



Antibacterial Resistance Leadership Group (ARLG)

**Fast Antibiotic Susceptibility Testing for Gram Negative Bacteremia Trial
(FAST)**

Protocol Number 20-0021

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**Statistical Analysis Plan
Version 2.0**

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INTRODUCTION

This is the Statistical Analysis Plan (SAP) for FAST, Fast Antibiotic Susceptibility Testing for Gram Negative Bacteremia Trial, an ARLG study. This SAP lays out the planned analyses for this study.

DOCUMENT HISTORY

- SAP Version 1.0 (22 DECEMBER 2023, FAST SAP_V1_22DEC2023.pdf)

FAST SAP Updates

1. Unevaluable subjects will be included in an analysis of rapid test performance
2. Difference between mITT and OE
3. Subgroups
4. Update Statisticians
5. Added VITEK before Reveal™
6. Updated ITT to be mITT
7. Updated categorization of gram-negative agents to include 1.5 and 4.5.
8. Updated time to antibiotics
9. Added KM methods
10. Added VITEK Reveal™ panel organisms
11. Fixed typos, capitalization, italics

LIST OF ABBREVIATIONS

ARLG	Antibacterial Resistance Leadership Group
AS	Antimicrobial Stewardship
AST	Antimicrobial Susceptibility Testing
BSI	Bloodstream Infection
CA	Categorical Agreement
CDC	Centers for Disease Control and Prevention
CLSI	Clinical and Laboratory Standards Institute
DCRI	Duke Clinical Research Institute
DMID	Division of Microbiology and Infectious Diseases
DOOR	Desirability of Outcome Ranking
DOOR MAT	Desirability of Outcome Ranking for Management of Antimicrobial Therapy
DSMB	Data and Safety Monitoring Board
EA	Essential Agreement
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FAST	Fast Antibiotic Susceptibility Testing for Gram Negative Bacteremia Trial
GNB	Gram-Negative Bacilli
ICU	Intensive Care Unit
ITT	Intention-to-Treat
IV	Intravenous
MDRO	Multi-Drug Resistant Organism
ME	Major Error
mE	Minor Error
MR	Medical Record
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
PI	Principal Investigator
qPitt	Quick Pitt Bacteremia Score
RCT	Randomized Controlled Trials
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDMC	Statistics and Data Management Center
SOC	Standard of Care
VME	Very Major Error

STUDY SCHEMA AND OBJECTIVES

DESIGN

Multi-center, multinational, prospective, randomized, controlled trial to evaluate the following strategies for hospitalized patients with confirmed gram-negative bacillus bacteremia:

- 1) Standard of care (SOC) antimicrobial susceptibility testing (AST); or
- 2) VITEK Reveal™, a rapid AST method, in addition to SOC AST

The VITEK REVEAL™ panel tests for AST for the following organisms:

- *Acinetobacter baumannii*
- *Citrobacter freundii*
- *Citrobacter koseri*
- *Enterobacter cloacae*
- *Escherichia coli*
- *Klebsiella aerogenes*
- *Klebsiella oxytoca*
- *Klebsiella pneumoniae*
- *Proteus mirabilis*
- *Pseudomonas aeruginosa*

DURATION

Up to 30 days post-Gram stain result

SAMPLE SIZE

900 unique subjects

POPULATION

Hospitalized adult and pediatric patients with bloodstream infections (BSIs) caused by gram-negative bacilli (GNB) detected on Gram staining will be eligible

NUMBER OF SITES

Up to 10 international sites

STRATIFICATION

By site and ICU status at the time of Gram stain result

PRIMARY OBJECTIVE

The primary objective is to compare clinical outcomes among subjects with GNB BSI who have bloodstream isolate AST determined using SOC vs. VITEK Reveal™ plus SOC methods.

SECONDARY OBJECTIVE

The secondary objective is to describe differences in antibiotic utilization up to 3 days post-Gram stain result among subjects with GNB BSI who have bloodstream isolate AST determined using SOC vs. VITEK Reveal™ plus SOC methods.

EXPLORATORY OBJECTIVES

Exploratory objectives will be to describe discrepancies between VITEK Reveal™ and SOC methods among subjects randomized to the VITEK Reveal™ arm, to describe clinician compliance with antibacterial stewardship (AS) recommendations in the VITEK Reveal™ versus SOC arms, and to describe the desirability of treatment selections in the VITEK Reveal™ versus SOC arms.

OUTCOME MEASURES

Primary Outcome Measures

1. The primary outcome measures of subject disposition and deleterious events will be collected to assess the composite 3-category DOOR outcome up to 30 days after the Gram stain result. The three-ordered levels of DOOR clinical outcomes from the best to the worst are:

- Alive without deleterious events
- Alive with at least one deleterious event (as listed in Table 1)
- Death

Table 1. Deleterious events for DOOR outcome

<u>Unsuccessful discharge:</u>	<u>Lack of clinical response:</u>	<u>Undesirable events</u>
• Not discharged from the index hospitalization • Readmission to hospital	• Relapse of bacteremia with the same species causing the index infection • Local suppurative complications not present at time of Gram stain result • Seeding distant sites with the same infecting organism after Gram stain result	• <u>Acquisition of hospital-acquired infection</u> ○ <i>Clostridioides difficile</i> ○ MDRO • <u>Renal failure that occurs after index bloodstream infection:</u> ○ Defined as three-fold or greater increase in serum creatinine or New renal replacement therapy started

Secondary Outcome Measures

1. All-cause in-hospital mortality up to 30 days of post Gram stain result.
2. Length of index stay in the hospital up to 30 days post Gram stain result, for those subjects alive at 30 days.
3. ICU admission up to 30 days post Gram stain result
4. New acquisition of Multi-Drug Resistant Organisms (MDRO) and/or *C. difficile* after Gram stain result and up to 30 days post Gram stain result. New acquisition is defined as detection of MDRO/*C. difficile* in subjects who do not have preceding clinical or surveillance cultures with these organisms in the prior 3 months. MDRO will be identified on routine clinical or surveillance samples using local laboratory diagnostic procedures and include:
 - Methicillin-resistant *Staphylococcus aureus*
 - Vancomycin-resistant *Enterococcus* species
 - 3rd generation cephalosporin-non-susceptible Enterobacterales
 - Carbapenem-resistant Enterobacterales, as defined by the CDC as resistant to imipenem, meropenem, doripenem, or ertapenem OR documentation that the isolate produces a carbapenemase
 - *P. aeruginosa* resistant to carbapenems/multi-drug resistant (resistant to aminoglycosides, cephalosporins, fluoroquinolones, and carbapenems)
 - Carbapenem-resistant *Acinetobacter* species
 - *Candida auris*
5. Time to effective antibiotic therapy within 3 days from Gram stain result, defined as treatment with an antibiotic to which the blood isolate is susceptible based on SOC AST.
6. Time to antibiotic escalation of gram-negative coverage in those who have antibiotic escalation within 3 days from Gram stain result.
 - Escalation: changing to a broader spectrum antibiotic (high number category in Table 2), or cessation of one or more antibiotics
7. Time to antibiotic de-escalation of gram-negative coverage in those who have antibiotic de-escalation within 3 days from Gram stain result.
 - De-escalation: changing to a narrower spectrum antibiotic (lower number category in Table 2), or cessation of one or more antibiotics

Table 2. Gram-negative agents

Category	Spectrum	Antibiotics
1	Narrowest	Ampicillin, cefazolin, Amoxicillin (IV, Oral), Cefazolin
1.5		Oral fluoroquinolones (ciprofloxacin, moxifloxacin, levofloxacin), Trimethoprim/Sulfamethoxazole (oral)
2		Amoxicillin/clavulanic acid, ampicillin/sulbactam, 2 nd generation cephalosporins, 3 rd generation cephalosporins (except ceftazidime), chloramphenicol, tetracyclines, trimethoprim/sulfamethoxazole (IV),
3		Aminoglycosides (amikacin, gentamicin, tobramycin), aztreonam, ceftaroline, ceftazidime, IV fluoroquinolones (ciprofloxacin, moxifloxacin, levofloxacin), fosfomycin (IV),
4	Broadest	Piperacillin/tazobactam, cefepime, ertapenem
4.5		Meropenem, imipenem, imipenem/cilastatin
5		Ceftazidime/avibactam, ceftolozane/tazobactam, imipenem/relebactam, cefiderocol, tigecycline, meropenem/vaborbactam, colistin, polymyxin B

Exploratory Analyses

- The 5-category DOOR clinical outcomes up to 30 days after Gram stain result. The five-ordered levels of DOOR from the best to worst are:
 - Alive without deleterious events
 - Alive with 1 deleterious event (as listed in Table 1)
 - Alive with 2 deleterious events
 - Alive with 3 deleterious events
 - Death
- Categorical agreement between VITEK Reveal™ and SOC testing among subjects who receive rapid testing using VITEK Reveal™ (VITEK Reveal™ arm only).
- Clinician compliance with AS recommendations measured by changes in antibiotics administered in accordance with at least one of the AS escalation/de-escalation recommendations.
- Desirability of treatment selections based on antibiotic spectrum and activity in relation to bloodstream isolate susceptibility profiles (DOOR MAT).

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A. General Analysis Considerations

Data summaries and analyses will be presented overall and by randomized arm.

To ensure participant confidentiality, listings of individual patient-level data will be minimized as much as possible during study monitoring and for analyses. If such data are provided, they will be indexed with a unique blinded identifier or with identifiers removed. Study dates will not be presented but provided as days/hours since randomization/Gram stain result, as appropriate.

Per protocol V4.0, subjects with the following scenarios will be considered unevaluable and will not be included in the primary analyses:

- For participants in both arms, if SOC culture methods do not yield a gram-negative organism (as was originally detected on Gram stain), the participant will be considered unevaluable.
- For participants randomized to the VITEK Reveal™ arm, if VITEK Reveal™ is initiated greater than 16 hours after the blood culture is flagged positive, the participant will be considered unevaluable. Sensitivity analyses will be performed to evaluate the impact of excluding these unevaluable participants.
- Subjects who died prior to randomization, had a history of blood culture with GNB within 7 days prior to randomization, or who were erroneously randomized due to laboratory issues such as spurious Gram stain results, will be considered unevaluable.

The unevaluable scenarios listed above are independent of patient status since Gram stain result. Post-randomization identification of these unevaluable subjects will not be considered a protocol deviation.

Additional exploratory analyses will be defined in a separate analysis plan.

B. Sample Size Consideration

Clinical outcomes up to 30 days post-Gram stain result will be compared using the DOOR. Data from the MERINO (Harris, et al., 2018) and RAPIDS-GN (Banerjee, et al., 2020) trials were used to inform the expected DOOR distribution. A nonparametric Wilcoxon rank sum test based on the DOOR distribution will be employed to test the null hypothesis that outcomes in the VITEK Reveal™ arm are not better than in the SOC arm, where this is defined as DOOR probability $\leq 50\%$, where DOOR probability is calculated by $\Pr(\text{more desirable outcome with rapid testing than SOC}) + 1/2\Pr(\text{outcome with rapid testing is equal to SOC})$ compared to the alternative hypothesis that outcomes in the VITEK Reveal™ arm are better than in the SOC arm. Based on the data from the RAPIDS-GN and MERINO trials, in the SOC arm, the following is expected: a 10%-12% mortality rate, about 32% percent of subjects alive with deleterious events, and the remaining 56%-58% of subjects alive without events. Assuming the difference between the arms in mortality is 4-5% and in being alive with no events is 9%, the DOOR probability is calculated to be between 54.8% and 55.1% (Table 3). With an unevaluable rate of 10%, 900 subjects (450 in each arm) will be enrolled in order to have at least 405 evaluable subjects in each arm. This will provide at least 80% power to reject the null hypothesis with 2.5% significance level for a one-sided test. Assuming that approximately 11% of bloodstream isolates will be “off-panel” and the rapid testing failure rate will be 11%, the planned sample size provides at least 70% power to detect a difference in the hypothesized DOOR distribution between the SOC and VITEK Reveal™ arm.

Table 3. DOOR outcome estimates and evaluable sample size

Scenario	SOC			VITEK Reveal™			DOOR probability
	Mortality	Deleterious events	Alive and no event	Mortality	Deleterious events	Alive and no event	
1	0.12	0.32	0.56	0.08	0.27	0.65	0.548
2	0.12	0.32	0.56	0.07	0.28	0.65	0.551
3	0.10	0.32	0.58	0.05	0.28	0.67	0.551

C. Statistical Monitoring Considerations

Routine statistical monitoring of accrual, study conduct, and data completion will be conducted by the statistical team. A monitoring report summarizing these components will be distributed by the statistical team monthly until the

completion of the study accrual; see sections listed below for details. The report containing the overall group only will be distributed to the core protocol team during the course of the study (see Sections H and H for details). With the exception of data availability, all other outcome-related data will not be available to the study team until the end of the study.

Additional monitoring and querying of all data will be conducted concurrently with the statistical monitoring report to ensure cross-form consistency and data quality. Some tables may be omitted in early monitoring reports if there are insufficient data to warrant inclusion.

Blinding: The primary service, including the treating provider, will be unaware of randomization assignment at the time of randomization; initial antibiotic choice will not be affected by arm assignment. Once VITEK Reveal™ results become available and/or AS recommendations are made, treating providers may become aware of randomization assignment. The AS team and laboratory technologists will not be blinded. The statistical team will not be blinded to arm assignment.

D. Antibiotic Data Review

Antibiotic administration data will be queried for all subjects with the following scenarios:

- Erroneous antibiotic date/time information (e.g., antibiotic start time came after the stop time);
- Antibiotics were started > 8 hours after Gram stain result.

E. Monitoring of Microbiology

The site Microbiology Laboratory Director is responsible for monitoring and reviewing the discordant AST results between the VITEK Reveal™ and standard test methods for subjects in the VITEK Reveal™ arm. AST discrepancies will be categorized according to Clinical Laboratory Standards Institute (CLSI), as follows:

- **Very major error (VME):** susceptible by VITEK Reveal™ and resistant by SOC AST.
- **Major error (ME):** resistant by VITEK Reveal™ and susceptible by SOC AST
- **Minor error (mE):** intermediate by one method and susceptible or resistant by the other method

A table will be provided during the interim analysis review summarizing the number and percent of Very major, Major, and Minor errors in the VITEK Reveal™ arm and for each bacteria-drug combination. If multiple susceptibility testing were performed, the later result will be used for summary.

F. Data and Safety Monitoring Review

The Data and Safety Monitoring Board (DSMB) will review accumulating data from FAST by treatment arm to ensure the validity and integrity of the trial and make a benefit-risk assessment. Safety events will not be followed or recorded because deleterious events from VITEK Reveal™ are not expected. The DSMB will review the study progress and focus on data quality, enrollment, and implementation of the SOC and VITEK Reveal™ strategies. See DSMB charter for more details.

G. Interim Analysis Considerations

There is no planned interim efficacy analysis involving a statistical test of the primary endpoint. As part of the benefit-risk analysis, one interim analysis is planned when at least 50% of subjects have been enrolled and their up to 30 days of post Gram stain follow-up have elapsed. Additional details on the interim analyses are found in the Statistical Monitoring Plan.

The predictive interval plots (PIPS) method will be used at an interim time point to predict 95% confidence intervals of the treatment effect at the end of the study. PIPS will be created for the primary endpoint based on the data collected up to the interim time point and modeled under the following four assumptions:

- The current trends in outcomes observed at the interim analysis continue to the end
- The alternative hypothesis (specified in Section 6.1) is true
- The null hypothesis (specified in Section 6.1) is true
- Best- and worst-case scenarios for the remaining outcomes

For each assumption, 10,000 complete datasets (N=900 subjects) will be simulated and used to calculate the probability of rejecting the null hypothesis for each scenario. Using the current trend, the remaining subjects will be simulated assuming outcomes continue to occur at the observed rates at the time of interim analysis. For the best-

case scenario, the remaining subjects will be simulated to have DOOR category 1 of alive with no events. For the worst-case scenario, the remaining subjects will be simulated as having DOOR category of 3 of death for 3-category DOOR outcome and DOOR category of 4 (for 3 deleterious events) for 5-category DOOR outcome.

By relying on prediction intervals, no statistical hypothesis testing is required; and thus, no statistical power is lost at the interim analysis.

The proposed timeline of interim analysis can be modified based on the input from the Data and Safety Monitoring Committee (DSMB). The Statistics and Data Management Center (SDMC) will prepare the interim analysis reports for DSMB review. Summary of PIPs statistics will be presented in tables and figures for 3-category and 5-category DOOR outcomes using ITT population. Other tables and figures from the main analyses and monitoring report will also be provided to the DSMB for interim analysis data review.

H. Final Analysis Considerations

The primary analysis will be conducted when data from the last participant enrolled has been received. The final analysis report will be distributed to the protocol team after the statistical team receives the final, locked data transfer from DCRI and validation of primary analyses and internal review at the statistical center are completed. The protocol team is defined in Section I.

The final analysis population will include subjects who were randomized.

I. Report Distribution List

Unless otherwise mentioned, distribution lists for monitoring and analysis reports are comprised of:

Protocol Team: Protocol Principal Investigator, Co-Principal Investigator, Protocol Clinician, Project Lead, Statisticians, Data Manager, Clinical Research Associate

Core Team: Protocol Principal Investigator, Co-Principal Investigator, Project Lead, Statisticians,

Table 4. Report Distribution Summary

Report	Frequency	Distribution List
Statistical Monitoring Report	Monthly	Protocol Team
Microbiologic Monitoring	Monthly	Protocol Team
Open Data Safety and Monitoring Report	Annually, or at the request of the DSMB	Core Team, DSMB members
Closed Data Safety and Monitoring Report	Annually, or at the request of the DSMB	DSMB members
Final Analysis Report	End of study per study timeline	Protocol Chair, Protocol Clinician, Project Lead

J. Application Validation

All study-specific programs for creation of derived datasets for derivation of the primary outcomes defined in this document will require application validation per GW ARLG guidelines, as appropriate; when applicable, requirements for independent results verifications of these datasets and application validation requirements for analysis programs are provided as annotations throughout the analysis plan.

K. Analysis Plan

Analysis population

The modified **Intention-to-Treat (mITT) Population** includes all randomized subjects, except for those who are considered unevaluable as defined in Section A. The primary analyses in this study will be based on the mITT population unless otherwise specified. Subjects randomized to the VITEK Reveal™ arm will be analyzed as randomized, including cases where the VITEK Reveal™ test does not return a result.

The **Organism Evaluable (OE) Population** will include the mITT population with evaluable, mono-microbial, gram-negative, on VITEK Reveal™ panel organisms as detected via SOC methods. The VITEK Reveal™ on-panel organisms are:

- *A. baumannii*
- *C. freundii*
- *C. koseri*
- *E. cloacae*
- *E. coli*
- *K. aerogenes*
- *K. oxytoca*
- *K. pneumoniae*
- *P. mirabilis*
- *P. aeruginosa*

The VITEK **Reveal™ Evaluable (RE) Population** will include the subjects randomized to the VITEK Reveal™ arm with non-missing VITEK Reveal™ panel results. This population includes participants who are considered unevaluable in Section A. As such, the RE population is not a subset of the mITT population. The purpose of the RE population is to compare the antibiotic susceptibility results via SOC testing and the VITEK Reveal™ panel, when both are available.

Reasons for exclusion from the screening set will be summarized with a total column; additional exclusions post-randomization will be summarized by randomized arms and reflected in the CONSORT diagram.

Statistical Considerations

Table summaries will present the mITT population characteristics overall and by randomized arms, unless otherwise specified. The primary analysis of this study is conducted on the mITT population.

Tables will be repeated for the OE population, limited to subjects in both arms who have an organism identified by SOC that is on the VITEK Reveal™ panel. This is considered an important subgroup.

All variables, as noted below, will be analyzed on a continuous scale or as categories or both as appropriate.

For continuous variables, summary statistics will include number of subjects, number of subjects with missing data, mean and standard deviation, median (Q1-Q3), and minimum and maximum.

For categorical variables, summary statistics will include number and percentage for each category. In calculating percentages, subjects with missing data will not be included in the denominator.

Unless otherwise specified, we will use the Wilcoxon rank sum test for comparing continuous outcomes and Fisher's exact test or Pearson's chi-squared test for comparing categorical outcomes.

Time to antibiotic change/escalation/de-escalation will be summarized using the methods of Kaplan-Meier. The randomized arms will be compared using the log rank test.

Statistical comparisons are presented with 95% confidence intervals. Statistical tests assume a two-sided $\alpha=0.05$ comparison. In the primary DOOR comparison, the VITEK Reveal™ arm will be considered superior to the SOC arm if the lower bound of the 95% confidence interval (CI) is above 50%. If the CI crosses 50%, the null hypothesis cannot be rejected.

Handling of missing data

After a subject is randomized, information about the subject's demographics, comorbid conditions, severity of illness, laboratory results, antibiotics, hospitalization, and outcomes will be obtained from the subject's medical

record and recorded into the study database. Incomplete and inconsistent results identified during monitoring review will be queried. All efforts will be made to minimize the missing data in the study database. Missing data for each domain will be summarized.

The effect that any missing data might have on results will be assessed via sensitivity analysis. If the pattern of missing data is different from the assumption, further sensitivity analyses will be provided that are tailored to the missing data pattern observed.

Given the nature of data collection, minimal missingness is expected. The primary analyses of DOOR outcomes will use available DOOR values in the mITT population. Sensitivity analyses of DOOR will include methods to account for missing data. All other analyses will be based on available results.

1. Study Population

1.1. Screen Failures

Table: Number (%) of screen failures at each site by reason, based on screening logs. Denominator of all screen failures will be all screened subjects, including those enrolled. Denominator for reason for screen failures will be total number who failed screening.

1.2. Accrual

Table: Enrollment by month, presented overall and by randomized arms

Note: Dates of first and last enrollments will be provided in a footnote to the table.

Table: Enrollment by site, presented overall and by randomized arms

Table: Enrollment by site, presented overall and by ICU status

Table: Enrollment by month, by site

Table: Enrollment by month, by treatment arm

Table: Enrollment by site, presented overall and by randomized arms and ICU status

Figure: Observed, cumulative and targeted accrual by month

Table: Eligibility - Number (%) ineligible/unevaluable at each site, with eligibility as defined in Section A.

Table: Eligibility - Number (%) ineligible/unevaluable by randomized arm with eligibility as defined in Section A.

Table: Unevaluable –with detailed reasons. Post-randomization unevaluable subjects will be listed by randomized arms and overall.

Table: Number (%) in each randomization stratum by randomized arms

Table: Study populations – Number (%) in the mITT, OE and RE populations, by randomized arm

1.3. Study Population Characteristics

Table: Demographics

a. Sex at birth: By category (male/female)

b. Self-reported race, ethnicity and race/ethnicity as defined by NIH reporting standards: By category

c. Current age on day of study entry (in years): Continuous and by age group (0-<2, 2-<19, 19-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-89, 90+)

1.4. Protocol deviations

Table: Number (%) of protocol deviations by deviation category and site, presented by overall and by randomized arms.

2. Study Status

Table: Number (%) by category of study status, by overall and sites.

CONSORT diagram: subject disposition and eligibility for analysis will be summarized in a CONSORT flow diagram.

3. Health Characteristics/Status at entry

- a. Admission duration prior to Gram stain result
- b. In ICU at time of Gram stain result
- c. On comfort care at time of Gram stain result or within 3 days of Gram stain result
- d. COVID testing results during index admission
- e. Charlson Comorbidity Score
- f. Age-adjusted Charlson Comorbidity Score

The scores for each comorbidity item is presented in Table 5. Number (%) of each component item will be listed. The calculated age-adjusted Charlson Comorbidity score, summation of all components, will be summarized as a continuous variable.

Table 5. Age-adjusted Charlson Comorbidity Score

Comorbidity	Score
• Myocardial infarction	+1
• Congestive heart failure	+1
• Cerebrovascular accident with mild or no residual deficits, or transient ischemic attack	+1
• Congestive heart failure	+1
• Peripheral vascular disease	+1
• Dementia	+1
• Chronic obstructive pulmonary disease	+1
• Connective tissue disease	+1
• Peptic ulcer disease	+1
• Hemiplegia	+2
• Renal disease (Cr >3, renal transplant, or uremia)	+2
• Mild liver disease (cirrhosis with no portal hypertension OR chronic hepatitis)	+1
• Moderate to severe liver disease (cirrhosis with portal hypertension)	+3
• Lymphoma	+2
• Leukemia	+2
• AIDS	+6
• Solid tumor last 5 Years; no known metastases	+2
• Solid tumor last 5 Years; with known metastases	+6
• Diabetes mellitus, no end-organ damage	+1
• Diabetes mellitus, with end-organ damage	+2
• Age categories	
<50 years old	0
50-59 years old	+1
60-69 years old	+2
70-79 years old	+3
≥80 years old	+4
g. Immunocompromising conditions	
• HIV	

- Solid organ transplant recipient
 - Cancer diagnosis within prior 1 year (excluding non-melanoma skin cancers)
 - Stem cell transplant recipient
 - Rheumatologic or inflammatory condition
 - Primary Immunodeficiency
 - Use of prednisone >2 weeks (if not for physiologic replacement)
 - No immunocompromising condition as listed above
- h. Quick Pitt (qPitt) Bacteremia Score (Severity of Illness)
The final qPitt will be calculated by adding all component scores and summarized as a continuous variable and as a categorical variable [mild (0,1), moderate (2,3), severe (4 or higher)]. Number (%) of subjects with each component will be listed.

Table 6. Quick Pitt Bacteremia score variable

Criterion	Points
• Temperature <36°C	+1
• Respiratory rate >25 breaths per minute or need for mechanical ventilation	+1
• Cardiac arrest	+1
• Altered mental status	+1
• Systolic blood pressure <90 mm Hg or vasopressor use	+1

- i. Source of bacteremia (from stewardship page)
Number (%) of subjects with each source of bacteremia will be listed.
- Urinary
 - Central venous catheter
 - Intra-abdominal infection
 - Lung
 - Skin/soft tissue
 - Bone/joint
 - Ears/eyes/nose/throat
 - Cardiovascular
 - Surgical site infection
 - Central nervous system
 - Other (with listing)
 - Unidentified
- j. Number of bacteremia sources, counting number of non-missing items other than 'unidentified' from 'source of bacteremia', will be listed.
- k. Number of bacteremia sources, including 'unidentified' from 'Source of Bacteremia', will be listed.

4. Microbiology

SOC tables will be presented by randomized arms. The VITEK Reveal™ diagnostic tables will only be presented for subjects randomized to the VITEK Reveal™ arm. These tables will be summarized once for participants in the VITEK Reveal™ arm of the mITT population and repeated for the RE population.

4.1. Standard of Care Methods (Subject Level)

Gram stain result reported in the EMR (from Microbiology SOC form)

Table: MALDI-ToF

- a. Did MALDI-ToF MS identify an organism that was reported in the electronic medical record (yes/no)
- If no, method used

- b. Was organism updated after the RAPID MALDI-ToF MS was entered (yes/no)
 - o Updated organism

Table: Number of organisms identified per subject

Table: Monomicrobial (yes/no)

Table: Number of gram negative bacilli (GNB) identified per subject

Table: Number of non-GNB (gram positive bacilli + others) identified per subject

Table: Did the participant have at least one on-panel organism identified?

Table: Organism identification: number (%) of total organisms identified with each organism will be listed.

Table: For each organism on the VITEK Reveal™ panel, number (%) of subjects in the mITT population with the organism identified.

4.2. Standard of Care Methods (Isolate Level)

Table: Hours to SOC Results

- a. Hours from Gram stain to organism identification reported in the EMR using SOC methods (hours)
- b. Hours from Gram stain to standard AST entered in the EMR

Table: Susceptibility for each antibiotic drug, by organism, among the Organism Evaluable population, including:

- Amikacin
- Ampicillin
- Ampicillin/sulbactam
- Aztreonam
- Cefazolin
- Cefepime
- Ceftazidime
- Ceftriaxone
- Ciprofloxacin
- Ertapenem
- Gentamicin
- Levofloxacin
- Meropenem
- Piperacillin/tazobactam
- Tobramycin
- Trimethoprim/sulfamethoxazole
- Other drugs (list by reported drug name)

Note: This will be limited to organisms from at least 10 subjects.

Table: Resistance by key drugs/classes (Isolate level):

- Carbapenem resistance
- Ceftriaxone resistance
- Ceftazidime resistance
- Cefuroxime resistance
- Cephalosporin resistance
- Resistance to a carbapenem or cephalosporin

Table: Resistance by key drugs/classes (Subject level) – In the subject level table, a subject with resistance in at least one isolate will be considered to have resistance to that drug:

- Carbapenem resistance

- Ceftriaxone resistance
- Ceftazidime resistance
- Cefuroxime resistance
- Cephalosporin resistance
- Resistance to a carbapenem or cephalosporin

4.3. VITEK Reveal™ results

Table: VITEK Reveal™ results reported in the EMR (from Microbiology Reveal form). *If answered as 'No', reasons for 'not-reported' will be listed (Denominators are the number of subjects with answers as 'No').*

Table: VITEK Reveal™ Organism identification: number (%) of subjects with each organism on the VITEK Reveal™ panel will be listed. The table will include the VITEK Reveal™ Evaluable population.

Table: Time to VITEK Reveal™ results

- Hours from Gram stain to VITEK Reveal™ AST test results completed
- Hours from Gram stain to VITEK Reveal™ results, as reported in the EMR

Table: VITEK Reveal™ Susceptibility for each drug by organism among the VITEK Reveal™ Evaluable population:

- Amikacin
- Ampicillin/clavulanate
- Ampicillin
- Aztreonam
- Cefepime
- Cefotaxime
- Ceftazidime
- Ceftazidime/avibactam
- Ceftazidime/clavulanate
- Ceftolozane/tazobactam
- Ciprofloxacin
- Ertapenem
- Gentamicin
- Imipenem
- Levofloxacin
- Meropenem
- Meropenem/vaborbactam
- Piperacillin
- Piperacillin/tazobactam
- Tigecycline
- Tobramycin
- Trimethoprim/Sulfamethoxazole

4.4. Microbiology mismatches – isolate level summaries, limited to the VITEK REVEAL™ evaluable population

Table: Antibiotic susceptibility testing errors (number (%) of subjects in each error type: VME, ME, and mE)

Table: Antibiotic susceptibility testing errors by bacterial species

Table: Antibiotic susceptibility testing errors by antibiotic

Table: Antibiotic susceptibility testing errors by site

Table: Listing of discrepancies, sorted by organism

Table: Listing of discrepancies, sorted by site

5. Antimicrobial Stewardship

Effective antibiotic definition:

- An antibiotic is considered to be effective if an isolate has tested susceptible to that antibiotic

Hours to antibiotic therapy considerations:

- Death is treated as a competing risk to antibiotic escalation/de-escalation
- If on an (effective) antibiotic at time of gram stain, time to effective therapy is time of gram stain (hours=0)
- If antibiotic therapy is not escalated/de-escalated, time to escalation/de-escalation will be censored at 72 hours.
- Day of gram stain is considered day 0. Time of gram stain result is considered to be time=0 hours.

5.1. Summary of Antibiotics

Table: Antibiotic Summary

- Number (%) of subjects who received any antibiotic within 3 days of gram stain result (yes/no)
- Number (%) of subjects who received any effective antibiotic within 3 days of gram stain result (yes/no)
- Number (%) of subjects who escalated gram-negative coverage within 3 days of gram stain (yes/no)
- Number (%) of subjects who de-escalated gram-negative coverage within 3 days of gram stain (yes/no)
- Number (%) of subjects whose first change between gram stain result and 3 days was:
 - Escalation of gram-negative coverage
 - De-escalation of gram-negative coverage
 - No change in gram-negative antibiotics
 - Did not receive gram-negative antibiotics in this time period
- Number of antibiotics received per participant within 3 days of gram stain result
- Number of effective antibiotics received per participant within 3 days of gram stain result

Table: For each GNB antibiotic received within 3 days of gram stain:

- Number (%) of subjects who received the antibiotics
- Number (%) of subjects who received the antibiotics and it was effective
- Number (%) of subjects receiving the antibiotic at 3 days or discharge if discharged alive prior to 3 days.

5.2. Time to effective antibiotic therapy

Table: Hours to effective antibiotic therapy within 3 days from Gram stain result, defined as hours from Gram stain result to treatment with an antibiotic to which the blood isolate is susceptible based on SOC AST, among all participants in the analysis (mITT, OE, subgroup)

Figure: Hours to effective antibiotic therapy within 3 days of gram stain result

5.3. Time to antibiotic change

Table: Hours from Gram stain result to first antibiotic escalation of gram-negative coverage within 3 days from Gram stain result, among all participants in the analysis (mITT, OE, subgroup). Escalation is defined as changing to a broader spectrum antibiotic (high number category in Table 2), or addition of one or more antibiotics.

Figure: Hours to first gram negative antibiotic escalation of gram-negative coverage within 3 days of gram stain result among all participants in the respective analysis

Table: Hours from gram stain result to first antibiotic de-escalation of gram-negative coverage within 3 days from gram stain result among all participants in the analysis (mITT, OE, subgroup). De-escalation is defined as changing to a narrower spectrum antibiotic (lower number category in Table 2), or cessation of one or more antibiotics).

Figure: Hours to first antibiotic de-escalation of gram-negative coverage within 3 days of gram stain result among all participants in the respective analysis.

Table: Hours from gram stain result to first antibiotic change (escalation or de-escalation) of gram-negative coverage within 3 days from gram stain result among all participants in the analysis (mITT, OE, subgroup). De-escalation is defined as changing to a narrower spectrum antibiotic (lower number category in Table 2), or cessation of one or more antibiotics).

Figure: Hours to first antibiotic change (escalation or de-escalation) of gram-negative coverage within 3 days of gram stain result among all participants in the respective analysis.

Table: Hours from gram stain result to first antibiotic change (escalation or de-escalation) of any antibiotic (including gram-negative, gram positive or anaerobic) within 3 days from gram stain result among all participants in the analysis (mITT, OE, subgroup).

Figure: Hours to first antibiotic change (escalation or de-escalation) of any antibiotic (including gram-negative, gram positive or anaerobic) within 3 days of gram stain result among all participants in the respective analysis.

5.4. Sensitivity Analyses - Time to antibiotic change

The analyses in section 5.3 will be repeated excluding changes in the 2 hours after gram stain result. This purpose of the sensitivity analysis is to avoid capturing changes due to the gram stain results.

5.5. Stewardship recommendations

Table: Stewardship recommendations:

- Number of stewardship recommendations made within 3 days for each subject, as a categorical variable (i.e. 1 recommendation, 2 recommendations, 3 recommendations, etc)
- Number (%) of subjects with each stewardship recommendation:
 - Any stewardship recommendation?
 - Intravenous to oral conversion
 - Narrow spectrum of therapy
 - Escalation of therapy
 - Dose optimization
 - Discontinuation of one or more antibiotics
 - Other
- Were stewardship recommendations accepted by treating physicians?

6. Clinical Outcomes

6.1. Primary analysis – three-category DOOR up to 30 days post Gram stain result

The primary outcome measure is the three-category DOOR, with deleterious event types listed in Table 1. The three-ordered levels of DOOR clinical outcomes from the best to worst with their corresponding outcome values are as follows:

- DOOR clinical outcome value = 1 for “Alive without deleterious events”
- DOOR clinical outcome value = 2 for “Alive with at least one deleterious event”
- DOOR clinical outcome value = 3 for “Death”

Detailed DOOR components, items, and data sources for DOOR are listed in Table 7. DOOR will be summarized as follows:

Table: summarizing number (%) of subjects with each level of DOOR outcome by randomized arm and total.

Table: Component outcomes of DOOR by randomized arm and total.

Figure: Bar chart of DOOR outcome distribution by randomized arm.

Figure: Bar chart of component outcomes by randomized arm.

Figure: Forest plot of the confidence interval estimates for the DOOR probability for the DOOR outcomes and respective components.

Figure: Forest plot of the DOOR probability for the primary outcome and sensitivity analysis outcomes.

Figure: Forest plot of the confidence interval estimates for the cumulative DOOR probability based on sequential dichotomization of the DOOR outcome.

The DOOR probability is calculated as the following:

$$\text{DOOR probability} = \Pr(\text{DOOR}_{\text{Reveal}} > \text{DOOR}_{\text{SOC}}) + \frac{1}{2} \Pr(\text{DOOR}_{\text{Reveal}} = \text{DOOR}_{\text{SOC}})$$

where $\Pr(\text{DOOR}_{\text{Reveal}} > \text{DOOR}_{\text{SOC}})$ is the probability of a more desirable DOOR outcome from VITEK Reveal™ than from SOC, and $\Pr(\text{DOOR}_{\text{Reveal}} = \text{DOOR}_{\text{SOC}})$ is the proportion of DOOR outcomes from the two arms that are the same.

Null hypothesis: outcomes in the VITEK Reveal™ arm are not better than the SOC arm (defined as DOOR probability $\leq 50\%$).

Alternative hypothesis: outcomes in the VITEK Reveal™ arm are better than the SOC ARM (DOOR probability $> 50\%$).

The DOOR outcome will be summarized by estimating the DOOR probability of a more desirable outcome in the VITEK Reveal™ arm compared to the SOC arm, with corresponding 95% Halperin's confidence intervals. Missing data for DOOR will not be imputed for the primary analysis as minimal missingness is expected. In addition, the DOOR outcome will be analyzed as follows: DOOR distribution by arms; cumulative difference (point estimate and confidence band) in DOOR categories for VITEK Reveal™ vs. SOC arms; point estimate and confidence interval of difference in mean partial credit between VITEK Reveal™ vs. SOC arms.

DOOR is defined by ranking all subjects, pooling together both VITEK Reveal™ and SOC arms, according to the 3-category DOOR clinical outcome values (lower is better). The ranking algorithm for DOOR is implemented as follows: a score variable is created that sums the DOOR category values.

Subjects are then ranked by the score, with the highest rank (1st) going to the participant with the lowest score, and the lowest rank going to the participant with the highest score. Tied scores result in a DOOR equal to the mean of the tied ranks.

Additional sensitivity analyses for DOOR are described in Section 7.2.

Table 7. Components and sources for DOOR outcome

Components	Items	Sources
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Death	Death	[Outcomes] page: "Dead" for question "Status at discharge from index hospitalization" OR "Yes" for question "Death within 30 days of gram stain and after discharge from index hospitalization"
Deleterious event type A – Unsuccessful discharge	Not discharged from index hospitalization	[Outcomes] page: 'Yes' if answered "No" for question "Was the subject discharged within 30 days of gram stain result?"
	Readmission to hospital	[Outcomes] page: 'Yes' if answered "Yes" for question "Was subject readmitted to the hospital within 30 days after gram stain?"
Deleterious event type B – Lack of clinical response	Relapse of bacteremia with the same species causing the index infection	[Outcomes] page: 'Yes' if answered "Yes" for question "Did the subject have a relapse of bloodstream infection with the same species within 30 days after gram stain?"
	Local suppurative complications not present at time of gram stain result	[Outcomes] page: 'Yes' if answered "Yes" for question "Did the subject have local suppurative complications not present at time of gram stain that developed within 30 days?"
	Seeding distant sites with the same infecting organism after gram stain result	[Outcomes] page: 'Yes' if answered "Yes" for question "Did the subject have seeding at distant sites within 30 days of gram stain with the same Gram negative organism identified in blood culture?"
Deleterious event type C – Undesirable events	Acquisition of hospital-acquired infection – C. difficile	[Outcomes] page: 'Yes' if answered "Yes" for question "Was hospital-onset C. difficile diagnosed after Gram Stain and up to 30 days later?"
	Acquisition of hospital-acquired infection – MDRO	[Outcomes] page: 'Yes' if answered "Yes" for questions "Were there positive cultures from any body site for healthcare-associated multidrug resistant organisms within 30 days after gram stain, acquired during index hospitalization?"
	Renal failure	[Outcomes] page: 'Yes' if answered "Yes" for "Did the subject have renal failure within 30 days after gram stain (defined as 3-fold greater increase in serum creatinine or new renal replacement therapy started)?"

Note: A deleterious event is one of the three event types: unsuccessful discharge, lack of clinical response, or undesirable events. Multiple clinical outcome items within the same deleterious event type are counted as one deleterious event. For example, if a participant has only "Relapse of bacteremia" and "Local suppurative complications", the participant has one deleterious event because both items are in the same event type "lack of clinical response".

Though all efforts will be made to minimize missingness, some missing data in the outcome page may occur:

- Subjects who are missing questions related to death are treated as "not known to be dead up to 30 days post gram stain result" and assumed to be "Alive"; supporting analyses will be performed to test the alternative assumption (treated as 'Death').
- Subjects who are alive and have at least one non-missing item as "Yes" for any of the deleterious event type will be assigned the DOOR clinical outcome value of 2 for the primary analysis; subjects who are alive and have some or all missing deleterious items and the non-missing deleterious event items all answered as "No" will be handled as follows:
 - If all deleterious event items are missing (e.g., all three items for the 'deleterious event type 3 - undesirable events' are missing), the subjects will be treated as *missing the outcome results*.
 - If not all deleterious event items are missing, the subjects will be treated as 'not known' to have the event item that is missing.

6.2. Hospitalization related outcome measures

1. All-cause in-hospital mortality

A table summarizing number (%) of all-cause in-hospital deaths up to 30 days after Gram stain result will be presented. In-hospital death includes subjects with “Dead” for “Status at discharge from index hospitalization” [OUTCOMES]. Additional deaths occurring after index discharge will not be included.

Days from Gram stain result to death among patients who died during index hospitalization will be summarized with n, mean, SD, median, Q1, Q3, min, and max.

Difference in in-hospital mortality at 30 days between the arms will be calculated, with 95% CI

Logistic regression adjusting for severity of illness (qPitt [mild (0,1), moderate (2,3), severe (4 or higher)].) and source of bacteremia will be used to evaluate in-hospital deaths up to 30 days.

2. Discharge status

A table summarizing number (%) of subjects alive/dead up to 30 days of gram stain will be presented.

3. Length of index stay

Length of index stay in the hospital up to 30 days after Gram stain result in days will be calculated as date of discharge minus date of gram stain result plus one day. Number of subjects, mean, SD, IQR, min, and max will be summarized.

4. ICU admission

Number (%) of subjects with or without ICU admissions up to 30 days after gram stain result will be presented.

5. Hospital readmissions

Number (%) of subjects with hospital readmissions to the index hospital up to 30 days after Gram stain result will be summarized.

6. Acquisition of newly-acquired *Clostridium difficile*

Both proportions and incidence rate of newly-acquired *Clostridium difficile* up to 30 days after Gram stain result will be summarized.

Proportion of newly-acquired *C. difficile* infection = Number (%) of infected subjects/mITT population

Incidence rate = Number of infections/Total study hospital days and normalized to/1,000 patient-days

Difference in proportion and difference in incidence rate between the randomized treatment arms will be calculated with 95% CIs.

7. Acquisition of newly acquired multidrug resistant organisms (MDROs)

Both proportions and incidence rate of newly acquired MDROs up to 30 days after Gram stain result will be summarized by overall and specimen source. Difference in proportion and difference in incidence rate, with 95% CIs will be calculated. Cultures that will be tracked include the following, from any specimen source, unless otherwise indicated:

- Methicillin-resistant *S. aureus*
 - Specimen type
- Vancomycin-resistant *Enterococcus* species
 - Specimen type
- Ceftriaxone non-susceptible Enterobacterales
 - Specimen type
- Carbapenem-resistant Enterobacterales (resistant to imipenem, meropenem, doripenem, or ertapenem OR documentation that the isolate possesses a carbapenemase)
 - Specimen type
- Multidrug resistant *P. aeruginosa* (resistant to aminoglycosides, cephalosporins, fluoroquinolones, and carbapenems)

- Specimen type
- Carbapenem-resistant *Acinetobacter* species
 - Specimen type
- *Candida auris*

6.3. Five-category DOOR up to 30 days post Gram stain result

The 5-category DOOR clinical outcomes from the best to worst are as follows:

- DOOR clinical outcome value = 1 for “Alive without deleterious events”
- DOOR clinical outcome value = 2 for “Alive with one deleterious event”
- DOOR clinical outcome value = 3 for “Alive with two deleterious events”
- DOOR clinical outcome value = 4 for “Alive with three deleterious events”
- DOOR clinical outcome value = 5 for “Death”

Data handling of the 5-category DOOR outcome will be similar to the primary analysis for 3-category DOOR outcome using the available data for DOOR probability, with corresponding 95% Halperin’s confidence intervals and will be summarized as follows:

Table: summarizing number (%) of subjects with each level of DOOR outcome by randomized arm and Total.

Table: Component outcomes of DOOR by randomized arm and Total.

Figure: Bar chart of DOOR outcome distribution by randomized arm

Figure: Bar chart of component outcomes by randomized arm

Figure: Forest plot of the confidence interval estimates for the DOOR probability for the DOOR outcomes and respective components.

Figure: Forest plot of the DOOR probability for the primary outcome and sensitivity analysis outcomes

Figure: Forest Plot of the Confidence Interval Estimates for the Cumulative DOOR Probability Based on Sequential Dichotomization of the DOOR Outcome

6.4. Exploratory Outcome - Desirability of treatment selections based on antibiotic spectrum and activity in relation to bloodstream isolate susceptibility profiles

The Desirability of Outcome Ranking for the Management of Antimicrobial Therapy (DOOR MAT, Wilson, et al., 2021) method will be used to assess the desirability of treatment selections based on antibiotic spectrum and activity in relation to bloodstream isolates susceptibility profiles. The analyses will include mITT population who have non-missing Gram-negative agents (as listed in Table 2), non-missing Gram-negative blood stream isolates, and at least one susceptibility testing results reported using SOC.

Additional details on the DOOR-MAT exploratory analysis will be described in a separate exploratory analysis plan.

7. Additional analyses

7.1. Subgroup analyses

A forest plot will be created showing the primary DOOR outcome and the DOOR outcome of each non-exploratory sub-group.

Subgroup analyses on the primary endpoint, outcome variables, time antibiotic modification variables, and, where appropriate, microbiologic variables will be performed for the following:

- 1)) Among subjects with infections due to on-panel Gram negative species (species included in the VITEK Reveal™ panel) as identified by SOC. This is the OE population.
- 2) By geographic locations:

- By each clinical site
- By country

3) Among subjects whose isolates have different phenotypic resistance patterns, specifically Enterobacterales that are 3rd generation cephalosporin non-susceptible and carbapenem resistant Enterobacterales, *Acinetobacter*, and *Pseudomonas* species.

- Enterobacterales resistant to at least one carbapenem
- Enterobacterales susceptible to carbapenems (not resistant to any tested carbapenems)
- Enterobacterales resistant to at least one cephalosporin (with and without resistance to a carbapenem)
- Enterobacterales susceptible to cephalosporins (not resistant to any tested cephalosporin)
- *Pseudomonas* species resistant to at least one carbapenem that is not ertapenem
- *Pseudomonas* species susceptible to all tested carbapenems, excluding ertapenem
- *Acinetobacter* species (alone) resistant to at least one carbapenem that is not ertapenem
- *Acinetobacter* species (alone) susceptible to at least one carbapenem that is not ertapenem

4) ICU

- In ICU at randomization
- Not in ICU at randomization

5) Immunocompromised

- Immunocompromised
- Not immunocompromised

6) Charlson Score

- Low Charlson Score (≤ 2)
- Higher Charlson Score (> 2)

7) Q Pitt Score

- Low Q Pitt Score (0,1)
- Higher Q Pitt Score (2+)

8) Sex

- Male
- Female

9) Age

- 0-29
- 30-49
- 50-59
- 60-69
- 70-79
- 80+

10) Source of bacteremia

- Urinary source
- Intra-abdominal
- Central venous catheter

Exploratory Subgroup analyses

- 1) Among subjects with blood culture growth (gram stain turned positive) during:
 - Day shift, as determined by local working hours at each site
 - Night shift
- 2) Participants not receiving comfort care at gram stain result or in the next 3 days, exploratory as this is a post-randomization variable.

7.2. Sensitivity analyses

1. Sensitivity analysis of the primary endpoint using inverse probability weighting for missing data

In cases where subjects in the m/TT population are *missing the outcome results* for determining DOOR outcome, inverse probability weighting (IPW) will be used to handle missing data for the primary analysis. Assuming the data are missing at random (MAR), the IPW approach weigh complete cases with the inverse of their probability of being a complete case. While subjects with missing DOOR outcome will not contribute to the DOOR analysis per se, their non-outcome data may still inform the fitting of the logistic regression model used to predict the probability of completeness which are used to calculate the weights.

Let Y_i represent the outcome of interest (ranking of the DOOR score with tie-breakers) for subject i .

The DOOR probability, incorporating IPW for adjusting for missing data, will be calculated as follows:

- 1) For labeling convenience, rename the DOOR score ranks from VITEK Reveal™ and SOC as 'group 1' and 'group 2' respectively. Weights from the VITEK Reveal™ arm are w_{1i} and w_{2i} for the SOC arm.
- 2) Compare the DOOR score ranks between groups and assign indicator value: starting with the first subject in group 1,
 - a. If an subject in group 1 has a smaller DOOR score rank than an subject in group 2 (more desirable DOOR outcome in the VITEK Reveal™ arm), the subject in group 1 is assigned an indicator value of 1.
 - b. If the first subject in group 1 has the same DOOR score rank as the subject in group 2 (equal DOOR outcome between both arms), the subject in group 1 is assigned an indicator value of $\frac{1}{2}$.
- 3) Calculate probability of being a complete case for each subject:
 - c. Create a non-missing data indicator L_i for each subject, $L_i=1$ for non-missing and $L_i=0$ for missing in the DOOR outcome;
 - d. Fit in a logistic regression model, including the following covariates of interest: age, qPitt score, and infection site;
 - e. Obtain the fitted probabilities of each subject π_i being complete: π_{1i} for subjects in group 1 and π_{2i} for subjects in group 2
- 4) For each pair of comparison in step 2, create the weight w_j as the inverse of the probability of both values in the pair being non-missing, i.e., $w_j = 1/(\pi_{1i} \times \pi_{2i})$ with j being the index for subjects in group 1.
- 5) For each pair of comparison in step 2, create the weighted indicator value as $w_ind_j = w_j \times indicator_j$
- 6) Repeat steps 2-5 for all observations in group 1.
- 7) The DOOR probability can then be obtained by $DOOR_prob_IPW =$ weighted average of all the indicator values in step 5, i.e., $DOOR_prob_IPW = \frac{\sum_j w_ind_j}{\sum w_j}$
- 8) The 95% confidence intervals for the DOOR probability will be constructed using Halperin's method (Halperin, 1989).

2. Sensitivity analysis of the primary endpoint using the worst and best case scenarios for missing data

In cases where subjects in the mITT population are missing outcome results for determining DOOR outcome, we will assume the best and worst case scenarios to check the robustness of the results.

1. Best case scenario: All subjects missing outcome data in the VITEK Reveal™ arm will be assumed to be in the category “Alive without deleterious events”. All subjects missing outcome data in the SOC arm will be assumed to have died.
2. Worst case scenario: All subjects missing outcome data in the VITEK Reveal™ arm will be assumed to have died. All subjects missing outcome data in the SOC arm will be assumed to be in the category “Alive without deleterious events”.
3. Sensitivity analysis using stabilized inverse probability weights to adjust for source of bacteremia, age-adjusted charlson score and qPitt score.

4. Sensitivity analysis of the primary endpoint using tiebreakers

To analyze DOOR with a tie-breaker variable, two variables will be used in separate sensitivity analyses:

- Survival days since gram stain will be used as the tie breaker for 30 day mortality and days of hospitalization since gram stain (shorter is better) will be used as the tie breaker for the other two DOOR categories.
- Sum of antibiotic spectrum of all antibiotics received in the first 3 days. A lower sum is better than a higher number.

5. Sensitivity analysis of primary endpoint including subjects with unevaluable VITEK Reveal™ results

For subjects who are randomized to the VITEK Reveal™ arm and whose VITEK Reveal™ assessment is initiated greater than 16 hours after the blood culture is flagged positive, the sensitivity analysis will include these subjects for the primary endpoint assessment.

6. Sensitivity analysis of primary endpoint by randomization strata

The van Elteren (vE) test (van Elteren, 1960), a stratified Wilcoxon-Mann-Whitney test, will be used to adjust for stratification by sites and by ICU status on the three-category DOOR outcome. A DOOR analysis stratified by sites and ICU status will be conducted

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