Protocol: INVEST

STATISTICAL ANALYSIS PLAN

EARLY ORAL STEP-DOWN ANTIBIOTIC THERAPY VERSUS CONTINUING INTRAVENOUS THERAPY FOR UNCOMPLICATED GRAM-NEGATIVE BACTERAEMIA (THE INVEST TRIAL)

Intervention: Oral Fluoroquinolones or Oral Trimethoprim-Sulfamethoxazole

Indication: Gram-negative Bacteraemia

Date: 16-Mar-2026

Principal Investigator:
Professor David Lye
Senior Consultant, Department of Infectious Diseases, Tan Tock Seng Hospital (TTSH)
Group Director (Research), Communicable Diseases Agency, Singapore

Trial Statistician:
Nabilah Rahman
Senior Biostatistician
Singapore Clinical Research Institute (SCRI)
Consortium for Clinical Research and Innovation, Singapore (CRIS)

APPROVAL

The undersigned hereby declare that they have prepared/examined the Statistical Analysis Plan and agree to its form and content. In addition, they confirm that to the best of their knowledge the Statistical Analysis Plan contains all information relevant for the conduct of Statistical Analysis of the study.

Prepared by: Trial Statistician

18-Mar-2026

Sign *Date*

Nabilah Rahman, Senior Biostatistician, SCRI

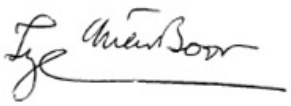
Reviewed by:

18-Mar-2026

Sign *Date*

Dr Mihir Gandhi, Head – Biostatistics, SCRI

Approved by: Principal Investigator



18-Mar-2026

Sign *Date*

Professor David Lye, Senior Consultant, TTSH & Group Director (Research), CDA

REVISION HISTORY

Version	Author	Date of Implementation	Description of Modification
2.0	Nabilah Rahman	16-Mar-2026	Pg 7 Introduction *Introduction improved.* Pg 7-11 Summary of Study Objectives and Endpoints *For secondary objective 3, added hospital in the home in the definition on total index hospitalisation to align with secondary objective 7.* *For secondary objective 4, endpoint changed to align to a similar study.* *For secondary objective 8, typo in endpoint corrected.* *For secondary objective 9, 10 and 11, details added to endpoints.* *Subgroup "Empiric therapy effectiveness" renamed to "Empiric therapy in-vitro effectiveness".* *Subgroup "Index pathogenic bacterial type" added in exploratory objective 2.* *Subgroup "Bacteraemia isolate at baseline" removed due to similarities to "Index pathogenic bacterial type"* Pg 11-17 Definitions of Outcomes *Details added for clarity, including definition of discontinuation.* Pg 12 Days Alive and Free from Antibiotics *Definition changed to align to a similar study.* Pg 12 Special Interest Treatment Related Adverse Events *Definition of liver function test abnormalities or acute kidney injury added. Description of monitoring of special interest AEs simplified.* Pg 14 EQ-5D Utility Value and EQ-VAS Value *Updated details on deriving utility values.* Pg 19 Study Population *Operational details removed.* Pg 24 Per-Protocol Population *Indicated source of protocol deviation data.*

			Pg 24 Safety Population *Time frame of receiving study drug to be included in safety population changed from "on first day" to "within 24 hours" to account for those randomised late in the night and hence receiving study drug the following day.* Pg 25 General Considerations *Added R software.* Pg 26-30 Final Analysis *Updated statistical analysis method to reflect changes in the following sections* - *Summary of Study Objectives and Endpoints* - *Definitions of Outcomes* *Empiric therapy in-vitro effectiveness subgroup updated to include interpretations details.* *Added alternative definition of multidrug-resistant and source of data for resistance of index Gram-negative bacteria.* *Index pathogenic bacterial type added as covariate for primary sensitivity analysis and other sensitivity analyses. Added decision in the event of collinearity between source of bacteremia and Index pathogenic bacterial type.* Pg 30-31 Safety Analysis *Improved section for clarity* *Pg Other Analysis* *Indicated that descriptive statistics will be reported for index pathogenic bacterial type.* Pg 33 Timing of Final Analysis *This section is added for clarity of expected analysis schedule.*

TABLE OF CONTENTS

List of Mock-Up Tables

List of Mock-Up Figures

List of Mock-Up Listings

1 Introduction

Gram-negative bacteraemia is the leading cause of healthcare-related bloodstream infections. Existing practice guidelines for treating Gram-negative bacteraemia include recommendations for antibiotic treatment duration but not the optimal route of antibiotic administration. Intravenous (IV) antibiotic therapy is the initial route of treatment for the majority of patients with Gram-negative bacteraemia. It is unclear whether outcomes will be non-inferior when patients convert to oral therapy from IV therapy after appropriate clinical response has been observed. The advantages of switching to oral therapy are evident, including no risk of catheter-associated adverse events, enhanced quality of life (QoL) with no discomfort resulting from IV catheters, reduced length of stay (LOS) in hospital and lower healthcare cost.

Whilst there are randomised controlled trials (RCTs) on duration of antibiotic therapy for Gram-negative bacteraemia (e.g. BALANCE, NCT02261506), no RCT has studied the efficacy of early oral stepdown therapy in Gram-negative bacteraemia within 72 hours of index blood culture collection. INVEST aims to fill knowledge gaps on oral stepdown therapy among clinically stable inpatients with uncomplicated Gram-negative bacteraemia. The study will evaluate clinical efficacy and economic impact of early stepdown to oral antibiotics within 72 hours from index blood culture over continuing IV therapy (for at least 24 hours post-randomisation).

This document intends to provide a detailed description of the statistical analysis plan for final analysis. Analysis plans for health economics outcomes will be covered in a separate document. Corresponding mock-up table, figure and listing (TFL) shells can also be found in this document. The final TFL may change without changes in reporting of the essential statistics.

2 Study Objectives and Endpoints

2.1 Summary

Objectives	Measures	
	Endpoints	Timepoint(s)
Primary objective		

To assess whether early oral stepdown arm is non-inferior to continuing IV therapy arm in terms of post-randomisation all-cause mortality. Hypothesis: The percentage of all-cause mortality in the early oral stepdown arm is at most 6% higher compared to the continuing IV therapy arm.		Percentage of all-cause mortality	Up to Day 30
Secondary objectives			
1	To compare post-randomisation all-cause mortality between early oral stepdown arm and continuing IV therapy arm.	Percentage of all-cause mortality	Up to Day 14, Up to Day 90
2	To compare survival time between early oral stepdown arm and continuing IV therapy arm from point of randomisation.	Hazard rate of survival	Up to Day 90
3	To compare post-randomisation duration of IV antibiotic therapy during total index hospitalisation (including outpatient parenteral antibiotic therapy (OPAT) and hospital in the home) between early oral stepdown arm and continuing IV therapy arm.	Median number of days on IV antibiotics therapy	Up to hospital discharge, up to Day 90
4	To compare post-randomisation total days alive and free from antibiotics between early oral stepdown arm and continuing IV therapy arm.	Median total days alive and free from antibiotics (both oral and IV) for surviving subjects Median total days alive and free from IV antibiotics for surviving subjects Median proportion of days alive and free from antibiotics (both oral and IV) for surviving	Up to Day 90 Up to Day 90 Up to Day 90

		subjects who discontinued Median proportion of days alive and free from IV antibiotics for surviving subjects who discontinued Median proportion of days alive and free from antibiotics (both oral and IV) for non-surviving subjects Median proportion of days alive and free from IV antibiotics for non-surviving subjects	 Up to Day 90 Up to Day 90 Up to Day 90
5	To compare post-randomisation special interest treatment related adverse events (AEs) between early oral stepdown arm and continuing IV therapy arm.	Percentage of subjects with each special interest AEs	Up to Day 90
6	To compare post-randomisation change in treatment strategy due to the reasons below, between early oral stepdown arm and continuing IV therapy arm: a) An adverse event deemed by the treating doctor to be of sufficient severity to change treatment strategy b) Presumed lack of efficacy of treatment strategy according to the judgement of treating doctor	Percentage of subjects who experienced change in treatment strategy Percentage of subjects who experienced change in treatment strategy due to adverse event Percentage of subjects who experienced change in treatment strategy due to presumed lack of efficacy	Up to Day 30 Up to Day 30 Up to Day 30

7	To compare total index hospitalisation time (including OPAT and hospital in the home) between early oral stepdown arm and continuing IV therapy arm.	Hazard rate of discharge alive	Up to Day 90
8	To compare post-randomisation number of days alive and not in hospital (including OPAT) between early oral stepdown arm and continuing IV therapy arm.	Median days alive and not in hospital (including OPAT)	Up to Day 90
9	To compare readmission (for any cause) between early oral stepdown arm and continuing IV therapy arm.	Percentage of subjects who were readmitted (for any cause)	Up to Day 90
10	To compare extended index hospitalization (> 14 days from randomisation) between early oral stepdown arm and continuing IV therapy arm.	Percentage of subjects who experienced extended index hospitalisation (> 14 days from randomisation)	Up to Day 90
11	To compare readmission (for any cause) or extended index hospitalisation between early oral stepdown arm and continuing IV therapy arm.	Percentage of subjects who were readmitted (for any cause) or experienced extended index hospitalisation	Up to Day 90
12	To compare QoL between early oral stepdown arm and continuing IV therapy arm.	Mean EQ-5D utility value Mean EQ-VAS value	Day 90 Day 90
Exploratory objectives			
1	To determine whether subjects in early oral stepdown arm have better overall clinical outcome than subjects in continuing IV therapy arm.	Probability of better desirability of utcome ranking (DOOR)	Day 30
2	To assess whether early oral stepdown arm is non-inferior to continuing IV therapy arm in terms of post-randomisation all-cause mortality within the following subgroups: a) Country grouped by region b) Age (< 70, ≥ 70) c) Gender (female, male)	Percentage of all-cause mortality	Up to Day 30

	d) Source of bacteremia at baseline (UTI, non-UTI) e) Empiric therapy *in-vitro* effectiveness (effective, not effective, unknown effectiveness) f) Resistance of index Gram-negative bacteria (multidrug-resistant, non-multidrug-resistance, unknown) g) Index pathogenic bacterial type (*Enterobacterales*, non-fermenters, others)		

2.2 Definitions of Outcomes

All-Cause Mortality
All-cause mortality is the primary outcome. A subject is determined to have experienced X-day all-cause mortality if there is a death date documented and the death date does not exceed X days from subject's date of randomisation. Fourteen-day, 30-day and 90-day all-cause mortality will be determined, with 30-day all-cause mortality being the primary endpoint of interest. Data for this outcome will be obtained from the REDCap study exit form.

Survival Time (Time to Death from Point of Randomisation)
Survival time in days will be calculated by taking a difference between death date and date of randomisation and subsequently adding 1 day. If subject has died, the death date will only be used if it does not exceed 90 days from date of randomisation. If subject has not died within 90 days from date of randomisation, survival time will be censored at Day 90. If subject discontinued within the 90 days from point of randomisation, survival time will be censored at date of last contact. A subject is said to have discontinued if he/she exited the trial due to the following reasons: lost to follow-up, withdrew consent, investigator's decision or study termination. Data for this outcome will be obtained from the REDCap randomisation form and study exit form.

Duration of IV Antibiotics Therapy
Duration of IV antibiotics therapy will be computed for subjects' total index hospitalisation (including OPAT and hospital in the home), stratified by subjects'survival status. For duration of IV antibiotics therapy until index hospital discharge (exclude OPAT), subject who experienced inpatient death will be grouped in the non-surviving group. For duration of IV antibiotics therapy until Day 90, subjects who died before or on Day 90 will be grouped in the non-surviving group. Counting of therapy duration will start from date of randomisation (i.e. empiric IV therapy will not be included). A subject would be considered

to be undergoing IV antibiotics therapy as long as subject has not completed prescribed regimen, even on days when subjects missed IV dose for index infection. The following formula will be used to compute the endpoint:

- Until hospital discharge (exclude OPAT)
  Duration of IV antibiotics therapy = {min[max(prescribed IV antibiotic end dates), date of index hospital discharge)] – min(prescribed IV antibiotic start dates) + 1} – (number of gap days between any IV regimen not because of omission)
- Until Day 90
  Duration of IV antibiotics therapy = {min[max(prescribed IV antibiotic end dates), date of Day 90)] – min(prescribed IV antibiotic start dates) + 1} – (number of gap days between any IV regimen not because of omission)

As IV therapy is most commonly administered while inpatient or during an OPAT visit, last date of contact and death date will be determined as antibiotic end date if subject discontinued or died before completing prescribed IV antibiotics. The dates in the formulae will be obtained from the REDCap randomisation form, prescribed study drug(s) form, antibiotic history form, before discharge form and study exit form.

Days Alive and Free from Antibiotics

To calculate total number of days alive and free from antibiotics, the days on which subject is on antibiotics regimen (regardless of indication) within 90 days post-randomisation will be subtracted from the total number of days observed in the subject. Total number of days observed for subjects who did not discontinue will be 90 days, counting from date of randomisation. For subjects who discontinued (including death) within 90 days post-randomisaiton, proportion of days alive and free from antibiotics will be reported instead. Discontinuation date and death date will be used to count the number of days observed to be used as the denominator for proportion. Subjects will be pooled in the following mutually exclusive manner for analysis: (1) Surviving group and completed 90 days, (2) surviving group but discontinued, (3) non-surviving group. Antibiotics-free status will be determined for (i) all antibiotics (both oral and IV) and (ii) IV antibiotics. Data for this outcome will be obtained from the REDCap randomisation form, prescribed study drug form, antibiotic history form and study exit form.

Special Interest Treatment Related Adverse Events

Special interest AEs is referred to as targeted/solicited AEs in the protocol. The following AEs are special interest AEs:

1. *C. difficile*-associated diarrhoea
2. Peripherally inserted central catheter and other central venous catheter complications
3. Liver function test abnormalities or acute kidney injury
   For criteria "AST or ALT > 3 × ULN and TBL > 2 × ULN or prothrombin time and international normalised ratio (PT-INR) > 1.5, if PT-INR measured (potential Hy's

law)", the case must be reported as an SAE (if baseline AST or ALT is ≤ ULN). If baseline AST or ALT is > ULN, the case that meets the following criteria must be reported as an SAE. AST or ALT > 3 × increase from baseline AST or ALT and TBL > 2 × increase from baseline TBL.

The following criteria will be used when assessing kidney injury:

- Grade 1: Creatinine > 1.5 to 2× baseline and < 350 µmol/L
- Grade 2: Creatinine > 2 to 3× baseline and < 350 µmol/L
- Grade 3: Creatinine > 3× baseline and/or > 350 µmol/L
- Grade 4: Dialysis (if previously not on dialysis)

If study drug regimen is ongoing, all special interest AEs will be monitored . If study drug regimen has been completed, only *C. difficile*-associated diarrhoea will be monitored up until the end of study at Day 90. An adverse event with 'possibly related' or 'related' relationship with treatment is considered a treatment-related AE.

For each treatment-related special interest AE, a binary variable will be created to indicate whether subject experienced the AE from date of randomisation to Day 90. Incidence of special interest AEs will be obtained from the REDCap AE form, under solicited AE.

Change in Treatment Strategy

Change in treatment strategy is defined as any escalation of treatment post-randomisation due to presumed lack of efficacy or adverse event. The following would not be considered as "change in treatment strategy":

1. Administering of another antibiotic on top of the randomised study drug regimen due to development of a secondary infection
2. Subject's non-compliance to definitive therapy of study drug post-randomisation
3. Additional antibiotics prescribed to subject days after definitive therapy of study drug has ceased
4. De-escalation to stepdown oral therapy in continuing IV therapy arm 24 hours after post-randomisation

A binary variable indicating whether subject experienced change in treatment strategy will be created based on the information in the antibiotic history form. This binary variable will be further differentiated by reason for change in treatment strategy (i.e. presumed lack of efficacy or adverse event). Reason for change in treatment strategy can be found in the REDCap adherence check form.

Total Index Hospitalisation Time (Time to Discharge Alive)

Discharge is defined as discharged from total index hospitalisation. Total index hospitalisation include index hospitalisation, OPAT and hospital in the home. Counting of days for the outcome starts from date of randomisation up to latest discharge from index

hospitalisation, OPAT and hospital in the home (i.e. difference between latest discharge date and date of randomisation with addition of 1 day), taking into account competing risk of mortality. IV treatment regimen end date for the index bacteraemia will be used as proxy for discharge date from OPAT and hospital in the home. If subject has not been discharged by Day 90, total index hospitalisation time will be censored at Day 90. If subject discontinued within the 90 days, total index hospitalisation time will be censored at date of last contact. Data for this outcome will be obtained from the REDCap randomisation form, before discharge form, study exit form, end of treatment form and antibiotic history form.

Number of Days Alive and Not in Hospital
Subject is considered to be not in hospital if he/she is not inpatient and discharged from OPAT. The following formula will be used to compute the endpoint: (discharge date 1 – admission date 2 + 1) + (discharge date 2 – admission date 3 + 1) + … + (discharge date X – min(death date, date at Day 90) +1). If subject died during index hospitalisation or OPAT, 0 days will be assigned to the subject's number of days alive and not in hospital. IV regimen start and end date will be used as proxy to determine subject's OPAT days. The dates in formulae will be obtained from the REDCap before discharge form, readmission form, end of treatment form and antibiotic history form.

Readmission (For Any Cause)
Readmission is defined as a new hospitalisation for any cause which occurs after discharge from the index hospitalisation. Using a binary variable, subjects will be indicated to have been readmitted if at least one readmission date is recorded from index hospitalisation discharge to Day 90. Data for this outcome will be obtained from REDCap readmission form.

Extended Index Hospitalisation (> 14 Days from randomisation)
Extended index hospitalisation is defined as > 14 days of hospital LOS starting from the day of randomisation (i.e. continued hospitalisation after 14 days). OPAT will not be included as LOS is not incurred there. LOS will be computed using the following formula: min(index discharge date, date at Day 90) – date of randomisation + 1. A binary variable indicating whether subject had extended index hospitalisation will be generated. Data for this outcome will be obtained from the REDCap randomisation form, before discharge form, readmission form.

Readmission or Extended Hospitalisation
Readmission and extended hospitalisation have been defined above. A binary variable indicating whether a subject was either readmitted or had extended index hospitalisation will be created.

EQ-5D Utility Value and EQ-VAS Value
The EQ-5D utility value and EQ-VAS value will be used to assess subject's QoL. The EQ-5D utility value will be derived from EQ-5D-5L questionnaire. The utility value reflects how

good a health state is based on the preferences of the general population. The EQ-VAS quantifies a respondent's perception of their overall current health on a range of 0 (the worst health one can imagine) to 100 (the best health one can imagine). The EQ-5D-5L questionnaire comprises of a short descriptive system questionnaire and EQ-VAS. The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five response levels indicating the severity level of problems experienced.

EQ-5D-5L country-specific value set will be used to derive the utility value of subjects. If EQ-5D-5L value set is not available for a country, the utility value of subjects recruited from the country will be derived from 5L to 3L crosswalk 'mapping'. The Singapore value set for EQ-5D-5L will be used to derive the utility value for subjects recruited from Singapore sites [1]. Data for this outcome will be obtained from the REDCap EQ-5D-5L form and the EQ-5D-5L (VAS) form.

Desirability of Outcome Ranking (DOOR)

DOOR is a composite ordinal outcome with five ranks. Rank 1 represents the most desirable outcome and rank 5 represents the least desirable outcome. In order to assign DOOR ranks to each subject, subjects are first given an event score of 0 to 3 based on whether subject experienced these events: (1) clinical failure, (2) infectious complications and (3) AEs or serious adverse events (SAEs) leading to study drug discontinuation. If a subject experienced none of the three events, he/she will be assigned event score of 0. If subject experienced all of the events, he/she will be assigned event score of 3. The definitions of clinical failure and infectious complications are as follows:

Clinical Failure in DOOR	**Infectious Complications in DOOR**
A subject will be considered to have experienced clinical failure if he/she satisfies one or more of the following index infection related events: o Extended duration of active antibiotics beyond 7–14 days, depending on planned duration of original regimen; o Addition of a rescue antibiotic including switching to an alternate, non-study antibiotic; o Additional unplanned therapeutic interventions	A subject will be considered to have experienced infectious complications if he/she satisfies one or more of the following index infection related events: o Bloodstream relapse due to the same index Gram-negative bacteria occurring any time between the completion of study drug intervention period and Day 30; o Distant seeding (i.e. growth of index Gram-negative bacteria in a distant sterile site different from the original source of infection) occurring any time between completion of study drug intervention period and Day 30; o Local suppurative complication (e.g. renal abscess in pyelonephritis,

	empyema in pneumonia) that was not present at the time of randomisation and occurring any time between completion of study drug intervention period and Day 30

On top of the event score, QoL measure based on functional bacteremia outcome score and all-cause mortality at Day 30 are also required to determine DOOR. All-cause mortality has been defined elsewhere in this document. Functional bacteraemia outcome score ranges from 0-7, with 0 being the least desirable and 7 being the most desirable. The change in functional bacteraemia outcome score measured at last day of study drug treatment from baseline functional bacteraemia outcome score will be used to tiebreak subjects with the same initial DOOR rank derived from the event score and mortality alone. The functional bacteraemia outcome score is assigned based on the following subject status:

Functional Bacteraemia Outcome Scoring System as Proxy for QoL	
7	Out of hospital; basically healthy; able to complete daily activities and has no healthcare interaction* since discharge from the index hospitalisation in the last 7 days
6	Out of hospital; moderate signs or symptoms of disease; unable to complete daily activities OR has required 1-2 healthcare interactions* since discharge from the index hospitalisation over the last 7 days
5	Out of hospital; significant disability; requires a high level of care and assistance daily OR has required more than two healthcare interactions* since discharge from the index hospitalisation over the last 7 days
4	Hospitalised but not requiring ICU
3	Hospitalised in ICU
2	Accommodated in a long-term ventilator unit
1	On palliative care in terminal phases of life (in hospital or at home)
0	Dead
*Healthcare interactions include home nursing visits, telehealth calls, emergency room visits and office visits.	

The ranking algorithm for DOOR is implemented in the following manner: Using the event score and mortality information, initial DOOR rank is determined based on subjects pooled from both arms. For alive subjects who have an event score of 0-3, initial DOOR rank of 1-4 will be assigned respectively. If the subject is dead, he/she will be assigned final DOOR ranks of 5. Initial DOOR ranks will be reassessed with change in functional bacteraemia outcome score as tiebreaker to derive the final DOOR rank. Change in functional bacteraemia outcome score divided by 10 will be added to initial DOOR rank to provided a temporary

score. Within each initial DOOR rank, subjects with temporary score higher than the minimum temporary score (i.e. subjects with larger improvement in QoL from baseline) in the rank will be re-assigned to a final rank that is one rank better. Subjects would not be reassigned more than once. In this study, DOOR is determined at Day 30. The table below summarises the DOOR scoring system:

Rank	Alive	How many of: 1) Clinical failure 2) Infectious complications 3) AEs or SAEs leading to study drug discontinuation	Quality-of-life
1	Yes	0 of 3	Tiebreaker based on change in functional bacteremia outcome score from baseline
2	Yes	1 of 3	
3	Yes	2 of 3	
4	Yes	3 of 3	
5	No	Any	QoL measure not used
Rank 1 – Alive without any of the following binary (yes/no) components: (1) evidence of clinical failure, (2) an infectious complication, or (3) any SAE or an AE leading to study drug discontinuation Rank 2 – Alive with one of the following binary (yes/no) components: (1) evidence of clinical failure, (2) an infectious complication, or (3) any SAE or an AE leading to study drug discontinuation Rank 3 – Alive with two of the following binary (yes/no) components: (1) evidence of clinical failure, (2) an infectious complication, or (3) any SAE or an AE leading to study drug discontinuation Rank 4 – Alive with all of the following binary (yes/no) components: (1) evidence of clinical failure, (2) an infectious complication, or (3) any SAE or an AE leading to study drug discontinuation Rank 5 – Death			

3 Study Design

INVEST is an international, multi-centre, randomised controlled, open-label, non-inferiority, phase 4 clinical trial which aims to assess clinical efficacy and economic impact of early stepdown to oral antibiotics (within 72 hours from index blood culture collection) versus continuing standard of care IV therapy (for at least another 24 hours post-randomisation). The study aims to recruit a total 720 clinically stable / non-critically ill patients with uncomplicated Gram-negative bacteraemia to be randomly assigned to either early oral stepdown arm or continuing IV therapy arm in a 1:1 allocation ratio. The non-inferiority margin is 6%. Due to the difference in administration routes between the standard (i.e.

continuing IV therapy) and intervention arms (i.e. early oral stepdown), the study has to be an open-label trial.

3.1 Study Drug

The study drugs in this trial are routinely used in clinical practice and will be dispensed from hospital pharmacy as per site institutional practice.

The early oral stepdown arm will receive fluoroquinolones or trimethoprim-sulfamethoxazole. Ciprofloxacin is the most common fluoroquinolone class of antibiotics for treatment of Gram-negative bacteraemia. Subjects on ciprofloxacin may not take concomitant drugs which can cause prolongation of QT interval (e.g. class IA or class III antiarrhythmics). The following recommended dosing rule will be used taking into account subject's renal function:

		Body Weight < 70 kg	**Body Weight ≥ 70 kg**
Ciprofloxacin	**Normal renal function or creatinine clearance > 50 mL/min**	500 mg every 12 hours	750 mg every 12 hours
	Creatinine clearance 30-50 mL/min	500 mg every 12 hours	
	Creatinine clearance 5-29 mL/min	500 mg every 24 hours	
	Haemodialysis or peritoneal dialysis	500 mg every 24 hours (after dialysis)	
Trimethoprim-sulfamethoxazole	**Normal renal function or creatinine clearance > 30 mL/min**	<u>Trimethoprim component</u> 5 mg/kg every 12 hours <u>Tablets</u> Maximum of 2 DS every 8 hours for creatinine clearance > 30 mL/min, every 12 hours for normal renal	
	Creatinine clearance > 15-30 mL/min	<u>Trimethoprim component</u> 2.5 mg/kg every 12 hours <u>Tablets</u> Reduce dose to ~50% of usual recommended dose*	
	Creatinine clearance < 15 mL/min	<u>Trimethoprim component</u> 2.5 mg/kg every 24 hours	

		Tablets Reduce dose to ~25 to 50% of usual recommended dose*
	Haemodialysis or peritoneal dialysis	Trimethoprim component 2.5 mg/kg every 24 hours (after dialysis)
*Possible recommended dose: (a) 2 SS tablets (1 DS tablet) every 24 hours or 3 times per week, (b) 2 SS tablets (1 DS tablet) every 12 hours, (c) 4 SS tablets (2 DS tablets) every 12 hours and (d) 4 SS tablets (2 DS tablets) every 8 hours. SS: Single strength trimethoprim-sulfamethoxazole (80 mg / 400 mg). DS: Double strength trimethoprim-sulfamethoxazole (160 mg / 800 mg).		

The antibiotics and antibiotic doses for continuing IV therapy arm will be determined by the subject's treating doctor. The IV antibiotic options will be based on their assessment of the 'best available treatment'. The treating doctor will also take into consideration subject's renal function when determining the IV antibiotics dosage and frequency.

The recommended treatment duration is 7 days of active antibiotics (including empiric therapy), although treatment regimen may be longer than 7 days due to regimen extension or requirement for prolonged regimen as clinically indicated. For the continuing IV therapy arm, the treating doctor may make a discretionary decision to convert subject to oral antibiotics therapy after at least 24 hours of IV therapy post-randomisation.

3.2 Study Population

As Gram-negative bacteraemia infections can be seen in a large range of clinical situations, the trial will recruit patients from all inpatient specialties in multiple countries.

A non-restrictive list of inclusion criteria will be used in this trial to create a generalisable cohort of subjects recruited to the trial.

Inclusion Criteria

1. ≥ 1 set of blood cultures positive for Gram-negative bacteraemia associated with evidence of infection;
2. Able to be randomised within 72 hours of index blood culture collection;
3. Age ≥ 18 years (≥ 21 in Singapore);
4. Latest Pitt bacteraemia score < 4;
5. Patient or legal representative is able to provide informed consent

Exclusion Criteria

1. Established uncontrolled focus of infection, including but not limited to:
    - Undrained abdominal abscess, deep seated intra-abdominal infection and other unresolved abdominal sources requiring surgical intervention
    - Central nervous system abscess (patients with focal neurology should have cranial CT prior to enrolment)
    - Undrained moderate-to-severe hydronephrosis;
2. Complicated infections, including but not limited to:
    - Necrotising fasciitis
    - Empyema
    - Central nervous system infections and meningitis
    - Endocarditis / endovascular infections;
3. Septic shock as defined by systolic blood pressure < 90 or mean arterial pressure < 70 mmHg despite adequate fluid resuscitation or need for inotropic/vasopressor support;
4. Polymicrobial bacteraemia involving Gram-positive pathogens or anaerobes (defined as either growth of ≥ 2 different microorganism species in the same blood culture, or growth of different species in ≥ 2 separate blood cultures within the same episode [< 48 hours] and with clinical or microbiological evidence of the same source);
5. Bacteraemia is due to a vascular catheter or intravascular materials (e.g. pacing wire, vascular graft) that cannot be removed;
6. Specific Gram-negative pathogens that cannot be effectively treated with fluoroquinolones or trimethoprim-sulfamethoxazole, including but not limited to, *Burkholderia* spp. and *Brucella* spp.;
7. Index Gram-negative bacteraemia with resistance to fluoroquinolones AND trimethoprim-sulfamethoxazole;
8. Hypersensitivity to fluoroquinolones AND sulphur drugs as defined by history of rash, urticaria, angioedema, bronchospasm, circulatory collapse or significant adverse reaction following prior administration;
9. Unable to consume or absorb oral medications for any reason or unsuitable for ongoing IV therapy (e.g. no intravenous access);
10. Severely immunocompromised in the opinion of the treating doctor, including but not limited to, medical conditions such as:
    - Active leukaemia or lymphoma
    - Aplastic anaemia
    - Bone marrow transplant within two years of transplantation or transplants of longer duration still on immunosuppressive drugs or with graft-versus-host disease
    - Congenital immunodeficiency
    - HIV/AIDS with CD4 lymphocyte count < 200
    - Neutropenia or expected post-chemotherapy neutropenia within 14 days from the time of screening, defined as absolute neutrophil count < 500 cells/μL;
11. Women who are known to be pregnant or breast-feeding;

12. Treatment is not with intent to cure the infection (i.e. palliative care);
13. Unable to collect patient's follow-up data for at least 30 days post-randomisation for any reason;
14. Treating doctor deems enrolment into the trial is not in the best interest of the patient;
15. Previous enrolment in this trial

3.3 Withdrawal and Replacement

Enrolled subjects may voluntarily withdraw their consent or be withdrawn by their legal representative at any time and for any reason without penalty.

A subject may also be withdrawn from the trial by the investigator for the following reasons:

- Termination of study
- Any new information becomes available that makes continuing trial participation unsafe

This decision must be discussed with the coordinating investigators.

Subjects who withdraw from the study will not be replaced. Subjects whose randomised treatment is changed due to an AE or treatment failure or an unintentionally fulfilled exclusion criterion will remain in the study for assessment of outcomes.

3.4 Randomisation

Subjects who meet eligibility criteria are randomised at equal allocation (1:1 ratio) to the early oral stepdown arm or continuing IV therapy arm. Permuted blocks of unequal length are used in the randomisation.

Randomisation is stratified by country. The day on which the randomisation occurred is considered as Day 1 of treatment. The allocated arms are not blinded to any party (i.e. open-label).

The randomisation list is prepared in advance by SCRI statisticians and upload to a central randomisation system. The randomisation system is maintained by SCRI research informatics team.

3.5 Sample Size Calculation

In a recent RCT comparing 7 days versus 14 days of antibiotic therapy for uncomplicated Gram-negative bacteraemia, 30-day all-cause mortality occurred in 4.9% of patients in the 7-day duration arm and 4.4% of patients in the 14-day duration arm [2]. In a recent retrospective multicentre study of a propensity score-matched cohort with monomicrobial Enterobacterales bacteraemia, 30-day all-cause mortality was 13.1% for patients who received early oral step-

down therapy and 13.4% for those who continued to receive IV therapy [3]. Accurate estimation of mortality (for this study) is complicated by significant variability in reported mortality of past studies – likely influenced by geography and isolate resistance phenotype. We assumed 30-day mortality of 8% in the standard and intervention arms of this study – determined as the approximate mid-range from the two aforementioned studies [2, 3]. With a 6% non-inferiority margin, a total of 720 patients are needed to achieve 80% power with a one-sided 0.025 α-level after adjustment for 5% drop-out. Based on an expected mortality of 80% under a hypothetical situation where bacteraemic patients received no antibiotic treatment [4, 5], the continuing IV therapy arm treatment would have reduced mortality by 72% (from 80% to 8%). The pre-specified 6% non-inferiority margin requires a 30-day mortality of ≤ 14% in the early oral stepdown arm, which preserves more than 90% of the 72% treatment effect of continuing IV therapy arm needed to conclude non-inferiority. This is in accordance with requirements by U.S. FDA on non-inferiority margin to maintain at least 50% of treatment effect of the standard treatment.

4 Trial Schedule

The full trial schedule can be found in the table below. Trial follow-up timepoints have a window period of 3 days.

Study activity	Screening	Antibiotic intervention			Follow up			As necessary [b]
	-72 hours to Day 1	Day 1-7[a]	Before hospital discharge	End of treatment (window period: 3 days)	Day 14 (±3 days)	Day 30 (±3 days)	Day 90 (±3 days)	
Check eligibility	x							
Informed consent	x							
Demographics	x							
Charlson comorbidity index	x							
Physical examination, complication screening (if suspected)	x		x					x
Randomisation		x						
Study drug[a]		x						
Antibiotic history[c]	x			x[d]		x[d]	x[d]	
Blood cultures[e]								x
Full blood count[f]	x		x					x
C-reactive protein	x		x					x
Renal & liver panel[g]	x		x					x

Adherence check[h]				x[d]				
Adverse event monitoring[i]		x	x	x[d]	x[d,j]	x[d,j]	x[d,j]	
Review mortality status					x[d]	x[d]	x[d]	
Review for development of complications, relapse and distant seeding						x[d]		
Review hospital admission and discharge summaries					x[d]	x[d]	x[d]	
Review health service/ resource utilisation cost[k]							x[d]	
Quality-of-life survey	x			x[d]			x[d]	

a – Recommended duration of active antibiotic treatment (including empiric therapy) is 7 days. Final day of study treatment may be as early as day 4 considering the 72 hours randomisation window, but will typically be between days 5 and 7. Regimen may be extended beyond 7 days if clinically indicated or treating doctor may prescribe a prolonged original regimen of >7 days according to his/her discretion.
b – According to the discretion of clinician if subject is still an inpatient
c – Document all antibiotics taken during this bacteraemia episode including empiric treatment, study drug and any additional antibiotics administered
d – Via telephone interview or home visit by the study team if subject has been discharged and information cannot be obtained via medical records or administrative sources
e – Blood cultures usually ordered if patient is febrile > 38°C in the last 24 hours during bacteraemia episode or if previous blood cultures remain positive or if any secondary infection is suspected
f – Full blood count includes white blood cells, neutrophils, platelets and haemoglobin
g – Renal panel includes sodium, potassium and creatinine; liver panel include alanine transaminase, aspartate transaminase, alkaline phosphatase and total bilirubin
h – Pill count for subjects on oral therapy and documentation of IV antibiotics administered for subjects on IV therapy; subject deemed compliant if ≥ 90% of prescribed antibiotics taken
i – Only AEs deemed by the treating doctor to be related to the study drug (from standard arm or intervention arm) will be documented in the CRF
j – Only targeted AEs will be monitored during the follow-up time points, such as *C. difficile*-associated diarrhoea, catheter-related complications, and liver and kidney function test abnormalities
k – Cost savings/effectiveness analyses will be performed in selected hospital sites

5 Analysis Populations

5.1 Modified Intention-to-Treat Population

All efficacy analyses will be carried out on a modified intention-to-treat (mITT) basis. The mITT population consists of randomised subjects excluding (i) those who did not have Day 30 mortality data, (ii) intervention arm subjects who did not receive any oral fluoroquinolones or oral trimethoprim-sulfamethoxazole post-randomisation and (iii) standard arm subjects who did not receive any IV antibiotics post-randomisation. These subjects will be grouped and analysed as per randomised arm.

5.2 Per-Protocol Population

As supportive analysis, the primary outcome will also be analysed on the per-protocol (PP) population. The PP population consists of subjects included in the mITT population but excluding those with major protocol deviation (PD) which may significantly affect the primary endpoint. The following will be considered as major PDs which may significantly affect the primary endpoint:

1. Administration of at least one dose of incorrect study drug;
2. Study drug compliance of below 90%;
3. Randomisation of ineligible participant

These subjects will be grouped and analysed as per randomised arm. Data on major PDs will be obtained from the central PD tracking log maintained by the Trial Management Group.

5.3 Intention-to-Treat Population

As sensitivity analysis, the primary outcome will also be analysed on the intention-to-treat (ITT) population if there is a difference of least 5% between ITT population size and the mITT population size. In ITT population analysis, subject who is missing mortality at any time point will be considered alive at that particular timepoint.

5.4 Safety Population

Safety analyses will be carried out on a treated basis. The treated population consists of all randomised subjects who continued study treatment (i.e. oral fluoroquinolones, oral

trimethoprim-sulfamethoxazole or IV antibiotics therapy) post-randomisation. These subjects will be grouped and analysed as actually treated:

Treated Arm	Criteria
Early oral stepdown	Subject received either oral fluoroquinolones or oral trimethoprim-sulfamethoxazole within 24 hours of treatment post-randomisation
Continuing IV therapy	Subject received IV antibiotics within 24 hours of treatment

6 Statistical Analysis

6.1 General Considerations

All statistical analyses will be carried out using either SAS version 9.4 or higher (Statistical Analysis System software, SAS Institute, North Carolina, USA) and/or R statistical software (v4.4.3 or later, R Core Team 2021).

Continuous variables will be summarised using descriptive statistics, i.e. mean, standard deviation (SD), median, lower quartile (Q1), upper quartile (Q3), minimum and maximum. Categorical variables will be summarised by frequency and percentage.

6.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics at screening will be presented in a summary table. Categorical variables will be summarised by frequency and percentage, and continuous variables will be summarised by descriptive statistics. No significance tests will be performed for between group comparisons. Clinical comparability will be assessed based on only the summary statistics presented.

6.3 Subject Disposition

The numbers of subjects screened, excluded, randomised, who completed each study timepoint, discontinued and included in each study populations will be presented in a CONSORT diagram.

6.4 Interim Analysis

Interim analyses have been performed for Data and Safety Monitoring Board (DSMB) review after the first 50, 100, and 350 subjects have completed 90-day study period or as determined by DSMB. The timing of additional interim analyses will be determined by the DSMB. The

interim analyses included both efficacy and safety endpoints. No hypothesis testing will be done for interim analyses.

DSMB may recommend discontinuation of subject enrolment to the trial if there is:

- Significant safety concern raised
- Observed difference in proportion of subjects reaching the primary endpoint exceeds the non-inferiority margin of 6%.

6.5 Final Analysis

6.5.1 Primary Efficacy Analysis

Primary efficacy analysis involves comparing incidence of all-cause mortality (binary) between the early oral stepdown arm and the continuing IV therapy arm. For each post-baseline timepoint (i.e. Day 14, 30, 90), risk difference in percentage of all-cause mortality and its corresponding 95% confidence interval (CI) will be reported. Chi-squared tests will be performed for statistical comparisons. Similarly, relative risk of all-cause mortality and its corresponding 95% CI will be reported. The continuing IV therapy arm will be the reference group for the risk differences and relative risks. As part of sensitivity analysis, generalised linear model (GLM) employing binomial distribution and identity link function will be performed for each post-baseline timepoint. The model will include treatment arm (early oral stepdown and continuing IV therapy; categorical) as an explanatory variable and the following covariates: country grouped by region (categorical), age group (< 70 and ≥ 70; categorical), gender (female and male; categorical), Charlson comorbidity index at baseline (< 3 and ≥ 3; categorical), Pitt bacteraemia total score at baseline (< 1 and ≥ 1; categorical), source of bacteremia (UTI and non-UTI; categorical), empiric therapy *in-vitro* effectiveness (effective, not effective, unknown effectiveness; categorical) and index pathogenic bacterial type (*Enterobacterales*, non-fermenters, others; categorical). Baseline covariates are measured at screening. The definitions of the covariate, source of bacteremia, empiric therapy *in-vitro* effectiveness and index pathogenic bacterial type, have been described in section 6.5.3. If collinearity is found between source of bacteremia and index pathogenic bacterial type, then only source of bacteremia will be retained between the two. In the event of non-convergence, only country grouped by region will be retained as covariate. Adjusted risk differences on all-cause mortality, its corresponding 95% CI and p-value will be estimated using the GLMs. Similarly, adjusted relative risk of all-cause mortality and its corresponding 95% CI will be estimated using GLM employing binomial distribution and log link function with the inclusion of the same covariates.

In the event that the incidence of all-cause mortality is limited, adjusted estimates for all-cause mortality will not be reported.

The primary endpoint is at Day 30. At Day 30, non-inferiority will be considered met if the upper limit of the 95% CI on the risk difference falls below the non-inferiority margin of 6%. If the upper limit of the 95% CI on the difference falls below zero, superiority will be considered met as special case of non-inferiority. Risk differences (adjusted and unadjusted) on all-cause mortality at Day 14 and 90 and its corresponding 95% CIs will also be reported as part of secondary objective 1.

6.5.2 Secondary Efficacy Analysis

For secondary objective 2, survival analysis will be performed on survival time. Survival curve of each treatment arm will be constructed using Kaplan-Meier method. Logrank test will be performed to compare the Kaplan-Meier curves of the two treatment arms and its p-value will be reported. Hazard ratio (HR), with continuing IV therapy arm as reference, and its 95% CI will be reported as well. As part of sensitivity analysis, stratified logrank test adjusting for country grouped by region (categorical), age group (< 70 and ≥ 70; categorical), gender (female and male; categorical), Charlson comorbidity index at baseline (< 3 and ≥ 3; categorical), Pitt bacteraemia total score at baseline (< 1 and ≥ 1; categorical), source of bacteremia (UTI and non-UTI; categorical), empiric therapy *in-vitro* effectiveness (effective, not effective, unknown effectiveness; categorical) and index pathogenic bacterial type (*Enterobacterales*, non-fermenters, others; categorical) will be performed to compare the Kaplan-Meier curves. The variables adjusted for the test will be amended to follow covariates eventually used for primary sensitivity analysis. P-value from the stratified logrank test will be reported together with adjusted HR and its corresponding 95% CI. Multivariate Cox proportional hazard (PH) regression model will be used to estimate the adjusted HR and its corresponding 95% CI. The multivariate Cox PH regression model will include the same covariates specified in section 6.5.1. Appropriateness of Cox PH regression model will be evaluated using plot of Schoenfeld residuals against survival time. Should there be at least one covariate not satisfying the PH assumption, "no-interaction" (i.e. estimated coefficients not varying by stratum) stratified Cox regression model will be used instead. The model will be stratified by strata formed after combining categories of all covariates which did not satisfy the PH assumption. Covariate(s) which satisfies the PH assumption will remain included in the stratified model. If the treatment indicator is found to not satisfy the PH assumption, time-varying HR will be obtained by the addition of treatment indicator by time interaction term in the Cox regression model. The time variable is obtained by partitioning the follow-up time into 30-day intervals. In the event of non-convergence, only country grouped by region will be retained as covariate and adjusted for in the stratified logrank test.

For secondary objective 7, Gray's test will be performed to compare the cumulative incidence function curves for discharge alive in the two treatment arms in the presence of mortality as competing risk. As part of sensitivity analysis, Fine and Gray's model will be used to analyse total index hospitalisation time with mortality treated as a competing risk while adjusting for the same covariates specified in section 6.5.1. Sub-distribution hazard ratios of discharge alive, together with its corresponding 95% CI, will be reported.

For secondary objective 12, EQ-5D utility value at Day 90 will be compared between the early oral stepdown arm and the continuing IV therapy arm. Mean difference in EQ-5D utility value, with the continuing IV therapy arm as reference, and its corresponding 95% CI will be reported. P-value from t-test will also be reported. As part of sensitivity analysis, adjusted mean difference in EQ-5D utility value and its corresponding 95% CI will be estimated from ordinary least square regression model. The model will include treatment arm (early oral stepdown and continuing IV therapy; categorical) as explanatory variable, and the same covariates specified in section 6.5.1 as well as EQ-5D utility value at baseline (continuous) as a covariate. The same analysis approach will be used for EQ-VAS value except that the model will adjust for EQ-VAS value at baseline (continuous) instead of EQ-5D utility value at baseline.

For secondary objective 3, 4 and 8, summary statistics (i.e. median, Q1 and Q3) of duration of IV antibiotics therapy, total days alive and free from antibiotics and ttnumber of days alive and not in hospital will be reported. Mann-Whitney U test will be performed to compare the outcomes between the treatment arms. Means and SDs of these outcomes will also be reported.

Analysis approach similar to primary efficacy analysis will be used for the following secondary outcomes: incidence of change in treatment strategy (binary; secondary objective 6), incidence of change in treatment strategy due to adverse event (binary; secondary objective 6), incidence of change in treatment strategy due to presumed lack of efficacy (binary; secondary objective 6), incidence of readmission for any cause (binary; secondary objective 9), incidence of extended index hospitalisation (binary; secondary objective 10) and incidence on readmission for any cause or extended index hospitalisation (binary; secondary objective 11). As these outcomes are dependent on subject's follow up duration up to Day 30 (secondary objective 6) and up to Day 90 (secondary objective 9-11), duration of follow up in days will be included as an offset term.

6.5.3 Exploratory Analysis

For exploratory objective 1, the analysis of DOOR ranking (ordinal) will follow the standard approach [6, 7]. Mann-Whitney U test will be performed on the DOOR rankings to determine the probability that a randomly selected subject assigned to early oral stepdown arm would have a better rank (i.e. desirable outcome), than a randomly selected subject assigned to the continuing IV therapy arm. The probability and its corresponding 95% CI will be reported.

Exploratory objective 2 involves subgroup analyses on incidence of 30-day all-cause mortality. There are a total of six pre-specified subgroup analyses on the primary endpoint of 30-day all-cause mortality:

a) Country grouped by region

b) Age group (< 70, ≥ 70)

c) Gender (female, male)

d) Source of bacteremia at baseline (UTI, non-UTI)
   Source of bacteremia at baseline will be determined by index blood culture result. Subject will be grouped under the "UTI" subgroup if urinary tract is found to be one of the sources of his/her bacteria infection. Subject will be grouped under the "non-UTI" subgroup if urinary tract is not one of the sources of his/her bacteria infection.

e) Empiric therapy *in-vitro* effectiveness (effective, not effective, unknown effectiveness)
   In-vitro Effectiveness of empiric therapy will be based on antibiotic susceptibilities test results of the antibiotics given as empiric therapy. The antibiotics susceptibilities will be interpreted according to local microbiology laboratory interpretations based on either CLSI or EUCAST criteria. For subjects who were given only one antibiotic as empiric therapy, the subject will be grouped under the "effective" subgroup if the antibiotic is found to be sensitive. If the antibiotic is found to be of intermediate or resistance sensitivity, , the subject will be grouped under the "not effective" subgroup. If antimicrobial susceptibility of the antibiotic was not tested, the subject will be grouped under the "unknown effectiveness" subgroup. For subjects who were given more than one antibiotic as empiric therapy, subject will be grouped under the "effective" subgroup if sensitive susceptibility result was observed in at least one of the antibiotics.

f) Resistance of index Gram-negative bacteria (multidrug-resistant, non-multidrug-resistance, unknown)

The index Gram-negative bacterial isolates will be shipped to a central laboratory for confirmatory testing to define multidrug-resistance via standardized phenotypic assays, genomic analyses or both, contingent on adequate study funding. For example, multidrug-resistance may be defined as follows:

- Extended-spectrum beta-lactamase (ESBL) or AmpC producing *Enterobacterales* isolates are considered multidrug-resistant. *Enterobacterales* demonstrating resistance to oxyimino-beta-lactam substrates (cefotaxime and ceftazidime) are also considered multidrug-resistant as they are likely to be ESBL or AmpC positive.
- *Pseudomonas* spp. isolates resistant to ≥ 3 of the following antimicrobial agents are considered multidrug-resistant: antipseudomonal penicillins (e.g. piperacillin), antipseudomonal cephalosporins (e.g. ceftazidime), fluoroquinolones (e.g. ciprofloxacin), carbapenems (e.g. imipenem, meropenem) and aminoglycosides.
- *Acinetobacter* spp. isolates resistant to ≥ 3 of the following antimicrobial agents are considered multidrug-resistant: imipenem (or meropenem), levofloxacin (or other fluoroquinolones), ceftazidime, colistin, tobramycin (or other aminoglycosides) and piperacillin–tazobactam.

Multidrug-resistance may also be broadly defined as follows: Resistant (R) or Intermediate (I) susceptibility to at least 3 different classes of antibiotics interpreted according to CLSI or EUCAST criteria.

g) Index pathogenic bacterial type (*Enterobacterales*, non-fermenters, others)
Pathogen type will be based on bacterial species identification from the index blood culture.
   - *Enterobacterales*: e.g., *E. coli*, Klebsiella, Salmonella, Proteus, Enterobacter, Shigella, Citrobacter, Serratia
   - Non-fermenters: e.g., Pseudomonas, Acinetobacter, Strenotrophomonas
   - Others

Analysis approach similar to primary efficacy analysis will be performed. Tests for interactions between randomised arm and the subgroup variable of interest will be performed. Risk differences, relative risks, corresponding 95% CIs, and p-values from the test for interactions will be presented in forest plots.

6.5.4 Safety Analysis

The term AE is understood to encompass serious AE (SAE). Monitoring for AEs should begin as soon as the study drugs are administered. Only AEs deemed by the treating/study doctor to be related or possibly related to the study treatment will be entered in the REDCap database. At the follow-up time points at days 14, 30 and 90, only targeted AEs

(*Clostridioides difficile* diarrhoea, catheter-related complications, liver and kidney function test abnormalities) will be monitored. If study drug treatment has ceased at the follow-up time points, the only solicited AE that needs to be monitored is *Clostridioides difficile* diarrhoea.

Monitoring for SAEs should start once the participant provides written consent to participate in the study and will occur throughout the study period. If there is an SAE, sites will populate the details in an SAE form and send for review and signed off prior to reporting. The data management team will then retrieve the relevant information from the form and key into a SAE tracking excel log. SAEs regardless of of relatedness will be keyed into the tracking log. As per country/institution's policy, SAEs will also be reported to ethics committee and regulatory authorities (e.g. in Singapore, SAEs that are unexpected and related or possibly related to study treatment needs to be reported; all deaths regardless of expectedness or relatedness also need to be reported).

An overview of treatment related AEs and all SAEs consisting of the number and percentage of subjects who experienced the events (along with number of events) will be provided for following categories by arms:

- AEs
- SAEs
- Treatment related AEs
- Treatment related grade 3-5 AEs
- Treatment related SAEs
- Solicited AEs
    - *C. difficile*-associated diarrhoea
    - Catheter-related complication
    - Liver function test abnormalities
    - Acute kidney injury
- Solicited grade 3-5 AEs
- Solicited SAEs

A summary of all treatment related AEs (including SAEs) term by grade and arm will also be provided. AE terms may be combined with advise from trial investigator. Number and percentage of subjects who experienced the AEs term (along with number of events) will be reported. Each preferred term will be further broken down into:

- Grade 1-2 AEs
- Grade 3-5 AEs
- SAEs

Listings of grade 3-5 treatment related AEs and SAEs will be provided indicating subject ID, randomised date, randomised arm, country, site, reported term, solicited type, event start date,

event end date, grade, relationship with treatment, expectedness, outcome, whether it is an SAE and seriousness criteria.

As part of secondary objective 5, number (events and subjects) and percentage of subjects who experienced each special interest treatment related AE will be reported. Fisher's exact test will be performed to compare the distribution of special interest treatment related AEs between the arms. P-values will be reported.

Laboratory safety measures (haematology and clinical chemistry assessments) at screening and before hospital discharge will be summarised by arms using summary statistics, and percentage of clinically significant (CS) results. A listing of subjects with at least one CS haematology or clinical chemistry result will be provided indicating subject ID, randomised arm, country, site, parameter and unit of measurement, timepoint at which the measurement was done, assessment result and whether result was abnormal or clinically significant.

6.5.5 Other Analysis

Data on blood samples collected, blood culture results, empiric therapy and treatment exposure will also be summarised.

Number and percentage of subjects with blood samples collected for blood culture, haematology and clinical chemistry will be summarised at screening, Day 1-7 and beyond Day 7. Total number of blood samples collected throughout the study for blood culture, haematology and clinical chemistry will also be summarised using descriptive statistics.

Blood culture results in terms of bacteraemia isolate and source of bacteremia will be summarised at screening and Day 1-7. Number and percentage of subjects with each bacteraemia isolate type, index pathogenic bacterial type and source of bacteremia will be reported.

The following subjects' empiric therapy and treatment exposure information will be summarised:

1. Antibiotics given for empiric therapy (categorical)
   Only top five antibiotics given as empiric therapy will be listed, with the rest being grouped under "Others".
2. Total number of days on empiric therapy
3. *In-vitro* effectiveness of empiric therapy (categorical)
   Definition has provided in section 6.5.3.
4. Total number of days on prescribed antibiotics, excluding empiric therapy (continuous)
   Computation is for antibiotics prescribed for definitive therapy and excludes empiric therapy. Definitive therapy includes treatment de-escalation.
5. Adherence to prescribed antibiotics (categorical)

6. Prescribed study antibiotics (categorical)
7. Site of administration of study drug (categorical)
8. Time to index hospital discharge from randomisation (day)
9. Time to index hospital discharge from index hospital admission (day).

Below are the formulae to be used for deriving continuous measure of adherence to prescribed antibiotics, which will then be dichotomised to give the categorical variable (i.e. ≥ 90% (compliant), < 90% (non-compliant)):

> Days on antibiotics$_{\text{early oral stepdown}}$ = [max(prescribed end dates) – min(prescribed start dates) + 1] + [de-escalation antibiotics end date – de-escalation antibiotics start date + 1] – (number of remaining pills from those given at discharge/daily dose).
> Days on antibiotics$_{\text{continuing intravenous}}$ = [max(prescribed end dates) – min(prescribed start dates) + 1] + [de-escalation antibiotics end date – de-escalation antibiotics start date + 1] – (number of doses omitted/daily dose).
>
> Subject considered to be 100% compliance if documented to have taken oral antibiotics (early oral stepdown) or IV antibiotics (continuing intravenous) as scheduled. Otherwise, the following formula will be used:
> Adherence$_{\text{early oral stepdown}}$ = [Days on antibiotics$_{\text{early oral stepdown}}$ / (max(prescribed end dates) – min(prescribed start dates) + 1] + [de-escalation antibiotics end date – de-escalation antibiotics start date) + 1]*100.
> Adherence$_{\text{continuing intravenous}}$ = [Days on antibiotics$_{\text{continuing intravenous}}$ / (max(prescribed end dates) – min(prescribed start dates) + 1] + [de-escalation antibiotics end date – de-escalation antibiotics start date) + 1]*100;

A listing of major PD will be provided indicating subject ID, randomised arm, country, site, category of the major PD (inclusion, exclusion and on study) and description of the major PD.

6.5.6 Timing of Final Analysis

Final analysis will be performed after the 720th participant has been randomised and completes the study's last visit or discontinues from the study, whichever earlier. The date of last patient last visit is expected to be in late July 2026.

Subgroup analysis by multidrugresistance will be an exploratory analysis to be performed separately, only after the index bacterial isolates have been consolidated from the participating sites in a central labarotory post-trial completion, for it to undergo standardised phenotypic analysis or genomic analysis or both, contingent on adequate study funding.

MOCK-UP TABLES

Table 1 Summary of Demographic and Baseline Characteristics

Population: Modified intention-to-treat*

Characteristic	Early Oral Stepdown (Intervention Arm) (N = XX)	Continuing Intravenous (Standard Arm) (N = XX)	Total (N = XX)
Demographics			
Country, n (%)			
Singapore	xx (xx.x)	xx (xx.x)	xx (xx.x)
Malaysia	xx (xx.x)	xx (xx.x)	xx (xx.x)
South Korea	xx (xx.x)	xx (xx.x)	xx (xx.x)
Australia	xx (xx.x)	xx (xx.x)	xx (xx.x)
…	xx (xx.x)	xx (xx.x)	xx (xx.x)
Israel	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing	xx (xx.x)	xx (xx.x)	xx (xx.x)
Age (years)			
M (missing)	xx (x)	xx (x)	xx (x)
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (Q1-Q3)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Sex, n (%)			
Female	xx (xx.x)	xx (xx.x)	xx (xx.x)
Male	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ethnicity, n (%)			
Chinese	xx (xx.x)	xx (xx.x)	xx (xx.x)
Malay	xx (xx.x)	xx (xx.x)	xx (xx.x)
Indian	xx (xx.x)	xx (xx.x)	xx (xx.x)
Korean	xx (xx.x)	xx (xx.x)	xx (xx.x)
…	xx (xx.x)	xx (xx.x)	xx (xx.x)
Others	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing	xx (xx.x)	xx (xx.x)	xx (xx.x)
Charlson Comorbidity Index at baseline			
Total score			
M (missing)	xx (x)	xx (x)	xx (x)

Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (Q1-Q3)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Charlson comorbidities, n (%)			
Myocardial infarction/coronary artery disease	xx (xx.x)	xx (xx.x)	xx (xx.x)
Congestive heart failure	xx (xx.x)	xx (xx.x)	xx (xx.x)
Peripheral vascular disease	xx (xx.x)	xx (xx.x)	xx (xx.x)
Cerebrovascular disease/transient ischaemic attack	xx (xx.x)	xx (xx.x)	xx (xx.x)
Dementia	xx (xx.x)	xx (xx.x)	xx (xx.x)
Chronic obstructive pulmonary disease	xx (xx.x)	xx (xx.x)	xx (xx.x)
Connective tissue disease	xx (xx.x)	xx (xx.x)	xx (xx.x)
Peptic ulcer disease	xx (xx.x)	xx (xx.x)	xx (xx.x)
Liver disease, mild	xx (xx.x)	xx (xx.x)	xx (xx.x)
Diabetes mellitus without complications	xx (xx.x)	xx (xx.x)	xx (xx.x)
Hemiplegia	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate to severe chronic kidney disease	xx (xx.x)	xx (xx.x)	xx (xx.x)
Diabetes mellitus with complications	xx (xx.x)	xx (xx.x)	xx (xx.x)
Any localized tumour	xx (xx.x)	xx (xx.x)	xx (xx.x)
Leukemia	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lymphoma	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate or severe liver disease	xx (xx.x)	xx (xx.x)	xx (xx.x)
Metastatic solid tumour	xx (xx.x)	xx (xx.x)	xx (xx.x)
Acquired immunodeficiency syndrome	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing	xx (xx.x)	xx (xx.x)	xx (xx.x)
Vital signs at baseline			
Temperature (Celsius)			
M (missing)	xx (x)	xx (x)	xx (x)
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (Q1-Q3)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Heart rate (beats/min)			

M (missing)	xx (x)	xx (x)	xx (x)
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (Q1-Q3)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Systolic blood pressure (mmHg)			
M (missing)	xx (x)	xx (x)	xx (x)
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (Q1-Q3)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Diastolic blood pressure (mmHg)			
M (missing)	xx (x)	xx (x)	xx (x)
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (Q1-Q3)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Respiratory rate (breaths/min)			
M (missing)	xx (x)	xx (x)	xx (x)
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (Q1-Q3)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Height (cm)			
M (missing)	xx (x)	xx (x)	xx (x)
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (Q1-Q3)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Weight (kg)			
M (missing)	xx (x)	xx (x)	xx (x)
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (Q1-Q3)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
BMI (kg/m^2)			
M (missing)	xx (x)	xx (x)	xx (x)
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (Q1-Q3)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Other measures at baseline			
Pitt bacteraemia total score			

M (missing)	xx (x)	xx (x)	xx (x)
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (Q1-Q3)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
EQ-5D-5L utility value			
M (missing)	xx (x)	xx (x)	xx (x)
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (Q1-Q3)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
EQ-VAS value			
M (missing)	xx (x)	xx (x)	xx (x)
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (Q1-Q3)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x

M: number of subjects with non-missing values; SD: standard deviation; Q1: lower quartile; Q3: upper quartile; n (%): number and percentage of subjects based on N.
*Note: Cross-walk algorithm will be used to calculate EQ-5D-5L utility value if value set for a country is not available. Modified intention-to-treat (mITT) population consists of randomised subjects excluding (i) those who did not have Day 30 mortality data, (ii) intervention arm subjects who did not receive any oral fluoroquinolones or oral trimethoprim-sulfamethoxazole post-randomisation and (iii) standard arm subjects who did not receive any IV antibiotics post-randomisation.

Table 2 Summary Statistics on Blood Samples Collected

Population: Modified intention-to-treat*

	Early Oral Stepdown (Intervention Arm) (N = XX)			Continuing Intravenous (Standard Arm) (N = XX)		
	Blood Culture[1]	Haematology[2]	Clinical Chemistry[3]	Blood Culture[1]	Haematology[2]	Clinical Chemistry[3]
Blood samples collected, n (%)						
Screening	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Day 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Day 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Day 3	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Day 4	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Day 5	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Day 6	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Day 7	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Beyond day 7	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Total blood samples collected						
M (missing)	xx (x)	xx (x)	xx (x)	xx (x)	xx (x)	xx (x)
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (Q1-Q3)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x

M: number of subjects with non-missing values; n (%): number and percentage of subjects based on N.

[1]Blood culture only required at screening. Blood cultures are usually ordered if patient is febrile >38°C in the last 24 hours during bacteraemia episode or if previous blood cultures remain positive or if any secondary infection is suspected.
[2]Haematological tests are required at screening and before hospital discharge. At other time points, it will be at the discretion of clinician if subject is still an inpatient.
[3]Clinical chemistry tests are required at screening and before hospital discharge. At other time points, it will be at the discretion of clinician if subject is still an inpatient.
*Note: Modified intention-to-treat (mITT) population consists of randomised subjects excluding (i) those who did not have Day 30 mortality data, (ii) intervention arm subjects who did not receive any oral fluoroquinolones or oral trimethoprim-sulfamethoxazole post-randomisation and (iii) standard arm subjects who did not receive any IV antibiotics post-randomisation.

Table 3 Blood Culture Results

Population: Modified intention-to-treat*

	Early Oral Stepdown (Intervention Arm) (N = XX)							
	Screening	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Was blood sample collected for culture?, n (%)								
No	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Bacteraemia isolate, n (%)								
Escherichia coli	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Klebsiella spp	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other enterobacterales	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Acinetobactor spp	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Pseudomonas spp	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Others	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Index pathogenic bacterial type, n (%)								
Enterobacterales	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Non-fermeters	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Others	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Source of bacteremia, n (%)								
Primary bacteraemia	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Urinary tract	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Gastrointestinal tract	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Respiratory tract	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Biliary tract	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Central venous catheter	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Skin or soft tissue	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Unknown source	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Others	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

	Continuing Intravenous (Standard Arm) (N = XX)							
	Screening	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Was blood sample collected for culture?, n (%)								
No	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Bacteraemia isolate, n (%)								
Escherichia coli	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Klebsiella spp	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other enterobacterales	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Acinetobactor spp	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Pseudomonas spp	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Others	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Index pathogenic bacterial type, n (%)								
Enterobacterales	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Non-fermenters	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Others	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Source of bacteremia, n (%)								
Primary bacteraemia	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Urinary tract	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Gastrointestinal tract	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Respiratory tract	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Biliary tract	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Central venous catheter	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Skin or soft tissue	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Unknown source	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Others	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Missing	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

n (%): number and percentage of subjects with blood sample collected for culture.
*Note: Blood culture only required at screening. Blood cultures are usually ordered if patient is febrile >38°C in the last 24 hours during bacteraemia episode or if previous blood cultures remain positive or if any secondary infection is suspected. Modified intention-to-treat population consists of randomised subjects excluding (i) those who did not have Day 30 mortality data, (ii) intervention arm subjects who did not receive any oral fluoroquinolones or oral trimethoprim-sulfamethoxazole post-randomisation and (iii) standard arm subjects who did not receive any IV antibiotics post-randomisation.

Table 4 Haematology

Population: Modified intention-to-treat*

	Early Oral Stepdown (Intervention Arm) (N = XX)		Continuing Intravenous (Standard Arm) (N = XX)	
	Screening	Before Hospital Discharge	Screening	Before Hospital Discharge
Haemoglobin (g/dL)				
M (missing)	xx (x)	xx (x)	xx (x)	xx (x)
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (Q1-Q3)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
CS, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
White blood cells (10^9/L)				
M (missing)	xx (x)	xx (x)	xx (x)	xx (x)
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (Q1-Q3)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
CS, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Platelets (10^9/L)				
M (missing)	xx (x)	xx (x)	xx (x)	xx (x)
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (Q1-Q3)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x

CS, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Neutrophils (absolute) (10^9/L)				
M (missing)	xx (x)	xx (x)	xx (x)	xx (x)
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (Q1-Q3)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
CS, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

M: number of subjects with non-missing values; SD: standard deviation; Q1: lower quartile; Q3: upper quartile; n (%): number and percentage of subjects based on N; CS: clinically significant.
*Note: Haematological tests are required at screening and before hospital discharge. At other time points, it will be at the discretion of clinician if subject is still an inpatient. Modified intention-to-treat population consists of randomised subjects excluding (i) those who did not have Day 30 mortality data, (ii) intervention arm subjects who did not receive any oral fluoroquinolones or oral trimethoprim-sulfamethoxazole post-randomisation and (iii) standard arm subjects who did not receive any IV antibiotics post-randomisation.

Table 5 Clinical Chemistry

Population: Modified intention-to-treat*

	Early Oral Stepdown (Intervention Arm) (N = XX)		Continuing Intravenous (Standard Arm) (N = XX)	
	Screening	Before Hospital Discharge	Screening	Before Hospital Discharge
C-reactive protein (nmol/L)				
M (missing)	xx (x)	xx (x)	xx (x)	xx (x)
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (Q1-Q3)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
CS, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Sodium (mmol/L)				
M (missing)	xx (x)	xx (x)	xx (x)	xx (x)
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (Q1-Q3)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
CS, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Potassium (mmol/L)				
M (missing)	xx (x)	xx (x)	xx (x)	xx (x)
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (Q1-Q3)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x

CS, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Creatinine (µmol/L)				
M (missing)	xx (x)	xx (x)	xx (x)	xx (x)
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (Q1-Q3)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
CS, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
ALT (SGPT) (U/L)				
M (missing)	xx (x)	xx (x)	xx (x)	xx (x)
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (Q1-Q3)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
CS, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
AST (SGOT) (U/L)				
M (missing)	xx (x)	xx (x)	xx (x)	xx (x)
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (Q1-Q3)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
CS, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
ALP (U/L)				
M (missing)	xx (x)	xx (x)	xx (x)	xx (x)
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)

Median (Q1-Q3)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
CS, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Total bilirubin (µmol/L)				
M (missing)	xx (x)	xx (x)	xx (x)	xx (x)
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (Q1-Q3)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
CS, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

M: number of subjects with non-missing values; SD: standard deviation; Q1: lower quartile; Q3: upper quartile; n (%): number and percentage of subjects based on M; CS: clinically significant.
*Note: Clinical chemistry tests are required at screening and before hospital discharge. At other time points, it will be at the discretion of clinician if subject is still an inpatient. Modified intention-to-treat population consists of randomised subjects excluding (i) those who did not have Day 30 mortality data, (ii) intervention arm subjects who did not receive any oral fluoroquinolones or oral trimethoprim-sulfamethoxazole post-randomisation and (iii) standard arm subjects who did not receive any IV antibiotics post-randomisation.

Table 6 Efficacy Analysis on Binary Outcomes in Terms of Risk Difference

Population: Modified intention-to-treat*

	Early Oral Stepdown (Intervention Arm) (N = XX)	Continuing Intravenous (Standard Arm) (N = XX)	Risk Difference (95% CI)	p-value[1]	[2]Adjusted Risk Difference (95% CI)	p-value[2]
Primary outcome						
14-day all-cause mortality, n (%) / M	xx (xx.x) / xx	xx (xx.x) / xx	x.x (x.x, x.x)	0.xxx	x.x (x.x, x.x)	0.xxx
30-day all-cause mortality, n (%) / M	xx (xx.x) / xx	xx (xx.x) / xx	x.x (x.x, x.x)	0.xxx	x.x (x.x, x.x)	0.xxx
90-day all-cause mortality, n (%) / M	xx (xx.x) / xx	xx (xx.x) / xx	x.x (x.x, x.x)	0.xxx	x.x (x.x, x.x)	0.xxx
Secondary outcome[3]						
[4]Change in treatment strategy, n (%) / M	xx (xx.x) / xx	xx (xx.x) / xx	x.x (x.x, x.x)	0.xxx	x.x (x.x, x.x)	0.xxx
[4]Change in treatment strategy due to AE, n (%) / M	xx (xx.x) / xx	xx (xx.x) / xx	x.x (x.x, x.x)	0.xxx	x.x (x.x, x.x)	0.xxx
[4]Change in treatment strategy due to presumed lack of efficacy, n (%) / M	xx (xx.x) / xx	xx (xx.x) / xx	x.x (x.x, x.x)	0.xxx	x.x (x.x, x.x)	0.xxx
[5]Readmission (for any cause), n (%) / M	xx (xx.x) / xx	xx (xx.x) / xx	x.x (x.x, x.x)	0.xxx	x.x (x.x, x.x)	0.xxx
[5]Extended index hospitalisation (> 14 days from randomisation), n (%) / M	xx (xx.x) / xx	xx (xx.x) / xx	x.x (x.x, x.x)	0.xxx	x.x (x.x, x.x)	0.xxx
[5]Readmission or extended index hospitalisation, n (%) / M	xx (xx.x) / xx	xx (xx.x) / xx	x.x (x.x, x.x)	0.xxx	x.x (x.x, x.x)	0.xxx

M: number of subjects with non-missing values; CI: confidence interval; AE: adverse event.
[1]Chi-squared test.

[2]Based on GLM employing binomial distribution and identity link function adjusting for country grouped by region (categorical), age group (categorical), gender (categorical), Charlson comorbidity index at baseline (categorical), Pitt bacteraemia total score at baseline (categorical), source of bacteremia (categorical), empiric therapy *in-vitro* effectiveness (categorical) and index pathogenic bacterial type (categorical).
[3]Duration of follow-up in days included as an offset term.
[4]Up to day 30.
[5]Up to day 90.
*Note: Risk difference = early oral stepdown arm – continuing intravenous arm. 30-day all-cause mortality is the primary endpoint. Modified intention-to-treat (mITT) population consists of randomised subjects excluding (i) those who did not have Day 30 mortality data, (ii) intervention arm subjects who did not receive any oral fluoroquinolones or oral trimethoprim-sulfamethoxazole post-randomisation and (iii) standard arm subjects who did not receive any IV antibiotics post-randomisation. The same table will be replicated for per-protocol (PP) population. PP population consists of subjects included in the mITT population but excluding those with major protocol deviation which may significantly affects the primary endpoint. The same table will be replicated for ITT population if there is a difference of least 5% between ITT population size and the mITT population size.

Table 7 Efficacy Analysis on Binary Outcomes in Terms of Relative Risk

Population: Modified intention-to-treat*

	Early Oral Stepdown (Intervention Arm) (N = XX)	Continuing Intravenous (Standard Arm) (N = XX)	Relative Risk (95% CI)	p-value[1]	[2]Adjusted Relaitve Risk (95% CI)	p-value[2]
Primary outcome						
14-day all-cause mortality, n (%) / M	xx (xx.x) / xx	xx (xx.x) / xx	x.x (x.x, x.x)	0.xxx	x.x (x.x, x.x)	0.xxx
30-day all-cause mortality, n (%) / M	xx (xx.x) / xx	xx (xx.x) / xx	x.x (x.x, x.x)	0.xxx	x.x (x.x, x.x)	0.xxx
90-day all-cause mortality, n (%) / M	xx (xx.x) / xx	xx (xx.x) / xx	x.x (x.x, x.x)	0.xxx	x.x (x.x, x.x)	0.xxx
Secondary outcome[3]						
[4]Change in treatment strategy, n (%) / M	xx (xx.x) / xx	xx (xx.x) / xx	x.x (x.x, x.x)	0.xxx	x.x (x.x, x.x)	0.xxx
[4]Change in treatment strategy due to AE, n (%) / M	xx (xx.x) / xx	xx (xx.x) / xx	x.x (x.x, x.x)	0.xxx	x.x (x.x, x.x)	0.xxx
[4]Change in treatment strategy due to presumed lack of efficacy, n (%) / M	xx (xx.x) / xx	xx (xx.x) / xx	x.x (x.x, x.x)	0.xxx	x.x (x.x, x.x)	0.xxx
[5]Readmission (for any cause), n (%) / M	xx (xx.x) / xx	xx (xx.x) / xx	x.x (x.x, x.x)	0.xxx	x.x (x.x, x.x)	0.xxx
[5]Extended hospitalisation (> 14 days from randomisation), n (%) / M	xx (xx.x) / xx	xx (xx.x) / xx	x.x (x.x, x.x)	0.xxx	x.x (x.x, x.x)	0.xxx
[5]Readmission or extended hospitalisation, n (%) / M	xx (xx.x) / xx	xx (xx.x) / xx	x.x (x.x, x.x)	0.xxx	x.x (x.x, x.x)	0.xxx

M: number of subjects with non-missing values; CI: confidence interval; AE: adverse event.

[1]Chi-squared test.
[2]Based on GLM employing binomial distribution and log link function adjusting for country grouped by region (categorical), age group (categorical), gender (categorical), Charlson comorbidity index at baseline (categorical), Pitt bacteraemia total score at baseline (categorical), source of bacteremia (categorical), empiric therapy *in-vitro* effectiveness (categorical) and index pathogenic bacterial type (categorical).
[3]Duration of follow-up in days included as an offset term.
[4]Up to day 30.
[5]Up to day 90.
*Note: Relative risk = early oral stepdown arm / continuing intravenous arm. 30-day all-cause mortality is the primary endpoint. Modified intention-to-treat (mITT) population consists of randomised subjects excluding (i) those who did not have Day 30 mortality data, (ii) intervention arm subjects who did not receive any oral fluoroquinolones or oral trimethoprim-sulfamethoxazole post-randomisation and (iii) standard arm subjects who did not receive any IV antibiotics post-randomisation. The same table will be replicated for per-protocol (PP) population. PP population consists of subjects included in the mITT population but excluding those with major protocol deviation which may significantly affects the primary endpoint. The same table will be replicated for ITT population if there is a difference of least 5% between ITT population size and the mITT population size.

Table 8 Efficacy Analysis on Quality of Life Measures

Population: Modified intention-to-treat*

	Unadjusted						Adjusted[2]					
	Early Oral Stepdown (Intervention Arm) (N = XX)		Continuing Intravenous (Standard Arm) (N = XX)		Difference		Early Oral Stepdown (Intervention Arm) (N = XX)		Continuing Intravenous (Standard Arm) (N = XX)		Difference	
Mean of secondary outcome	M	Estimate (95% CI)	M	Estimate (95% CI)	Estimate (95% CI)	p-value[1]	M	Estimate (95% CI)	M	Estimate (95% CI)	Estimate (95% CI)	p-value
EQ-5D utility value	xxx	xx (xx, xx)	xxx	xx (xx, xx)	xx (xx, xx)	0.xxx	xxx	xx (xx, xx)	xxx	xx (xx, xx)	xx (xx, xx)	0.xxx
EQ-VAS value	xxx	xx (xx, xx)	xxx	xx (xx, xx)	xx (xx, xx)	0.xxx	xxx	xx (xx, xx)	xxx	xx (xx, xx)	xx (xx, xx)	0.xxx

M: number of subjects with non-missing values; CI: confidence interval.
[1]T test.
[2]Based on OLS adjusting for baseline value (continuous), country grouped by region (categorical), age group (categorical), gender (categorical), Charlson comorbidity index at baseline (categorical), Pitt bacteraemia total score at baseline (categorical), source of bacteremia (categorical), empiric therapy *in-vitro* effectiveness (categorical) and index pathogenic bacterial type (categorical).
*Note: Difference = early oral stepdown arm – continuing intravenous arm. Modified intention-to-treat (mITT) population consists of randomised subjects excluding (i) those who did not have Day 30 mortality data, (ii) intervention arm subjects who did not receive any oral fluoroquinolones or oral trimethoprim-sulfamethoxazole post-randomisation and (iii) standard arm subjects who did not receive any IV antibiotics post-randomisation. The same table will be replicated for per-protocol (PP) population. PP population consists of subjects included in the mITT population but excluding those with major protocol

deviation which may significantly affects the primary endpoint. The same table will be replicated for ITT population if there is a difference of least 5% between ITT population size and the mITT population size.

Table 9 Efficacy Analysis on Other Continous Outcomes

Population: Modified intention-to-treat*

	Early Oral Stepdown (Intervention Arm) (N = XX)			Continuing Intravenous (Standard Arm) (N = XX)			p-value[1]
	M	Median (Q1-Q3)	Mean (SD)	M	Median (Q1-Q3)	Mean (SD)	
Duration of IV antibiotics therapy up to hospital discharge in surviving subjects	xxx	xx.x (xx.x-xx.x)	xx.x (xx.x)	xxx	xx.x (xx.x-xx.x)	xx.x (xx.x)	0.xxx
Duration of IV antibiotics therapy up to hospital discharge in non-surviving subjects							
Duration of IV antibiotics therapy up day 90 in surviving subjects	xxx	xx.x (xx.x-xx.x)	xx.x (xx.x)	xxx	xx.x (xx.x-xx.x)	xx.x (xx.x)	0.xxx
Duration of IV antibiotics therapy up day 90 in non-surviving subjects							
Total days alive and free from antibiotic in surviving subjects	xxx	xx.x (xx.x-xx.x)	xx.x (xx.x)	xxx	xx.x (xx.x-xx.x)	xx.x (xx.x)	0.xxx
Proportion of days alive and free from antibiotic in surviving subjects who discontinued	xxx	0.xx (0.xx-0.xx)	0.xx (0.xx)	xxx	0.xx (0.xx-0.xx)	0.xx (0.xx)	0.xxx
Proportion of days alive and free from antibiotic in non-surviving subjects	xxx	0.xx (0.xx-0.xx)	0.xx (0.xx)	xxx	0.xx (0.xx-0.xx)	0.xx (0.xx)	0.xxx
Total days alive and free from IV antibiotic in surviving subjects	xxx	xx.x (xx.x-xx.x)	xx.x (xx.x)	xxx	xx.x (xx.x-xx.x)	xx.x (xx.x)	0.xxx
Proportion of days alive and free from IV antibiotic in surviving subjects who discontinued	xxx	0.xx (0.xx-0.xx)	0.xx (0.xx)	xxx	0.xx (0.xx-0.xx)	0.xx (0.xx)	0.xxx

Proportion of days alive and free from IV antibiotic in non-surviving subjects	xxx	0.xx (0.xx-0.xx)	0.xx (0.xx)	xxx	0.xx (0.xx-0.xx)	0.xx (0.xx)	0.xxx
Number of days alive and not in hospital (including OPAT)	xxx	xx.x (xx.x-xx.x)	xx.x (xx.x)	xxx	xx.x (xx.x-xx.x)	xx.x (xx.x)	0.xxx

M: number of subjects with non-missing values; Q1: lower quartile; Q3: upper quartile; SD: standard deviation.
[1]Based on Mann-Whitney U test.
*Note: Modified intention-to-treat (mITT) population consists of randomised subjects excluding (i) those who did not have Day 30 mortality data, (ii) intervention arm subjects who did not receive any oral fluoroquinolones or oral trimethoprim-sulfamethoxazole post-randomisation and (iii) standard arm subjects who did not receive any IV antibiotics post-randomisation. The same table will be replicated for per-protocol (PP) population. PP population consists of subjects included in the mITT population but excluding those with major protocol deviation which may significantly affects the primary endpoint. The same table will be replicated for ITT population if there is a difference of least 5% between ITT population size and the mITT population size.

Table 10 Survival Analysis

Population: Modified intention-to-treat*

	Early Oral Stepdown (Intervention Arm) (N = XX)	Continuing Intravenous (Standard Arm) (N = XX)	p-value
Survival			
Event, n (%)	xx.x (xx.x)	xx.x (xx.x)	-
Censored, n (%)	xx.x (xx.x)	xx.x (xx.x)	-
HR (95% CI)[1]	xx.x (xx.x-xx.x)		0.xxx
Adjusted HR (95% CI)[2]	xx.x (xx.x-xx.x)		0.xxx
Discharged alive with competing risk of mortality[3]			
Sub-distribution HR for discharge alive (95% CI)	xx.x (xx.x-xx.x)		0.xxx

n (%): number and percentage of subjects based on N; HR: hazard ratio; CI: confidence interval.
[1]Based on Cox proportional-hazard (PH) without covariates. P-value based on logrank test.
[2]Based on Cox proportional-hazard (PH) adjusting for country grouped by region (categorical), age group (categorical), gender (categorical), Charlson comorbidity index at baseline (categorical), Pitt bacteraemia total score at baseline (categorical), source of bacteremia (categorical), empiric therapy *in-vitro* effectiveness (categorical) and index pathogenic bacterial type (categorical). P-value based on stratified logrank test.
[3]Based on Fine and Gray's model adjusting for country grouped by region (categorical), age group (categorical), gender (categorical), Charlson comorbidity index at baseline (categorical), Pitt bacteraemia total score at baseline (categorical), source of bacteremia (categorical), empiric therapy *in-vitro* effectiveness (categorical) and index pathogenic bacterial type (categorical).
*Note: Modified intention-to-treat (mITT) population consists of randomised subjects excluding (i) those who did not have Day 30 mortality data, (ii) intervention arm subjects who did not receive any oral fluoroquinolones or oral trimethoprim-sulfamethoxazole post-randomisation and (iii) standard arm subjects who did not receive any IV antibiotics post-randomisation. The same table will be replicated for per-protocol (PP) population. PP population consists of subjects included in the mITT population but excluding those with major protocol deviation which may significantly affects the primary

endpoint. The same table will be replicated for ITT population if there is a difference of least 5% between ITT population size and the mITT population size.

Table 11 Empiric Therapy and Treatment Exposure

Population: Modified intention-to-treat*

	Early Oral Stepdown (Intervention Arm) (N = XX)	Continuing Intravenous (Standard Arm) (N = XX)
Antibiotics given for empiric therapy[1], n (%)		
Ampicillin	xx (xx.x)	xx (xx.x)
…	xx (xx.x)	xx (xx.x)
Others	xx (xx.x)	xx (xx.x)
Missing	xx (xx.x)	xx (xx.x)
Total number of days on empiric therapy[2]		
M (missing)	xx (x)	xx (x)
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
Median (Q1-Q3)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)
Min, Max	xx.x, xx.x	xx.x, xx.x
In-vitro effectiveness of empiric therapy[3], n (%)		
Effective	xx (xx.x)	xx (xx.x)
Not effective	xx (xx.x)	xx (xx.x)
Unknown effectiveness	xx (xx.x)	xx (xx.x)
Missing	xx (xx.x)	xx (xx.x)
Total number of days on prescribed antibiotics, excluding empiric therapy (day)[4,5]		
M (missing)	xx (x)	xx (x)
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
Median (Q1-Q3)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)
Min, Max	xx.x, xx.x	xx.x, xx.x
Adherence to prescribed antibiotics[4,6], n (%)		
M (missing)	xx (x)	xx (x)
≥ 90% (compliant)	xx (xx.x)	xx (xx.x)
< 90% (non-compliant)	xx (xx.x)	xx (xx.x)
Prescribed study antibiotics, n (%)		
Ciprofloxacin (oral)	xx (xx.x)	-
Trimethoprim-Sulfamethoxazole (oral)	xx (xx.x)	-
Others (oral)	xx (xx.x)	-
Ceftriaxone	-	xx (xx.x)
Ceftazidime	-	xx (xx.x)
Cefepime	-	xx (xx.x)
Cefazolin	-	xx (xx.x)

Meropenem/other carbapenem	-	xx (xx.x)
Amoxicillin-Clavunalate	-	xx (xx.x)
Piperacillin-Tazobactam	-	xx (xx.x)
Others (IV)	-	xx (xx.x)
Missing	xx (xx.x)	xx (xx.x)
Sites of administration of study drugs, n (%)		
Inpatient	xx (xx.x)	xx (xx.x)
Inpatient and home	xx (xx.x)	xx (xx.x)
Outpatient	xx (xx.x)	xx (xx.x)
Inpatient and outpatient	xx (xx.x)	xx (xx.x)
Missing	xx (xx.x)	xx (xx.x)
Time to index hospital discharge from randomisation (day)		
M (missing)	xx (x)	xx (x)
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
Median (Q1-Q3)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)
Min, Max	xx.x, xx.x	xx.x, xx.x
Time to index hospital discharge from index hospital admission (day)		
M (missing)	xx (x)	xx (x)
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
Median (Q1-Q3)	xx.x (xx.xx-xx.xx)	xx.x (xx.xx-xx.xx)
Min, Max	xx.x, xx.x	xx.x, xx.x

M: number of subjects with non-missing values; SD: standard deviation; Q1: lower quartile; Q3: upper quartile; n (%): number and percentage of subjects based on N.
[1]Only top five antibiotics will be listed. The rest will be grouped under "Others".
[2]Days exclude gaps in antibiotics prescriptions.
[3]For subjects given more than one antibiotics for empiric therapy, therapy will be considered "Effective" if at least one sensitive response was observed.
[4]Antibiotics prescribed for definitive therapy. Definitive therapy includes treatment de-escalation.
[5]Ommitted pills or doses weighted over daily frequency were considered as days on which subject was not antibiotics.
[6]Subject considered to be 100% compliance if documented to have taken oral antibiotics (early oral stepdown) or IV antibiotics (continuing intravenous) as scheduled. Total number of days on prescribed antibiotics, excluding empiric therapy, is the numerator.
*Note: Modified intention-to-treat population consists of randomised subjects (i) those who did not have Day 30 mortality data, (ii) intervention arm subjects who did not receive any oral fluoroquinolones or oral trimethoprim-sulfamethoxazole post-randomisation and (iii) standard arm subjects who did not receive any IV antibiotics post-randomisation.

Table 12 Overall Summary of Adverse Events by Treatment

Population: Treated*

	Early Oral Stepdown (Intervention Arm) (N = XX)		Continuing Intravenous (Standard Arm) (N = XX)		Total (N = XX)	
	n (%)	nAE	n (%)	nAE	n (%)	nAE
Adverse event category						
AEs[1,2]	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
SAEs[3]	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Treatment related AEs[1,4]	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Treatment related grade 3-5 AEs[1,4]	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Treatment related SAEs[4]	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Solicited AEs[1,2]	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Solicited grade 3-5 AEs[1,2]	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Solicited SAEs[3]	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
C. difficile associated diarrhoea	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Catheter-related complication	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Liver function test abnormalities	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx

Acute kidney injury	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx

AEs: adverse events; SAEs: serious adverse events; n (%): number (percent) of subjects; nAE: number of adverse events.
[1]Includes SAEs.
[2]For non-serious events, only treatment related ones have been included in this table.
[3]Both treatment and non-treatment related SAEs included.
[4]Treatment related adverse event is defined as AE or SAE with 'possibly related' or 'related' relationship with treatment.
*Note: The term adverse event means it includes serious adverse events. Treated population consists of all randomised subjects who continued study treatment (i.e. oral fluoroquinolones, oral trimethoprim-sulfamethoxazole or IV antibiotics therapy) post-randomisation

Table 13 Summary of Treatment Related Adverse Event Terms

Population: Treated*

	Early Oral Stepdown (Intervention Arm) (N = XX)					
	Grade 1-2		Grade 3-5		SAE	
	n (%)	nAE	n (%)	nAE	n (%)	nAE
[Adverse event term #1]	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
…						
[Adverse event term #X]	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
	Continuing Intravenous (Standard Arm) (N = XX)					
	Grade 1-2		Grade 3-5		SAE	
	n (%)	nAE	n (%)	nAE	n (%)	nAE
[Adverse event term #1]	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
…						
[Adverse event term #X]	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx

n (%): number (percent) of subjects; nAE: number of adverse events; SAE: serious adverse event.
*Note: The term adverse event means it includes serious adverse events. Treatment related adverse event is defined as AE or SAE with “possibly related” or “related” relationship with treatment. Treated population consists of all randomised subjects who continued study treatment (i.e. oral fluoroquinolones, oral trimethoprim-sulfamethoxazole or IV antibiotics therapy) post-randomisation.

Table 14 Comparison of Special Interest Treatment Related Adverse Events

Population: Treated*

n (%) / nAE	Early Oral Stepdown (Intervention Arm) (N = XX)	Continuing Intravenous (Standard Arm) (N = XX)	p-value[1]
C. difficile-associated diarrhoea	xx (x.xx) / xxx	xx (x.xx) / xxx	0.xxx
Catheter-related complications	xx (x.xx) / xxx	xx (x.xx) / xxx	0.xxx
Liver function test abnormalities or acute kidney injury	xx (x.xx) / xxx	xx (x.xx) / xxx	0.xxx

n (%): number (percent) of subjects; nAE: number of adverse events.
[1]Fisher's exact test.
Note: Treated population consists of all randomised subjects who continued study treatment (i.e. oral fluoroquinolones, oral trimethoprim-sulfamethoxazole or IV antibiotics therapy) post-randomisation.

MOCK-UP FIGURES

Figure 1 Patient Disposition – CONSORT Diagram

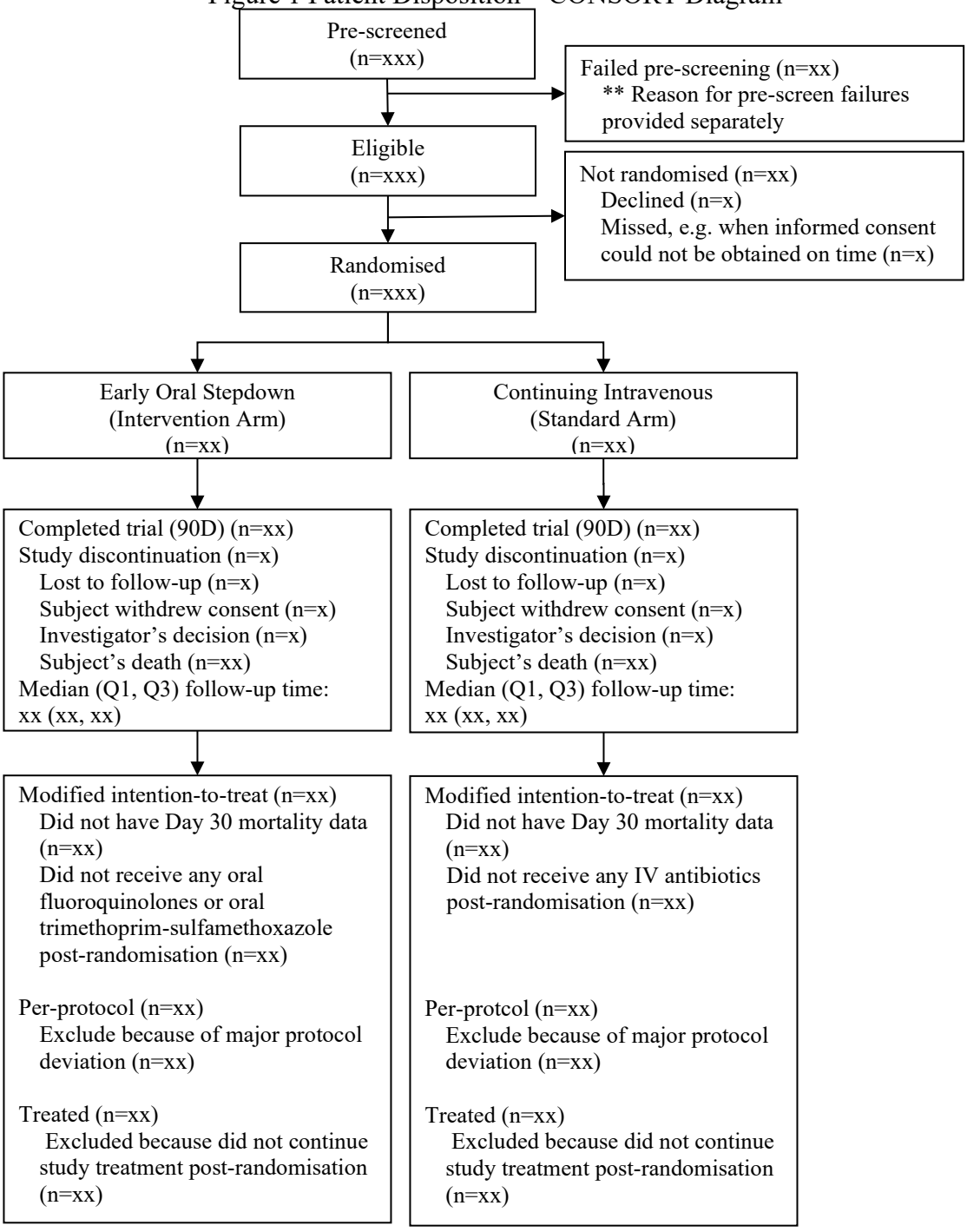
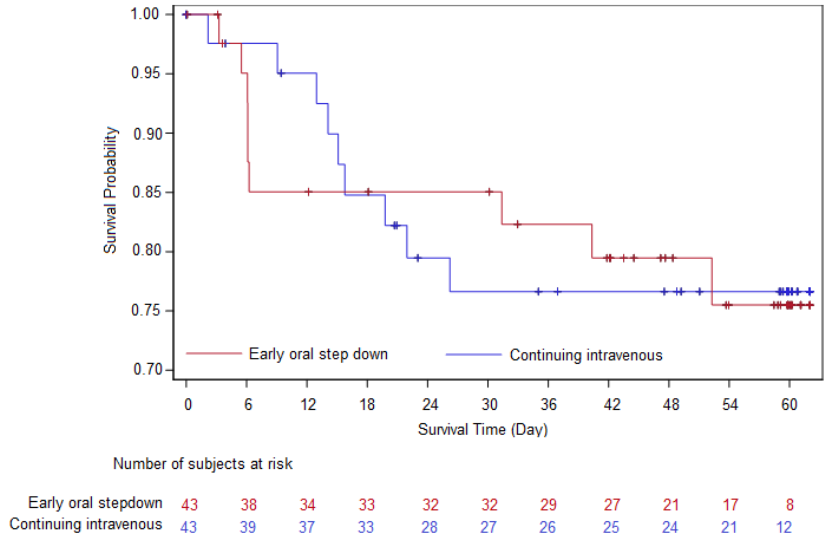


Figure 2 Kaplan-Meier Estimate For Survival

Population: Modified intention-to-treat*



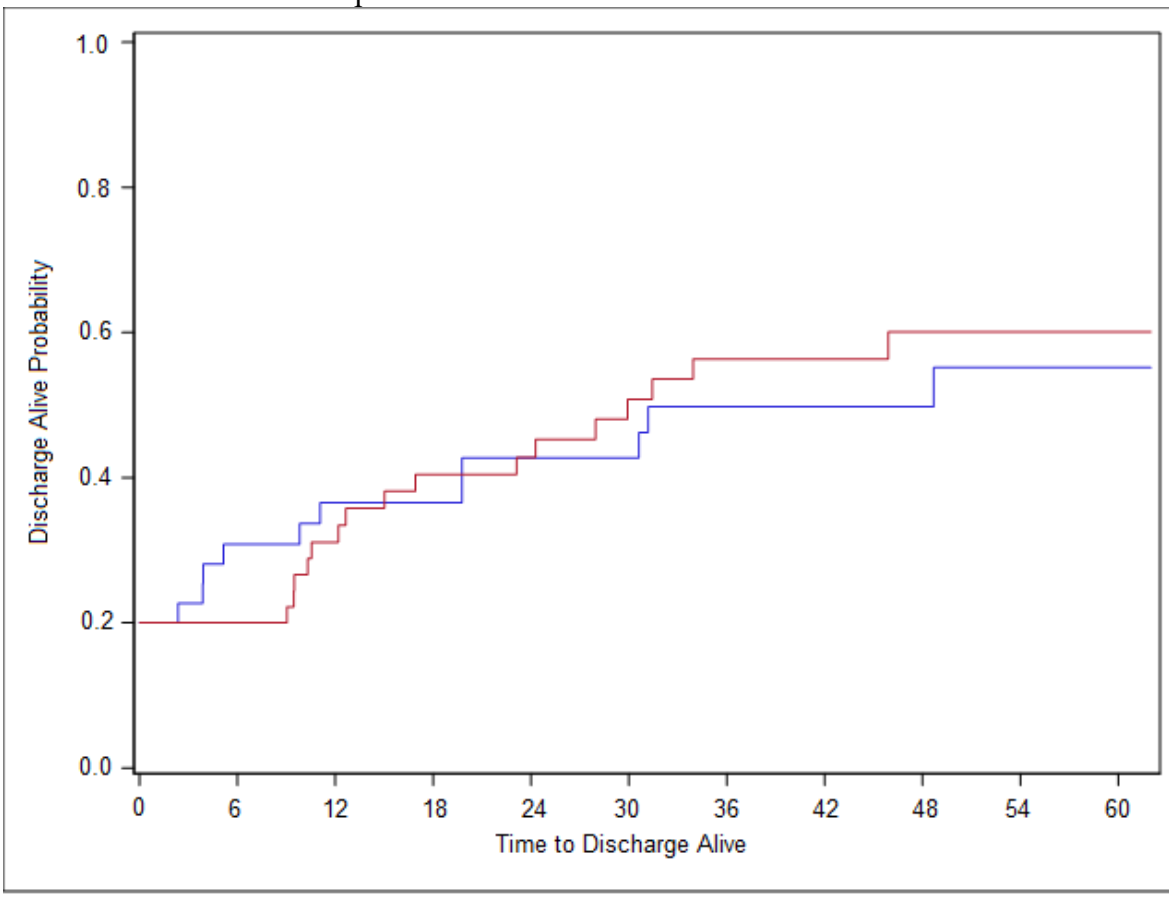
Number of subjects at risk

Early oral stepdown	43	38	34	33	32	32	29	27	21	17	8
Continuing intravenous	43	39	37	33	28	27	26	25	24	21	12

*Note: Modified intention-to-treat (mITT) population consists of randomised subjects excluding (i) those who did not have Day 30 mortality data, (ii) intervention arm subjects who did not receive any oral fluoroquinolones or oral trimethoprim-sulfamethoxazole post-randomisation and (iii) standard arm subjects who did not receive any IV antibiotics post-randomisation. The same figure will be replicated for per-protocol (PP) population. PP population consists of subjects included in the mITT population but excluding those with major protocol deviation which may significantly affects the primary endpoint. The same figure will be replicated for ITT population if there is a difference of least 5% between ITT population size and the mITT population size.

Figure 3 Cumulative Incidence of Discharge Alive from Fine and Gray's model

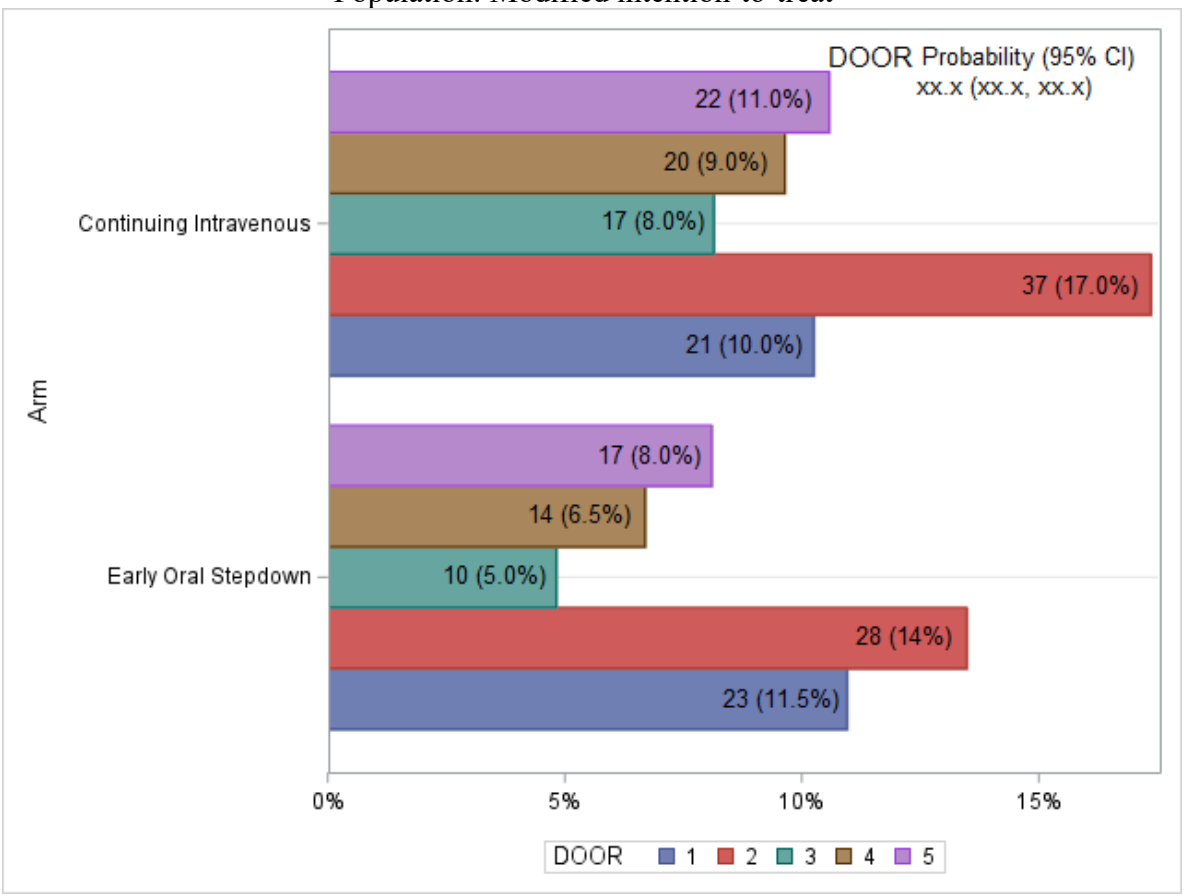
Population: Modified intention-to-treat*



*Note: Modified intention-to-treat (mITT) population consists of randomised subjects excluding (i) those who did not have Day 30 mortality data, (ii) intervention arm subjects who did not receive any oral fluoroquinolones or oral trimethoprim-sulfamethoxazole post-randomisation and (iii) standard arm subjects who did not receive any IV antibiotics post-randomisation. The same figure will be replicated for per-protocol (PP) population. PP population consists of subjects included in the mITT population but excluding those with major protocol deviation which may significantly affects the primary endpoint. The same figure will be replicated for ITT population if there is a difference of least 5% between ITT population size and the mITT population size.

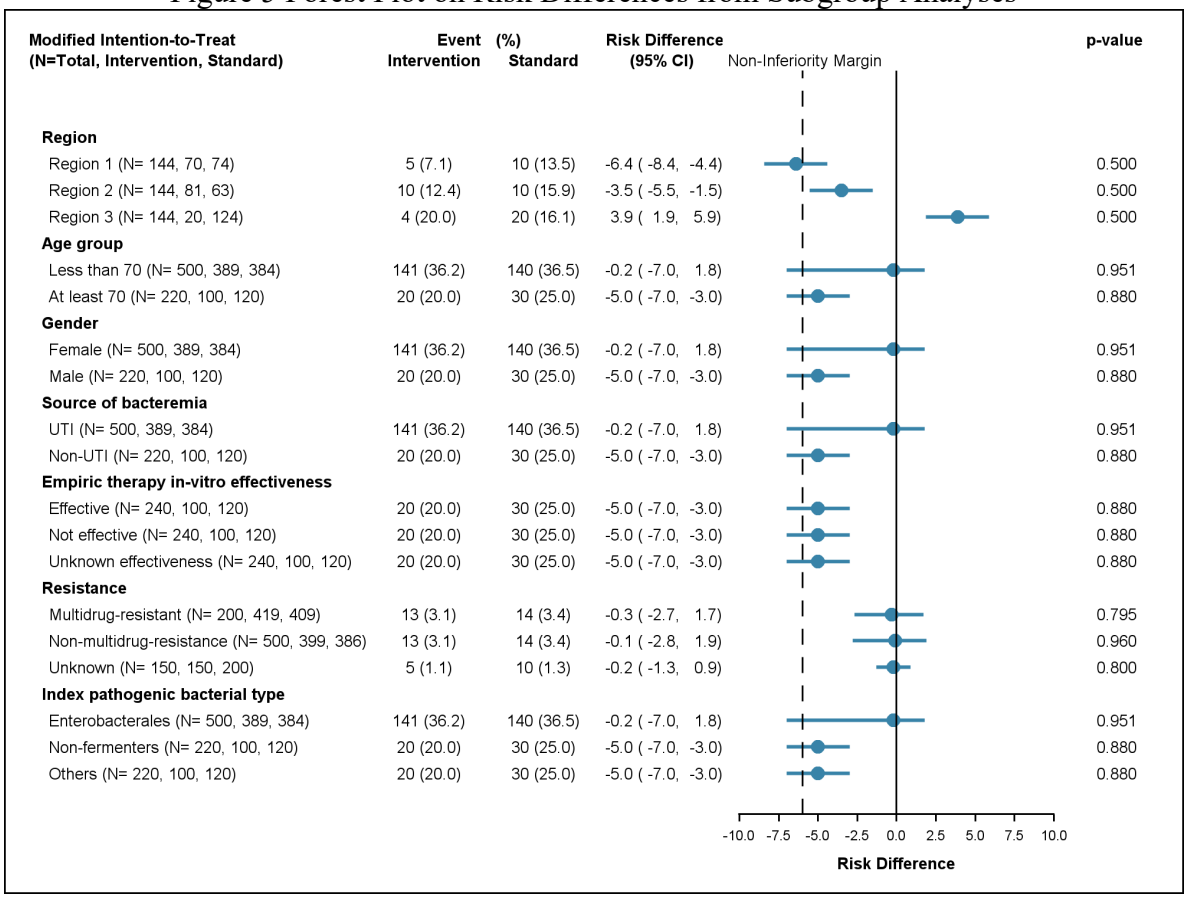
Figure 4 Distribution of DOOR Ranking by Arm

Population: Modified intention-to-treat*



DOOR: desirability of outcome ranking; CI: confidence interval.
*Note: Modified intention-to-treat (mITT) population consists of randomised subjects excluding (i) those who did not have Day 30 mortality data, (ii) intervention arm subjects who did not receive any oral fluoroquinolones or oral trimethoprim-sulfamethoxazole post-randomisation and (iii) standard arm subjects who did not receive any IV antibiotics post-randomisation.

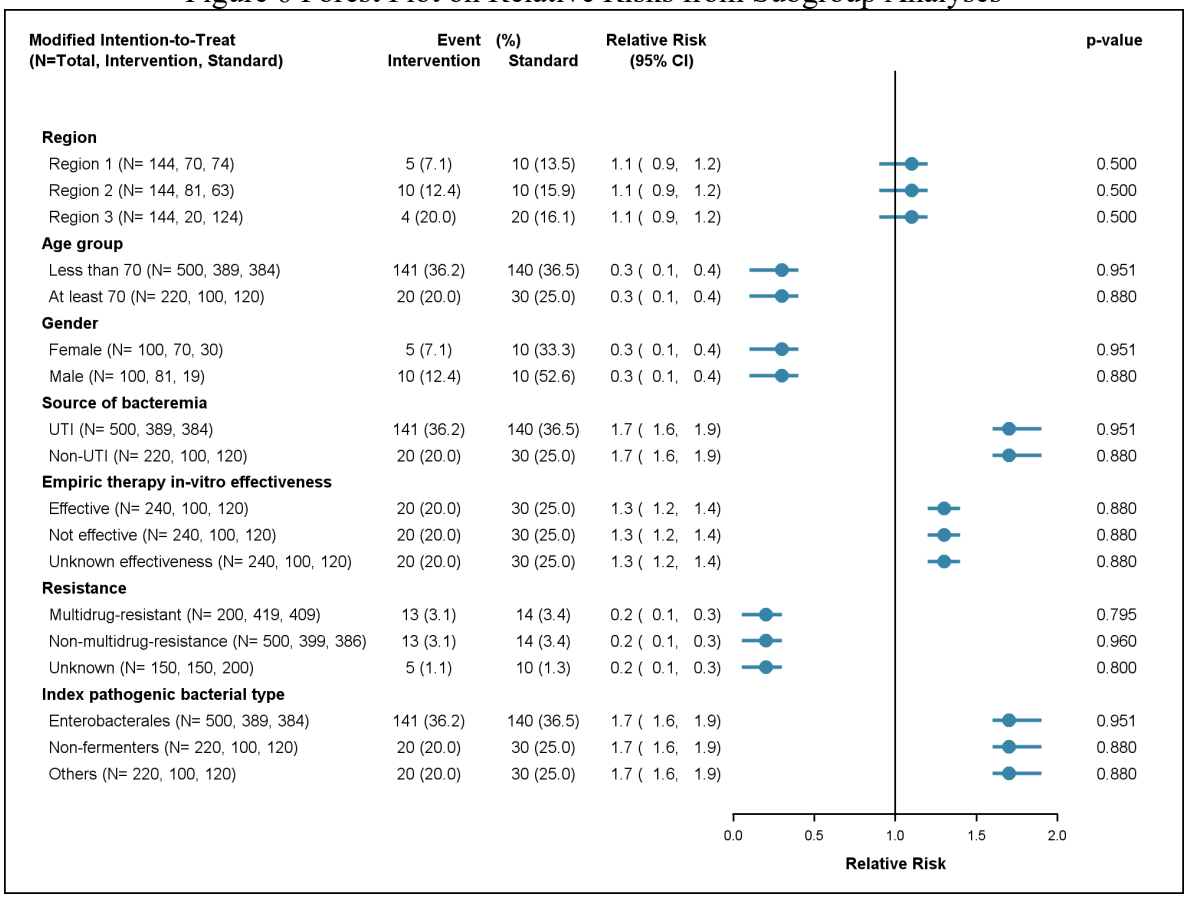
Figure 5 Forest Plot on Risk Differences from Subgroup Analyses



Intervention: early oral stepdown arm; standard: continuing intravenous arm; event: 30-day all-cause mortality; CI: confidence interval.

Note: Modified intention-to-treat (mITT) population consists of randomised subjects excluding (i) those who did not have Day 30 mortality data, (ii) intervention arm subjects who did not receive any oral fluoroquinolones or oral trimethoprim-sulfamethoxazole post-randomisation and (iii) standard arm subjects who did not receive any IV antibiotics post-randomisation.

Figure 6 Forest Plot on Relative Risks from Subgroup Analyses



Intervention: early oral stepdown arm; standard: continuing intravenous arm; event: 30-day all-cause mortality; CI: confidence interval.
Note: Modified intention-to-treat (mITT) population consists of randomised subjects excluding (i) those who did not have Day 30 mortality data, (ii) intervention arm subjects who did not receive any oral fluoroquinolones or oral trimethoprim-sulfamethoxazole post-randomisation and (iii) standard arm subjects who did not receive any IV antibiotics post-randomisation.

MOCK-UP LISTINGS

Listing 1 Listing of Grade 3-5 Treatment Related Adverse Events

Population: Treated*

Subject ID	Randomisation Date	Treatment Arm	Country	Site	Reported Term	Type of Solicited Adverse Event	Relationship to Study Treatment	Expected?	Event Start Date	Event End Date	Action Taken to Study Treatment
SGPXXX	DD MM YYYY	Early Oral Stepdown (Intervention Arm)	Singapore	xxx	[AE X]	-	XXX	No	DD MM YYYY	DD MM YYYY	XXX
MYSXXX	DD MM YYYY	Continuing Intravenous (Standard Arm)	Malaysia	xxx	[AE X]	XXX	XXX	Yes	DD MM YYYY	DD MM YYYY	XXX
…											

*Note: Treated population consists of all randomised subjects who continued study treatment (i.e. oral fluoroquinolones, oral trimethoprim-sulfamethoxazole or IV antibiotics therapy) post-randomisation

Listing 2 Listing of Serious Adverse Events

Population: Treated*

Subject ID	Randomisation Date	Treatment Arm	Country	Site	Reported Term	Type of Solicited Adverse Event	Seriousness Criteria	Relationship to Study Treatment	Expected?	Event Start Date	Event End Date	Action Taken to Study Treatment
SGPXXX	DD MM YYYY	Early Oral Stepdown (Intervention Arm)	Singapore	xxx	[AE X]	-	XXX	XXX	Yes	DD MM YYYY	DD MM YYYY	XXX
TXCXXX	DD MM YYYY	Continuing Intravenous (Standard Arm)	Malaysia	xxx	[AE X]	XXX	XXX	XXX	No	DD MM YYYY	DD MM YYYY	XXX
…												

*Note: Treated population consists of all randomised subjects who continued study treatment (i.e. oral fluoroquinolones, oral trimethoprim-sulfamethoxazole or IV antibiotics therapy) post-randomisation.

Listing 3 Listing of Subjects with at Least One Clinically Significant Haematology or Clinical Chemistry Result

Population: Treated*

Subject ID	Treatment Arm	Country	Site	Parameter (Unit)	Timepoint	Lab Result	Abnormal?	Clinically Significant Result?
SGPXXX	Early Oral Stepdown (Intervention Arm)	Singapore	xxx	Haemoglobin (g/dL)	Screening	xxx	Yes	Yes
					Before hospital discharge	xxx	No	No
MYSXXX	Continuing Intravenous (Standard Arm)	Malaysia	xxx	C-reactive protein (nmol/L)	Baseline	xxx	No	No
					Before hospital discharge	xxx	Yes	Yes
…								

*Note: Treated population consists of all randomised subjects who continued study treatment (i.e. oral fluoroquinolones, oral trimethoprim-sulfamethoxazole or IV antibiotics therapy) post-randomisation.

Listing 4 Major Protocol Deviations

Subject ID	Treatment Arm	Country	Site	Category	Description
SGPXXX	Early Oral Stepdown (Intervention Arm)	Singapore	xxx	Inclusion	
MYSXXX	Continuing Intravenous (Standard Arm)	Malaysia	xxx	On study	
…					

REFERENCES

[1] N. Luo, T. Vasan, L. Cheng, Z. Yang, K. Rand, Y. Cheung and J. Thumboo, "Developing an EQ-5D-5L Value Set for Singapore," *Pharmacoeconomics,* 2025.

[2] M. de Kraker, V. Jarlier, J. Monen, O. Heuer, N. van de Sande and H. Grundmann, "The changing epidemiology of bacteraemias in Europe: trends from the European Antimicrobial Resistance Surveillance System," *Clin Microbiol Infect,* vol. 19, no. 9, pp. 860-868, 2012.

[3] P. Tamma, A. Conley, S. Cosgrove, A. Harris, E. Lautenbach, J. Amoah, E. Avdic, P. Tolomeo, J. Wise, S. Subudhi, J. Han and A. R. L. Group, "Association of 30-Day Mortality With Oral Step-Down vs Continued Intravenous Therapy in Patients Hospitalized With Enterobacteriaceae Bacteremia," *JAMA Intern Med,* vol. 179, no. 3, p. 316–323, 2019.

[4] W. MacNeal and F. Frisbee, "One Hundred Patients with Staphylococcus Septicemia Receiving Bacteriophage Service," *American Journal of the Medical Sciences,* vol. 191, no. 2, pp. 179-195, 1936.

[5] T. Mendell, "Staphylococcic Septicemia - A Review of Thirty-Five Cases, with Six Recoveries, Twenty-Nine Deaths and Sixteen Autopsies," *Arch Intern Med,* vol. 63, no. 6, pp. 1068-1083, 1939.

[6] J. Howard-Anderson, W. Dai, D. Yahav, T. Hamasaki, A. Turjeman, F. Koppel, E. Franceschini, C. Hill, Z. Sund, H. Chambers, F. Jr, H. Boucher, S. Evans, M. Paul, T. Holland, S. Doernberg and A. R. L. Group, "A Desirability of Outcome Ranking Analysis of a Randomized Clinical Trial Comparing Seven Versus Fourteen Days of Antibiotics for Uncomplicated Gram-Negative Bloodstream Infection," *Open Forum Infect Dis,* vol. 9, no. 6, 2022.

[7] S. Evans, D. Rubin, D. Follmann, G. Pennello, W. Huskins, J. Powers, D. Schoenfeld, C. Chuang-Stein, S. Cosgrove, V. Jr, E. Lautenbach and H. Chambers, "Desirability of Outcome Ranking (DOOR) and Response Adjusted for Duration of Antibiotic Risk (RADAR)," *Clinical Infectious Diseases,* vol. 61, no. 5, pp. 800-806, 2015.

[END OF THE DOCUMENT]