STUDY PROTOCOL

PROTOCOL TITLE:

Early oral step-down antibiotic therapy versus continuing intravenous therapy for uncomplicated Gram-negative bacteraemia (the INVEST trial)

PROTOCOL VERSION: 10.0
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Investigator Protocol Agreement Page

- I confirm agreement to conduct the study in compliance with the protocol, International Conference on Harmonisation Guideline for Good Clinical Practice (ICH-GCP) and applicable local regulations.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study and maintain the appropriate records and documentation required.
- I agree to ensure that all site staff involved in the conduct of the study will be appropriately trained and informed of their responsibilities and obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Principal Investigator Name:

Investigator Signature	Date

Key Information & Synopsis

Key Information of the Study	
Study title	Early oral step-down antibiotic therapy versus continuing intravenous therapy for uncomplicated Gram-negative bacteraemia (the INVEST trial)
Domain Specific Review Board identifier	2021/00764
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Study duration (patient recruitment and follow up)	Oct 2021 – Mar 2026
Overarching coordinating centre / Study sponsor	Tan Tock Seng Hospital, Singapore
Overarching coordinating network	Singapore Infectious Disease Clinical Research Network
Collaborating bodies	Singapore Clinical Research Institute
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Trial Steering Committee	Site Principal Investigators (PIs) are ex officio members of the Trial Steering Committee. Prof David Paterson, Director of ADVANCE-ID, is the independent Chairperson of the committee.
Study Synopsis	
Background	The incidence of Gram-negative bacteraemia is rising globally, and remains a major cause of morbidity and mortality for hospitalised patients. Although practice guidelines provide general recommendations for treatment duration for Gram-negative bacteraemia, the optimal route of administration is yet to be definitively defined. The majority of patients with Gram-negative bacteraemia initially receive intravenous (IV) antibiotic therapy. However, it remains unclear whether patients can step down to oral antibiotics after appropriate clinical response has been observed without compromising outcomes. Although the efficacy of early oral step-down therapy versus continuing IV therapy for uncomplicated Gram-negative bacteraemia is unknown, the advantages of oral therapy are evident. Compared with IV therapy, oral therapy eliminates the risk of catheter-associated adverse events, enhances patient quality of life, and reduces total healthcare costs.
Purpose of study	Current management of uncomplicated Gram-negative bacteraemia entails a duration of IV antibiotic therapy with limited evidence to guide oral conversion. We aim to evaluate the clinical efficacy and economic impact of early step-down 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) for clinically stable / non-critically ill inpatients with uncomplicated Gram-negative bacteraemia.
Hypothesis	- Early step-down to oral fluoroquinolones or trimethoprim-sulfamethoxazole will be clinically non-inferior to continuing IV

	antibiotic therapy - Early oral step-down therapy will result in lower health resource and service utilisation costs compared with continuing IV therapy
Primary outcome	Compare the all-cause mortality at day 30 post-randomisation in patients from the standard arm versus intervention arm.
Key secondary outcomes	Compare between standard and intervention arms: - All-cause mortality at days 14 and 90 - Number of days on IV therapy in the total index hospitalisation (including outpatient parenteral antibiotic therapy [OPAT]) for surviving participants from the time of randomisation until i. hospital discharge and ii. day 90 - Adverse events by day 90, including *Clostridioides difficile*-associated diarrhoea, catheter-related complications, and liver function test abnormalities or acute kidney injury - Time to being discharged alive from the total index hospitalisation (including OPAT and hospital-in-the-home) by day 90 - Health economic evaluation by day 90, including estimation of total healthcare cost as well as assessment of patient's quality of life and number of quality adjusted life years saved
Exploratory outcome	Composite outcome for Desirability Of Outcome Ranking (DOOR)
Study design	This is an international, multicentre, randomised controlled, open-label, phase IV, non-inferiority trial with a non-inferiority margin of 6%. Eligible participants must be clinically stable / non-critically ill inpatients over the age of 18 (21 in Singapore) with uncomplicated Gram-negative bacteraemia. Randomisation into the intervention or standard arms will be performed with 1:1 allocation ratio according to a randomisation list prepared in advance using a secure online randomisation system. Randomisation will be stratified by country and random sequence will be generated using random permuted blocks of unequal length. Participants randomised to the intervention arm (within 72 hours from index blood culture collection) will be immediately converted to an oral fluoroquinolone (most commonly, ciprofloxacin) or trimethoprim-sulfamethoxazole. In the event of microbiological or clinical failure of the oral antibiotic treatment, escalation to IV antibiotics may be initiated at any time point post-randomisation. Participants randomised to the standard arm should continue to receive IV therapy for at least another 24 hours post-randomisation before clinical re-assessment and decision making by the treating doctor. All study drugs (and dosage) would be those routinely used in clinical practice and will be ordered/dispensed from the hospital pharmacy as per site institutional practice. The recommended treatment duration is 7 days of active antibiotics (including empiric therapy), although treatment regimen may be longer than 7 days if clinically indicated. Participants may be discharged home or to OPAT at any time post-randomisation.
Inclusion criteria	- ≥1 set of blood cultures positive for GNB associated with evidence of infection - Able to be randomised within 72 hours of index blood culture collection - Age ≥18 years (≥21 in Singapore)

	- Latest Pitt bacteraemia score <4 - Patient or legal representative is able to provide informed consent
Exclusion criteria	- Established uncontrolled focus of infection (e.g. undrained abdominal abscess) - Complicated infections (e.g. necrotising fasciitis) - Septic shock - Polymicrobial bacteraemia - Bacteraemia due to vascular catheter or intravascular materials that cannot be removed - Specific Gram-negative pathogens that cannot be effectively treated with fluoroquinolones or trimethoprim-sulfamethoxazole (e.g. *Burkholderia, Brucella*) - Index GNB with resistance to fluoroquinolones AND trimethoprim-sulfamethoxazole - Hypersensitivity to fluoroquinolones AND sulpha drugs - Unable to consume or absorb oral medications for any reason or unsuitable for ongoing IV therapy (e.g. no intravenous access) - Severely immunocompromised - Women who are known to be pregnant or breast-feeding - Treatment is not with intent to cure the infection - Unable to collect patient's follow-up data for at least 30 days post-randomisation - Treating doctor deems enrolment into trial is not in the best interest of the patient - Previous enrolment in this trial
Sample size	Assuming a 30-day mortality of 8% in the standard and intervention arms, with 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. Recruitment will take place in numerous hospital sites from Singapore, Australia, United Kingdom, Malaysia, South Korea, Israel, Turkey, Lebanon, Greece, Spain, Italy and Taiwan.
Statistical analyses	Primary analysis will be performed on the modified intention-to-treat (mITT) population, which consists of all randomised patients excluding (i) those who did not have 30-day all-cause mortality data, (ii) intervention arm patients who did not receive any oral fluoroquinolones or oral trimethoprim-sulfamethoxazole post-randomisation, and (iii) standard arm patients who did not receive any IV antibiotics post-randomisation. Risk difference of 30-day all-cause mortality and its 95% confidence interval between intervention and standard arms will be estimated and compared using chi-squared test. If the upper limit of the 95% confidence interval falls below the 6% non-inferiority margin, clinical non-inferiority will be concluded. Economic viability will be assessed through health economic evaluation according to ITT principle from healthcare system and patient perspectives. For base case analysis, private rate of each resource utilisation will be applied to calculate the average cost and savings. The health economic analysis will have two components: - If results confirm clinical non-inferiority, a cost saving analysis

	will be conducted to estimate the economic impact of the new treatment regimen - If results fail to confirm clinical non-inferiority, a cost effectiveness analysis will be conducted to estimate the incremental cost effectiveness ratio (ICER) by comparing the difference in cost and clinical outcomes as well as quality-of-life between the two treatment arms (ICER=ΔC/ΔE)

Contents

1. BACKGROUND AND RATIONALE

1.1. General Introduction

The incidence of Gram-negative bacteraemia is rising globally, and remains a major cause of morbidity and mortality for hospitalised patients. *Enterobacterales*, particularly *Escherichia coli* and *Klebsiella pneumoniae*, are currently the predominant pathogens isolated from blood, overtaking the Gram-positive *Staphylococcus aureus* as the major cause of bacteraemia.[1,2] Although practice guidelines provide general recommendations for antibiotic treatment duration for Gram-negative bacteraemia, the optimal route of administration is yet to be definitively defined.[3] The majority of patients with Gram-negative bacteraemia initially receive intravenous (IV) antibiotic therapy. However, it remains unclear whether patients can step down to oral therapy after appropriate clinical response has been observed without compromising outcomes. Doctors must exercise judgement based on multiple factors such as severity of disease, host immune status, anticipated adherence, and predicted adequacy of drug absorption and infection-site penetration. Limited data suggesting conversion to oral therapy is effective and safe are generally restricted to Gram-negative bacteraemia secondary to urinary tract infection (UTI).[4–7] Although the efficacy of early oral step-down therapy versus continuing IV therapy for uncomplicated Gram-negative bacteraemia (not limited to urinary tract sources) is unknown, the advantages of oral therapy are evident. Compared with IV therapy, oral therapy eliminates the risk of catheter-associated adverse events such as venous thrombosis, phlebitis, line breakage and catheter-associated bloodstream infections.[8,9] Oral therapy enhances patient quality of life by eliminating discomfort associated with IV catheters, enabling mobility and reducing length of stay (LOS) in hospital.[8,9] The healthcare cost of oral therapy is lower compared with IV therapy as there are no charges associated with placement/maintenance of central lines or drug preparation and administration.[8,10]

1.2. Rationale and justification for the Study

Tamma *et al* recently compared patient outcomes from early oral step-down therapy (within the first 5 days of treatment) versus continued IV therapy for monomicrobial *Enterobacterales* bacteraemia.[7] This retrospective multicentre study involved a 1:1 propensity score-matched cohort of 4,967 unique cases. Key eligibility criteria included: effective antibiotics administered from day 1 until treatment discontinuation, appropriate source control and clinical response by day 5. The authors found that 30-day all-cause mortality was not significantly different between 739 patients who received oral step-down therapy versus 739 on continued IV therapy (HR 1.03, 95% CI 0.82–1.30). This suggested conversion to oral therapy may be an efficacious option for patients who received appropriate source control and demonstrated favourable clinical response to the initial IV therapy. Additionally, patients who stepped down to oral therapy were discharged from hospital an average of 2 days earlier than those who continued IV therapy (5 [IQR 3–8] days vs. 7 [IQR 4–14] days; $p < 0.001$).

In an earlier retrospective single-centre study of *Enterobacterales* bacteraemia from the urinary tract, Rieger *et al* compared outcomes between 135 patients who transitioned early to oral therapy (median 4 days of IV therapy) versus 106 patients who continued to receive IV therapy.[4] The composite outcome consisted of treatment failure defined by escalation to IV antibiotic from oral antibiotic, change in antibiotic due to worsening clinical status, and readmission due to the same UTI and/or bacteraemia within 30 days of discharge. The key eligibility criterion was positive urine and blood cultures collected within 24 hours with the same *Enterobacterales*

pathogen. Treatment failure was not significantly different between patients who received only IV antibiotics versus those who received IV-oral antibiotics (3.8% [95% CI 1.0–9.4%] vs. 8.2% [95% CI 4.1–14.1%]; $p = 0.19$). Similar to Tamma *et al,*[7] the authors reported that patients who transitioned early to oral therapy were discharged from hospital approximately 2 days earlier than patients who continued to receive IV therapy (4.6 [IQR 3.1–7.8] days vs. 7.1 [IQR 4.0–17.5] days; $p < 0.001$).

a. Rationale for the Study Purpose

No randomised controlled trial (RCT) has been conducted to assess the efficacy of early oral step-down therapy for uncomplicated Gram-negative bacteraemia that are not limited to urinary tract sources. High-bioavailability oral antibiotics such as fluoroquinolones or trimethoprim-sulfamethoxazole have been utilised for Gram-negative bacteraemia based on clinical and pharmacokinetics/pharmacodynamics (PK/PD) data.[11–13] However, the use of fluoroquinolones and trimethoprim-sulfamethoxazole increases the risk of potential adverse effects including *Clostridioides difficile*-associated diarrhoea.[13–15] As a result, interest has been spurred in the role of oral β-lactams that have low-to-moderate bioavailability. The question of whether oral β-lactams can be used as an efficacious alternative to oral fluoroquinolones or trimethoprim-sulfamethoxazole for Gram-negative bacteraemia is controversial.

Many doctors assume that patients who switch to oral fluoroquinolones or trimethoprim-sulfamethoxazole are less likely to experience treatment failure compared with patients who switch to oral β-lactams. This is due to the higher bioavailability and more favourable PK/PD profile of fluoroquinolones and trimethoprim-sulfamethoxazole compared with β-lactams. This assumption is supported by the retrospective study of Kutob *et al,* which investigated whether varying bioavailabilities of different oral antibiotics affected outcomes for Gram-negative bacteraemia predominantly from the urinary tract.[16] The authors found the risk of treatment failure was higher in patients who received antibiotics with low-to-moderate bioavailability compared to those who received antibiotics with high bioavailability.

However, in another retrospective study by Mercuro *et al,* clinical success was similar between patients who received oral fluoroquinolones and those who received oral β-lactams as step-down therapy for *Enterobacterales* bacteraemia.[17] Likewise, in the earlier described study by Tamma *et al,* the authors found no difference in 30-day mortality between patients who switched to high-bioavailability agents versus those who switched to low-bioavailability agents.[7] It is noteworthy the studies by Kutob *et al,* Mercuro *et al* and Tamma *et al* were underpowered to determine whether bioavailability of oral antibiotics is crucial for successful treatment of Gram-negative bacteraemia.[7,16,17]

b. Rationale for Doses Selected

In view of the uncertainty associated with high-bioavailability versus low-bioavailability agents for Gram-negative bacteraemia, our team decided the oral step-down arm of this RCT will consist only of fluoroquinolones or trimethoprim-sulfamethoxazole. This conservative decision (in not testing oral β-lactams) is supported by a recent review article highlighting many oral β-lactams have short half-life requiring frequent dosing that may negatively impact patient adherence.[18] Furthermore, the dose of oral β-lactams (unlike IV β-lactams) required to attain specific PD targets is still unclear and the determination of minimum inhibitory concentration of

oral β-lactams is not routinely performed in many hospitals.[18] This conundrum is further complicated in clinical scenarios when dose adjustments are needed for patients with renal impairment.[18] A recent systematic review and meta-analysis revealed infection recurrence occurred more frequently in Gram-negative bacteraemic patients transitioned to oral β-lactams compared with oral fluoroquinolones, although all-cause mortality was not significantly different between the β-lactams group versus fluoroquinolones or trimethoprim-sulfamethoxazole group.[19]

In this RCT, the recommended doses of oral antibiotics to be used in the intervention arm for patients with normal renal function would be ciprofloxacin 750 mg twice daily (if body weight ≥70 kg) or ciprofloxacin 500 mg twice daily (if body weight <70 kg) or trimethoprim-sulfamethoxazole 5 mg/kg (for trimethoprim component) every 12 hours up to a maximum trimethoprim-sulfamethoxazole (160 mg / 800 mg; double strength) two tablets twice daily. Ciprofloxacin is the most common fluoroquinolone class of antibiotics for treatment of Gram-negative bacteraemia. For patients in the standard arm, the IV antibiotic dose will be determined by the patient's treating doctor (e.g. ceftriaxone 2 g daily, cefazolin 2 g three times daily). 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. Treatment duration is not the focus/subject of this trial as there is one ongoing RCT (BALANCE, NCT02261506) investigating optimal duration of antibiotic therapy for Gram-negative bacteraemia. The study drugs are routinely used in clinical practice and will be ordered/dispensed from the hospital pharmacy as per site institutional practice.

c. Rationale for Study Population

Current management of uncomplicated Gram-negative bacteraemia typically entails a duration of IV antibiotic therapy with limited evidence from prospective studies to guide oral conversion. In this RCT, we aim to evaluate the clinical efficacy and economic impact of early step-down to oral antibiotics (within 72 hours from the time of index blood culture collection) versus continuing IV therapy (for at least another 24 hours post-randomisation) for clinically stable / non-critically ill inpatients with uncomplicated Gram-negative bacteraemia. As these infections can be seen in a large range of clinical situations spanning all hospital departments and patient populations, the study logically requires recruitment of patients from all areas of the hospital system. Gram-negative bacteraemias are usually treated in admitted patients and therefore inclusion of outpatients is not applicable.

d. Rationale for Study Design

Recent data from a multicentre, propensity score-matched, retrospective study suggested 7 days of antibiotics may be sufficient for treatment of uncomplicated *Enterobacterales* bacteraemia.[20] Consistent with this, recently completed RCTs demonstrated non-inferiority of 7 days versus 14 days of antibiotic treatment for uncomplicated Gram-negative bacteraemia.[21,22] Therefore, switching to oral therapy on day 7 or later will not be meaningful as it is likely that sufficient IV antibiotics would have already been administered. In this study, we propose 3 days (72 hours from the time of index blood culture collection) as the cut-off time frame for switching to oral therapy for patients randomised to the intervention arm. This proposed randomisation window of 72 hours from index blood culture collection is supported by the observational analyses of

Rieger *et al,* Kutob *et al* and Mercuro *et al,* where patients typically received 3–5 days of IV therapy prior to oral step-down therapy.[4,16,17] The options for oral therapy in this study are fluoroquinolones or trimethoprim-sulfamethoxazole – selected due to their extensive use in clinical practice with well-established safety and efficacy across a plethora of infections. For example, in one of the aforementioned RCTs studying treatment duration for uncomplicated Gram-negative bacteraemia, >70% (across both study arms) received oral fluoroquinolones among the subjects who transitioned to step-down therapy.[21] For patients randomised to the standard arm, the continuing IV antibiotic therapy should be maintained for at least 24 hours post-randomisation before clinical re-assessment and decision making by the treating doctor. At the doctor's discretion, patients in the standard arm may be converted to oral antibiotic therapy (after continuing the IV therapy for at least 24 hours post-randomisation). This data on oral antibiotic switch for patients in the standard arm will be recorded in the case report form (CRF). This study will help inform local and international practice guidelines on optimal antibiotic management for uncomplicated Gram-negative bacteraemia. A finding of non-inferiority in clinical efficacy of oral fluoroquinolones or trimethoprim-sulfamethoxazole versus IV antibiotics may translate to wider adoption of a more cost-effective treatment strategy that reduces hospital LOS as well as better patient-centred outcomes and satisfaction.

2. HYPOTHESIS AND OBJECTVES

2.1. Hypothesis

We hypothesise in clinically stable / non-critically ill patients with uncomplicated Gram-negative bacteraemia that:

1. Early step-down to oral fluoroquinolones or trimethoprim-sulfamethoxazole will be non-inferior to continuing IV antibiotic therapy in the primary outcome of 30-day all-cause mortality, and
2. Early oral step-down therapy will result in significantly lower health resource/service utilisation and associated costs compared with continuing IV therapy.

2.2. Primary Objectives

Compare the all-cause mortality at day 30 post-randomisation in patients from the standard arm versus intervention arm.

2.3. Secondary Objectives

Compare between standard and intervention arms:

1. All-cause mortality at days 14 and 90 from the time of randomisation
2. Duration of survival from the time of randomisation until day 90
3. Number of days on IV antibiotic therapy in the total index hospitalisation (including outpatient parenteral antibiotic therapy [OPAT]) for surviving participants from the time of randomisation until i. hospital discharge and ii. day 90
4. Number of days alive and free of antibiotics (i. for all antibiotics and ii. for IV antibiotics) between the time of randomisation and day 90
5. Adverse events from the time of randomisation until day 90 including:
   - *C. difficile*-associated diarrhoea
   - Peripherally inserted central catheter and other central venous catheter complications (such as catheter-related bloodstream infection, catheter-related superficial or deep

venous thrombosis/thrombophlebitis, catheter blockage, and exit site infection) requiring line removal during index hospitalisation (including OPAT) from the time of randomisation
   - Liver function test abnormalities or acute kidney injury (defined in section 12.1)
6. Change in treatment strategy (e.g. switch to IV antibiotics from allocated oral antibiotics or vice versa) between the time of randomisation and day 30 due to:
   - An adverse event deemed by the treating doctor to be of sufficient severity to change treatment strategy
   - Presumed lack of efficacy of treatment strategy according to the judgement of treating doctor
7. Time to being discharged alive from the total index hospitalisation (including OPAT and hospital in the home) between the time of randomisation and day 90 (note: any death occurrence within 90 days will be considered '90 days')
8. Number of days alive and not in hospital (including OPAT) between the time of randomisation and day 90
9. Readmission or extended hospitalisation by day 90. Readmission is defined as a new hospitalisation for any cause or a return to ambulatory hospital services occurring after discharge from the index hospitalisation. Extended hospitalisation is defined as >14 days of hospital LOS starting from the day of randomisation.
10. Health economic evaluation, including estimation of total healthcare cost (from healthcare system and patient perspective)* and assessment of patient's quality of life via EQ-5D by day 90

    **Cost savings/effectiveness analyses will be performed in selected hospital sites*

    <u>Exploratory outcome</u>

    Composite Desirability Of Outcome Ranking (DOOR) outcome comprising:
    - All-cause mortality at day 30 from the time of randomisation
    - Clinical failure as defined by one or more of the following related to the index infection:
        - Extended duration of active antibiotics beyond 7–14 days, depending on planned duration of original regimen
        - Addition of a rescue antibiotic including switching to an alternate, non-study antibiotic
        - Additional unplanned therapeutic interventions
    - Infectious complications as defined by one or more of the following related to the index infection:
        - Bloodstream relapse due to the same index Gram-negative bacteria (GNB) occurring any time between the completion of study drug intervention period and day 30
        - Distant seeding (i.e. growth of index GNB 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
        - 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
    - Presence of adverse events or serious adverse events (SAEs) that lead to study drug discontinuation
    - Quality-of-life by functional status, calculated as change from baseline functional bacteraemia outcome score (measured on the day of randomisation) to functional bacteraemia outcome score measured on the last day of study drug treatment

Table 1. Functional bacteraemia outcome scoring system.

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

Table 2. Composite 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 QoL functional bacteremia outcome score
2	Yes	1 of 3	
3	Yes	2 of 3	
4	Yes	3 of 3	
5	No	Any	

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

2.4. Potential Risks and Benefits:

a. End Points - Efficacy

Early switch to oral antibiotics (within 72 hours from the time of index blood culture collection) may be clinically non-inferior to continuing IV antibiotic therapy (for at least another 24 hours post-randomisation). The recommended treatment duration for both study arms 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. The benefits of oral therapy over IV therapy include elimination of risk of catheter-associated adverse events, enhancement of patient's quality of life, and reduction of healthcare associated costs.

b. End Points – Safety

All the study drugs would be commonly used in clinical practice for Gram-negative pathogens. We will not be exposing participants to excess risk by study inclusion beyond the risks involved in standard therapeutic decisions and clinical management. The main risk for patients randomised to the intervention arm is that oral antibiotics may not be as efficacious compared with IV antibiotics for treatment of Gram-negative bacteraemia. In the event of microbiological or clinical failure of the oral antibiotic treatment, escalation to IV antibiotics may be initiated at the discretion of the treating doctor at any time point post-randomisation. Antibiotic escalation will not be considered a protocol deviation.

3. STUDY POPULATION

3.1. List the number of subjects to be enrolled

A total of 720 participants will be enrolled in this study. Recruitment in Singapore will be carried out in Tan Tock Seng Hospital, National University Hospital, Singapore General Hospital, Changi General Hospital, Ng Teng Fong General Hospital and Sengkang General Hospital. Recruitment will also be carried out in several overseas sites in Australia (Royal Brisbane and Women's Hospital, Gold Coast University Hospital, John Hunter Hospital, Royal Melbourne Hospital, Princess Alexandra Hospital), Malaysia (University Malaya Medical Centre, Hospital Universiti Kebangsaan Malaysia, Ampang Hospital, Sungai Buloh Hospital), South Korea (Samsung Medical Center, Seoul National University Bundang Hospital), United Kingdom (Imperial College Healthcare NHS Trust, London North West University Healthcare NHS Trust, Chelsea and Westminister NHS Foundation Trust Hospitals), Israel (Sheba Medical Centre, Rambam Hospital), Turkey (Medipol Mega University Hospital), Lebanon (American University of Beirut Medical Centre), Greece (University General Hospital of Patras), Spain (Hospital del Mar), Italy (IRCCS Policlinico di Sant'Orsola, University Alma Mater Studiorum, University Hospital of Pisa, IRCCS San Raffaele Hospital, Monaldi Hospital) and Taiwan (Taichung Veterans General Hospital).

3.2. Criteria for Recruitment

Potential study participants will be identified on the basis of positive blood cultures by liaison between the investigators and the clinical microbiologists. The following information will be transcribed into the screening log by a study team member at the time of referral: date and time the blood culture was collected, hospital record number, participant's name and date of birth, and the date and time referral was received. No "cold-calling" will be performed. The investigator will only approach the patient or his/her legal representative on invitation by the treating team (who will also have been notified of the blood culture results by the clinical microbiologist). The treating team will have the rationale of the study explained to them by the study investigator(s) before any patient contact occurs. On invitation by the treating team, the patient will be approached by a study team member to evaluate suitability for inclusion (by review of medical records and discussion with treating team) and have the study explained to him/her and be offered an opportunity to be enrolled. This will only occur after written material has been provided, and the patient has had time to consider and ask questions to the study team or the treating team. Informed consent will be obtained prior to performing any research-related procedures.

3.3. Inclusion Criteria

Inclusion criteria will be non-restrictive allowing a representative and generalisable cohort of eligible participants including elderly patients:

1. ≥1 set of blood cultures positive for GNB 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

3.4. Exclusion Criteria

Exclusion criteria include:

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 GNB 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

a. Withdrawal Criteria

Subjects may voluntarily withdraw their consent from study participation at any time and for any reason without penalty. A subject may also be withdrawn from participation in the study for the following reasons:

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

Handling of withdrawals

An early termination occurs when an enrolled subject withdraws consent to participate in the study, regardless of circumstances, prior to the primary outcome assessment at day 30. The reason(s) for early termination should be reflected in the source documentation and on the applicable CRF. In all cases, the reasons why a participant is withdrawn must be recorded in detail and entered into the CRF.

b. Subject Replacement

Patients who withdraw from the study will not be replaced. Patients whose randomised treatment is changed due to an adverse event or treatment failure or an unintentionally fulfilled exclusion criterion will remain in the study to assess outcomes and for safety analysis regardless of study arm allocation.

4. TRIAL SCHEDULE

Table 3. Trial schedule of study activities.

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 participant 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 participant 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 participants on oral therapy and documentation of IV antibiotics administered for participants on IV therapy; participant deemed compliant if ≥90% of prescribed study antibiotics taken

i – Only adverse events deemed by the treating and/or study doctor to be related or possibly related to the study drug (from standard arm or intervention arm) will be documented in the CRF

j – Only targeted adverse events 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. STUDY DESIGN

5.1. Summary of Study Design

This study is designed as an international, multicentre, randomised controlled, open-label, phase IV, non-inferiority trial with a non-inferiority margin of 6%. Eligible participants must be clinically stable / non-critically ill inpatients over the age of 18 (21 in Singapore) with uncomplicated Gram-negative bacteraemia. Randomisation into the intervention or standard arms will be performed with a 1:1 allocation ratio. Participants randomised to the intervention arm (within 72 hours from the time of index blood culture collection) will be immediately converted to oral therapy. Participants randomised to the standard arm should continue to receive IV therapy for at least 24 hours post-randomisation before clinical re-assessment and decision making by the treating doctor. At the doctor's discretion, patients in the standard arm may be converted to oral antibiotic therapy (after continuing the IV therapy for at least 24 hours post-randomisation). This data on oral antibiotic switch for patients in the standard arm will be recorded in the CRF. All study drugs (and dosage) would be those routinely used in clinical practice and will be ordered/dispensed from the hospital pharmacy as per site institutional practice. 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. Participants may be discharged home or to OPAT at any time post-randomisation according to the discretion of the treating doctor. At day 30 post-randomisation, participants will be assessed for the primary outcome of all-cause mortality. The key secondary outcome is health economic evaluation including estimation of total healthcare cost (from healthcare system and patient perspective) to determine the economic impact of early oral step-down therapy. Health services/resource utilisation and related cost data over the entire duration of the study will be collected from medical records or administrative sources whenever possible. A health outcome analysis will be conducted to assess patients' quality of life and the number of quality adjusted life years saved.

6. METHODS AND ASSESSMENTS

6.1. Randomisation and Blinding

Randomisation may occur if eligibility criteria have been met and informed consent has been obtained. Participants will be randomly assigned to either standard or intervention arms in a 1:1 ratio according to a randomisation list prepared in advance using a secure online randomisation system hosted by Singapore Clinical Research Institute. Randomisation will be stratified by country (Singapore, Australia, Malaysia, South Korea, United Kingdom, Israel, Turkey, Lebanon, Greece, Spain, Italy and Taiwan) to ensure balance between study arms across countries. Random sequence will be generated using random permuted blocks of unequal length. The day of randomisation is considered day 1 of treatment and the last dose of study drug to be given for the day is the dose next due prior to 23:59 hr (i.e. the last scheduled dose prior to midnight). As the drugs in the standard and intervention arms have different routes of administration, this will be an open-label study.

6.2. Contraception and Pregnancy Testing

Women who are known to pregnant will not be enrolled into the study. As the intervention period is short (typically 4–7 days) and occurring during a hospital admission, it is not anticipated that contraceptive advice is relevant.

6.3. Study Visits and Procedures

a. Screening Visits and Procedures

The screening visit will include:

- Eligibility assessment (including a urine pregnancy test if applicable)
- Written informed consent
- Documentation of demographics
- Documentation of Charlson comorbidity index and antibiotic history since admission
- Vital signs measurement and physical examination, such as measurement of blood pressure and heart rate as well as cardiovascular, respiratory and abdominal examination
- Radiographic findings (if any)
- Baseline blood tests including full blood count (FBC; white blood cells, neutrophils, platelets, haemoglobin), C-reactive protein (CRP), renal panel (sodium, potassium, creatinine) and liver panel (alanine transaminase [ALT], aspartate transaminase [AST], alkaline phosphatase [ALP], total bilirubin [TBL])
- Blood culture results and antibiotic sensitivities of bacteraemia isolate

- EQ-5D quality-of-life survey

Screening for metastatic complications will be undertaken if symptoms or examination findings are suggestive. Randomisation must be achieved within 72 hours of the positive blood culture collection.

b. Study Visits and Procedures

If participant is randomised to intervention arm, the first dose of the oral antibiotic will be administered by the ward nursing staff, and the participant may either remain as inpatient or be discharged to home. If participant is randomised to standard arm, administration of the IV 'best available treatment' antibiotic should continue for at least 24 hours post-randomisation, which may be done as inpatient or in OPAT. The recommended treatment duration for both study arms 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. Participants will be monitored by the clinical team in the hospital as per institutional practice until discharged, which typically entails standardised clinical assessments such as adverse event monitoring, physical examination, and complication screening (if suspected). Blood cultures may be repeated on any day during the study period according to the discretion of the treating doctor to ensure clearance of bacteraemia especially if there is persistent fever or if previous blood cultures remain positive or if any secondary infection is suspected.

Before a participant is discharged from hospital, the standardised clinical assessments (physical examination, review of adverse events, complication screening [at treating doctor's discretion]) and blood tests (FBC, CRP, renal and liver panels) should be performed again.

At the end of study drug treatment (window period: 3 days), the study team will:
- Check for adherence to treatment regimen (pill count for participants in intervention arm and documentation of IV antibiotics administered for participants in standard arm)
- Review and document all antibiotics taken as well as adverse events experienced since randomisation
- Request for completion of the quality-of-life survey

The above study procedures may be conducted via telephone interview or home visit by the study team if participant has been discharged from hospital and information cannot be obtained from medical records or administrative sources.

On day 14 (±3 days) and/or day 30 (±3 days), the study team will review and document:
- Mortality status of the participant (days 14 and 30)
- Specific adverse event occurrence, if any, since the last study review (days 14 and 30)
- Development of complications, relapse and distant seeding (day 30)
- Hospital admission and discharge summaries (days 14 and 30)
- Any antibiotics taken since the end of the study drug treatment regimen (day 30)

The above procedures may be conducted via telephone interview or home visit by the study team if participant has been discharged from hospital and information cannot be obtained from medical records or administrative sources.

c. Final Study Visit:

On day 90 (±3 days), the study team will review and document:
- Mortality status of the participant
- Specific adverse event occurrence, if any, since the last study review
- Any antibiotics taken since the last study review
- Hospital admission and discharge summaries since the last study review
- Health services/resource utilisation and related cost data for the entire study duration (applicable only to selected hospital sites)

On day 90 (±3 days), the study team will also request for completion of the quality-of-life survey by the participant. The above procedures may be conducted via telephone interview or home visit by the study team if participant has been discharged from hospital and information cannot be obtained from medical records or administrative sources.

d. Post Study Follow up and Procedures

There is no requirement for post study follow-up or procedures.

e. Discontinuation Visit and Procedures

Participants or legal representatives have the right to choose to withdraw from the study at any time. The investigator may also discontinue a participant from the study or from treatment if deemed appropriate. The decision to withdraw a participant from the study must be discussed with the coordinating investigators. If a participant withdraws consent from study participation and withdraws consent for collection of future information, no further evaluations will be performed and no additional data will be collected. The study team may retain and continue to use any data or samples collected before such withdrawal of consent. Participants who abscond will continue to be followed, if possible, until the end of the trial to avoid missing data. Participants withdrawn from the treatment by the treating or study doctors will continue to be followed up to the end of the trial to avoid missing data and will be used in the analysis if they satisfy the analysis population definitions. Withdrawn participants will not be replaced. If a participant is withdrawn, the reason will be recorded in the database and source documents. Participants who deviate from intervention protocols, including premature discontinuation of study related antibiotic therapy, will continue to have primary and secondary endpoint assessments for analysis.

f. Laboratory studies

An aliquot of the initial index blood culture isolate (as a suspension of pure bacterial colonies) will be stored at -80°C in glycerol and nutrient broth or in Microbank™ at each hospital site microbiology laboratory as per standard practice. These bacterial isolates may be retrieved later for confirmatory susceptibility testing and genetic analysis for mechanisms of resistance. Any subsequent Gram-negative bacteraemia isolates that show resistance to the randomised antibiotic can be stored at the discretion of the site PI and microbiology laboratory, but is not mandated in the protocol.

7. TRIAL MATERIALS

7.1. Trial Product (s)

The oral antibiotic options in the intervention arm are fluoroquinolones (most commonly, ciprofloxacin) or trimethoprim-sulfamethoxazole. They will be administered from each site's pharmacy. Patients on ciprofloxacin may not take concomitant drugs that can cause prolongation of QT interval (e.g. class IA or class III antiarrhythmics) on a case-by-case basis determined by the site doctors who will make the final decision as per their clinical discretion. The IV antibiotic options in the standard arm will be determined by the treating doctor at the study site based on their assessment of the 'best available treatment' (e.g. ceftriaxone, cefazolin, meropenem) for the Gram-negative bacteraemia episode. All the study drugs are routinely used in clinical practice and will be ordered/dispensed from the hospital pharmacy as per site institutional practice.

There is considerable variation in clinical practice with regard to the total antibiotic duration and more specifically the duration of IV therapy for Gram-negative bacteraemia. Recent data from RCTs and a propensity score-matched retrospective study support the adoption of shorter course (approximately 7 days of active antibiotics counting from the day of index blood culture collection) therapy for uncomplicated Gram-negative bacteraemia.[20–22] 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.

7.2. Storage and Drug Accountability

All the study drugs will be stored and administered in accordance with standard pharmacy procedures. Storage conditions, temperature monitoring and accountability of the study drugs will be as per hospital pharmacy policy.

8. TREATMENT

8.1. Rationale for Selection of Dose

The dosage, frequency and administration of study drugs for patients in the standard arm will be determined by the treating doctor according to their hospital site's clinical practice as well as consideration of patient's renal function.

The recommended doses of oral antibiotics to be used in the intervention arm would be ciprofloxacin 750 mg twice daily (if body weight ≥70 kg) or ciprofloxacin 500 mg twice daily (if body weight <70 kg) or trimethoprim-sulfamethoxazole 5 mg/kg (for trimethoprim component) every 12 hours up to a maximum trimethoprim-sulfamethoxazole (160 mg / 800 mg; double strength) two tablets twice daily. Doses may be adjusted in the setting of renal dysfunction according to the recommendations in Tables 2, 3 and 4.

Table 2. Recommended starting and maintenance doses of ciprofloxacin for patients with impaired renal function.

Creatinine clearance (mL/min)	Dose of ciprofloxacin
>50	750 mg every 12 hours (for patients <70 kg, dose at 500 mg every 12 hours)
30–50	500 mg every 12 hours
5–29	500 mg every 24 hours
Haemodialysis or peritoneal dialysis	500 mg every 24 hours (after dialysis)

Table 3. Recommended starting and maintenance doses of trimethoprim-sulfamethoxazole for patients with impaired renal function (weight based adjustments).

Creatinine clearance (mL/min)	Dose of trimethoprim-sulfamethoxazole
>30	5 mg/kg (for trimethoprim component) every 12 hours
15–30	2.5 mg/kg every 12 hours
<15	2.5 mg/kg every 24 hours
Haemodialysis or peritoneal dialysis	2.5 mg/kg every 24 hours (after dialysis)

Table 4. Recommended starting and maintenance doses of trimethoprim-sulfamethoxazole for patients with impaired renal function (tablet based adjustments).

Creatinine clearance (mL/min)	If usual recommended dose is 2 SS[a] tablets (1 DS[b] tablet) every 24 hours or 3 times per week	If usual recommended dose is 2 SS tablets (1 DS tablet) every 12 hours	If usual recommended dose is 4 SS tablets (2 DS tablets) every 12 hours	If usual recommended dose is 4 SS tablets (2 DS tablets) every 8 hours
>30	No dose adjustment	No dose adjustment	No dose adjustment	No dose adjustment
15–30	Reduce dose to ~50% of usual dose. Example: 1 SS tablet every 24 hours or 3 times per week	Reduce dose to ~50% of usual dose. Example: 2 SS tablets once, followed by 1 SS tablet every 12 hours	Reduce dose to ~50% of usual dose. Example: 2 SS tablets every 12 hours	Reduce dose to ~50% of usual dose. Example: 3 SS tablets every 12 hours
<15	Reduce dose to ~25 to 50% of usual dose. Use with caution and appropriate monitoring. Example: 1 SS tablet every 24 hours or 3 times per week	Reduce dose to ~25 to 50% of usual dose. Use with caution and appropriate monitoring. Example: 2 SS tablets once, followed by 1 SS tablet every 12 or	Reduce dose to ~25 to 50% of usual dose. Use with caution and appropriate monitoring. Example: 2 SS tablets every 12 hours OR 2 SS tablets once,	Reduce dose to ~25 to 50% of usual dose. Use with caution and appropriate monitoring. Example: 3 SS tablets every 12 hours or 24 hours

		24 hours	followed by 1 SS tablet every 12 hours	

[a] Abbreviation: SS, single strength (trimethoprim-sulfamethoxazole 80 mg / 400 mg)
[b] Abbreviation: DS, double strength (trimethoprim-sulfamethoxazole 160 mg / 800 mg)

8.2. Study Drug Formulations

Study drugs in the standard arm will be administered intravenously while study drugs in the intervention arm will be administered orally.

8.3. Study Drug Administration

Patients randomised to the standard arm will receive an IV antibiotic deemed to be the 'best available treatment' by the treating doctor. Patients randomised to the intervention arm will receive either oral fluoroquinolones (most commonly, ciprofloxacin) or oral trimethoprim-sulfamethoxazole. The participant's drug charts (electronic and/or paper) will be reviewed for compliance with study treatment. Any missed dose(s) and non-study drugs administered will be recorded in the CRF.

8.4. Specific Restrictions / Requirements

Patients on ciprofloxacin may not take concomitant drugs that can cause prolongation of QT interval (e.g. class IA or class III antiarrhythmics) on a case-by-case basis determined by the site doctors who will make the final decision as per their clinical discretion.

8.5. Blinding

This will be an open-label study as the drugs in the standard and intervention arms have different routes of administration.

8.6. Concomitant therapy

Concomitant antibiotics taken by the participant will be documented in the CRF.

8.7. Safety Monitoring Plan

A Data and Safety Monitoring Board (DSMB) comprising two independent ID doctors and an independent statistician will be established prior to commencing the study. An interim analysis, including efficacy and safety endpoints, will be performed after the first 50, 100 and 350 subjects have completed the 90-day study period or as determined by DSMB. A DSMB Charter detailing the required interim analysis will be prepared at the beginning of the trial. If there is a significant safety concern raised or the observed difference in proportion of patients reaching the primary endpoint exceeds the non-inferiority margin of 6%, the DSMB may recommend the trial should be stopped. The timing of additional interim analyses will be determined by the DSMB.

8.8. Complaint Handling

Complaints may be made to the PI or approving institutional review board (IRB) / ethics committee (EC). Complaints will be handled according to the normal procedures in operation at the recruiting hospital.

9. DATA ANALYSIS

9.1. Data Quality Assurance

Clinical record forms will be monitored by an independent monitoring team to ensure data quality and accuracy. In addition, the study may be audited by regulatory authorities who must be allowed access to CRF, source documents and other study files.

9.2. Data Entry and Storage

A trial database using the REDCap data management system will be developed with a secured web hosting facility. The CRF will collect clinical and laboratory related information, and will contain validation ranges for each variable to minimise data entry errors. The database will include information on demographics, underlying illnesses, antibiotic history, baseline and follow-up laboratory data including microbiologic data, and assessments of vital signs and adverse events for the purpose of clinical outcome assessment. Data on hospital admission and discharge summaries will also be recorded. Source of bacteraemia, if known, will be noted. Trial data will be stored in a re-identifiable manner in the database using a unique screening number for each participant. For each potential participant screened (even those who are not eligible), the screening CRF will be completed by the site PI or their delegate. For each participant enrolled, CRF must be completed. This also applies to records for those participants who fail to complete the study. The site PI should ensure the accuracy, completeness and timeliness of the data entered into the CRF and in all required reports. A comprehensive validation check program will verify the data and automatically generate discrepancies for resolution by the investigator. Manual discrepancies can also be raised if necessary. The study team will manage the data and will conduct quality control of the data following their own standard operating procedures. Missing data or suspected errors will be raised as data queries (by the data management team and monitor) and will be resolved prior to database lock and analysis. An audit trail will be maintained for tracking purposes. The Clinical Study Report(s) and all analyses performed as well as the final data set will be archived together according to standard operating procedures.

10. SAMPLE SIZE AND STATISTICAL METHODS

10.1. Determination of Sample Size

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.[21] In a recent retrospective multicentre study of 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.[7] 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.[7,21] 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,[23,24] the standard 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 intervention arm, which preserves more than 90% of the 72% treatment effect of standard arm treatment 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.

10.2. Statistical and Analytical Plans

The primary analysis for this study will be performed on the modified intention-to-treat (mITT) population, which consists of all randomised patients excluding (i) those who did not have 30-day all-cause mortality data, (ii) intervention arm patients who did not receive any oral fluoroquinolones or oral trimethoprim-sulfamethoxazole post-randomisation, and (iii) standard arm patients who did not receive any IV antibiotics post-randomisation. Risk difference of 30-day all-cause mortality and its 95% confidence interval between intervention and standard arms will be estimated and compared using chi-squared test. If the upper limit of the 95% confidence interval falls below the 6% non-inferiority margin, non-inferiority will be concluded for early oral step-down therapy relative to continuing IV therapy. As a special case of non-inferiority, if the upper limit of the 95% confidence interval falls below zero, superiority will be declared for early oral step-down therapy. Supportive analysis of the primary endpoint will be performed with the per-protocol population, which consists of patients included in the mITT population excluding those with major protocol deviation that may significantly affect the primary endpoint. The following will be considered as major protocol deviations:

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

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 the ITT population size and the mITT population size. In the ITT population analysis, any subjects who are missing mortality data at any time point will be considered alive at that particular time point.

Superiority of early oral step-down therapy over continuing IV therapy will be evaluated with respect to outcomes such as LOS in hospital, as well as infection and health economic outcomes. Secondary outcome measures expressed as proportions will be compared between intervention and standard arms using chi-squared test, and risk difference as well as relative risk of the outcome measures will be calculated together with its 95% confidence interval. Mean difference and its 95% confidence interval will be provided for secondary outcome measures that are on interval scale, and comparison between study arms will be done using a two-sample t-test.

Subgroup analysis of the primary endpoint will also be performed as part of exploratory analysis although the study power in subgroups may be low. The subgroups include a) countries grouped by region, b) age group (< 70 years, ≥ 70 years), c) gender (female, male), d) source of

bacteraemia at baseline (UTI, non-UTI), e) bacteraemia isolate at baseline (*Escherichia coli*, Klebsiella spp, others), f) empiric therapy effectiveness (effective, not effective, unknown effectiveness), and g) resistance of index Gram-negative bacteria (multidrug-resistant, non-multidrug-resistance, unknown). The definitions of multidrug resistance are below.

- 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.

In addition to exploring the efficacy and safety of early oral step-down therapy, this study will also analyse the economic viability of the proposed approach through a health economic evaluation according to ITT principle from healthcare system as well as patient perspectives. For base case analysis, private rate of each resource utilisation will be applied to calculate the average cost and savings. The health economic analysis will have two components:

1. If the RCT results confirm the non-inferiority of early oral step-down therapy relative to continuing IV therapy, a cost saving analysis will be conducted to estimate the economic impact of the new treatment regimen;
2. If the RCT results fail to confirm the non-inferiority, a cost effectiveness analysis will be conducted to estimate the incremental cost effectiveness ratio (ICER) by comparing the difference in cost and clinical outcomes as well as quality-of-life between the two treatment arms (ICER=ΔC/ΔE).

To address possible variations in patient medical conditions and outcomes, a series of one-way sensitivity analyses will be conducted to address the potential impact of each parameter uncertainty and assess the robustness of study estimations for generalisability. Based on the sensitivity analysis, tornado plot will be generated to assess how much influence each of the variables have on the overall model. Additionally, probabilistic sensitivity analysis using the Monte Carlo simulation will be performed. Simulated results will be plotted in the cost-effectiveness plane to present the distribution of cost-effectiveness ratios. Cost-effectiveness acceptability curves will be generated to assess the probability variations of accepting each strategy by changing the threshold of willingness-to-pay.

11. ETHICAL CONSIDERATIONS

11.1. Informed Consent

The site PI is responsible for obtaining IRB/EC approval for the protocol, and ensuring the participant information sheet and informed consent form (ICF) are in compliance with local regulatory requirements prior to enrolling any participant into the study. The approval letter/document must clearly identify the protocol and all documents approved by the IRB/EC.

These include the version number and date of the protocol as well as the version number and date of the participant information sheet and ICF. The site PI must also obtain approval for any amendments to the protocol or participant information sheet and ICF. The site PI must comply with all IRB/EC and regulatory reporting requirements for adverse events, study status updates, end of study reports, and must agree to abide by any IRB/EC conditions of approval. The site PI (or designee) is responsible for ensuring freely given consent by each potential participant prior to the conduct of any protocol-specific procedures. The site PI may delegate the task of obtaining consent to appropriately qualified co-investigator(s). Consent must be documented by the participant's dated signature on the participant information sheet and ICF together with the dated signature of the person conducting the consent discussion.

If the participant is illiterate or a translator is required, an impartial witness should be present during the entire consent discussion. Once the discussion is complete, the participant must sign and date the ICF, if capable. The impartial witness must also sign and date the ICF along with the person who conducts the consent discussion. If the participant does not have the capacity to consent, the written consent from a legal representative must be obtained. Capacity to consent should be assessed using the same process that is used when assessing consent capacity for treatment in the general hospital setting. This will take into account any potential legal authorities already in place and the patient's baseline presentation. Capacity will be assessed in consultation with the treating team and the family if applicable. The investigator responsible for the consent process is responsible for ensuring the participant has the capacity to consent.

A copy of the signed and dated participant information sheet and ICF must be given to the participant prior to study participation. The participant or his/her legal representative must be informed in a timely manner of any new information that becomes available during the course of the study that may affect his/her willingness to continue study participation.

This study shall be conducted in accordance with the ethical principles laid out in the Declaration of Helsinki (most current issued version) and the National Statement on Ethical Conduct in Research Involving Humans (most current issued version).

12. SAFETY MEASUREMENTS

12.1. Definitions

An adverse event is defined in the ICH-GCP as "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment."

An elective procedure not reflecting a worsening of a known underlying medical condition is not considered an adverse event, and therefore will not be considered an SAE despite requiring hospitalisation. However, complications of a procedure will be considered an adverse event and may be considered an SAE if hospitalisation is prolonged (or any other SAE criteria is met). A hospitalisation or prolongation of a hospitalisation for reasons other than an adverse event would not be considered an SAE.

Adverse events include any occurrences that are new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities. Concurrent medical conditions present at baseline that worsen will

be considered as adverse events. Lack of efficacy, aggravation, or relapse of current infection are not an adverse event in the study and therefore also not an SAE (except death).

Events will be reviewed and classified by the site PI. The relationship of the event to the study drug and whether the event is an expected event or not will be assessed using the listing of adverse effects contained in the summary of product characteristics for the antibiotics used.

The treating team has the primary responsibility for reviewing laboratory test results and determining whether an abnormal value in an individual study participant requires action. In general, abnormal laboratory results without clinical significance (based on clinical judgment) should not be recorded as adverse events. However, laboratory value changes requiring therapy or adjustment in prior therapy are considered adverse. The investigators should liaise closely with the treating teams and remain aware of any such adverse events.

SAE are defined as an adverse event that:
• is fatal
• is life threatening (places the participant at immediate risk of death)
• requires inpatient hospitalisation or prolongation of existing hospitalisation
• results in persistent or significant disability/incapacity
• is a congenital anomaly/birth defect
• other significant medical hazard

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)

Death within 30 days from time of randomisation is the primary outcome measure of the study, and death within 14 and 90 days are the secondary outcome measures. Given the variability of mortality associated with Gram-negative bacteraemia (approximately 5–12%), death itself cannot be considered an 'unanticipated' event.

If any member of the trial team becomes aware of an unexpected death or SAE at any stage of the trial, the PI will be alerted. The PI should report all deaths and relevant SAEs as appropriate to their local regulatory authority, and all deaths and adverse events that are related or possibly related to the study treatment will be recorded and reported in the final analysis. Unforeseen adverse events will be discussed with collaborating investigators at other centres; such information will be reviewed by regular teleconference.

12.2. Collecting, Recording and Reporting of "Unanticipated Problems Involving Risk to Subjects or Others" – UPIRTSO events to the National Healthcare Group (NHG) Domain Specific Review Board (DSRB)

UPIRTSO events and SAEs are defined below. Events will be reviewed and classified by the site PI or other investigator. Severity will be classified using a standard set of criteria for grading adverse events (Common Terminology Criteria for Adverse Events version 5.0). The relationship of the event to the study drug and whether the event is an expected event or not will be assessed using the listing of adverse effects contained in the summary of product characteristics for the antibiotics used.

Any events that are unexpected (in terms of severity or frequency), that can reasonably be attributed to the drug under study and that may expose other subjects to harm will be reported. UPIRTSO events refers to problems, in general, to include any incident, experience, or outcome (including adverse events) that meets ALL of the following criteria:

Unexpected
In terms of nature, severity or frequency of the problem as described in the study documentation (e.g. Protocol, Consent documents, etc).

Related or possibly related to participation in the research
Possibly related means there is a reasonable possibility that the problem may have been caused by the procedures involved in the research; and

Risk of harm
Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognised.

Reporting Timeline for UPIRTSO Events to the NHG DSRB:

Urgent Reporting: All problems involving local deaths, whether related or not, should be reported immediately – within 24 hours after first knowledge by the local PI.

Expedited Reporting: All other problems must be reported as soon as possible but not later than 7 calendar days after first knowledge by the local investigator

12.3. Collecting, Recording and Reporting of Serious Adverse Events (SAEs) to the Health Science Authority (HSA)

Medical and scientific judgment should be exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalisation. However, if it is determined that the event may jeopardise the subject and/or may require intervention to prevent one of the other adverse event outcomes, the important medical event should be reported as serious. All SAEs that are unexpected and related to the study drug will be reported to HSA. The investigator will be responsible for informing HSA no later than 15 calendar days after first knowledge that the case qualifies for expedited reporting. Follow up information will be actively sought and submitted as it becomes available. For fatal or life-threatening cases, HSA will be notified as soon as possible but no later than 7 calendar days after first knowledge that a case qualifies, followed by a complete report within 8 additional calendar days.

12.4. IRB Review

All relevant documents will be approved by the National Healthcare Group (NHG) Domain Specific Review Board (DSRB) before trial initiation in Singapore (or the respective IRB/EC for the other international participating sites).

12.5. Confidentiality of Data and Patient Records

All study findings and documents will be regarded as confidential. The site PIs, co-investigators and other study personnel must not disclose such information without prior written approval from the chief PI. Subject confidentiality will be strictly maintained to the extent possible under the law and local hospital policy. Identifiable information will be removed from any published data.

13. PUBLICATIONS

The data obtained from all participating sites will be pooled and analysed together as soon as possible after trial completion. Individual researchers will not publish data from the trial until the main study publication has been released. The trial steering committee will form the main writing committee.

14. RENTENTION OF TRIAL DOCUMENTS

The PI will keep any records, study files or source documentation for a minimum of 6 years after the completion of the trial before being destroyed or erased. These documents may be retained for a longer period if required by the applicable regulatory requirements or institutional policy.

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