Is ≥ 18 yrs of age.
3. If subject has an intravenous catheter in place, then the subject and his/her primary health care provider must agree to have the catheter removed within 5 days of initial blood culture draw, with the exception of those subjects who meet criteria for simple CoNS bacteremia as defined in Table 1. The catheter may be retained in those subjects with simple CoNS bacteremia.
4. Has blood stream infection defined as at least one blood culture positive for *S. Aureus* or CoNS. In most cases, vancomycin (or other study drug alternative) will have been started prior to randomization. Enrollment windows depend on clinical classification as follows:
 - a. *identification of CoNS and classification as simple per Table 1* – must be randomized within 3 calendar days of the start of treatment effective for the baseline infecting pathogen
 - b. *identification of CoNS and classification as uncomplicated per Table 1* – must be randomized within 4 calendar days of the start of treatment effective for the baseline infecting pathogen
 - c. *identification of S. Aureus* – must be randomized within 12 calendar days of the start of treatment effective for the baseline infecting pathogen .
5. *This criterion has been removed.*
6. Women of child bearing potential must have a negative urine and/or serum pregnancy test.
7. All patients of reproductive potential must be abstinent or agree to use double-barrier contraception while receiving study (algorithm-based or SOC) treatment.

5.2 Patient Exclusion Criteria

All patients meeting any of the exclusion criteria at randomization will be excluded from study participation.

1. Has known or suspected complicated staphylococcal infection at the time of randomization.
2. Weigh ≥ 200 kg.
3. Has non-removable intravascular foreign material at the time a positive blood culture was drawn (e.g., intracardiac pacemaker or cardioverter/defibrillator wires, hemodialysis access grafts, cardiac prosthetic valve, valvular support ring). Exception: coronary stents, inferior vena cava (IVC) filters in place >6 weeks, patients with pacemakers whose baseline infecting pathogen is a CoNS, vascular stents in place for > 6 weeks, non-hemodialysis grafts in place >90 days and hemodialysis grafts not used within past 12 months and not previously infected are eligible for randomization. Arthroplasties and other extravascular devices, e.g. synthetic hernia repair mesh, and non-arthroplasty orthopedic prostheses including pins or plates, are acceptable as long as there are no signs or symptoms of foreign material-related infection at the time of randomization.
4. *This criterion has been removed.*
5. Has a moribund clinical condition such that there is a high likelihood of death or cardiac surgery during the next three days.
6. Has shock or hypotension (supine systolic blood pressure < 80 mmHg) or oliguria (urine output < 20 mL/h) unresponsive to fluids or pressors within four hours.
7. Has received an investigational antibacterial agent with antistaphylococcal activity within 30 days prior to randomization.
8. Has a documented history of significant allergy or intolerance to all protocol-approved antibiotics anticipated to be effective for their infection.
9. Has an infecting pathogen with confirmed reduced susceptibility to vancomycin (MIC > 2 $\mu\text{g/mL}$), if known. Note: If reduced susceptibility to vancomycin is discovered after enrollment, the patient will be treated with daptomycin (if pathogen is susceptible). Patient will remain in study as appropriate and be evaluated in the ITT analysis, but will be excluded from PP analyses.
10. For *S. Aureus* patients, is severely neutropenic (absolute neutrophil count $< 0.100 \times 10^3/\text{mm}^3$) or is anticipated to develop severe neutropenia (absolute neutrophil count $< 0.100 \times 10^3/\text{mm}^3$) during the study treatment period due to prior or planned chemotherapy. CoNS patients with neutropenia are eligible to be enrolled.

11. *This criterion has been removed.*
12. Has previously known HIV infection with a nadir CD4+ count of < 100 cells/mm³ within the past 12 months.
13. Is considered unlikely to comply with study procedures or to return for scheduled post-treatment evaluations.
14. Is pregnant or trying to get pregnant, nursing, or lactating.
15. Has known or suspected septic arthritis, osteomyelitis, pneumonia or other metastatic focus of infection. CoNS patients with pneumonia and not being treated, or anticipated to start treatment, with antibiotics effective for the baseline infecting pathogen can be included.
16. Has polymicrobial blood stream infection including at least one non-staphylococcal species, except AFTER consultation with the Clinical Medical Monitor at DCRI. Note that it is possible that a subject may not have a known polymicrobial bloodstream infection at the time of randomization, but additional pathogen(s) can subsequently be isolated from the initial blood culture. These patients will be eligible to remain in the trial. Please also note that patients with *S. aureus* plus CoNS will follow the treatment pathway for *S. aureus*.
17. *This criterion has been removed.*
18. Is hemodialysis dependent or has end stage renal disease (CrCl < 30 cc/min).
19. Developed *S. aureus* blood stream infection within 72 hours of percutaneous coronary revascularization
20. Received of any of the following antibiotics for 7 or more of the 10 calendar days immediately preceding the calendar day that the initial positive blood culture was drawn:
 - a. If methicillin susceptibility of the isolate is unknown at the time of enrollment: vancomycin; daptomycin; telavancin; tigecycline; linezolid (in either oral or IV administration); quinupristin/dalfopristin; piperacillin/tazobactam; penicillin; nafcillin; oxacillin; cloxacillin; cefazolin, ceftriaxone, ceftaroline, dalbavancin, oritavancin, and tedizolid levofloxacin or equivalent fluoroquinolone (in either oral or IV administration)
Note: ciprofloxacin is not an exclusion criteria.
 - b. If the staphylococcal isolate is known to be methicillin resistant: vancomycin; daptomycin; telavancin; tigecycline; linezolid (in either oral or IV administration), quinupristin/dalfopristin, dalbavancin, oritavancin, and tedizolid ceftaroline.

Note: patients who have developed bacteremia after at least 7 days of prophylaxis with oral antibiotics have by definition failed prophylaxis and the oral antibiotic can be deemed non-effective for the index bacteremia. Oral antibiotics that have failed as

prophylaxis in this manner will not be considered exclusionary or count towards the number of antibiotic days but must be stopped upon randomization.

21. Has previously participated in this study.

5.3 Source of Blood Stream Infection

5.3.1 Baseline Infecting Pathogen

The staphylococcus reported by the local microbiology laboratory isolated from a blood culture meeting the parameters of inclusion criterion # 4 that triggered evaluation for study participation will be defined as the Baseline Infecting Pathogen.

5.3.2 Definition of Catheter-associated Blood Stream Infection

The current protocol will evaluate an algorithm-based treatment strategy for the treatment of staphylococcal blood stream infection, many of which will be catheter-associated infections. Definitions of these conditions are provided below. Ideally, the studies in this condition could be limited to confirmed catheter-associated staphylococcal blood stream infection. However, based on our previous published experience^{18,19,25,26,29,30,31} and on the experiences of previous trials^{27,28} enrollment of patients with confirmed catheter-associated infections is extremely difficult. There are several important issues contributing to this fact. First, catheters have already been removed from many of these patients by the time that the blood cultures have turned positive and they are being screened for study participation. Thus, catheter-culture techniques are no longer possible. Second, not all centers perform quantitative catheter or blood cultures. Thus, these important data are not available.

Because the presence of catheter-associated blood stream infection is difficult to confirm, we are also including patients who do not have a catheter, as well as patients who do have a catheter and in whom this infection is suspected clinically, but confirmation is not possible. The inclusion of patients with suspected catheter-associated staphylococcal blood stream infection serves two important purposes. First, it avoids the prohibitively high screen:enroll ratios experienced by recent clinical trials requiring confirmed infection^{27,28}. Second, it strengthens the clinical relevance of this study by better reflecting current clinical practice. In this way, the study findings will be more generalizable to routine clinical care.

Note that “catheter” refers to any type of intravascular catheter, including peripheral catheters, peripherally-inserted central catheters (PICC); central venous catheters (short-term central venous catheters, vascath); cuffed, tunneled central lines (eg, Perm-cath, Hickman catheters), and peripheral arterial catheters.

Confirmed catheter-associated staphylococcal blood stream infection will be defined as the isolation of staphylococci in a patient with 1) “an intravascular device and ≥ 1 positive blood culture of blood samples obtained from the peripheral vein, clinical manifestations of infection (e.g., fever, chills, and/or hypotension), and no apparent source for bloodstream infection (with the exception of the catheter); and 2) at least one of the following: “a positive result of semiquantitative (> 15 colony forming units [cfu] per catheter segment) or quantitative ($> 10^2$ cfu per catheter segment) catheter culture, whereby the same organism (species and antibiogram) is isolated from a catheter segment and a peripheral blood sample; simultaneous quantitative cultures of blood samples with a ratio of $> 5:1$ (central venous catheter [CVC] vs peripheral); or a differential time to positivity (i.e., a positive result of culture from a CVC is obtained at least 2 hours earlier than is a positive result of culture from peripheral blood).²⁰

Suspected catheter-associated staphylococcal blood stream infection will be defined as the isolation of staphylococci in a patient with an intravascular device, or a patient who has had an intravascular device removed within 5 days of initial blood culture drawn, and clinical suspicion of catheter-associated infection, but without any quantitative or semiquantitative culture confirmation as present in patients with confirmed infection.

5.3.3 Definition of Nosocomial, Health Care-Associated and Community-Acquired Bloodstream Infection

The protocol will also evaluate the management of bloodstream infections from diverse settings, including those that are nosocomial, non-nosocomial but health care-associated, and those that are community-acquired. In accordance with accepted practice³², these terms are defined as follows:

Nosocomial bloodstream infection will be defined as a positive blood culture obtained from a patient who has been hospitalized for 48 hours or longer. If a patient has been transferred from another hospital, the duration of inpatient stay will be calculated from the date of the first hospital admission.

Health care-associated bloodstream infection will be defined as a positive blood culture obtained from a patient at the time of presentation, or within 48 hours of presentation, if the patient also fulfills any of the following criteria:

- Received intravenous therapy at home; received wound care or specialized nursing care through a health care agency, family, or friends; or had self-administered intravenous medical therapy in the 30 days before the bloodstream infection.
- Attended a hospital or hemodialysis clinic or received intravenous chemotherapy in the 30 days before the bloodstream infection.
- Was hospitalized in an acute care hospital for 2 or more days in the 90 days before the bloodstream infection.

- Resided in a nursing home or long-term care facility.

Community-acquired bloodstream infection will be defined as a positive blood culture obtained at the time of presentation, or within the 48 hours after presentation, for patients who do not fit the criteria for a health care-associated infection.

5.4 Treatment Assignment Procedures

5.4.1 Randomization Procedures

Randomization will be 1:1 Algorithm vs SOC in permuted randomized blocks by site. The randomization plan will be generated by a Duke Clinical Research Institute (DCRI) statistician. Site personnel will randomize patients through an automated system. The subject will be assigned a randomization number, which will be a combination of a two-digit site number and a four-digit patient number starting with 0001 and continuing sequentially.

5.4.2 Masking Procedures

The study personnel will not be blinded to study intervention group. However, CEC adjudicators will be blinded to treatment assignment. The CEC Coordinator will ensure that the data is blinded when provided to CEC members for review and adjudication.

5.4.3 Reasons for Withdrawal

A study patient will be discontinued from participation in the study for the following reasons:

- The patient develops a serious adverse event (SAE) possibly related to study drug or algorithm, and continuation in the study would jeopardize best clinical practice.
- Patient withdraws consent at any time during the study.
- Physician caring for the patient (not necessarily a study investigator) feels withdrawal is in the patient's best interest.
- Pregnancy
- Administrative reasons necessitating discontinuation (such as patient discontinues medical treatment against medical advice; patient lost to follow-up).

Complicated infection is a protocol exclusion; however, it is not reason to withdraw the patient when diagnosed after randomization.

5.4.4 Handling of Withdrawals

A premature discontinuation occurs when an enrolled patient ceases participation in the study, regardless of circumstances, prior to the final TOC. All patients prematurely discontinuing from

the study, regardless of cause, must receive a final evaluation at the time of withdrawal, will be classified as non-evaluable, and will be analyzed as a “Failure” in the efficacy analyses. The reason(s) for early discontinuation should be reflected in the source documentation and on the Study Termination Record of the eCRF. If a patient withdrawing from the study has an ongoing AE at the time of withdrawal, the AE will be followed for 72 hours after the last dose of study treatment; an ongoing SAE will be followed until resolved or stabilized.

5.4.5 Termination of Study

The Executive Committee shall have the right to terminate this study at its discretion with written notice to the institution and the site investigator. The investigator or institution shall have the right to terminate this study at its discretion with written notice to the Executive Committee or its designee. DMID/NIAID shall also have the right to terminate the study at any time.

Possible reasons for termination of the study include, but are not limited to:

Unsatisfactory enrollment with respect to quantity or quality

Inaccurate or incomplete data collection

Falsification of records

Failure to adhere to the protocol

At the request of a local IRB

A situation may arise that could lead a local IRB to suspend or terminate a study at their site. If the reason for the suspension or termination is specific to that site, it will not impact the status of the study at other sites.

6 STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

6.1 Antibiotic Treatment and Dosage

6.1.1 Algorithm Treatment with Intravenous Vancomycin

Vancomycin will be reconstituted with 20mL of sterile water for injection USP or 0.9% Sodium Chloride, diluted with 200mL of diluent (5% dextrose or 0.9% Sodium Chloride, or as per standard practice at each participating site, and administered as an IV infusion over 60 minutes every 12 hours or as per local practice to achieve desired vancomycin trough levels.

Vancomycin will be dosed by local standard practice, but it is recommended that it be dosed to achieve a goal trough of 15 - 20 mcg/ml in accordance with published guidelines.³³ Trough levels are not required, but if done should be checked within thirty minutes prior to the infusion of the fourth dose, and again prior to the fourth dose after any changes in dose. Toxicity to vancomycin intravenous will be monitored by performing hematology and chemistry tests outlined in Section 8.15, and as clinically indicated to conform to published guidelines.³³

6.1.2 Alternatives to Intravenous Vancomycin

In the appropriate clinical settings, vancomycin alternative agents that are commercially available, approved by the study protocol, and FDA-approved for US sites and/or EMEA-approved for the site in Spain will also be acceptable for use in the algorithm arm. For patients in the SOC arm, the primary provider has unrestricted choice of antibiotics. It is preferable that all patients be treated with vancomycin. However, vancomycin alternatives may be used if the bloodstream staphylococcal isolate is methicillin-susceptible, if the isolate has reduced susceptibility to vancomycin, or if the patient develops, or has an existing, intolerance or allergy to vancomycin, as outlined below. In addition, any antibiotic may be utilized in SOC patients in order to follow standard clinical practice.

Appropriate settings for **vancomycin alternatives** include the following:

- Replacement of vancomycin with intravenous antistaphylococcal penicillin (e.g., penicillin, nafcillin, oxacillin, cloxacillin) or first generation cephalosporin (cefazolin) for patients with methicillin susceptible staphylococcal infections.
- Use of daptomycin (US) or Cubicin (Spain) (dosed per standard of care in patients in the SOC arm and at 6mg/kg IV once daily, or according to patient renal function per package insert, for patients in the algorithm arm) when methicillin-resistant staphylococcal bloodstream infection has been identified and if vancomycin cannot be used due to the development of vancomycin allergy or intolerance, reduced vancomycin susceptibility (vancomycin MIC \geq 2 μ g/ml for *S. aureus*), AE/SAE potentially related to vancomycin, or other extenuating circumstances that would require withdrawal of the patient from the trial (these circumstances should be discussed with the Clinical Medical Monitor who will subsequently discuss with the DMID Medical Monitor).

For these clinical settings, dosing recommendations for each vancomycin alternative agent is provided in Table 2:

Table 2: Vancomycin Alternatives by Clinical Setting*

Antibiotic	Dosing	Comments
Vancomycin alternative antibiotics for methicillin susceptible staphylococci		
US - Nafcillin, oxacillin Spain – Cloxacillin	2 gm q 4h IV, or equivalent dosing through continuous infusion, in algorithm arm (dosing per SOC in SOC arm)	Preferred agents for MSSA and susceptible CoNS. If penicillin-allergic or intolerant, may use vancomycin instead
Penicillin	4 million units q4h IV or equivalent dosing through continuous infusion, in algorithm arm (dosing per SOC in SOC arm)	
Cefazolin	1.5 gm q 6h IV or equivalent, e.g. 2 gm q 8h IV**, renally dose-adjusted per package insert	In the US, may use for <i>S. aureus</i> only, per FDA indication. In Spain, may use for any methicillin-susceptible staphylococci

Vancomycin alternative antibiotics for methicillin resistant staphylococci

US - Daptomycin*** Spain – Cubicin	6 mg/kg IV q 24h in algorithm arm (dosing per SOC in SOC arm)	Use only if unable to give vancomycin due to allergy, intolerance, elevated vancomycin MIC, or AE/SAE
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*any antibiotic may be utilized in SOC patients in order to follow standard clinical practice

**recommended dose per package insert is 1-1.5 g q 6h IV, which is equivalent to the 2 gm q 8h IV recommended by current guidelines, and less than the 12 g/day maximum dose allowed per package insert

***FDA-Approved for *S. aureus* bacteremia and right-sided endocarditis, including infections caused by methicillin resistant *S. aureus*.

6.2 Duration of Antibiotics

All vancomycin alternatives will be considered in calculating antibiotic days. In the event that two antibiotics are used in empiric treatment of presumed staphylococcal sepsis, when both drugs are administered concomitantly only the duration of vancomycin will be considered when calculating antibiotic days. In the rare event that two antibiotics are administered concomitantly and neither is vancomycin, the effective antistaphylococcal antibiotic will be considered when calculating antibiotic days (per Section 6.3.1 use of combination antistaphylococcal treatment is not permitted in either treatment group). In the event that two antibiotics with documented efficacy based on the susceptibility profile of the bloodstream isolate are added sequentially, including as part of empiric therapy, the total duration of effective antistaphylococcal treatment with one or more agent will be used for calculations.

The following sections clarify durations of antibiotics for algorithm-treated patients only. Patients in the SOC treatment arm will be managed according to the judgment of the primary treating physician. If patients were given empiric treatment prior to speciation and susceptibility testing and the empiric treatment was found not to be effective for the baseline infecting pathogen, those days will not be counted towards duration of treatment or as antibiotic days. Similarly, if patients were given oral prophylaxis with antibiotics for at least 7 days and developed the index bacteremia regardless, these oral antibiotics will not be counted towards antibiotic days prior to randomization.

6.2.1 Coagulase Negative Staphylococcus

Patients randomized to Algorithm-based treatment will be treated according to the type of staphylococcal infection present. Patients with CoNS blood stream infection will be categorized into simple or Uncomplicated treatment groups. In some cases, complicated staphylococcal infections may develop after randomization in patients with CoNS blood stream infection.

Simple: Patients randomized to Algorithm-based treatment who meet criteria for simple coagulase negative staphylococcal blood stream infection (as defined in Table 1) may have received up to 3 (+1) calendar days of vancomycin, or protocol approved alternative. Upon randomization to Algorithm-based treatment, antibiotic treatment for the index bacteremia in patients who meet criteria for simple CoNS must be discontinued. If the patient has not received any antibiotic treatment for the index bacteremia prior to randomization, no treatment will be started. In the simple CoNS algorithm patients who do not receive any antibiotic treatment, End Of Therapy will be defined as the day that the patient was randomized

Uncomplicated: Algorithm patients meeting criteria for uncomplicated CoNS blood stream infection (as defined in Table 1) will receive 5 (-/+1) calendar days of vancomycin or protocol-approved vancomycin alternative as defined in Section 6.1.2.

Complicated: Algorithm patients who develop complicated CoNS blood stream infection after randomization but before the completion of study treatment for their baseline bacteremia clinical

classification (i.e. Simple CoNS, Uncomplicated CoNS) will receive 7 - 28 (-/+2) calendar days of treatment with vancomycin or a protocol-approved vancomycin alternative antibiotic. This wide range of possible treatment durations reflects the heterogeneity of complicated coagulase negative staphylococcal infections. For example, a patient with CoNS blood stream infection on 2 separate calendar days but without signs of metastatic infection may be treated for as few as 7 days, whereas endocarditis would be treated for up to 28 days. Precise duration of treatment will be determined by local standard practice.

6.2.2 *S. aureus*

Uncomplicated: Algorithm patients meeting criteria for Uncomplicated *S. aureus* infection (as defined in Table 1) will receive 14(-/+2) calendar days of treatment with vancomycin or one of the protocol-approved alternatives defined in Section 6.1.2.

Complicated: Patients who develop complicated *S. aureus* infection after enrollment and before the completion of study treatment for the baseline bacteremia clinical classification will receive 28 – 42 (-/+2) calendar days of treatment with vancomycin or one of the acceptable alternatives as defined in Section 6.1.2. As with coagulase negative staphylococcal infections, there is considerable heterogeneity of *S. aureus* infections leading to different durations of treatment. For example, complicated bacteremia without endocarditis could be treated for 28 days, whereas endocarditis would be treated for 42 days.

6.3 Criteria for Change of Antibiotic Treatment

Changes in antibiotic treatment in the standard of care (SOC) treatment arm will be based upon local SOC. The number of days of antibiotic use will include vancomycin or alternatives taken starting the day the baseline blood culture sample was collected.. Replacements for vancomycin will continue to count for total antibiotic days for secondary analysis. As stated above, however, if patients were given empiric treatment prior to speciation and susceptibility testing and the empiric treatment was found not to be effective for the baseline infecting pathogen, those days will not be counted towards duration of treatment or as antibiotic days. Similarly, if patients were given oral prophylaxis with antibiotics for at least 7 days and developed the index bacteremia regardless, these oral antibiotics will not be counted towards duration of treatment or antibiotic days prior to randomization.

Algorithm-based group changes in treatment will be allowed in the following circumstances:

- a. replacing vancomycin (or alternative drug) with anti-staphylococcal penicillin or first-generation cephalosporin (cefazolin) for patients infected with methicillin susceptible staphylococci
- b. replacing antistaphylococcal antibiotic with daptomycin due to intolerance, allergic reaction, drug resistance, or adverse effect;

- c. other reasons for changing treatment to one of the protocol identified alternative antibiotics will be allowed if approved by the coordinating center helpline physician.

6.3.1 Combination Therapies

Use of combination antistaphylococcal treatment (e.g., addition of gentamicin and/or rifampin to vancomycin) is not permitted in the algorithm group.

6.3.2 Concomitant Medications

Empiric treatment for Gram-negative pathogens is allowable. These agents will not be counted when calculating antibiotic days unless: 1) susceptibility testing of the bloodstream staphylococcal isolate reveals that the staphylococcus is susceptible to the antibiotic, and 2) the patient is not receiving other protocol approved antistaphylococcal treatment (e.g., methicillin-susceptible staphylococcal bloodstream isolate from a patient receiving empiric beta-lactam treatment for gram-negative infection). Aminoglycosides, including gentamicin, are prohibited for combined treatment of staphylococcal blood stream infection as addressed above. Aminoglycosides are prohibited for treatment of suspected or confirmed Gram-negative bacterial infections unless: 1) no other alternatives are available, and 2) its use for the treatment of a Gram-negative bacterial infection is approved by the coordinating center helpline physician.

6.3.3 Safety Monitoring

Clinical and laboratory evaluations of safety will be carried out as specified in the Schedule of Events in Sections 8.8-8.12 and in Section 8.14.1.

6.3.4 Acquisition

All drugs will be provided by the local hospital pharmacy.

6.3.5 Formulation, Packaging, and Labeling

Formulation, packaging, and labeling of vancomycin and vancomycin alternatives will be as per marketed drug and available from the local hospital pharmacy stock.

6.3.6 Product Storage and Stability

All drugs will be provided from the local hospital pharmacy, where they will be stored and prepared according to product labeling. Only drugs that have not expired will be administered to study patients.

6.4 Dosage, Preparation and Administration of Study Intervention

If done, recommended vancomycin trough levels for the algorithm arm will be consistent with published treatment guidelines (e.g., vancomycin trough levels of 15 - 20 ug/mL).³²

Refer to manufacturer package insert for dosage, preparation and administration instructions for study medication. The local pharmacy or site study staff will prepare study drug according to manufacturer package insert

6.5 Accountability Procedures for the Study Intervention/Investigational Product(s)

Study drug will be accounted for by local pharmacy standard practices and procedures. Pharmacies will be required to keep a drug accountability log per pharmacy procedures.

6.6 Assessment of Patient Compliance with Study Intervention/Investigational Product

Dose and frequency of study drug will be captured in the EDC system. Protocol compliance will be assessed during on-site monitoring visits and periodically by viewing data. Noncompliance issues will be documented and addressed with the site PI. After discharge, or during outpatient treatment for CoNS patients who were not admitted, site study personnel will contact patients actively taking study drug 2 times per week to assure they are compliant with prescribed dose.

6.7 Concomitant Medications/Treatments

Concomitant medications will be recorded in the Electronic Data Management system (EDC). After discharge, or during outpatient treatment for CoNS patients who were not admitted, study staff will contact patients 2 times per week and inquire about concomitant medication usage and enter into the EDC system. The exception to this is patients who are assigned to the 5-day treatment algorithm who will be called for this information every other weekday (to avoid the need for weekend calls). The information reported to study staff by the patient during these contacts will be considered source. Antibiotics will be captured from the day of baseline blood culture collection to trial termination; all other drug classes below will be captured only from randomization through end of treatment.

The following classes of concomitant medications will be captured:

- Antimicrobials
- Aspirin
- Anticoagulants
- Statins

7 STUDY SCHEDULE

7.1 Screening

Site personnel will follow local site procedures to obtain permission to monitor blood culture results daily. The investigator or designee will evaluate the patient's eligibility to enter the study based on the bacteriology results, clinical signs and symptoms, the clinician's judgment and the inclusion/exclusion criteria.

Patients who meet all inclusion criteria and none of the exclusion criteria will be eligible to be randomized and will receive either algorithm (defined in Section 8.2) or SOC (defined in Section 8.3) treatment.

7.2 Subject Consent

All patients (or the patient's LAR) must sign and date the current approved Informed Consent Form (ICF) before any study related procedures or tests are performed or any data is entered into the EDC system. A patient may be consented at the time of report of gram positive cocci in clusters i.e. positive for staphylococcal infection, if all other available data indicates that the patient is eligible for the study. Patients cannot be randomized, however, until all inclusion criteria have been met and all exclusion criteria have been assessed and it is determined that the patient does not meet any of the exclusion criteria.

7.3 Randomization/Enrollment

Treatment assignment will be by randomization (see Section 5.4.1). Refer to Schedule of Events sections 8.7, 8.8 and 8.10 for Enrollment procedures.

7.4 Schedule of Assessments

For patients assigned to algorithm-based treatment and the standard of care-based treatment, the Schedule of Events tables are provided in Sections 8.7 through 8.11. Patients will be seen at the Enrollment visit and, if hospitalized, daily until the Inpatient End of Treatment visit (IEOT) ± 2 days. Patients discharged while still on treatment will have a Discharge Visit (DV) up to 2 days prior to or on the day of discharge. Some CoNS patients may be treated solely as outpatients. These patients will only have IEOT/DV visit procedures performed if they have an in-person clinic visit as part of their treatment plan between the enrollment visit and the end of treatment. Subjects on treatment as outpatients, or continuing treatment after discharge, will then be monitored for compliance with study antibiotics and for concomitant medication and adverse event information by twice-weekly telephone calls from site study personnel during study treatment. Site study personnel will call the patient on the day study treatment is scheduled to end (± 2 days) to confirm actual drug discontinuation date, and to collect

concomitant medication and adverse event information. If the site study personnel are unable to contact the subject via telephone, required data obtained from the medical records is acceptable but not preferred. The site should document all attempts to contact the subject in the study records.

All subjects will undergo an early TOC assessment by clinic visit, which is preferred, or by telephone call at 14 - 4 + 10 days for CoNS or 21 - 4 + 10 days for *S. aureus* after completion of study antibiotic treatment. All subjects will undergo a final TOC assessment by clinic visit, which is preferred, or by telephone call at 28 - 4 + 10 days for CoNS or 42 - 4 + 10 days for *S. aureus* after completion of study antibiotic treatment. . If the site study personnel are unable to contact the subject via telephone, required data obtained from the medical records is acceptable but not preferred. The site should document all attempts to contact the subject in the study records. Subjects who, at the time of the phone call(s) or clinic visit(s), state that they have any signs or symptoms of potentially continuing infection will be referred to their primary care physicians for further evaluation as needed, with a subsequent follow-up call made to the patient to establish the results of that evaluation.

If a patient is readmitted to the hospital after treatment ends, the patient or family member should notify study staff of the reason for readmission. Patients readmitted before final TOC assessment for infection due to a staphylococcus that is identical to the Baseline Infecting Pathogen on the basis of speciation, antimicrobial susceptibility testing, and/or genotyping will be considered treatment failures and discontinued from the study. If bacterial genetic testing is not done, the patient will be considered a treatment failure and discontinued from the study. If patient was admitted for reasons other than staphylococcal infection, study staff will continue to contact patient or family member with patient's permission to obtain follow-up information for the duration of the study. If the patient dies before final TOC, a family member should notify the study staff of the reason for death, if otherwise unknown. If a patient is lost to follow up prior to final TOC, all attempts should be made by study staff to determine if the patient died prior to final TOC since death is an important patient outcome.

If patients fail or are determined non-evaluable prior to the scheduled final TOC visit, all applicable TOC assessments can be conducted at the time of failure or non-evaluable determination and the patient can be classified as completing (failure) or terminating (non-evaluable) the study at that time.

A Schedule of Events for complicated infection is provided in the protocol and applies only to those patients diagnosed with complicated infection, as defined in Section 3.2.3.6, after randomization but before completion of study treatment for the baseline bacteremia clinical classification.

7.5 Early Termination Visit

If patient terminates the study early for any reason, the TOC assessment should be performed at the time of termination. Only safety and outcome data will be collected during early termination visits for patients terminating early due to administrative reasons. These patients will be classified as 'Non-Evaluable' per Section 3.2.3.1. All TOC data will be collected for patients terminating early due to an outcome of 'Failure'.

7.5.1 Replacement Procedures

Patients who discontinue after randomization will not be replaced.

8 STUDY PROCEDURES/EVALUATIONS

8.1 Algorithm Based Treatment

Algorithm based treatment will be based upon the clinical classification of staphylococcal infection present. Patients with CoNS infections will be categorized into Simple or Uncomplicated treatment groups and all eligible *S. aureus* patients will have Uncomplicated infections. In some cases, complicated staphylococcal infections may develop or be discovered after enrollment. Definitions of the different categories are listed in Table 1.

8.2 Standard of Care Treatment

For the purposes of this trial, Standard of Care treatment will consist of routine care as provided by the patient's primary provider. Therefore there will not be a mandatory treatment regimen, such as that advocated by the IDSA guidelines. The goal in this trial is not to compare algorithm-based care to published guidelines (which are in any event often not followed⁴⁴), as the algorithm-based recommendations mimic the guideline recommendation by design. Instead, the goal of this trial is to compare algorithm-based care to routine care as it is currently practiced. Thus, for example, a patient in the SOC group may or may not have treatment guided by an infectious disease consultant. Additionally, for those patients in the SOC group, selection of the antibiotic for treatment of the staphylococcal infection will be at the discretion of the primary provider. Standard practices for treatment of staphylococcal bloodstream infection are outlined below but are not mandatory for those patients on the SOC group.

It is important to point out that the current protocol does not deprive patients of standard treatment. Thus, patients with complicated infections in both the algorithm-based treatment group and those receiving SOC treatment will have identical durations of antibiotic treatment. Instead, the algorithm-based treatment strategy uses clinically rational, evidence-based^{29,30} criteria to identify patients without complicated infection and justify the decision to stop unnecessary antibiotics in these patients. In this way, the algorithm-based treatment strategy will reduce overall antibiotic use without compromising patient care.

While there are no absolute guidelines for treatment of staphylococcal blood stream infection, there are some general practices followed in most centers to treat these infections. These standard practices are outlined below.

In the absence of extenuating circumstances, patients with methicillin-susceptible staphylococcus should be treated with an antistaphylococcal penicillin or first-generation cephalosporin in place of vancomycin.

Standard general practices for duration of antibiotic treatment for *S. aureus* blood stream infection²

*Uncomplicated: 14 to 28 days

*Complicated: 28 to 42 days

Standard general practices for durations of antibiotic treatment for CoNS blood stream infection²

*Simple: 4 days

*Uncomplicated: 10 days

*Complicated: 7 to 28 days

*As defined in Table 1.

8.3 Simple CoNS Blood Stream Infection

We anticipate that a significant portion of the blood cultures included in this group will represent contaminants rather than clinically significant blood culture results. However, the clinical interpretation of a blood culture result as a contaminant generally occurs 36 – 48 hours after the initial blood culture was obtained, when Gram positive cocci in clusters have been isolated, but not yet speciated. During this period, many patients are treated with empiric vancomycin or other effective vancomycin alternative due to the adverse impact of delayed effective antimicrobial treatment on the outcome of patients with *S. aureus* bloodstream infection.³⁴ To account for this clinical reality, our treatment algorithm has allowed for a range of treatment days. If a patient has been taking study antibiotic empirically before enrollment in the trial, the number of treatment days will be counted beginning at the day that empirical treatment with an antibiotic effective for the baseline infecting pathogen was started, and no earlier than the time bacteremia was suspected i.e. the day that the index blood culture was drawn. In this way, patients with simple CoNS blood stream infection randomized to the algorithm-based treatment arm will have antibiotics appropriately discontinued, while those for whom parenteral antibiotics are appropriate will be treated accordingly. Importantly, this design avoids the counterproductive scenario of recipients of algorithm-based treatment being mandated to receive antibiotics that they would otherwise not receive.

8.4 Further Speciation of CoNS

The decision to treat CoNS isolated from the blood stream can be influenced by the species of the organism. For example, the isolation of *Staphylococcus lugdunensis* from the blood stream is virtually always clinically significant and requires treatment³⁴. However, the cost-effectiveness of routine speciation of CoNS from blood cultures is controversial, and thus CoNS speciation is not performed at all medical centers. In the current trial, CoNS speciation is performed at some, but not all participating sites. For this reason, CoNS speciation is preferred and should be requested for enrolled subjects but is not mandated. However, susceptibility testing is required for the baseline infection pathogen for all subjects, as this is critical for evaluating PENS antibiotics.

The interpretation of different species of staphylococci from different sets of blood cultures is an important consideration. Only the initial isolate in the discordant pairs will be considered as clinically significant except in the following circumstances: 1) at least one of the isolates is *S. lugdunensis*. In this situation, *S. lugdunensis* will be considered clinically significant; 2) one staphylococcal isolate is grown from a blood culture obtained from venipuncture and the second staphylococcal isolate of a different species is grown from a blood culture obtained from an indwelling venous catheter. In this setting the peripheral culture will be considered as clinically significant; 3) any other clinical setting which the site investigator and/or the patient's primary physician considers relevant in the determination of a clinically significant organism.

In situations where *S. aureus* and at least one culture of CoNS staphylococci are isolated from two different sets of blood cultures, the patient will receive the *S. aureus* treatment.

8.5 Storage of Isolates

An important strength of this proposal is the planned storage of baseline staphylococcal bloodstream isolates from patients enrolled in the trial who provided consent for future use of their samples. These isolates will be saved, frozen at -70°C to -80°C, and shipped to Dr. Fowler's laboratory at Duke University. Alternatively, isolates may be lyophilized. The availability of these isolates will allow for additional analyses (e.g., vancomycin MIC determination [see Section 8.6.1], genotyping, and pathogenesis studies). With the subject's (or LAR's) consent, subcultures of isolates may be sent from Dr. Fowler's laboratory to study PIs upon request for future testing. No human genetic testing will be performed as part of the current study or future studies/testing. Dr. Fowler's laboratory personnel have extensive experience in linking individual study data with bacterial isolates,^{36,37,38,39} as well as shipping and receipt of pathogens according to appropriate regulations. All shipments will be documented.

Isolates will be labeled with patient number and date of sample and stored at -80°C in Dr. Fowler's laboratory until required for analysis. Additional details regarding collection, labeling, and storage of isolates will be contained in the Manual of Procedures (MOP).

8.5.1 Vancomycin Minimum Inhibitory Concentration (MIC)

A growing body of evidence suggests that higher vancomycin MICs – even within levels interpreted as susceptible for staphylococci - in staphylococcal blood stream isolates may be associated with a worse overall clinical outcome.⁴⁰ However, the clinical significance of these findings is not yet fully established. Thus, vancomycin MIC values are not routinely made clinically available at all of the participating sites in this trial. In order to uniformly address the potential impact of bacterial vancomycin MIC values on the clinical outcome of patients treated with this antibiotic, all baseline bloodstream isolates from enrolled patients will be retained by the participating sites and shipped to Dr. Fowler's laboratory. Once in Dr. Fowler's lab, vancomycin MICs will be determined for all isolates using broth micro dilution methods.

Potential associations between vancomycin MIC values and clinical outcome will then be assessed as part of Exploratory Efficacy analyses.

8.6 Consideration of Vancomycin Levels

In accordance with consensus guidelines published in 7/2009, vancomycin should be dosed to attain target troughs of 15-20 mcg/ml.³² Trough levels should be obtained just prior to the fourth dose, at steady-state conditions. However, in light of ongoing controversy regarding the efficacy of this practice, it will not be mandatory to follow this suggested vancomycin monitoring schedule. If vancomycin levels are obtained as part of clinical care, the results will be collected as part of study data.

8.7 Schedule of Events: Simple CoNS Blood Stream Infection

If Randomized to Algorithm, the total treatment period is 0 – 3 (+1) Days

Day ^a	Baseline	Enrollment	Treatment ^{m,n,o}		Follow-up	
			Daily to IEOT/D V ^b	IEOT/D V ^b	Early TOC ^c Assessment 14-4+10 days ^d	Final TOC Assessment 28-4 + 10 days ^e
Informed Consent		X				
Medical History		X				
Antibiotic / Medication History		X				
Vital Signs ^f		X	X	X		
Physical Exam (PE)		X		X	X	X
Height, Weight ^g		X				
Clinical Assessment ^h		X	X	X		
Blood Culture	X ^a	X 48-168 hours after initial positive blood culture was collected				
CBC with differential, Comprehensive metabolic panel ⁱ		X ^p		X ^p		
Pregnancy Test (urine or serum)		X				
Randomization		X ^a				
Study Medication Administration	(X) ^o	(X) ^o	X	X		
Concomitant Antibiotics ^k			X	X	X	X
Safety ^l			X	X	X	X

- a. Patients must have at least one blood culture positive for CoNS and classification of simple and have received no more than 3 calendar days of medication effective for their baseline infecting pathogen prior to randomization. Baseline bloodstream isolates will be collected and stored for shipment until the end of the study, or earlier if requested.
- b. Inpatient End of Treatment (IEOT) or Discharge Visit (DV), whichever occurs first. The IEOT can be ± 2 days; the DV can be done up to two calendar days prior to discharge. Some CoNS patients may be treated solely as outpatients. These patients will only have IEOT/DV visit procedures performed if they have an in-person clinic visit as part of their treatment plan between the enrollment visit and the end of treatment. Subjects on treatment as outpatients, or continuing treatment after discharge, will receive a phone call from the site on the day treatment is scheduled to end (± 2 days) to confirm drug discontinuation date, and collect con med and AE information. In the simple CoNS algorithm patients who do not receive any antibiotic treatment for their index bacteremia, End Of Therapy will be defined as the day that the patient was randomized.
- c. Test of Cure (TOC). If patients fail or are determined non-evaluative prior to the scheduled TOC visit, all applicable final TOC assessments can be conducted at the time of failure or non-evaluative determination and the patient can be classified as completing (failure) or terminating (non-evaluative) the study at that time.
- d. 14 - 4 + 10 days after last dose of study drug, by clinic visit (preferred) or telephone call (required data obtained from the medical records is acceptable but not preferred). Perform PE only if clinic visit.
- e. 28 - 4 + 10 days after last dose of study drug, by clinic visit (preferred) or telephone call (required data obtained from the medical records is acceptable but not preferred). Perform PE only if clinic visit.
- f. Vital signs are blood pressure, heart rate and temperature; record the most clinically significant measurement for that date.
- g. Record weight and height at enrollment only. Use weight and height from admission; if none available measure at enrollment.
- h. Clinical Assessment is done by PI or designated SI and involves clinical judgment based upon all clinical aspects of care (e.g. labs, ECG and/or ECHO if clinically indicated, clinical symptoms).
- i. If repeat culture is positive, patient meets criteria for complicated infection and will be managed according to table 8.9.
- j. CBC with differential and comprehensive metabolic panel includes the tests listed in Section 8.14.1. If these tests were not run as standard of care prior to randomization, they should be requested at the time of randomization
- k. Empiric treatment for Gram-negative pathogens is allowable; these agents will not be counted when calculating antibiotic days unless susceptibility testing of the bloodstream staphylococcal isolate reveals that the staphylococcus is susceptible to the antibiotic and the patient is not receiving other antistaphylococcal treatment (e.g., methicillin-susceptible staphylococcal bloodstream isolate from a patient receiving empiric beta-lactam treatment for gram-negative treatment).
- l. Collect all AEs leading to study drug withdrawal and all SAEs.
- m. Suggest to measure trough vancomycin levels prior to 4th dose and at steady state.
- n. For subjects on treatment as outpatients, or continuing treatment after discharge, study staff will call patient twice per week and on the scheduled end of treatment day (± 2 days) to confirm drug discontinuation date, concomitant medication usage, and AE information.
- o. If empiric treatment was started prior to randomization and this treatment is effective for the baseline infecting pathogen, these treatment days will count towards the total treatment duration. In patients randomized to algorithm in the simple CoNS group, antibiotic treatment for the index bacteremia must be discontinued upon randomization. If the patient has not received any antibiotic treatment for the index bacteremia prior to randomization, no treatment will be started.
- p. Labs within 14 days of enrollment. Differential required only at Enrollment. For comprehensive metabolic panel AST (SGOT) is not required.

8.8 Schedule of Events: Uncomplicated CoNS Blood Stream Infection

If Randomized to Algorithm, the total treatment period is 5 (-/+1) Days

Day ^a	Baseline	Enrollment	Treatment ^{m,n,o}		Follow-up	
			Daily to IEOT/DV ^b	IEOT/DV ^b	Early TOC ^c Assessment 14-4+10 days ^d	Final TOC ^c Assessment 28-4+10 days ^e
Informed Consent		X				
Medical History		X				
Antibiotic / Medication History		X				
Vital Signs ^f		X	X	X		
Height/Weight ^g		X				
Physical Exam		X		X	X	X
Clinical Assessment ^h		X	X	X		
Blood Culture	X ^a	X 48- 168 hours after initial positive blood culture was collected				
CBC with differential, Comprehensive metabolic panel ⁱ		X ^p		X ^p		
Pregnancy Test (urine or serum)		X				
Randomization		X				
Study Medication Administration	(X) ^o	(X) ^o	X	X		
Concomitant Antibiotics ^k			X	X	X	X
Safety ^l			X	X	X	X

- a. Patients must have at least one blood culture positive for CoNS, meet the classification for uncomplicated, and have received no more than 4 calendar days of medication effective for their baseline infecting pathogen prior to randomization. Baseline bloodstream isolates will be collected and stored for shipment until the end of the study, or earlier if requested.
- b. Inpatient End of Treatment (IEOT) or Discharge Visit (DV), whichever occurs first. The IEOT can be ± 2 days; the DV can be done up to two calendar days prior to discharge. Some CoNS patients may be treated solely as outpatients. These patients will only have IEOT/DV visit procedures performed if they have an in-person clinic visit as part of their treatment plan between the enrollment visit and the end of treatment.
- c. Test of Cure (TOC). If patients fail or are determined non-evaluative prior to the scheduled TOC visit, all applicable final TOC assessments can be conducted at the time of failure or non-evaluative determination and the patient can be classified as completing (failure) or terminating (non-evaluative) the study at that time.
- d. 14 - 4 + 10 days after last dose of study drug, by clinic visit (preferred) or telephone call (required data obtained from the medical records is acceptable but not preferred). Perform PE only if clinic visit.
- e. 28 - 4 + 10 days after last dose of study drug, by clinic visit (preferred) or telephone call (required data obtained from the medical records is acceptable but not preferred). Perform PE only if clinic visit.
- f. Vital signs are blood pressure, heart rate and temperature; record the most clinically significant measurement for that date.
- g. Record height and weight at enrollment only. Use height and weight from admission; if none available, measure at enrollment.
- h. Clinical Assessment is done by PI or designated SI and involves clinical judgment based upon all clinical aspects of care (e.g. labs, ECG and/or ECHO if clinically indicated, clinical symptoms).
- i. If repeat cultures positive, patient meets criteria for complicated infection and will be managed according to table 8.9. Blood cultures will be repeated every 1-2 days until all cultures obtained within the past 48 hours have remained negative.
- j. CBC with differential and comprehensive metabolic panel includes the tests listed in Section 8.14.1. If these tests were not run as standard of care prior to randomization, they should be requested at the time of randomization.
- k. Empiric treatment for Gram-negative pathogens is allowable; these agents will not be counted when calculating antibiotic days unless susceptibility testing of the bloodstream staphylococcal isolate reveals that the staphylococcus is susceptible to the antibiotic and the patient is not receiving other antistaphylococcal treatment (e.g., methicillin-susceptible staphylococcal bloodstream isolate from a patient receiving empiric beta-lactam treatment for gram-negative treatment).
- l. Collect AEs leading to study drug withdrawal and all SAEs.
- m. Suggest to measure trough vancomycin levels prior to 4th dose and at steady state.
- n. For subjects on treatment as outpatients, or continuing treatment after discharge, study staff will call patient twice per week and on the scheduled end of treatment day (± 2 days) to confirm drug discontinuation date, concomitant medication usage, and AE information.
- o. If empiric treatment was started prior to randomization and this treatment is effective for the baseline infecting pathogen, these treatment days will count towards the total treatment duration.
- p. Labs within 14 days of enrollment. Differential required only at Enrollment. For comprehensive metabolic panel AST (SGOT) is not required.

8.9 Schedule of Events – Complicated CoNS Blood Stream Infection

Reminder: Complicated infection is an enrollment exclusion; however, it is not reason to withdraw a patient when diagnosed after randomization. This schedule of events applies only to those patients diagnosed with complicated infection after randomization but before completion of study treatment for the baseline bacteremia clinical classification. Complicated CoNS identified after completion of study treatment for the baseline bacteremia clinical classification will be considered a “New Complicated Staphylococcal Infection” will be retained in their original group and counted as a Treatment Failure.

If Randomized to Algorithm, the total treatment period is 7-28 (-/+2) Days

Day	Treatment ^{i,k}			Follow-up	
	Daily to IEOT/DV ^a	Weekly to IEOT/DV ^a	IEOT/DV ^a	Early TOC ^b Assessment 14+/-4 days ^c	Final TOC ^b Assessment 28- 4 + 10 days ^d
Vital Signs ^e	X		X		
Physical Exam		X	X	X	X
Clinical Assessment ^f	X ^l		X		
Blood Culture ^g	Repeat every 1-2 days until all negative for 48 hours.				
CBC with differential, Comprehensive metabolic panel		X ^k	X ^k		
Study Medication Administration ^h	X		X		
Concomitant Antibiotics ^j	X		X	X	X
Safety ⁱ	X		X	X	X

- a. Inpatient End of Treatment (IEOT) visit or Discharge Visit (DV), whichever comes first. The IEOT visit can be ± 2 days; the DV can be done up to two calendar days prior to /discharge.
- b. Test of Cure (TOC). If patients fail or are determined non-evaluable prior to the scheduled TOC visit, all applicable final TOC assessments can be conducted at the time of failure or non-evaluable determination and the patient can be classified as completing (failure) or terminating (non-evaluable) the study at that time.
- c. 14 - 4 + 10 days after last dose of study drug by clinic visit (preferred) or telephone call (required data obtained from the medical records is acceptable but not preferred). Perform PE only if clinic visit.
- d. 28 - 4 + 10 days after last dose of study drug by telephone call or clinic visit (preferred) or telephone call (required data obtained from the medical records is acceptable but not preferred). Perform PE only if clinic visit.
- e. Vital signs are blood pressure, heart rate and temperature; record the most clinically significant measurement for that date.
- f. Clinical Assessment is done by PI or designated SI and involves clinical judgment based upon all clinical aspects of care (e.g. labs, ECG and/or ECHO if clinically indicated, clinical symptoms).
- g. Blood culture(s) will be repeated every 1-2 days until all cultures obtained within the past 48 hours have remained negative.
- h. Empiric treatment for Gram-negative pathogens is allowable; these agents will not be counted when calculating antibiotic days unless susceptibility testing of the bloodstream staphylococcal isolate reveals that the staphylococcus is susceptible to the antibiotic and the patient is not receiving other antistaphylococcal treatment (e.g., methicillin-susceptible staphylococcal bloodstream isolate from a patient receiving empiric beta-lactam treatment for gram-negative treatment).
- i. Collect AEs leading to study drug withdrawal and all SAEs.
- j. Suggest to measure trough vancomycin levels prior to 4th dose and at steady state. If on treatment after discharge, study staff will call patient 2 times per week and on the scheduled end of treatment day (± 2 days) to confirm drug discontinuation date, concomitant medication usage, and AE information. Clinical assessments performed daily while inpatient and on treatment
- k. Labs within 14 days of enrollment. Differential required only at Enrollment. For comprehensive metabolic panel AST (SGOT) is not required.

8.10 Schedule of Events – Uncomplicated *S. aureus* Blood Stream Infection

If Randomized to Algorithm, the total treatment period is 14 (-/+2) Days

Day ^a	Baseline	Enrollment	Treatment ^{n,o,p}			Follow-up	
			Daily to IEOT/DV ^b	Weekly to IEOT/DV ^b	IEOT/DV ^b	Early TOC ^c Assessment 21-4 + 10 days ^d	Final TOC ^c Assessment 42-4+10 days ^e
Informed Consent		X					
Medical History		X					
Antibiotic / Medication History		X					
Vital Signs ^f		X	X		X		
Height/Weight ^g		X					
Physical Exam		X		X	X	X	X
Clinical Assessment ^h		X	X ^q		X		
Blood Culture ^a	X	X 24-72 hours following initial blood culture collection					
CBC with differential, Comprehensive metabolic panel ^j		X ^r		X ^r	X ^r		
Pregnancy Test (urine or serum)		X					
Echocardiogram (Algorithm Only) ^k			Within 10 calendar days of start of treatment				
Randomization		X					
Study Medication Administration	(X) ^p	(X) ^p	X		X		
Concomitant Antibiotics ^l		X	X		X	X	X
Safety ^m		X	X		X	X	X

- a. Patients must have at least one blood culture positive for *S. aureus* and have received no more than 12 days of treatment effective for their baseline infecting pathogen prior to randomization. Baseline bloodstream isolates will be collected and stored for shipment until the end of the study, or earlier if requested.
- b. Inpatient End of Treatment (IEOT) or Discharge Visit (DV), whichever occurs first. The IEOT can be ± 2 days; the DV can be done up to two calendar days prior to discharge
- c. Test of Cure (TOC). If patients fail or are determined non-evaluable prior to the scheduled TOC visit, all applicable final TOC assessments can be conducted at the time of failure or non-evaluable determination and the patient can be classified as completing (failure) or terminating (non-evaluable) the study at that time.
- d. 21 - 4 + 10 days after last dose of study drug, by clinic visit (preferred) or telephone call (required data obtained from the medical records is acceptable but not preferred). Perform PE only if clinic visit.
- e. 42 - 4 + 10 days after last dose of study drug, by clinic visit (preferred) or telephone call (required data obtained from the medical records is acceptable but not preferred). Perform PE only if clinic visit.
- f. Vital signs are blood pressure, heart rate and temperature; record the most clinically significant measurement for that date.
- g. Record weight at Enrollment only. Use height and weight from admission; if none available, measure at enrollment.
- h. Clinical Assessment is done by PI or designated SI and involves clinical judgment based upon all clinical aspects of care (e.g. labs, ECG, TTE, TEE, clinical symptoms).
- i. Blood culture(s) will be repeated every 1-2 days until all cultures obtained within the past 48 hours have remained negative. If repeat culture is positive, patient meets criteria for complicated infection and will be managed according to algorithm 8.11.
- j. CBC with differential and comprehensive metabolic panel includes the tests listed in Section 8.14.1. If these tests were not run as standard of care prior to randomization, they should be requested at the time of randomization
- k. Echocardiography (TEE preferred) mandated for algorithm *S. aureus* within 10 calendar days of start of study treatment.
- l. Empiric treatment for Gram-negative pathogens is allowable; these agents will not be counted when calculating antibiotic days unless susceptibility testing of the bloodstream staphylococcal isolate reveals that the staphylococcus is susceptible to the antibiotic and the patient is not receiving other antistaphylococcal treatment (e.g., methicillin-susceptible staphylococcal bloodstream isolate from a patient receiving empiric beta-lactam treatment for gram-negative treatment).
- m. Collect AEs leading to study drug withdrawal and all SAEs.
- n. Suggest to measure trough vancomycin levels prior to 4th dose and at steady state.
- o. If on treatment after discharge study staff will call patient 2 times per week and on the scheduled end of treatment day (± 2 days) to confirm drug discontinuation date, concomitant medication usage, and AE information.
- p. If empiric treatment was started prior to randomization and this treatment is effective for the baseline infecting pathogen, these treatment days will count towards the total treatment duration.
- q. Clinical assessments performed daily while inpatient and on treatment
- r. Labs within 14 days of enrollment. Differential required only at Enrollment. For comprehensive metabolic panel AST (SGOT) is not required.

8.11 Schedule of Events – Complicated *S. aureus* Blood Stream Infection

Reminder: Complicated *S. aureus* blood stream infection is an enrollment exclusion; however, it is not reason to withdraw patient when diagnosed after randomization. This schedule of events applies to those patients diagnosed with complicated infection after randomization but prior to completion of study treatment for the baseline bacteremia clinical classification. Patients with Complicated *S. aureus* blood stream infection identified after completion of study treatment for the baseline bacteremia clinical classification will be defined as having a New Complicated Staphylococcal infection will be retained in their original group and counted as a Treatment Failure.

If Randomized to Algorithm, the total treatment period is 28-42 (-/+2) Days

Day	TREATMENT ^{k,l}			FOLLOW-UP	
	Daily to IEOT/DV ^a	Weekly to IEOT/DV ^a	IEOT/DV ^a	Early TOC ^b Assessment 21-4+10 days ^c	Final TOC ^b Assessment 42-4+10 days ^d
Vital Signs ^e	X		X		
Physical Exam		X	X	X	X
Clinical Assessment ^f	X ^j		X		
Blood Culture ^g	Repeat every 1-2 days until negative for 48 hours.				
CBC with differential, Comprehensive metabolic panel		X ^m	X ^m		
Echocardiogram (Algorithm only) ^h	Within 10 calendar days of start of treatment				
Study Medication Administration	X		X		
Concomitant Antibiotics ⁱ	X		X	X	X
Safety ^j	X		X	X	X

- a. Inpatient End of Treatment (EOT) or discharge, whichever occurs first. The IEOT can be ± 2 days; the DV can be done up to two calendar days prior to discharge.
- b. Test of Cure (TOC). If patient fails or is determined non-evaluable prior to the scheduled TOC visit, all applicable final TOC assessments can be conducted at the time of failure or non-evaluable determination and the patient can be classified as completing (failure) or terminating (non-evaluable) the study at that time.
- c. 21 - 4 + 10 days after last dose of study drug, by clinic visit (preferred) or telephone call (required data obtained from the medical records is acceptable but not preferred). Perform PE if clinic visit.
- d. 42 - 4 + 10 days after last dose of study drug, by clinic visit (preferred) or telephone call. Perform PE if clinic visit.
- e. Vital signs are blood pressure, heart rate and temperature; record the most clinically significant measurement for that date.
- f. Clinical Assessment is done by PI or designated SI and involves clinical judgment based upon all clinical aspects of care (e.g. labs, ECG, TTE, TEE, clinical symptoms).
- g. Blood culture(s) will be repeated every 1-2 days until all cultures obtained within the past 48 hours have remained negative.
- h. Echocardiography (TEE preferred) mandated for algorithm *s. aureus* within 10 calendar days of the start of treatment.
- i. Empiric treatment for Gram-negative pathogens is allowable; these agents will not be counted when calculating antibiotic days unless susceptibility testing of the bloodstream staphylococcal isolate reveals that the staphylococcus is susceptible to the antibiotic and the patient is not receiving other antistaphylococcal treatment. Clinical assessments performed daily while inpatient and on treatment (e.g., methicillin-susceptible staphylococcal bloodstream isolate from a patient receiving empiric beta-lactam treatment for gram-negative treatment).
- j. Collect AEs leading to study drug withdrawal, and all SAEs .
- k. Suggest to measure trough vancomycin levels prior to 4th dose and at steady state.
- l. If on treatment after discharge study staff will call patient 2 times per week and on the scheduled end of treatment day (± 2 days) to confirm drug discontinuation date, concomitant medication usage, and AE information.
- m. Labs within 14 days of enrollment. Differential required only at Enrollment. For comprehensive metabolic panel AST (SGOT) is not required.

8.12 Standard of Care Assessments

Both the Standard of Care and Algorithm treatment arm will have the same assessments and data collected with the exception of the echocardiography. The echocardiogram (TEE preferred) is not obligatory in the Standard of Care treatment group but is mandatory in the Algorithm group for patients with cultures positive for *S. aureus*. Refer to Sections 8.7 through 8.11 for the Schedule of Events for all subjects, based on the subject's infecting pathogen and clinical classification.

8.13 Safety and Efficacy Evaluations

Efficacy will be determined based upon the patient's clinical and bacteriologic results on the days designated by the group to which the patient is randomized. Safety will be evaluated by collecting and comparing all AEs leading to study drug withdrawal, and all SAEs, in the algorithm-based treatment and SOC treatment.

The DMID Medical Monitor will review all SAEs on an ongoing basis and will also review all occurrences of persisting and relapsing infection. In addition, the DSMB will meet and review reported AEs and SAEs as outlined in their charter.

8.13.1 Clinical Events Committee (CEC)

In addition to the investigator evaluation of clinical outcomes, a CEC consisting of three adjudicators will be established. These three CEC adjudicators are Board Certified Infectious Diseases Physicians with particular expertise in bacterial infections. They will be responsible for: 1) establishing the presence and significance of PENS antibiotics; 2) evaluating patient outcome in a randomly selected cohort of study patients; and 3) adjudicate death for attribution.

All investigator identified potential PENS occurrences will be reviewed by the CEC using source documents and specifically designed study documents will be completed by the Site Study Coordinator.

Outcomes will be defined as "Success," "Failure", or "Non-evaluable" for the ITT population and as "Success", or "Failure" for the PP population, using definitions in Section 3.2.3.1 and 3.2.3.2, and will be assessed at a TOC telephone call or clinic visit at TOC assessment. Outcome assignment will be based on relevant hospital records, outpatient records, and study coordinator data. At least 50 patients or ~ 12 patients per year for the 4 years of study enrollment will be adjudicated to address the potential confounding effect of open label design. If there is a disagreement in outcome between the CEC committee and site PI/SI, then the CEC decision on outcome will be used in the final analysis. For example, if PI/SIs assessment is cure and CECs assessment is treatment failure, then the patient will be considered a treatment failure in analysis.

The CEC charter will be developed, and the committee and the process will be defined in the charter. The committee chair will be responsible for ensuring accuracy and compliance with the charter. Five percent of all the cases reviewed in the first session will be reviewed again as a quality control effort to evaluate internal consistency of the group interpretation; any inconsistencies will be resolved by the group under the direction of the adjudication chair.

8.14 Laboratory Evaluations

8.14.1 Clinical Laboratory Evaluations

Baseline blood culture(s) will have been drawn and a positive result of *S. Aureus* or CoNS reported, prior to randomization. Blood and urine specimens for laboratory determinations will be collected at the Enrollment visit and at intervals determined on the Schedule of Events in Sections 8.7 through 8.11, based on the subject's baseline pathogen and clinical classification..

Specimens will be submitted for analysis as per the instructions of the individual hospital laboratory. These laboratories will be intended to evaluate both 1) potential AEs and 2) therapeutic response. Hematologic and chemistry laboratories will be obtained to evaluate for possible AEs. Blood cultures will be obtained to monitor therapeutic response. The following parameters will be measured:

- Hematology: hemoglobin, hematocrit, WBC count (with differential), and platelet count, at Enrollment, then according to the Schedule of Events in Sections 8.7-8.11, and then as clinically indicated.
- Chemistry: alkaline phosphatase, BUN (reported only if done), calcium (reported only if done), creatinine, glucose, potassium, ALT (SGPT), sodium, total bilirubin, obtained collectively within a comprehensive metabolic panel at Enrollment, then according to the Schedule of Events in Sections 8.7-8.11, and then as clinically indicated.
- Urine or serum pregnancy screen at Enrollment only.
- Blood cultures at Baseline, then as specified by the Schedule of Events in Sections 8.7-8.11, and then as clinically indicated.
- Creatinine clearance will be calculated at the enrollment visit using the Cockcroft-Gault or Modification of Diet in Renal Disease study (MDRD) formula and should be noted in the source documentation.
- Transesophageal Echocardiogram (TEE) or Transthoracic Echocardiogram (TTE) is mandated only for algorithm patients with cultures positive for *S. aureus*. The TEE is preferred.
- Electrocardiograms (ECG) are not mandated and will only be performed if part of clinical assessment.

- It will not be mandatory to obtain vancomycin levels, but if these are obtained, the results will be collected as part of study data.

8.14.1.1 Echocardiogram

Echocardiography will be performed on all algorithm subjects with a baseline blood culture positive for *S. aureus*. The TEE is preferred over the TTE. The echocardiogram will be interpreted by the site's echocardiographer as per standard clinical practice⁴¹ and the interpretation must be kept in the investigator's file. In addition, the de-identified echo study recorded on CD will be sent to DCRI and be reinterpreted by an experienced echocardiographer at the DCRI Echocardiography Core Laboratory. The echocardiographer will be blinded to the clinical details of the patient.

The following selection criteria will be used to determine which study is reinterpreted:

- a. If a single protocol required echocardiogram is performed, it will be sent for reinterpretation.
- b. If multiple echocardiograms are performed then the study that is the most diagnostic for endocarditis will be sent for reinterpretation.
- c. If multiple echocardiograms are performed, but none are diagnostic, then the first study following the initial diagnosis of *S. aureus* bacteremia will be sent for reinterpretation. If both a TTE and TEE have been performed, and none are diagnostic, then the first TEE following initial diagnosis of *S. aureus* bacteremia will be sent for reinterpretation.

A comparison between the site and central echocardiogram readings will be performed. If there are discrepancies, then only the site interpretation will be reported on the eCRF and used for clinical decision-making at the study site. Patient outcome at final TOC for those patients randomly selected for CEC adjudication of outcome, will also be assessed by the CEC using the interpretation of the Echocardiography Core Laboratory to ensure that no bias is introduced by the fact that the onsite clinicians interpreting the echocardiogram know the clinical condition of the patient. See Section 8.13.1.

Echocardiography may also be performed for clinical assessments and read by site echocardiographer **per standard clinical practice**, but a CD recording should not be submitted as it will not be reinterpreted by the central Core Laboratory.

8.14.2 Procedures to be Followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings

If the following abnormal laboratory values are found, they will be followed at least weekly until resolution or until stable:

- 1) WBC <2000/mm³

- 2) renal impairment, as defined by an increase in creatinine by at least 50% or 0.5 mg/dL over baseline value, whichever is greater
- 3) platelet count <60,000/mm³
- 4) AST or ALT >5x upper limit of normal if the patient is on an antistaphylococcal penicillin.

Other abnormal laboratory test values will be managed according to routine clinical care. TEE/TTE results consistent with infective endocarditis will be managed according to the cohort to which the subject was randomized; other TEE/TTE abnormalities will be managed according to routine clinical care.

8.14.3 Special Assays or Procedures

Baseline staphylococcal bloodstream isolates will be analyzed as part of this protocol to determine vancomycin minimum inhibitory concentration. In addition, the baseline bloodstream isolates will be stored for potential future additional studies if patients agree. There is a section in the ICF for patients to indicate if they choose to “opt out” of storage for future testing.

8.14.4 Specimen Preparation, Handling, and Shipping

All baseline staphylococcal isolates from study patients will be shipped to Dr. Fowler’s laboratory for storage until required for additional analyses. The bloodstream staphylococcal isolate from the initial positive blood culture of each study patient will be stored, frozen at -70°C to -80°C or lyophilized and batch shipped to Dr. Fowler’s laboratory at Duke University at the following address:

Vance G. Fowler, Jr. MD, MHS
Division of Infectious Diseases
Department of Medicine
Room 1546, Stead Bldg
Duke University Medical Center
Durham, NC 27710
(Lab) 919-668-3369 Office: 919-613-5678

Additional details regarding collection, storage, packing and shipping of isolates will be contained in the Manual of Operating Procedures (MOP).

9 SPECIFICATION OF SAFETY PARAMETERS

9.1 Adverse Events

Site investigator is responsible for monitoring the safety of patients enrolled into the study at the study sites. All adverse events should be documented in the patient's medical record and managed as standard practice. All AEs should be followed by the site until satisfactory resolution or until the investigator deems the event to be chronic and/or the patient to be stable. At each visit the study staff, with investigator oversight, will review the patient's medical record and determine if there have been any AEs leading to study drug withdrawal or serious adverse events (SAEs) and will then collect all pertinent information for entry into the eCRF. All AEs leading to study drug withdrawal, and all SAEs will be documented by the sites and will be reviewed by the Data Safety Monitoring Board (see Section 9.5)

9.2 Methods and Timing for Assessing, Recording, and Evaluating Safety Parameters

9.2.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation where a patient is administered a pharmaceutical product. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product. AEs also include any worsening (i.e., any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug (vancomycin or protocol permitted alternative drug) and abnormal laboratory findings considered by the reporting investigator to be clinically significant.

All SAEs, and AEs leading to study drug withdrawal, must be graded for severity and relationship to study drug.

Severity of Event: Clinicians will use the following guidelines to quantify intensity of the event reported.

- **Mild:** events require minimal or no treatment and do not interfere with the patient's daily activities.
- **Moderate:** events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe:** events interrupt a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

- **Life threatening:** any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

Changes in the severity of an AE should be documented but only the most severe level of intensity is to be captured on the eCRF. AEs characterized as intermittent require documentation of onset and duration of each episode. If the AE is deemed “Life Threatening” or meets any other criteria in Section 9.2.2, then the event is reported as a “Serious Adverse Event” (see section 9.2.2 for definition and Section 9.3.1 for reporting requirements).

Relationship to Study Intervention: The investigator should use the following definitions when assessing causality of an AE to study medication:

- **Not associated:** an AE that has no or little temporal relationship to trial drug or has a definite alternative etiology (only SAEs of this category will be recorded on the eCRFs).
- **Associated:** an AE commonly associated with this drug class; or that has a temporal relationship to study medication and/or reappeared on re-challenge; and/or no alternative etiology exists or is apparent (only AEs leading to study drug withdrawal and SAEs of this category will be recorded on the eCRFs).

Lack of efficacy will not be reported as associated to study drug but may satisfy the definition of treatment failure.

9.2.2 Serious Adverse Events

An SAE is any AE that results in any of the following outcomes:

- Death
- Life-threatening
- Persistent or significant disability or incapacity
- Inpatient hospitalization or prolongation of existing hospitalization
- Congenital abnormality or birth defect
- Important medical event

Life-threatening means that the patient or subject was, in the view of the investigator, at immediate risk of death from the AE as it occurred. It does not include an AE that, had it occurred in a more severe form, might have caused death.

Persistent or significant disability/incapacity means that the event resulted in permanent or significant and substantial disruption of the patient’s ability to carry out normal life functions.

Important medical event is any medical event that may not result in one of the above outcomes, but may jeopardize the health of the study participant or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of SAEs.

9.3 Reporting Procedures

9.3.1 Non Serious and Serious Adverse Events

Sites will record all AEs leading to study drug withdrawal, and all SAEs, occurring from study drug initiation (time of first dose of study drug) for all treatment subjects through final TOC assessment regardless of their association to study drug on the AE eCRF. In the case of subjects with simple CoNS who do not receive any study drug (i.e. the “zero days” subjects), sites will record all SAEs occurring from randomization through final TOC assessment.

All AEs leading to study drug withdrawal, and all SAEs, will be followed by the site until satisfactory resolution or until the investigator deems the event to be chronic and/or the patient to be stable regardless if the patient is continuing the study.

All SAEs will be reported by completing the AE/SAE eCRF page in INFORM within 24 hours of knowledge of the event. The initial report must be as complete as possible, including details of the SAE, and provide an investigator assessment of severity and the causal relationship between the event and the investigational product. Information not available at the time of the initial reporting must be documented on SAE eCRF page in Inform within 24 hours of knowledge of the information.

DCRI Safety Surveillance, the DMID Medical Monitor and the DMID Pharmacovigilance designee will receive a real-time automated SAE email notification when data is entered or changed on the SAE eCRF in InForm. DCRI Safety Surveillance will be responsible for reviewing SAE eCRF data, querying sites within InForm for additional or missing SAE data, and generating SAE reports. SAEs confirmed to meet protocol specific reporting criteria will be forwarded to DMID Pharmacovigilance within 1 business days of receipt. DMID Pharmacovigilance will process all SAE reports and forward to the DMID Medical Monitor. DMID Pharmacovigilance will forward any additional SAE queries to DCRI Safety Surveillance to be entered into InForm clinical database.

Questions about SAE reporting can be referred to DCRI Safety Surveillance at **919-668-8624, or at 866-668-7799 (North America only)**.

Other supporting documentation of the event may be requested by DCRI Safety Surveillance and should be provided as soon as possible.

All SAEs and all AEs leading to study drug withdrawal will be followed by the site until satisfactory resolution or until the investigator deems the event to be chronic and/or the patient to be stable. DCRI Safety Surveillance will follow all reported SAEs until resolved

or stabilized or until the trial database lock. For any ongoing SAE after database lock, the sites will be instructed to forward follow-up information directly to DMID Pharmacovigilance. If the event resolves during the study or follow-up period, a resolution date should be documented on the AE eCRF.

9.3.2 Reporting of Pregnancy

Pregnant patients are excluded from enrolling in this trial and participants are strongly discouraged from becoming pregnant while enrolled in the trial. If a study participant does become pregnant during the course of the study, the site will follow the pregnancy through 8 weeks post-live delivery or elective or natural termination of the pregnancy, whichever occurs first. If an SAE occurs in conjunction with the pregnancy the SAE must be reported as described in section 9.3.1 above.

Upon notification of pregnancy the site will obtain a Pregnancy Outcome Tracking (POT) form from DCRI Safety Surveillance by calling **919-668-8624, or at 866-668-7799 (North America only)**. The form should be completed with as much information as is available and faxed to DCRI Safety Surveillance at the number provided on the form. The site will provide updated information on the POT as it becomes available through the final outcome of the pregnancy and for ≥ 8 weeks after delivery via fax to DCRI Safety Surveillance as above.

DCRI Safety Surveillance will forward all Pregnancy Outcome Tracking forms to DMID Medical Monitor and DMID Pharmacovigilance designee within 1-2 business days of receipt

Vancomycin is an approved drug, and thus, the risk to the fetus and newborn known slightly better than an unapproved drug, but is still not well defined. It is not known if vancomycin can affect reproduction capacity (Baxter Healthcare Corporation, Vancomycin Hydrochloride Injection Package insert revised February 2009). In one controlled clinical study, vancomycin was administered to pregnant women. One infant had conductive hearing loss, but this was not attributed to vancomycin. The size of the trial is not reported in the package insert.

Sexually active female participants must use an effective method of birth control during the study. Non-estrogen-containing birth control medications or double-barrier contraception will be recommended for all female participants of childbearing potential. The ICF must indicate that the investigator has reviewed information about pregnancy prevention for all women of childbearing potential. A serum or urine β -HCG will be performed at enrollment.

The consent form will include what is known about mutagenic and teratogenic effects of vancomycin from reproductive toxicity studies in animals, with the statement that this information has had limited predictive value for effects in humans. The consent form will

indicate that exposure to vancomycin may involve unforeseeable risks to a fetus. The ICF must include names and telephone numbers for study contacts that the participant can call if she becomes pregnant, suspects she may be pregnant, has missed her period or it is late, or has had a change in her usual menstrual cycle. Any participant who becomes pregnant during the study will be withdrawn immediately and referred for obstetrical care.

The primary physician caring for the patient will oversee any changes to treatment, for example changing antibiotics, as appropriate. Vancomycin is classified as a FDA Category C in pregnancy, whereas daptomycin is FDA Category B. Thus, daptomycin is the recommended antibiotic in this study for staphylococcal bacteremia in pregnant patients, unless individual circumstances intervene.

9.4 Type and Duration of Follow-up of Patients after Adverse Events

Any clinical findings in the final examination, including clinically significant laboratory abnormalities, must be followed, whether the patient completes the study or discontinues prematurely for any reason, until satisfactory resolution or until the investigator deems the event to be chronic and/or the patient to be stable. See Section 9.3.1 for detailed information regarding follow-up timelines of SAE and AEs.

9.5 Safety Oversight

An independent DSMB will be established by NIAID to monitor safety data. The DSMB will operate under the rules of a DMID-approved charter that will be written at the organization meeting of the DSMB. At this time, each data element that the DSMB needs to assess safety will be clearly defined. There will be several safety data reviews during the conduct of the study, which will take place, at a minimum, after approximately 125, 250, and 350 patients have enrolled and completed the final TOC visit. In addition the DSMB may hold more frequent meetings if determined necessary for any reason and the DSMB will also be involved in the planned sample size re-estimation outlined in Section 11.2.3. The DSMB will advise DMID of its recommendations. The DMID and DSMB will also review periodic reports generated from CEC adjudication meetings.

Either the study Executive Committee, DMID or the investigator may terminate the study at any time based on safety concerns.

9.6 Halting Rules

The Data and Safety Monitoring Board (DSMB) will define halting rules in their charter.

The DSMB will consider stopping the trial if one or more of the following conditions occur:

1. In the patients with simple or uncomplicated bacteremia, there is evidence that the incidence of SAEs in the algorithm group is $\geq 20\%$ higher than the standard of care group (SOC) and is not by chance alone (defined as P-value <0.05).
2. In patients with simple or uncomplicated infections, the incidence of persisting and/or relapsing infections is $\geq 20\%$ higher in the algorithm group than the SOC group and is not by chance alone (defined as P-value <0.05).

See section 3.2.3.2 and 3.2.3.3 for definitions of persisting and relapsing infection.

3. In all randomized patients, there is $\geq 20\%$ difference in the death rate between the SOC and algorithm group and is not by chance alone (defined as P-value <0.05).

To assure adequate data is available, halting rule analysis will be performed prior to DSMB meetings after 125, 250 and 350 patients have enrolled and completed the Test of Cure visit. The DSMB will evaluate the halting rule results during regularly scheduled DSMB meetings and will decide if the trial may proceed or should be stopped during each meeting.

10 CLINICAL MONITORING

10.1 Site Monitoring Plan

A universal monitoring plan was developed by DCRI. The monitoring plan will be updated as needed to address the changing needs of the study. The DCRI Lead CRA or designee will train both the DCRI and Aptiv Solutions (formerly SRA International) monitors on all versions of the clinical monitoring plan to assure consistency in monitoring activities.

The investigator will make available to the CRA the eCRFs, source documents, patients' medical records, signed consent forms, and all other study related documents. The investigator will be responsible for reviewing eCRFs, providing missing or corrected data, approving all changes performed on his/her data, and signing the appropriate eCRF(s).

11 STATISTICAL CONSIDERATIONS

11.1 Study Hypotheses

11.1.1 Primary

The primary study objective is to demonstrate that the clinical efficacy of algorithm-based treatment of patients with staphylococcal blood stream infection is noninferior to current SOC. Based on the primary study endpoint of clinical outcome (cure rate), a non-inferiority hypothesis will be tested using a two-sided alpha of 0.05; a non-inferiority margin of 15%, at least 80% power, an assumed cure rate of 75%, and an estimated drop-out rate of 28%. Note that non-inferiority is sometimes considered a one-sided equivalence.⁴²

11.1.2 Secondary

The secondary study objective is to demonstrate that algorithm-based treatment of patients with staphylococcal blood stream infection can decrease antibiotic days when compared to current SOC. Based on the number of days of antibiotic use, a superiority hypothesis will be tested at the 5% level of significance.

11.2 Sample Size Considerations

11.2.1 Assumptions

With a sample size of 500 patients (i.e., 362 patients after 28% dropout), we would have at least 90% power for establishing non-inferiority based on two-sided test at 5% assuming that (1) equal cure rate of 75% and (2) a non-inferiority margin of 15%. See Table 3 below. In order to validate these assumptions, and to confirm the appropriate target number of patients, a blinded sample size re-estimation was performed after 250 patients were enrolled and completed the TOC visit DSMB's recommendation for sample size increase was made based on a conservative sensitivity analysis approach to account for variability associated with the observed difference in cure rates at interim. This recommendation will be confirmed at the next blinded sample size re-estimation when 350 patients have been enrolled and completed the TOC visit.. The sample size re-estimation will be reviewed by the DSMB. If the sample size re-estimation performed at 350 patients enrolled confirms that at least 80% power can be achieved, the total patient target may adjusted In the unlikely event that at least 80% power cannot be achieved with 500 patients enrolled, the DSMB will provide recommendations and the Executive Committee will determine an appropriate course of action.

11.2.2 Sample Size Calculation

Sample size calculation was performed based on the primary study endpoint of clinical outcome (cure rate). The proposed study is powered to establish non-inferiority in clinical

outcome (cure rate) between the proposed treatment algorithm group and the SOC group⁴³.

Table 3: Sample Sizes Required for Establishing Noninferiority of the Proposed Treatment Algorithm to the Standard of Care

Cure Rate		Sample Size Required			
		80% Power		90% Power	
Margin	Equal Cure Rate of both Treatments	One-sided* Test at 2.5%	Two-sided** Test at 5%	One-sided Test at 2.5%	Two-sided Test at 5%
10%	75%	590	644	790	812
	80%	504	550	674	694
	85%	402	438	536	552
15%	75%	262	286	352	362****
	80%	224	244	300	308
	85%	178	196	240	246

Note:

* One-sided test for noninferiority at the 2.5% level of significance.

** One side of a two-sided test for equivalence at the 5% level of significance (i.e., each side is 2.5%).

*** Sample sizes are not adjusted for dropouts.

**** the original sample size of 500 patients (362 patients after a 28% predicted dropout) was intended to achieve 90% power. The blinded sample size re-estimation will be performed with the goal of achieving at least 80% power.

11.2.3 DSMB Efficacy Review

No interim analysis for efficacy is planned. DSMB safety reviews are outlined in Section 9.5.

11.3 Final Analysis Plan

11.3.1 Study Population

The primary analysis will be performed based on both the ITT population and the PP population.

The **ITT population** is defined as all randomized patients.

The **PP population** includes randomized patients EXCLUDING those that meet any of the following criteria:

- a) Received a PENS antibiotic
- b) Did not undergo removal of intravascular catheter suspected to be infected. Note that patients with simple CoNS bacteremia may retain the catheter; all other patients should have their catheter(s) removed.
- c) Had blood stream infection with a vancomycin-resistant staphylococcus; or a staphylococcus resistant to protocol-identified alternative drugs if these were used
- d) Discontinued study medication prematurely for reasons other than clinical failure
- e) Did not undergo final TOC assessment
- f) Did not comply with all Patient Inclusion Criteria as listed in 5.1.
- g) Violated any Patient Exclusion Criteria as listed in 5.2.
- h) Died within 3 days of randomization.
- i) Were classified as non-evaluable

PPE Population: Patients from the PP population who did not have complicated staphylococcal infection.

Patients who discontinue after randomization will not be replaced.

11.3.2 Statistical Methods

For continuous variables, descriptive statistics such as the number of patients, mean, standard deviation, median, minimum, and maximum will be generated. For discrete variables, the number and percentage of patients in each category will be provided. Unless otherwise noted, any tests of hypotheses are two-sided and the nominal level of significance will be 0.05. No intra-block correlation will be assumed in statistical analysis of the collected data.

Missing efficacy data will be handled as follows: subjects who had missing values in efficacy variable at final TOC will be considered as treatment failure for both the ITT analyses and the PP analyses. For assessment of the primary endpoint, missing values will be counted as missing, and will be imputed by early TOC for the sensitivity analysis.

11.3.3 Baseline Comparability

Patient disposition in terms of the number and percent of patients enrolled by site will be tabulated. The number of patients randomized, number completing the study, and reasons for discontinuation will be summarized by treatment group within each cohort. Patient demographics and baseline characteristics such as age, weight, route of acquisition of infection (nosocomial, health-care associated and community-acquired) and comorbid conditions will be tabulated and compared across treatment groups within

each cohort. All comparisons will be performed by use of the CMH test for categorical variables and two-way ANOVA for continuous variables.

11.3.4 Primary Analysis

The primary efficacy analysis is to compare cure rate between the proposed treatment algorithm and the overall SOC treatment.

Point estimates and the corresponding 95% confidence intervals for the cure rate in each treatment will be calculated. The large sample z-test for comparing the two proportions will be performed to test the inferiority with the pre-specified non-inferiority margin. The CMH test and ANOVA or ANCOVA will also be performed to compare the difference of the intrinsic differences in the clinical experiences and practices at each site, characteristics of enrolled patients (including route of acquisition of infection), and variations in administering antibiotic dosing schemas as appropriate. Such variations may relate to site-specific practices involving vancomycin dosing, for example, whether troughs are followed or utilized. If there is statistically significant difference for the above parameters among the sites detected, the logistic regression model with the confounding factor of site and the above parameters, which had significant difference among sites, will be used to comparing the cure rate between treatments.

Because safety will also be assessed as a primary endpoint in this trial, safety will be evaluated by comparing all SAEs in the algorithm-based treatment and SOC treatment.

11.3.5 Secondary Analysis

The secondary analysis is to compare the days of antibiotic use between the proposed treatment algorithm and the SOC treatment for the PP population.

Patients in the simple or uncomplicated cohort who develop New Complicated staphylococcal infections after the completion of study treatment for their baseline clinical classification of bacteremia will be retained in their original group and counted as failure. They will be included in the PP analyses as treatment failures and their antibiotic days for their original grouping (e.g., the clinical group to which they had been assigned *before* being defined as having complicated infection) will be included in the Secondary analysis.

Patients in the simple or uncomplicated cohort who develop complicated staphylococcal infection after randomization but prior to the completion of effective treatment for their baseline clinical classification of bacteremia should remain in the PP analysis. Cure will be determined at their TOC visit. These patients will be regrouped in the complicated bacteremia population of the algorithm and will be excluded in the duration of treatment analysis.

Point estimates and the corresponding 95% confidence intervals for the difference in the days of antibiotic use between the proposed treatment algorithm and the SOC will be calculated. If statistically significant differences for the parameters among the sites are detected, ANCOVA will be performed to compare the days of antibiotic use between treatments with the confounding factor of site and the above parameters that have significant differences among sites.

11.3.6 Sensitivity Analysis

Sensitivity Analysis will be performed in the same manner as primary efficacy analyses to count the missing values as “missing” and the missing outcomes will be imputed by early TOC.

11.3.7 Exploratory Analyses

The exploratory analyses include comparisons of the treatment effects for the endpoints cure rate, days of antibiotic use and days to discontinuation using survival analysis methods for the following diagnostics subgroups in the ITT and PP populations, respectively:

1. Cohort of Coagulase Negative Staphylococcus
2. Sub-cohort within Coagulase Negative Staphylococcus and simple case
3. Sub-cohort within Coagulase Negative Staphylococcus and uncomplicated case
4. Cohort of *S. aureus* Bacteremia
5. Sub-Cohort within *S. aureus* Bacteremia and uncomplicated case

In addition, potential associations between vancomycin MIC values and clinical outcomes (e.g., cure rates, duration of bacteremia on treatment, and incidence of development of new complicated staphylococcal infection) will be assessed as part of exploratory efficacy analyses.

11.3.8 Safety Assessment

Because safety will also be assessed as a primary endpoint in this trial, safety will be evaluated by comparing all SAEs in the algorithm-based treatment and SOC treatment.

Collected AEs will be tabulated and ordered by decreasing frequency for all patients. Separate tabulations will list events according to seriousness, severity, and possible association with study drug. If appropriate, the incidence of AEs will be compared by Fisher’s exact test. Special attention will be given to patients who discontinued treatment because of AEs as well as those who had an SAE.

For the clinical laboratory data, descriptive statistics (with classes for below, within, and above the normal range) will be generated for all tests performed during the study. The McNemar test or Stuart-Maxwell test may be performed to determine whether a significant shift in laboratory data occurred after treatment began. Vital signs will also be analyzed. Results will be summarized for each time point and for changes in each variable from Enrollment visit and during each interval between assessments.

Extent of exposure to study medication will be presented in terms of treatment duration and mean daily dose.

A summary table will be provided for dose compliance.

11.3.9 Statistical Software Package

Statistical analyses will be performed using Version 9.2 (or newer version) of SAS® on a UNIX operating system at DCRI.

12 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

During monitoring visits, the site will make their computer and/or high speed Internet access available to the CRAs, so that they may verify the data entries with the source documentation. At the conclusion of the study, each enrolling site will be provided with a compact disc (CD) containing PDF files of both the individual patient's data and the audit trail (changes made to the database). This will be maintained at the site according to the requirements for records retention.

All data collected in the context of this study will be stored and evaluated in such a way as to guarantee patient confidentiality in accordance with the legal stipulations applying to confidentiality of data. Study records and regulatory documents will be retained at the study site, along with adequate source documentation, according to NIH requirements. All source documents must be available for monitor review. The source document is the first place information is documented. Source documents include but are not limited to patient charts, lab reports, medication administration records, echocardiograms, etc. All study records must be available for inspection by Duke Clinical Research Institute, DMID, or their authorized representatives, and the NIH.

13 QUALITY CONTROL AND QUALITY ASSURANCE

The DCRI will submit a protocol specific CQMP template to DMID for review and acceptance. This template will be provided to sites who will enter site specific information onto the CQMP and implement the quality management activities. The CQMP policy describes elements to assist sites, conducting DMID-supported clinical research with developing, implementing, and evaluating such a plan. DMID makes available through the NIAID public website adaptable sample quality management plan templates and tools to meet the specific site/protocol needs.

<https://www.dmidcroms.com/CRS/QM/SitePages/Qualitymanagement.aspx>

13.1 Local (site) plans for Quality Assurance and Quality Control

See Section 10.1 for details on the DCRI site monitoring plan.

All sites conducting research under the sponsorship of the DMID are required to have a plan in place for assuring the quality of the research being conducted.

Each site should have a quality management plan which describes:

- How data will be evaluated for compliance with the protocol and for accuracy in relations to source documents.
- The documents to be reviewed (eg. CRFs, clinic notes) who is responsible, and the frequency for reviews should be identified, either in a formal quality management plan or in their SOPs.
- Site study staff will receive protocol and Good Clinical Practice training during the investigator meeting. This training will be reinforced during initiation visits, interim monitoring visits, and via phone as needed. In addition, site will be trained on entry of data into the EDC system (Inform) via web cast and during the investigator meeting. Site will describe clinic training requirement of staff in their formal quality management plan and/or SOPs. Documentation of all training must be made available to DMID or designee upon request.

The following DMID QMP documents are available on the DMID Clinical Research Operations Management and Support (CROMS) website to help guide sites.

- DMID Quality Management Plan – Standard Operation Procedure
- Quality Management Plan, version-controlled, template
- Chart Review Tool, template
- Regulatory File Review Tool, template
- Quality Management Summary Report, template
- Quality Management Plan Fact Sheet.

13.2 Investigator Obligations

The investigator(s) will ensure that this study is conducted in full conformity with the principles of the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR 46 and/or ICH E6; 62 Federal Register 25691 (1997). The PI/Institution will hold a current FWA issued by OHRP for federally funded research.

13.2.1 Documentation

The investigator must provide the following to Duke University Medical Center prior to the start of the study:

- A fully executed contract and agreement between the investigator and the Duke University Medical Center.
- The Investigator's Statement page of this protocol signed and dated by the investigator, and all subsequent amended protocol versions.
- Copy of the completed Site Staff Delegation & Signature Log
- Copy of training on all approved protocol versions for all study staff listed on the Site Staff Delegation & Signature Log
- Curriculum vitae for the site PI and all sub-investigators including a copy of their medical license
- A copy of the original IRB approval letter for conducting the study protocol. Renewals must be submitted at yearly intervals, if the study is ongoing. All subsequent modifications must be submitted and approved by the IRB, as described in Section 18.2.
- Copy of the IRB/EC-approved ICF.
- FDA IRB registration confirmation (IORG number).
- A copy of the HIPAA authorization form (US only, may be included in site specific ICF).
- DHHS Federalwide Assurance Number or roster of IRB membership.
- Laboratory certifications and normal ranges.
- Copies of Financial Disclosures for the site PI and all sub-investigators.
- Copy of Human Subject Protection training completion certificate for all study staff listed on the Site Staff Delegation & Signature Log.
- Copy of NIH Computer Security Awareness Training completion certificate for all study staff responsible for eCRF data entry.
- Copy of InForm training for all study staff responsible for eCRF entry.

13.2.2 Performance

The investigator must demonstrate reasonable efforts to consent qualified patients for the study.

13.2.3 Use of Investigational Materials

The study medication is an approved drug for this indication and will be supplied from the hospital pharmacy.

13.2.4 Electronic Case Report Forms

All data relating to the study will be entered into eCRFs to be provided by Duke Medical Center. Data will be entered from the patient's medical records and other source documentation such as lab reports into the eCRF. Source documentation will be maintained at the site. The investigator is responsible for the data entered into the eCRF, and for verifying that all data entries in the eCRFs are accurate and correct.

14 ETHICS/PROTECTION OF HUMAN SUBJECTS

14.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in the Declaration of Helsinki, The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6; 62 Federal Regulations 25691 (1997).

The Investigator must ensure that patients or their legally acceptable representatives are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate. An investigator shall provide the patient or representative sufficient opportunity to consider whether or not to participate in the study and minimize any coercion of the patient to participate. The consent form must include all elements required by CFR 21 Part 50.25, 45 CFR 46, and the local IRB.

14.2 Institutional Review Board/Ethics Committee

Before initiating this study, the protocol, site-specific ICFs, HIPAA forms, recruitment materials, and other relevant information will be reviewed by a properly constituted IRB/EC at each participating clinical site. A copy of the signed and dated IRB/EC approval at each clinical site will be retrieved prior to site activation and archived at the DCRI. Any amendments to the protocol, other than simple administrative and typographical changes, must be approved by each IRB/EC before they are implemented. The sites will seek annual renewals of their IRB approvals in accordance with local procedures.

This study will be carried out in full compliance with FDA guidelines for Good Clinical Practices (GCPs). Approval by the IRB prior to the start of the study will be the responsibility of the investigator. A copy of the approval letter must be supplied to Duke Medical Center along with a roster of IRB members or DHHS General Assurance Number. During the course of the study, the investigator shall make timely and accurate reports to the IRB on the progress of the study, at intervals not exceeding one year (or as appropriate), and notify the IRB of SAEs or other significant safety findings.

14.2.1 Amendments to the Protocol

Any amendment to this protocol will be provided to the investigator in writing by Duke Medical Center. No protocol amendment may be implemented (with the exceptions noted below) before it has been approved by the Institutional Review Board (IRB) and the signature page, signed by the investigator, has been received by Duke Medical Center. Where the protocol is amended to eliminate or reduce the risk to the patient, the amendment may be implemented before IRB review and approval. However, the IRB must be informed in writing of such an amendment and approval obtained within reasonable time limits. Deviating from the protocol is permitted only if absolutely necessary for the safety or clinical management of the patient, and must be immediately reported to the Duke Clinical Research Institute.

14.3 Informed Consent Process

The informed consent must contain all of the elements of informed consent; the HIPAA authorization must contain all of the core elements and mandatory statements as defined in the code of federal regulations. Signed copies of the informed consent and HIPAA authorization forms will be given to the subject or LAR and the signed originals of both documents will be placed in the investigator's study files.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Extensive discussion of risks and possible benefits of this treatment will be provided to the subjects and their families. Consent forms describing in detail the study interventions/products, study procedures, and risks are given to the subject and written documentation. Informed consent and HIPAA authorization is required prior to starting any study-specific procedures. HIPAA language may be part of the Informed Consent document or in a separate document. Consent and HIPAA forms will be IRB-approved and the subject will be asked to read and review the document(s). Upon reviewing the document, the Investigator will explain the research study to the subject and answer any questions that may arise. The subject (or LAR) will indicate their consent by signing the informed consent document prior to any procedures being done specifically for the study. The subject (or LAR) should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. If the patient is unable to provide written informed consent, then verbal assent must be obtained if required by applicable regional regulations e.g. for the mentally impaired, and written consent obtained from the LAR in accordance with the appropriate State Laws, where applicable. The subject may withdraw consent at any time throughout the course of the trial. Signed copies of the Informed Consent and HIPAA authorization form will be placed in the investigator's study files. A copy of the informed consent document will be given to the subject (or LAR) for their records. The rights and welfare of the subject or LAR will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

DCRI and/or DMID will provide the Investigator, in writing, any new information that bears significantly on the subject's risk to participate in this study. This new information will be communicated by the Investigator to subjects who consent to participate in the trial in accordance with IRB requirements. The informed consent document will be updated and subjects will be reconsented, if necessary.

Site staff may employ IRB-approved recruitment efforts prior to the subject consenting; however, before any protocol-specific procedures are performed to determine protocol eligibility, an informed consent form must be signed. Subjects or their LAR will be given a copy of all consent forms that they sign.

By signing the informed consent form, the subject agrees to complete all evaluations required by the trial, unless the subject withdraws voluntarily or is terminated from the trial for any reason, and adverse events will be followed as described in Section 9.4 of this protocol.

Required elements of the Informed consent per Code of Federal Regulations, Title 21, Volume 1, Part 50, Subpart B, revised April 1, 2009, follow:

1. A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
2. A description of any reasonably foreseeable risks or discomforts to the subject.
3. A description of any benefits to the subject or to others which may reasonably be expected from the research.
4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
5. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records.
6. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
7. An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.
8. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

When appropriate, one or more of the following elements of information shall also be provided to each subject:

1. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.
2. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.
3. Any additional costs to the subject that may result from participation in the research.
4. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
5. A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.
6. The approximate number of subjects involved in the study.

The informed consent requirements in these regulations are not intended to preempt any applicable Federal, State, or local laws which require additional information to be disclosed for informed consent to be legally effective. Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable Federal, State, or local law.

Informed Consent/Assent Process (in Case of a Minor)

As patients must be 18 years or older to enroll in the study (inclusion criterion no.1); informed consent/assent process for minors is not applicable.

14.4 Exclusion of Women, Minorities, and Children (Special Populations)

Children under the age of 18 years will not be enrolled in this study, because the investigational intervention is a treatment algorithm based on adult-dosing guidelines for vancomycin (or acceptable vancomycin substitutes), and the comparison will be SOC based on treatment of adult patients .

14.5 Patient Confidentiality

All patient records will be identified only by code number. Patients' names are not to be transmitted to Duke Medical Center. The investigator will keep a Master Patient List, on which the identification number and full name, address, and telephone number of each patient is kept.

Patient confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genotyping of bacteria isolates in addition to the clinical information relating to participating patients.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any third party with the exception of the NIAID.

The study monitor or other authorized representatives of the sponsor, the NIAID and DMID may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the patients in this study. The clinical study site will permit access to such records.

14.6 Study Discontinuation

Duke University Medical Center and the NIAID reserve the right to terminate the study in its entirety or at a specific site, at any time.

14.7 Future Use of Stored Specimens

Isolates will be stored for future testing, including bacterial genetic testing of patient samples, with patient's (or LAR's) informed consent. This is optional and patients may be enrolled in the study but "opt out" of future testing of stored specimens. Specimens will be labeled only with patient numbers, sample numbers, date of collection and name of isolate. No personal information such as initials, date of birth, etc, will be recorded on the specimen or shipping form.

15 DATA HANDLING AND RECORD KEEPING

The investigator is responsible for the integrity and accuracy of the data. The investigator must ensure completeness, legibility, and timeliness of the data reported. In addition, the PI must review and sign off electronically to verify data accuracy. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. **DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL SOURCE DOCUMENTS.**

15.1 Data Management Responsibilities

DCRI will submit a Data Management Plan to DMID for review. The plan must meet both DCRI and DMID expectations. The plan will be finalized by key staff at DMID and DCRI.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. During the study, the investigator must maintain complete and accurate documentation for the study.

Investigators are responsible for reviewing and signing off on all data entered into the EDC system by study staff.

15.2 Data Capture Methods

Qualified study staff at each site will perform primary data collection from source-document reviews. DCRI will perform clinical monitoring, including review of eCRFs with verification to the source documentation.

This study will use web-based electronic CRFs (eCRFs) developed through a validated, ERES-compliant platform (21 CFR Part 11). Prior to initiation of the trial, each site will be contacted as to computer availability, hardware specifications, and internet connectivity, to evaluate the capacity of the site to use this type of data collection system. The investigator's site staff who will be entering data, will receive training on the system; after which, each person will be issued a unique user identification and password.

For security reasons, and in compliance with regulatory guidelines, it is imperative that only the person who owns the user identification and password access the system using their own unique access codes. Access codes are non-transferable. Site personnel who have not undergone training may not use the system and will not be issued user identification and password until appropriate training is completed.

15.3 Types of Data

All data relating to the study will be entered into the eCRFs. Data will be entered from the patient's medical records into the eCRF. Patient's medical records will be maintained at the site and considered the source documents for this clinical trial. The investigator is responsible for the data recorded on the eCRF, and for verifying that all data entries in the eCRFs are accurate and correct.

15.4 Timing/Reports

Data will be collected on an ongoing basis and the CRA and the site management team will review the eCRFs on a continuous basis throughout the trial. The CRA will monitor each site approximately 4 times per year. This schedule may be altered depending on enrollment and site need. The electronic data will be reviewed by the site management team prior to the visits and between visits. There will be several safety data reviews after 125, 250, and 350 patients have enrolled in the study.

Safety and efficacy data with written summaries will be generated and sent to DMID for the final study report.

15.5 Study Records Retention

It is recommended that investigators retain all records and documents (including electronic data capture materials) pertaining to the conduct of the study for at least 6 years after submission of the final study report in the event follow up is necessary to help determine any potential hazards to patients who took part in these studies. The investigator agrees to obtain DMID agreement prior to disposal, moving, or transferring of any study-related records. Additionally, if the investigator retires, relocates, or for other reasons withdraws from the responsibility of the study, then another investigator must be assigned if the study is still active. Any new investigator must be approved by DMID and DCRI.

Data generated by the methods described in the protocol will be recorded in the patient's medical records and/or study progress notes. Data may be transcribed legibly on case report forms supplied for each patient or directly inputted into an electronic system or any combination thereof. The investigator and DCRI will mutually agree upon the storage format for the retention of electronic data.

The investigator will agree to provide access to the office, clinic, and/or hospital records of all patients entered in this study. Access inspection of these records may be required by the DCRI, DMID, and/or their representative(s) at the time of each monitoring visit. In addition, all records may be subject to inspection by other health authorities. The investigator shall make accurate and adequate written progress reports to the IRB/IEC at appropriate intervals, not exceeding one year. The investigator shall make an accurate

and adequate final report to the IRB/IEC within three months after completion or termination of the study.

15.6 Protocol Deviations

A protocol deviation is defined as an event where the investigator or site personnel did not conduct the study according to the protocol.

Investigators are required to obtain prior approval from the Clinical Medical Monitor before initiating deviations from the protocol, except where necessary to protect the life or physical well-being of a patient in an emergency. Prior approval is generally not expected in situations where unforeseen circumstances are beyond the investigator's control, (e.g., patient was not reached for a follow-up telephone call or clinic visit, sample lost by laboratory, etc.); however, the event is still considered a deviation.

Deviations will be reported to DCRI within 3 business days by Investigator, Study Coordinator, or Monitors knowledge of deviation, whichever occurs first, regardless of whether medically justifiable, preapproved by the Clinical Medical Monitor, or taken to protect the patient in an emergency. DCRI will batch report deviations to DMID once per week.

The IRB/EC will be informed of all protocol changes by the investigator in accordance with applicable regulations and the IRB/EC's established procedures. No deviations of any type from the protocol will be made without complying with all the IRB/EC's established procedures.

Investigators will maintain documentation of the dates and reasons for each deviation from the protocol.

15.7 Patient Privacy

The Executive Committee affirms the patient's right to protection against invasion of privacy. Only a patient identification number will identify patient data retrieved by the Executive Committee. However, in compliance with US federal and/or local regulations, the Executive Committee requires the investigator to permit the Executive Committee's representatives and, when necessary, representatives of the NIAID to review and/or copy any medical records relevant to the study. By law, the NIAID are required to maintain confidentiality.

The Executive Committee will ensure that the use and disclosure of protected health information obtained during a research study complies with the HIPAA Privacy Rule. The Rule provides US federal protection for the privacy of protected health information by implementing standards to protect and guard against the misuse of individually identifiable health information of patients participating in Clinical Trials. "Authorization" is required from each research patient, i.e., specific permission granted by an individual to

a covered entity for the use or disclosure of an individual's protected health information. A valid authorization must meet the implementation specifications under the HIPAA Privacy Rule. Authorization may be combined in the Informed Consent document (approved by the IRB/EC) or it may be a separate document (approved by the IRB/EC or designated privacy board [PB]), or provided by the investigator or Executive Committee (without IRB/EC or PB approval). It is the responsibility of the investigator and institution to obtain such waiver/authorization in writing from the appropriate individual.

16 PUBLICATION POLICY

A Publication Policy will be developed by the Executive Committee to ensure all publications meet DMID goals. The study sponsor, DMID has designated the DCRI PI to serve as the "Responsible Party" and register, update and report basic results of the trial to the "clinicaltrials.gov", which is sponsored by the National Library of Medicine, The trial will be registered prior to enrollment.

Members of the Executive Committee (e.g., *the principal investigators from each site as well as the study principal investigator and co-investigator*) and/or the CEC committee will be primarily responsible for creation, review, and submission of publications and presentations relating to the major aspects of the study and approved ancillary analyses within a timely fashion after completion of the study.

The manuscript containing the overall study results as well as future manuscripts containing analyses of trial data will be distributed to the NIH according to present guidelines/requirements. Submitted publications will conform to international standards for biomedical manuscripts, including those regarding authorship. The final analysis and manuscript will take approximately six months to complete.

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