



Antibacterial Resistance Leadership Group (ARLG)

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

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Antibacterial Resistance Leadership Group (ARLG)

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STATEMENT OF COMPLIANCE

The study will be carried out in accordance with the Protocol and as required by the following:

- Applicable International Council for Harmonisation (ICH) guidelines
- ICH GCP E6R2 (Good Clinical Practice [GCP])
- NIH Clinical Terms of Award
- Applicable National, State, and Local Regulations and Guidance

SIGNATURE PAGE

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 governmental regulations and ICH guidelines.

Site Investigator:

Signed: _____ Date: _____

Name

Title

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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
CRO	Contract Research Organization
DCRI	Duke Clinical Research Institute
DMID	Division of Microbiology and Infectious Diseases
DOOR	Desirability of Outcome Ranking
DOOR MAT	Desirability of Outcome Ranking for the Management of Antimicrobial Therapy
DOOR STEPP	Desirability of Outcome Ranking with Subpopulation Treatment Effect Pattern Plot
DSMB	Data and Safety Monitoring Board
EA	Essential Agreement
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EU	European Union
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FAST	Fast Antibiotic Susceptibility Testing for Gram Negative Bacteremia Trial
GCP	Good Clinical Practice
GNB	Gram Negative Bacilli
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICU	Intensive Care Unit
ID	Identification
IEC	Independent or Institutional Ethics Committee
IRB	Institutional Review Board
ITT	Intention-to-Treat
IV	Intravenous
MALDI-TOF MS	Matrix-assisted Laser Desorption/Ionization Time of Flight Mass Spectrometry
MDRO	Multi-Drug Resistant Organism
ME	Major Error

List of Abbreviations - *continued*

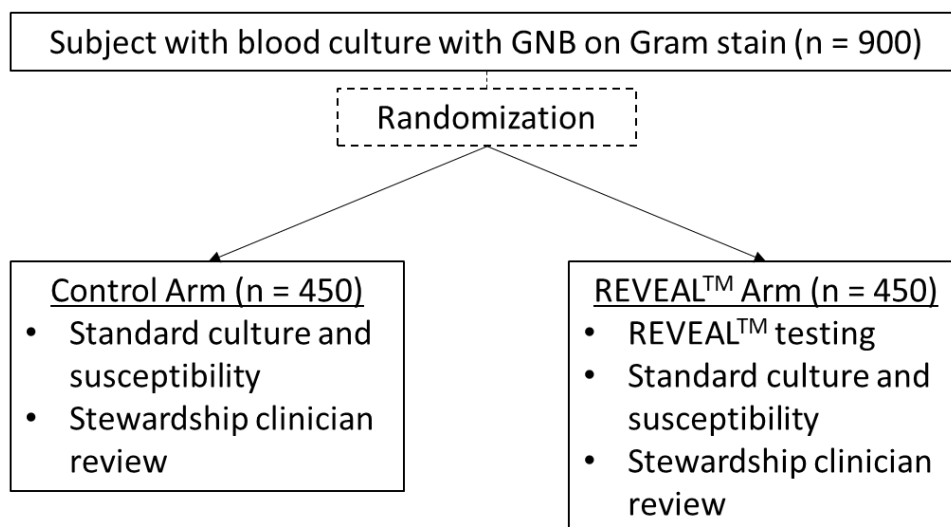
mE	Minor Error
MIC	Minimum Inhibitory Concentration
MOP	Manual of Procedures
MR	Medical Record
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PI	Principal Investigator
PIPS	Predictive Interval Plots
PMP	Project Management Plan
PO	Oral
QA	Quality Assurance
QC	Quality Control
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
US	United States
VME	Very Major Error

PROTOCOL SUMMARY

- Title:** Fast Antibiotic Susceptibility Testing for Gram Negative Bacteremia Trial (FAST)
- Study Description:** This study is a 2-arm, multicenter, multinational, prospective, randomized, controlled clinical trial. Hospitalized subjects with blood cultures growing Gram negative bacilli (GNB) will be randomized 1:1 to have the positive blood cultures characterized using standard of care (SOC) antimicrobial susceptibility testing (AST) vs. a rapid AST method known as REVEAL™ in addition to SOC AST. The purpose of the FAST trial is to evaluate whether use of a rapid phenotypic AST improves clinical outcomes compared to use of SOC AST methods in clinical settings with high resistance rates.
- Study Population:** A total of 900 adult and pediatric subjects hospitalized with bloodstream infections (BSIs) caused by GNB
- Number of Sites:** Up to 10 international sites
- Study Duration:** Approximately 48 months
- Duration of Participation:** Up to 30 days
- Objectives:**
- Primary:
- To compare clinical outcomes among subjects with GNB BSI who have bloodstream isolate AST determined using REVEAL™ vs. SOC methods.
- Secondary:
- 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 REVEAL™ vs. SOC methods.

Exploratory:

- To describe discrepancies between REVEAL™ and SOC methods among subjects randomized to the REVEAL™ arm.
- To describe clinician compliance with Antimicrobial Stewardship (AS) recommendations in the REVEAL™ vs. SOC arms.
- To describe the desirability of treatment selections in the REVEAL™ vs. SOC arms.

Figure 1. Schematic of Study Design

1 KEY ROLES

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2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Gram negative bacilli (GNB) cause up to one-third of bloodstream infections (BSIs) worldwide. Ineffective therapy for GNB BSIs is associated with mortality rates in excess of 30%.¹⁻⁷ More rapid determination of the antimicrobial susceptibility characteristics of bacteria causing BSI may lead to earlier pathogen-directed antimicrobial therapy, more optimal antibiotic utilization, improved clinical outcomes, and less emergence of resistance. The Antibacterial Resistance Leadership Group (ARLG) has pioneered the use of randomized controlled trials (RCTs) to evaluate the clinical impact of rapid identification (ID) and AST of bacteria from blood cultures.^{8,9} The recently completed RAPIDS-GN trial was an RCT conducted at two United States (US) centers to compare performance characteristics and clinical impact of a rapid identification and phenotypic AST method vs. standard of care (SOC) methods in subjects with GNB-BSI.⁹ RAPIDS-GN demonstrated that compared to conventional testing, a rapid phenotypic AST method implemented with antimicrobial stewardship (AS) led to significantly faster antibiotic modifications for treatment of GNB-BSI, and enabled antibiotic escalations to occur almost 2 days faster for subjects with antimicrobial-resistant infections. The RAPIDS-GN study was performed in areas with low prevalence of antimicrobial resistance and was not sufficiently powered to detect differences in clinical outcomes. The RAPIDS-GN data support the conduct of the FAST trial, an international clinical utility study in several sites with a high prevalence of multi-drug resistant GNB, to assess the clinical impact of rapid AST in settings where it is likely to have the greatest impact.

2.2 Rationale

The rapid AST method that will be used in the FAST trial is VITEK® REVEAL™ (bioMérieux, Marcy-l'Étoile, France),¹⁰ which uses small molecule sensor technology to detect growth of bacterial populations by measuring volatile metabolites, and provides AST results in ~5 hours. REVEAL™ is approved for clinical use in the European Union (EU) and in progress for approval in Israel, and provides minimum inhibitory concentrations (MICs) for 23 antibiotics (see [Table 1](#)) and 10 Gram negative species (see [Table 2](#)), that together account for ~90% of organisms causing Gram negative BSIs. The performance of the REVEAL™ system has been evaluated against 104 Gram negative clinical isolates and compared to Sensititre™ (Thermo Fisher Scientific) and VITEK 2 (bioMérieux) reference methods. REVEAL™ had 97% essential agreement (EA) and 96% categorical agreement (CA) with VITEK 2, and 98% EA and 96% CA with Sensititre with a 1.2% very major error (VME) rate. As compared to standard disk diffusion, the REVEAL™ system showed 96% CA, with 3%, 2% and 2% minor errors (mE), major errors (ME) and VMEs, respectively, when evaluated using 81 positive blood cultures from patients with Gram negative bacteremia. The REVEAL™ system has also been evaluated against 317

carbapenem-resistant GNB from the Centers for Disease Control (CDC) isolate bank and detected carbapenem resistance in 312/317 (98%) isolates. REVEAL™ detected carbapenem resistance in 204/205 of the carbapenemase-producing isolates and 108/112 of the non-carbapenemase-producing organisms. Use of REVEAL™ requires little technologist training, and sample preparation takes less than 3 minutes.

While novel and rapid blood culture diagnostics can provide faster organism ID and AST compared to standard methods, their clinical impact is unclear, and has not been assessed in prospective clinical trials (other than the prior ARLG BCID and RAPIDS-GN trials).^{8,9} The FAST trial will add to the data acquired from previous studies and evaluate whether use of a rapid phenotypic AST method improves outcomes compared to use of conventional methods *in clinical settings with high resistance rates*.

Table 1. Antibiotics for which REVEAL™ provides MICs using either European Committee on Antimicrobial Susceptibility Testing (EUCAST) or Clinical and Laboratory Standards Institute (CLSI) breakpoints

amikacin	cefoxitin	ertapenem	piperacillin
amoxicillin/clavulanic acid	ceftazidime	gentamicin	piperacillin/ tazobactam
ampicillin	ceftazidime/ avibactam	imipenem	tigecycline
aztreonam	ceftazidime/ clavulanic acid	levofloxacin	tobramycin
cefepime	ceftolozane/ tazobactam	meropenem	trimethoprim/ sulfamethoxazole
cefotaxime	ciprofloxacin	meropenem/ vaborbactam	

Table 2. Gram negative organism-types for which REVEAL™ provides antibiotic MICs

<i>Acinetobacter baumannii</i> (species and complex)	<i>Escherichia coli</i>	<i>Pseudomonas aeruginosa</i>
<i>Citrobacter freundii</i>	<i>Klebsiella aerogenes</i>	<i>Proteus mirabilis</i>
<i>Citrobacter koseri</i>	<i>Klebsiella oxytoca</i>	
<i>Enterobacter cloacae</i> (species and complex)	<i>Klebsiella pneumoniae</i> (species and complex)	

2.3 Potential Risks and Benefits

Results of this study have implications for diagnosis, management, and outcomes of GNB and will inform future efforts to develop blood culture diagnostics and integrate them into clinical care. Findings will be applicable to regions of the world with high endemic drug resistance among GNB. The minimal risks associated with participation in this study are outweighed by the significant knowledge to be gained through the proposed research.

2.3.1 Potential Risks

This study poses minimal risk to subjects. This study will use the results of blood samples collected for routine clinical care and does not involve any blood draws for research. All subjects randomized to the REVEAL™ arm will also have blood culture evaluation using SOC methods. REVEAL™ has been approved for use in the EU. The study will be conducted in countries where it is approved for use and will be implemented for its approved indication and according to the manufacturer's instructions. The purpose of the study is not to address whether the technology works, but to determine if it adds value to patient care.

This study poses minimal risk of breach of privacy or confidentiality. Only coded information will be collected, and the study will have measures in place to protect privacy. The study protocol, documentation, data, and all other information generated will be maintained in a secure manner and will be kept confidential. Database access will be limited to study personnel issued a unique user identification and password. Study personnel will enter data at each site. No information concerning the study or the data will be released to any third party without prior written approval of the sponsor.

All enrolled subjects will have antibiotic management overseen by local AS clinicians. Thus, participation in the study will not adversely affect the welfare of subjects enrolled in the study.

2.3.2 Known Potential Benefits

While there is no direct benefit to subjects at this time, results from this study will be used to assess a potential benefit and inform strategies to improve diagnostic testing for GNB bacteremia.

3 OBJECTIVES

3.1 Primary Objective

To compare clinical outcomes among subjects with GNB BSI who have bloodstream isolate AST determined using REVEAL™ vs. SOC methods.

3.2 Secondary Objective

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 REVEAL™ vs. SOC methods.

3.3 Exploratory Objectives

- To describe discrepancies between REVEAL™ and SOC methods among subjects randomized to the REVEAL™ arm
- To describe clinician compliance with AS recommendations in the REVEAL™ vs. SOC arms
- To describe the desirability of treatment selections in the REVEAL™ vs. SOC arms

4 STUDY DESIGN

This study is a 2-arm, multicenter, multinational, prospective, randomized, controlled clinical trial. Approximately 900 hospitalized subjects with GNB in blood cultures will be randomized to have positive blood cultures characterized using SOC AST vs. REVEAL™ in addition to SOC AST. The primary objective of this study is not to evaluate REVEAL™ for its diagnostic accuracy, but rather to determine whether its use in the clinical setting can improve clinical outcomes, according to the Objectives in Section 3.

Eligible subjects will be identified based on results of blood cultures (with growth of GNB) collected for clinical indications. All laboratory testing will occur in local clinical microbiology laboratories. Screening will occur according to eligibility criteria (Section 5), and eligible subjects will be randomized in a 1:1 ratio to one of two arms. The primary service, including the treating provider, will be unaware of arm assignment at the time of randomization, so initial antibiotic choice by the treating provider will not be affected by arm assignment. The treating provider for each subject will make all treatment decisions. There will be no blood draws, tests, or procedures performed solely for research purposes.

For all subjects in both arms, matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS) will be used as the standard clinical organism identification method, and local SOC AST of GNB from positive blood cultures will be performed. All subjects in both arms of the study will undergo prospective audit and feedback by the local AS clinicians according to institutional practices. The AS clinicians and laboratory technologists will not be blinded to arm assignment.

After a subject is randomized, information about the subject's demographics, comorbid conditions, severity of illness, laboratory results, administered antimicrobials, and whether the subject is on comfort care will be obtained from the subject's medical record (MR) and recorded into the study database according to [Appendix A – Schedule of Activities](#) in Section 17. Final outcomes for each enrolled subject will be gathered from the MR.

5 STUDY POPULATION

5.1 Selection of the Study Population

Hospitalized subjects from participating sites who are screened and meet the eligibility criteria will be enrolled in the study. Any eligible subject who has a GNB BSI may be enrolled into this study. Unevaluable subjects (as defined in Section 10.2) will not be replaced. Partial data on these subjects, including microbiology results and certain baseline data, will be retained.

5.2 Inclusion/Exclusion Criteria

Inclusion Criteria:

1. Positive blood culture with Gram stain showing GNB
2. Hospitalized at the time of Gram stain result
3. Enrolled within 16 hours of blood culture positivity

Exclusion Criteria:

1. Positive blood culture for GNB within the prior 7 days (if known at the time of Gram stain result)
2. Deceased at the time of Gram stain result
3. Gram-positive bacilli, Gram-positive cocci, Gram-negative cocci, yeast, fungi, or multiple morphologies of GNB detected on Gram stain of blood culture
4. Previous enrollment in this study

6 STUDY PROCEDURES

6.1 Randomization Procedures

Subjects meeting enrollment criteria will be assigned, in a 1:1 ratio using permuted blocks, to one of the two arms: (1) SOC AST Control Arm or (2) REVEAL™ Arm. The randomization scheme will be stratified by site for all sites and by intensive care unit (ICU) status at the time of the Gram stain result. The treating provider for each subject will make all treatment decisions. The date and time of Gram stain result must be recorded.

Once the study arm is assigned, the Study Coordinator, the AS team, and other relevant study team member(s), as appropriate per site processes, will be notified which arm the subject has been randomized to.

Sites are responsible for notifying appropriate agencies of reportable infectious diseases per institutional policies.

6.2 Blinding

Primary service/provider: The primary service, including the treating provider, will be unaware of arm assignment at the time of randomization, so initial antibiotic choice will not be affected by arm assignment. Once REVEAL™ results become available and/or AS recommendations are made, treating providers may become aware of arm assignment.

The AS team and laboratory technologists will not be blinded.

6.3 Standard of Care (SOC) AST

For all subjects in both arms, matrix-assisted laser desorption/ionization time of MALDI-TOF MS will be used as the standard clinical organism identification method and local SOC AST of GNB from positive blood cultures will be performed.

6.4 Rapid AST with REVEAL™

For subjects randomized to the REVEAL™ arm, testing will be performed according to the manufacturer's instructions and reported in the subject's medical record and/or reported to the subject's treating provider. Gram negative bacilli/antibiotic combinations not reported by REVEAL™, but routinely reported by the local Microbiology Laboratory using SOC testing, will be added to the final AST report for study subjects. These data will be collected on the eCRF.

Any disagreement in results between the REVEAL™ and the SOC AST will be reviewed by the Microbiology Laboratory Director and reported in the subject's eCRF in the study Electronic Data Capture (EDC) system according to Section 6.4.1. The primary team caring for the subject will be notified of any disagreement between the REVEAL™ and the SOC AST results; additional susceptibility testing may be performed per clinical practice, as needed.

REVEAL™ must be initiated within 16 hours after the blood culture bottle is flagged positive.

6.4.1 Monitoring of Discordant Results

The site Microbiology Laboratory Director will be responsible for monitoring and reviewing discordant results between the REVEAL™ and SOC methods for subjects in the REVEAL™ arm, as per routine clinical care. In this study, AST discrepancies will be categorized according to CLSI or EUCAST, as follows:

- **Very major error (VME):** Susceptible by REVEAL™ and resistant by SOC AST.
- **Major error (ME):** Resistant by REVEAL™ and susceptible by SOC AST.
- **Minor error (mE):** Intermediate by one method and susceptible or resistant by the other method.

Sites will record all results in the subject's eCRF in the study EDC system.

Discrepancies between the REVEAL™ and SOC results will be handled as noted in Section 6.4.

6.5 Antimicrobial Stewardship

All subjects in both arms of the study will undergo standard audit and feedback by institutional AS programs. The AS provider will review the subject's microbiology results and MRs. The AS provider will follow local or national treatment guidelines and contact the appropriate provider if modifications to therapy are indicated at any time following notification of positive Gram stain result, organism identification, and/or AST results. If the AST result is ready when the AS provider is unavailable (e.g., in the evening or on a weekend), the AS team will review the MRs and make recommendations as soon as possible, but no later than the beginning of the next working day. Escalation and de-escalation recommendations made by AS providers will be recorded in the study database. Recommendations can be directly entered into the database by the AS provider or designee to serve as an electronic source when another source document is not available.

In addition to standard audit and feedback, other routine institutional AS activities will continue, such as implementation of institutional treatment guidelines, prior authorization of restricted antibiotics, review of subjects on selected antibiotics with feedback to clinicians, and daily review of specific culture results.

6.6 Study Assessments

For this study, all information (measurement and assessment results) will be taken from the MR or other hospital system, as appropriate.

6.6.1 Demographics, Admission Information, Medical History

Subject demographics, admission information, comorbid conditions, antibiotic therapy, severity of illness markers, and clinical outcomes will be collected. Refer to the MOP for details.

6.6.2 Quick Pitt Bacteremia Score

Components of the quick Pitt Bacteremia Score (qPitt) will be collected, including temperature, mechanical ventilation, cardiac arrest, mental status, and hypotension.^{11,12,13}

6.6.3 Comfort Care

Whether a subject is on comfort care at the time of Gram stain result or within 3 days of Gram stain result will be recorded, as determined by review of the primary physician team notes and any relevant consultations (e.g., Palliative Care).

6.6.4 Antibiotic and Other Medication Administration

Antibiotics and other medications will be administered as prescribed by the treating provider. The following information will be collected from the MR or other hospital system, as appropriate:

- Antibiotic(s) [targeting Gram negative, Gram positive, and other bacteria], including start and stop dates, if within 3 days of Gram stain result

6.6.5 Microbiology

The following data will be collected from the subject's MR (or other hospital system as appropriate):

- Organism identification to species, genus, or complex level
- Source of bacteremia
- AST results using SOC (see Section 6.3)
- AST results using REVEAL™ (for subjects in REVEAL™ arm)
- Date and time of Gram stain result
- Date and time of organism identification and AST using SOC (see Section 6.3)
- Date and time of organism AST using REVEAL™ (for subjects in the REVEAL™ arm)
- Acquisition of hospital-acquired *Clostridioides difficile*/multi-drug resistant organisms (MDRO) detected on clinical/surveillance cultures (Section 8.1.2)

6.6.6 Record DOOR events/outcomes

The following data will be collected from the subject's MR (or other hospital system as appropriate):

- Subject disposition: alive or dead AND not in hospital or in hospital (not discharged or re-admitted)
- Deleterious events (for the DOOR outcome), refer to [Table 3](#) for the list of deleterious events

7 STUDY SCHEDULE

7.1 Screening

The following procedures will be done at screening:

- Record date and time of gram stain result
- Evaluation of Inclusion/Exclusion Criteria (Section [5.2](#))

7.2 Enrollment/Baseline

The following procedures will be done after randomization. Note, all activities that require recording can be recorded in the database at any time through the subject's Final Visit:

- Perform AST based on assigned arm (SOC or REVEAL™)
- Record in the EDC:
 - Demographics
 - Medical history
 - Components of qPitt
 - Whether subject is on comfort care
 - Antibiotic administration details
 - Admission information (ICU status must be collected and recorded in the database at enrollment/baseline, Day 0)
 - Source of bacteremia, if available

7.3 Follow-up Visits

The following information will be collected through review of the MR (or other hospital system, as appropriate) and recorded in the EDC database for the following time points: 1, 2, and 3 days after Gram stain result. Note that these data can be recorded in the database at any time through the subject's Final Visit:

- Record antibiotic administration details
- Record results of blood culture organism identification
- Record results of AST
- Record AS provider escalation/de-escalation recommendation
- Record source of bacteremia

7.4 Final Visit

Any of the following data that occurs up to 30 days after Gram stain will be recorded in the EDC:

- Source of bacteremia
- Results of blood culture organism identification
- Results of AST
- Date of discharge; or if not discharged, the date of the 30 day after Gram stain evaluation
- Deleterious events/outcomes (Section [6.6.6](#)), including mortality and hospital readmission
- ICU admission

8 ASSESSMENT OF OUTCOME MEASURES

8.1 Specification of the Appropriate Outcome Measures

8.1.1 Primary Outcome Measures

The primary outcome measures of subject disposition and deleterious events will be collected, in order to assess the DOOR outcome up to 30 days after Gram stain result (See Statistical Considerations; Section 10).¹⁴

The composite 3-category DOOR outcome will assess three deleterious events (unsuccessful discharge, lack of clinical response, and undesirable events) (Table 3) in addition to survival up to 30 days after Gram stain result. The primary DOOR outcome measure is defined using three ordered levels. From best to worst, they are:

1. Alive without deleterious events
2. Alive with at least 1 deleterious event that is listed in Table 3
3. Death

Table 3. Deleterious events for DOOR outcome

<u>Unsuccessful discharge:</u>	<u>Lack of clinical response:</u>	<u>Undesirable events</u>
• Not discharged from 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>C. difficile</i> – MDRO • <u>Renal failure that occurs after index bloodstream infection:</u> – Three-fold or greater increase in serum creatinine^{15,16} – New renal replacement therapy

8.1.2 Secondary Outcome Measures

- All-cause in-hospital mortality up to 30 days post Gram stain result
- Length of index stay in the hospital up to 30 days post Gram stain result, for those subjects alive at 30 days. Length of stay will be calculated as date of discharge minus date of Gram stain result.

-
- ICU admission up to 30 days post Gram stain result
 - New acquisition of 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: resistant to imipenem, meropenem, doripenem, or ertapenem OR documentation that the isolate produces a carbapenemase¹⁷
 - *Pseudomonas aeruginosa* resistant to carbapenems/multi-drug resistant (resistant to aminoglycosides, cephalosporins, fluoroquinolones, and carbapenems)¹⁸
 - Carbapenem-resistant *Acinetobacter* species
 - *Candida auris*
 - Time to effective antibiotic therapy within 3 days from Gram stain result, defined as treatment with an antibiotic (or antibiotic class) to which the blood isolate is susceptible based on SOC AST.
 - 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 (higher number category in [Table 4](#)), addition of one or more antibiotics, or conversion of oral (PO) to intravenous (IV) route.
 - 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 4](#)), cessation of one or more antibiotics, or changing from an IV to PO route of appropriate drug (i.e., IV to PO ciprofloxacin or levofloxacin).
-

Table 4. Gram negative agents

Category	Spectrum	Antibiotics
1	Narrowest	Ampicillin, cefazolin
2	Narrow	Amoxicillin/clavulanic acid, ampicillin/sulbactam, 2 nd generation cephalosporins, 3 rd generation cephalosporins (except ceftazidime), tetracyclines, trimethoprim/sulfamethoxazole
3	Medium	Aminoglycosides (amikacin, gentamicin, tobramycin), aztreonam, ceftaroline, ceftazidime, fluoroquinolones (ciprofloxacin, moxifloxacin, levofloxacin), fosfomycin
4	Medium broad	Piperacillin/tazobactam, cefepime, ertapenem
5	Broadest	Anti-pseudomonal carbapenems (imipenem/cilastatin, meropenem), ceftazidime/avibactam, ceftolozane/tazobactam, imipenem/relebactam, cefiderocol, tigecycline, meropenem/vaborbactam, colistin, polymyxin B

8.1.3 Exploratory Outcome Measures

- The 5-category DOOR up to 30 days after Gram stain result. The five-ordered levels of DOOR clinical outcomes from best to worst are:
 - Alive without deleterious events
 - Alive with 1 deleterious event that is listed in [Table 3](#)
 - Alive with 2 deleterious events that are listed in [Table 3](#)
 - Alive with 3 deleterious events that are listed in [Table 3](#)
 - Death
- Categorical agreement between REVEAL™ and SOC testing among subjects who receive rapid testing using REVEAL™ (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).

9 CLINICAL MONITORING

9.1 Site Monitoring/Oversight Plan

Site monitoring will be conducted to ensure that the human subject protection, study procedures, laboratory, use of the testing method, and data collection processes are of high quality and meet the sponsor, ICH E6 and, when appropriate, regulatory guidelines. This section provides a general description of how site monitoring will be conducted. A separate monitoring/oversight plan document will be developed to describe who will conduct the monitoring, what frequency, and at what level of detail monitoring will be conducted.

The monitoring/oversight plan will follow risk-based and quality by design principles per ICH E6. The plan will include both remote and in-person monitoring scenarios, as appropriate. The plan will include what will be monitored and who will be responsible for conducting monitoring visits.

The sponsor has ethical, legal, and scientific obligations to carefully follow this study in accordance with established research principles and applicable regulations. The investigator, as part of his/her responsibilities is expected to cooperate with the sponsor in ensuring that the study adheres to the protocol and GCP requirements.

As part of the concerted effort to fulfill these obligations, the coordinating center's monitor (or designee) will visit the site(s), either remotely or in-person, during the study in accordance with the monitoring/oversight plan set forth for this trial. The investigator will permit the monitor to perform monitoring visits for the study as frequently as is deemed necessary and provide access to MRs/source documents to ensure that data are being recorded adequately, that data are verifiable and that protocol adherence is satisfactory. Monitor access to medical and research records will follow locally allowable processes. For example, direct patient MR access may not be allowed or access to such records may require pre-approval and de-identification prior to viewing by the monitor.

Monitoring visits will include, but are not limited to, review of regulatory files, eCRFs, MRs, medical and laboratory reports, and protocol and GCP compliance. Site monitors will have access to each participating site, study personnel, and all study documentation according to the site monitoring/oversight plan. Study monitors will meet with site principal investigators (PIs) to discuss any problems and actions to be taken, and will document site visit findings and discussions.

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Considerations

Clinical outcomes through 30 days post-Gram stain result will be compared using the DOOR. Data from the MERINO and RAPIDS-GN trials were used to inform the expected DOOR distribution.^{9,19} The MERINO trial has important differences from FAST, but provides useful data for this trial. The MERINO trial enrolled subjects with ceftriaxone-non-susceptible, piperacillin/tazobactam-susceptible, and meropenem-susceptible bloodstream isolates. The FAST trial will enroll subjects with bacteremia due to any type of GNB. Optimal antibiotic therapy in MERINO was initiated at 48-72 hours after onset of sepsis, while in FAST, the rapid test may allow for initiation of optimal therapy up to 2 days sooner with additional potential survival benefit. Thus, FAST may lead to timely, effective antibiotic treatment and mortality benefit in a substantial portion of enrolled subjects.

A nonparametric Wilcoxon rank sum test based on the DOOR distribution will be employed to test the null hypothesis that outcomes in the 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 $\text{Pr}(\text{more desirable outcome with rapid testing than SOC}) + 1/2\text{Pr}(\text{outcome with rapid testing is equal to SOC})$ compared to the alternative hypothesis that outcomes in the 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 5). 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 REVEAL™ arm.

Table 5. DOOR outcome estimates and evaluable sample size

Scenario	SOC			REVEAL™			DOOR probability
	Mortality	Deleterious events	Alive and no events	Mortality	Deleterious events	Alive and no events	
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	0.1	0.32	0.58	0.05	0.28	0.67	0.551

10.2 Analysis Plan

Details of all planned statistical analyses will be described in the Statistical Analysis Plan (SAP).

Analyses will be performed based on the intention-to-treat (ITT) principle. The ITT analysis set includes all randomized subjects, except for those who are considered unevaluable as defined below:

- If standard culture methods do not yield a Gram-negative organism (as was originally detected on Gram stain), the culture result will be reported in the electronic Case Report Form (eCRF), and the subject will be considered unevaluable.
- Deceased at time of Gram stain result and history of blood culture with GNB within 7 days prior to randomization (if known at randomization) are exclusion criteria. However, it is possible that this information may not be known or confirmed before randomization. As such, subjects who meet either of these exclusion criteria following randomization will be considered unevaluable.
- Additionally, subjects whose blood cultures are found to have had erroneous Gram stain results in the laboratory will be considered unevaluable. Post-randomization identification of these unevaluable subjects will not be considered a protocol deviation.

Unevaluable subjects will be included in an analysis of rapid test performance.

A modified intention-to-treat (mITT) population, including subjects who meet all eligibility criteria and no exclusion criteria will be used to evaluate all other outcomes. Subjects randomized to the REVEAL™ arm will be included in the analyses even if REVEAL™ does not return a result. This effectively evaluates the strategy of REVEAL™ application.

Descriptive statistics (e.g., percentages, means, standard deviations, medians, quantiles) and graphical summaries (e.g., histogram, boxplots) will be reported to describe and display the distribution of important outcomes. The DOOR outcome will be summarized by estimating the DOOR probability, with corresponding 95% confidence intervals. 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 REVEAL™ vs. SOC arms; point estimate and confidence interval of difference in mean partial credit between REVEAL™ vs. SOC arms.

The Desirability of Outcome Ranking approach for the Management of Antimicrobial Therapy (DOOR MAT) was devised to assess the desirability of treatment selections based on antibiotic spectrum and activity in relation to susceptibility profiles.²⁰ The selected antibiotics will be grouped into categories of increasing spectrum, and the susceptibility profile for each isolate will be established according to the susceptibility to each antibiotic category ([Table 4](#)). Scores (defined by a partial credit scoring system) will be assigned to each category based on the desirability of the treatment selection and be analyzed as means and standard deviations (SD) for REVEAL™ and SOC arms. The narrowest spectrum antibiotic to which an isolate is susceptible is the most desirable treatment. Comparisons between the arms will be made using the t-test. The proportion of bacteremia cases receiving over, under and optimal treatment will

be compared between REVEAL™ vs SOC arms based on Chi-squared test. All tests will use a p-value <0.05 with a two-sided test. Details will be described in the SAP.

A pairwise ordering regression²¹ will be used for the ordinal DOOR outcome to adjust for additional covariates. The dependent variable for this analysis will be the observed DOOR level at Day 30. The variable of interests will be use of REVEAL™ vs SOC. Other independent variables such as, but not limited to, randomization strata, immunocompromised status, duration of hospitalization, subject age, gender, and source of bacteremia (urinary/non-urinary) will be adjusted in the model. Logistic regression adjusting for severity of illness and source of bacteremia will be employed to evaluate death at day 30. The Kaplan-Meier method will be used to estimate the survival curves of the time to first antibiotic modification outcome, and the log-rank test will be used to compare the curves between the arms. A proportional hazard model will be used to adjust for clinical factors (e.g., comorbid conditions, severity of illness, and source of bacteremia) to evaluate the time to first antibiotic modification outcome.

Treatment interactions with severity of illness based on the source of bacteremia and the qPitt will be evaluated to inform subgroup analyses. Subgroup analyses will be performed to evaluate the rapid testing method among subjects 1) across geographic locations, 2) whose isolates have different phenotypic resistance patterns, 3) with infections due to on-panel Gram negative species (species included in the REVEAL™ panel), and 4) whose blood cultures turned positive during day vs. night shift. Details regarding subgroup analysis will be included in the SAP.

Endpoints could be missing for subjects who are lost to follow-up or who are missing information in their MR or other hospital document. The effect that any missing data might have on results will be assessed using the inverse probability weighting algorithm to adjust for potential selection bias. The sensitivity analyses including available data and assumption of worst and best case scenarios will be used to check the robustness of the results.

10.3 Planned Interim Analysis

Details of all planned statistical analyses including the interim analyses will be described in the SAP.

The core protocol team will receive monthly reports monitoring study accrual, study conduct, and completeness of eCRFs.

There is no planned interim efficacy analysis involving a test of the primary endpoint. When at least 50% of subjects have been enrolled and at least 30 days for follow-up have elapsed, 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 study.²² PIPS will be created for the primary endpoint based on the data collected up to the interim time point and conditional on scenarios for data to be collected in the remainder of the study. The proposed timelines can be altered based on the input from the Data and Safety Monitoring Board (DSMB). The Statistics and Data Management Center (SDMC) will conduct these analyses and compile the reports for the DSMB.

10.3.1 Data and Safety Monitoring Board (DSMB)

The FAST trial will be reviewed at least annually by a DSMB. The DSMB membership will be composed of investigators and statisticians that are not currently associated with the ARLG or the FAST protocol. The DSMB will review accumulating data from FAST by treatment arm to ensure validity and integrity of the trial and make a benefit-risk assessment.²³ Safety events will not be followed or recorded as deleterious events from REVEAL™ are not expected. The DSMB will review study progress and focus on data quality, enrollment, and implementation of the SOC and REVEAL™ strategies. The study statisticians will prepare a report for the DSMB that will include baseline summaries, data quality and completeness, and will address issues concerning viability and appropriate execution of the protocol such as accrual and invalid or unobtainable results via either SOC or REVEAL™ by site and by organism. The DSMB will make recommendations to the ARLG Executive Committee regarding trial continuation.

11 ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will maintain appropriate research records for this trial, in compliance with Section 4.9 of ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. Each site will permit authorized representatives of the sponsor(s), US National Institutes of Health – Division of Microbial and Infectious Diseases (DMID), and national and local regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a study necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, and subject files and records kept at the laboratories.

12 QUALITY CONTROL AND QUALITY ASSURANCE

The Duke Clinical Research Institute (DCRI) will implement a Project Management Plan (PMP) to define principles that will result in best clinical research practice in compliance with the overall goals of the trial.

As specified in the PMP, the DCRI will transfer site management, site monitoring, and medical monitoring activities to a Contract Research Organization (CRO) with in-country capabilities. The CRO partner is responsible for implementing quality assurance (QA) and quality control (QC) activities and the DCRI will remain responsible for overseeing these activities as detailed in the PMP. The CRO will implement a Monitoring Plan to ensure protocol training, data quality and data security at participating sites are being undertaken.

Following local standard operating procedures (SOPs) for quality management, and the study-specific laboratory manual, each participating site is responsible for conducting routine QA and QC activities to internally monitor study progress and protocol compliance. The site PI will provide direct access to all study-related sites, source data/data collection forms, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by regulatory authorities. The site PI will ensure all study personnel are appropriately trained and applicable documentations are maintained on site and sent to the delegated CRO partner for review and filing. Following the above mentioned quality plan, site monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Following the data management plan, quality control procedures will be implemented, beginning with the data entry system, and data quality control checks will be generated and run on the database. Any missing data or data anomalies will be communicated to the participating site(s) for clarification and resolution. The DCRI will provide direct access to the dataset for the purposes of monitoring, and auditing by the sponsor, and inspection by local and foreign regulatory authorities.

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

The investigator will ensure that the study will be conducted in accordance with all applicable national, regional, and local regulations. The study does not involve direct interaction with human subjects, and all outcome data will be obtained as part of routine clinical care.

The purpose of this study is not to test the REVEAL™ performance characteristics, but rather to evaluate whether the use of this assay in combination with local AS programs will lead to improvement in subjects' clinical outcomes. A waiver of informed consent from the site's reviewing Independent Ethics Committee (IEC) will be requested.

13.1 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

Each participating institution must provide for the review and approval of this protocol by an appropriate IRB/IEC registered with the US government's Office of Human Research Protections (OHRP). Any amendments to the protocol must also be approved by the IRB/IEC before they are placed into use. In both the US and in other countries, only institutions holding a current US Federal-Wide Assurance issued by OHRP may participate.

13.2 Waiver of Informed Consent

A waiver of informed consent will be requested, consistent with local and national regulations. If local and/or national regulations do not allow a waiver of consent, a locally approved consent process will be utilized.

13.3 Exclusion of Special Populations

Fetuses will not be included, as their blood cultures are not obtained during routine clinical care. Other vulnerable populations such as neonates, pregnant women, children, prisoners, or institutionalized individuals will not be selectively recruited/excluded. Enrollment of pediatric subjects is not required if it is not feasible at a study site.

13.4 Subject Confidentiality and Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study and may be used for ad hoc secondary analyses. These data will be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures/access, accidental/unlawful destruction, or accidental loss/alteration will be put in place. Sponsor personnel whose responsibilities require access to personal data will agree to keep the identity of participating subjects confidential.

Subject 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 in addition to the clinical information relating to participating subjects.

Database access will be limited to study personnel who are issued a unique user identification and password. Data will be entered at each site by study personnel. 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 unauthorized third party without prior written approval of the sponsor. Study records may be reviewed in order to meet international, national, regional, or local regulations. Reviewers may include regulatory agencies, the sponsor, IRB/IEC, the DCRI, or the NIH.

14 DATA HANDLING AND RECORD KEEPING

14.1 Data Management Responsibilities

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

The site staff who will be entering data into the EDC 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 persons who own the user identification and passwords access the system using their own unique access codes. Access codes are nontransferable. 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.

14.2 Data Capture Methods

This study will use the RAVE electronic data capture system.

14.3 Types of Data

Types of data include demographics, medical history, blood culture isolate identification and AST, information from medical records, and antibiotic treatment.

14.4 Study Records Retention

Study records are to be retained per local or national regulations. At a minimum, study records and documents pertaining to the conduct of this study will be kept for a minimum of 6 years after final reporting and/or publication of primary manuscript.

At the end of the study, an anonymized copy of the database will be stored in the ARLG data repository for future use.

14.5 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol/GCP requirements. The noncompliance may be on the part of either the investigator or the study site staff. It is the responsibility of the site to use continuous vigilance to identify deviations. Post-randomization identification of unevaluable subjects as detailed in Section [10.2](#) is not considered a protocol deviation.

Each investigator must adhere to the study protocol as detailed in the study protocol document. Each investigator will be responsible for enrolling only those subjects who have met all protocol eligibility criteria.

According to ICH/GCP sections 4.5.2 through 4.5.4, the following should be noted:

4.5.2: “The investigator should not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), change of telephone number(s)).”

4.5.3: The investigator or designee should document and explain any deviation from the approved protocol.

Instructions for reporting subject-specific protocol deviations in RAVE can be found in the eCRF Instructions.

15 PUBLICATION POLICY

Following completion of the study, the investigator may publish the results of this research in a scientific journal under the oversight of the ARLG Publications Committee.

The ARLG Publications Committee comprises representatives of the network cores, thought-leaders, SDMC, and is responsible for generation and coordination of the publications that report scientific findings of the network. All public presentations (abstracts, manuscripts, slides and text of oral/other presentations, and text of any transmission through any electronic media) by participating investigators, participating institutions, SDMC, and ARLG that use ARLG data and are intended to represent the ARLG or are supported by the ARLG will be reviewed by the Publications Committee per the Publications Committee charter and must include the following statement **“Research reported in this publication was supported by the National Institute of Allergy And Infectious Diseases of the National Institutes of Health under Award Number UM1AI104681. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.”**

The Publications Committee guarantees that the study results are presented by experts in the field that have working knowledge of the study design, implementation, data synthesis/analysis, and interpretation. The committee goals are to ensure that any confidential or proprietary information is protected, and that all appropriate statistical analyses have been included.

The ARLG Publications Committee will adhere to the trials registration policy adopted by the International Committee of Medical Journal Editors (ICMJE) member journals. This policy requires that all applicable clinical trials be registered in a public trials registry such as [ClinicalTrials.gov](https://clinicaltrials.gov), which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. It is the responsibility of the PI to register this trial in an acceptable registry. Any clinical trial starting enrollment after 01 July 2005 must be registered either on or before the onset of subject enrollment.

The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention/comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Studies designed for other purposes, such as to study pharmacokinetics/major toxicity (e.g., Phase 1 trials), would be exempt from this policy.

All investigators funded by the NIH must submit or have submitted for them to the National Library of Medicine's PubMed Central an electronic version of their final, peer-reviewed manuscripts upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication. The NIH Public Access Policy ensures the public has access to the published results of NIH-funded research. It requires investigators to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication. Further, the policy stipulates that these papers must be accessible to the public on PubMed Central no later than 12 months after publication. Refer to: <http://publicaccess.nih.gov/>

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17 APPENDIX A – SCHEDULE OF ACTIVITIES

Table 6. Schedule of Activities

Activity	Screening	Enrollment/baseline (Day 0)	Day 1	Day 2	Day 3	Day 30
Record date & time of gram stain result	X					
Evaluation of inclusion/exclusion criteria	X					
Randomization		X				
Perform AST based on assigned arm ¹		X				
Record demographics		X ²				
Record medical history		X ²				
Record components of qPitt		X ²				
Record comfort care		X ²				
Record antibiotic administration or other medication details		X ²	X ²	X ²	X ²	
Record admission information		X ³				
Record source of bacteremia		X ²	X ²	X ²	X ²	X ⁴
Record results of blood culture organism identification			X ²	X ²	X ²	X ⁴
Record results of AST			X ²	X ²	X ²	X ⁴
Record AS provider escalation/de-escalation recommendation			X ²	X ²	X ²	
Record date of discharge						X
Record DOOR events/outcomes						X
Record readmission occurrence						X

¹ REVEAL™ AST must be initiated within 16 hours after the blood culture bottle is flagged positive.

² Data can be recorded in RAVE for a subset of Day 0 data and Day 1, 2, and 3 time points at the Final Visit by reviewing the MR.

³ ICU status must be collected and record in RAVE at Day 0 for randomization

⁴ Including results from Day 4 up to Day 30.