COVER Page

The **B**eta-**L**actam **I**nfusio**N** **G**roup

BLING III Study

A phase III randomised controlled trial of continuous beta-lactam infusion compared with intermittent beta-lactam dosing in critically ill patients

Protocol Number: TGI-CCT254643

Version Number: 6.0

Date: 01April 2022

ClinicalTrials.gov Register: NCT03213990

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The George Institute for Global Health

A collaboration between The George Institute for Global Health and critical care researchers around the world.

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1. Protocol synopsis

Title	A phase III randomised controlled trial of continuous beta-lactam infusion compared with intermittent beta-lactam dosing in critically ill patients
Short title	The Beta-Lactam InfusioN Group (BLING) III study
Design	Prospective, multicentre, open, phase III, randomised controlled trial (RCT)
Primary outcome	All-cause mortality within 90 days after randomisation
Secondary outcomes	1. Clinical cure at Day 14 post randomisation 2. New acquisition, colonisation or infection with a multi-resistant organism or *Clostridium difficile* diarrhoea up to 14 days post randomisation 3. All-cause ICU mortality 4. All-cause hospital mortality
Tertiary outcomes	1. ICU length of stay 2. Hospital length of stay 3. Duration of mechanical ventilation in ICU up to 90 days after randomisation 4. Duration of renal replacement therapy up to 90 days after randomisation
Intervention	The administration of beta-lactam antibiotic will be randomised to either continuous infusion or intermittent infusion over 30 minutes for the treatment course for up to 14 days after randomisation while the patient is in the ICU. The choice of beta-lactam antibiotic, either piperacillin-tazobactam or meropenem, and the dose and dosing interval (i.e. the dose the patient will receive in 24 hours) will be determined by the treating physician prior to randomisation.
Sample size	7,000 patients and extended at sites participating in the PKPD study until 600 patients are recruited into the PK-PD study or for a period of 6 months following recruitment of the 7,000th participant, whichever occurs first
Inclusion criteria	1. Patient has a documented site of infection or strong suspicion of infection 2. Patient is expected to be in the ICU the day after tomorrow 3. Patient has been commenced on piperacillin-tazobactam or meropenem to treat the episode of infection 4. Giving piperacillin-tazobactam or meropenem by intermittent infusion or continuous infusion is considered equally appropriate for the patient 5. One or more organ dysfunction criteria in the previous 24 hours i. MAP < 60 mmHg for at least 1 hour ii. Vasopressors required for > 4 hours iii. Respiratory support using supplemental high flow nasal prongs, continuous positive airway pressure, bilevel positive airway pressure or invasive mechanical ventilation for at least 1 hour iv. Serum creatinine concentration > 220 µmol/L or >2.49 mg/dL

1. Protocol synopsis (Cont')

Exclusion criteria	1. Patient age is less than 18 years 2. Patient has received piperacillin-tazobactam or meropenem for more than 24 hours during current infectious episode 3. Patient is known or suspected to be pregnant 4. Patient has a known allergy to piperacillin-tazobactam, meropenem or penicillin 5. Patient is requiring renal replacement therapy at the time of randomisation, including renal replacement therapy for chronic renal failure 6. The attending physician or patient or surrogate legal decision maker is not committed to advanced life-support, including mechanical ventilation, dialysis and vasopressor administration, for at least the next 48 hours 7. Patient's death is deemed imminent and inevitable 8. Patient has previously been enrolled in BLING III

2. Administrative information

2.1. Chief investigator

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2.3. BLING III management structure

Terms of Reference for the BLING III Management Committee are defined in the BLING III Management Committee Charter. Management committee membership:

1. Professor Jeffrey Lipman (CHAIR), Professor and Head, Anaesthesiology and Critical Care, University of Queensland, QLD, Australia
2. Professor Stephen Brett, Consultant in Intensive Care Medicine, Imperial College Healthcare NHS Trust and Professor of Critical Care, Department of surgery and Cancer, Imperial College London, United Kingdom
3. Dr Menino Osbert (Os) Cotta, Research Fellow, Department of Intensive Care Medicine, Royal Brisbane and Women's Hospital, QLD, Australia
4. Associate Professor Joshua Davis, Infectious Diseases Physician, John Hunter Hospital, NSW, Australia
5. Professor Jan De Waele, Surgical Intensivist, Department of Critical Care Medicine, Ghent University Hospital, Belgium
6. Dr Joel Dulhunty, Research Fellow, Department of Intensive Care Medicine, Royal Brisbane and Women's Hospital, QLD, Australia
7. Professor Simon Finfer, Professorial Fellow, Critical Care Program, The George Institute for Global Health, NSW, Australia
8. Dr Serena Knowles, Operations Lead, Critical Care Program, The George Institute for Global Health, NSW, Australia
9. Dr Shay McGuinness, Director of Research and Specialist Intensivist, Cardiothoracic & Vascular Intensive Care Unit, Auckland City Hospital, New Zealand
10. Professor John Myburgh, Director, Critical Care Program, The George Institute for Global Health, NSW, Australia
11. Professor David Paterson, Infectious Diseases Physician, Royal Brisbane and Women's Hospital, QLD, Australia

12. Professor Sandra Peake, Senior Staff Specialist, Department of Intensive Care Medicine, The Queen Elizabeth Hospital, SA, Australia
13. Ms Dorrilyn Rajbhandari (BLING III study Project Manager), Critical Care Program, The George Institute for Global Health, NSW, Australia
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15. Professor Jason Roberts, Pharmacist Consultant, Royal Brisbane and Women's Hospital, and Professor of Medicine and Pharmacy, The University of Queensland, QLD, Australia
16. Professor Claire Roger, Intensive Care Physician, Surgical Intensive Care Unit, Nimes University Hospital, Nimes, France
17. Dr Charudatt Shirwadkar, Intensive Care Specialist, Blacktown Hospital, NSW, Australia
18. Ms Therese Starr (Research Coordinator), Department of Intensive Care Medicine, Royal Brisbane and Women's Hospital, QLD, Australia
19. Dr Colman Taylor, Research Fellow, Critical Care Program, The George Institute for Global Health, NSW, Australia

2.4. Funding

This study is funded by an Australian National Health and Medical Research Council (NHMRC) project grant (APP1121481). Funding will be sought from additional funding bodies for study costs outside of Australia.

2.5. Role of funding bodies

The study will be designed and conducted, and the results analysed, presented and published by the investigators independent of the funding agencies**.**

2.6. Trial registration

This protocol has been registered on the following clinical trial registry; ClinicalTrials.gov Register: NCT03212990

2.7. Consumer engagement/patient and public involvement

Consumer engagement has been and will be sought to inform study procedures and information materials for patients, families and the community. The Royal Brisbane and Women's Hospital Consumer Advisory Group has reviewed a number of study documents prior to submission to the lead (Australian) Human Research Ethics Committee (HREC) and will continue to be consulted as needed throughout the study.

3. Introduction

3.1. Background and rationale

Defined as life-threatening organ dysfunction due to infection,[1] sepsis is a major cause of mortality worldwide.[2-5] Gram-positive and Gram-negative bacteria, either alone or in combination with other pathogens, are the leading cause of sepsis.[6]

Recent longitudinal data from Australia and New Zealand show the incidence of sepsis-related admissions to the Intensive Care Unit (ICU) is on the rise with 2,700 patient admissions in 2000 increasing to over 12,500 in 2012.[7] Rising rates of sepsis have also been reported internationally.[8]

Hospital costs for each episode of severe sepsis have been estimated at USD 19,330 (AUD 27,500) in a United States study to Euro 35,185 (AUD 53,700) in a European study,[8,9] with no comparable data available from Australia and New Zealand.

Hospital mortality from severe sepsis in Australia and New Zealand has shown an annual absolute rate reduction of 1.3%, trending downwards from 35.0% in 2000 to 18.4% in 2012.[7] Data from other developed countries have also shown similar, although not as profound, annual reductions in sepsis mortality,[3,10] and wide variations in absolute hospital mortality (20-50%).[2,3,11] However, although mortality rates are observed to be decreasing, the steady increase in sepsis incidence means that the number of people dying of sepsis is more than ever before and continues to rise.[6] Worldwide estimates report that the number of people dying from sepsis each year is similar to the number of people dying from acute myocardial infarction, and far exceeds deaths as a result of Human Immunodeficiency Virus, breast cancer or stroke.[6] Therefore, sepsis is a major public health concern and there is a worldwide imperative to define interventions and strategies to reduce morbidity and mortality.

Early use of effective antibiotic therapy against the initiating infection is central in the treatment of patients with sepsis.[12] One important class of antibiotics commonly used to treat infection in patients with sepsis are beta-lactam antibiotics. A multicentre point prevalence study of antibiotic usage in patients admitted to ICUs in Australia and New Zealand showed that beta-lactam antibiotics, such as meropenem and piperacillin-tazobactam, were the most commonly prescribed antibiotic class for the treatment of proven or suspected infections.[13] Meropenem and piperacillin-tazobactam were also the two most commonly prescribed beta-lactam antibiotics in a prospective, multinational pharmacokinetic point-prevalence study conducted in 68 ICUs across 10 countries.[14]

3.2. Theoretical rationale

Since the late 1930s, beta-lactam antibiotics have been administered via intermittent infusion. However, there is a strong biological precedent that this mode of administration may be substantially less effective than administration via the use of continuous infusion in some clinical conditions.[15,16] Also known as time-dependent killing, beta-lactam antibiotics display maximal bacterial killing when concentrations of the antibiotic remain above four times the minimum inhibitory concentration (MIC) of the infective bacterial pathogen for 100% of the dosing interval.[17] As highlighted in a recent editorial in *Intensive Care Medicine*, "the body of evidence suggests that application of this strategy [continuous infusion] may be best in severe infections, in patients with normal renal function and lung infections, and when less susceptible pathogens are isolated or suspected" (**Figure 1**).[18]

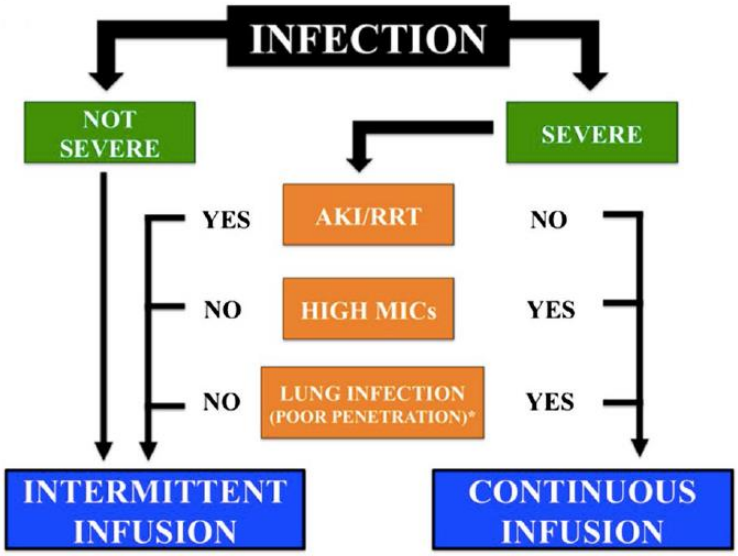


Figure 1. *Patients hypothesised to have the highest likelihood to benefit from continuous infusion of beta-lactam antibiotics (extract from Taccone et al.)*[18]

3.3. Current evidence

Recent human trials have shown that administration of beta-lactam antibiotics by continuous infusion significantly increases the likelihood of concentrations being maintained above the MIC of pathogens (**Figure 2**). The BLING I trial showed that plasma concentrations were more likely to exceed the bacterial MIC in the continuous arm compared with the intermittent arm (82% vs. 29%; p = 0.01) and found a higher clinical cure rate in the continuous group compared with the intermittent group (70% vs. 43%; p = 0.037).[19] A recent single centre randomised controlled trial (RCT) also reported an increased microbiological eradication of the pathogen in the continuous group compared to the intermittent group (91% vs. 78%; p = 0.02).[20] Additionally, these investigators found continuous infusion of the beta-lactam antibiotic to be an independent predictor of microbiological success (Odds Ratio = 2.98; 95% confidence interval [CI] 1.05-8.44).

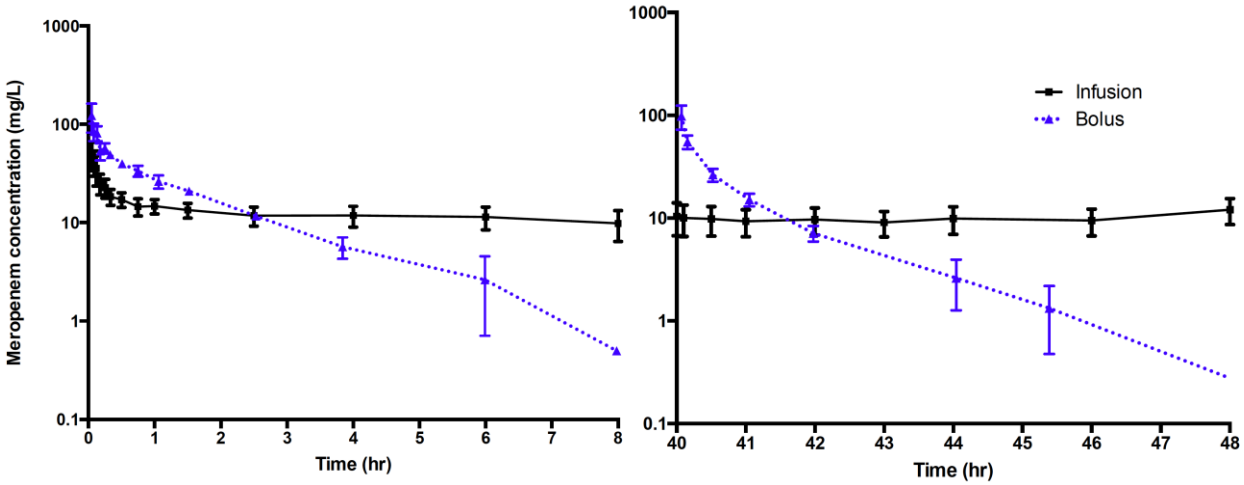


Figure 2. *Higher plasma concentrations are maintained with continuous infusion (black line) compared with intermittent dosing (dotted blue line)*[21]

Although improved microbiological eradication has been demonstrated with continuous infusion of beta-lactam antibiotics, there is limited evidence that these improvements translate to better patient

outcomes. Three previous meta-analyses of RCTs have not demonstrated that use of continuous beta-lactam antibiotic infusions is superior to intermittent administration in terms of clinical cure and survival, although studies to date have been small and underpowered, even when pooled.[17,22,23] A more recent meta-analysis that also included observational studies found a lower mortality in the continuous group (Risk ratio = 0.59; 95% CI 0.41-0.83).[24] Current human trials, however, have primarily been conducted in non-critically ill patient groups, with an overall mortality rate of only 6.4%,[24] which is lower than that observed in critically ill patients with sepsis. Additionally, all but one study included in a meta-analysis by our group used higher doses in the intermittent arm.[17]

In view of the above limitations associated with previous RCTs, a prospective, multicentre, double-blind, double-dummy, phase II RCT (BLING II) was conducted in 25 ICUs in Australia, New Zealand and Hong Kong (n = 432).[25,26] While there was no significant difference in the primary endpoint of alive ICU-free days at Day 28, an absolute difference in hospital mortality of 4.3% in favour of the continuous group (p = 0.28) and a similar directional trend at ICU discharge (2.2%, p = 0.54) and Day 90 (1.8%, p = 0.67) was observed.[26] In participants who received the study drug for 3 or more days, thereby representing a population with a higher degree of illness, there was a 7.4% absolute difference in Day 90 mortality in the continuous group (p = 0.17). Furthermore, an individual patient-data meta-analysis of multicentre RCTs conducted to date comparing continuous and intermittent infusion of beta-lactam antibiotics reported lower hospital morality censored at Day 30 in the continuous infusion group compared with the intermittent infusion group (19.6% vs. 26.3%; Relative Risk = 0.74; 95% CI 0.56-1.00, p = 0.045).[27] The difference in hospital mortality (**Figure 3**) remained after controlling for baseline factors in multivariate analysis (**Figure 4**).

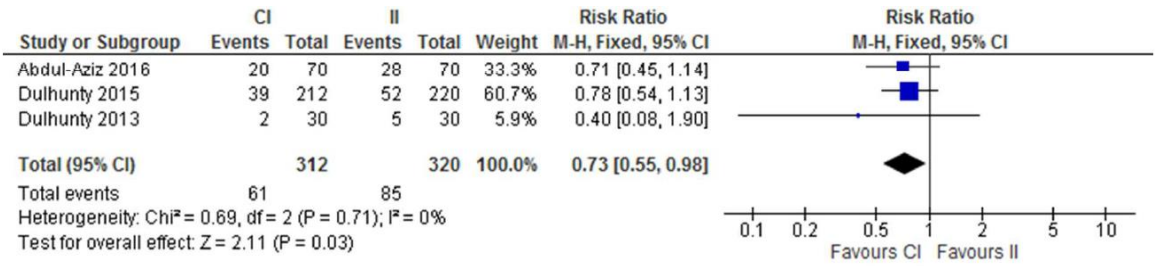
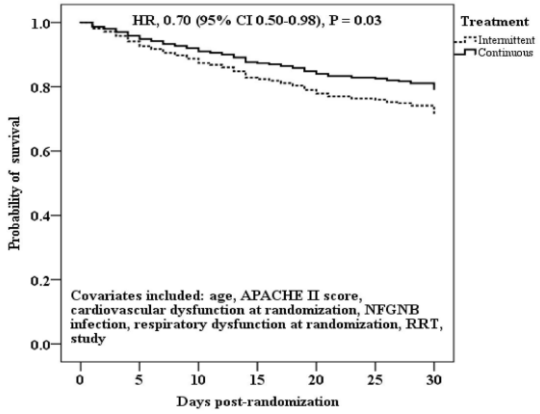


Figure 3. *Difference in hospital mortality and 95% confidence interval for continuous infusion (CI) versus intermittent infusion (II)*[27]



Abbreviations: *APACHE*, Acute Physiology and Chronic Health Evaluation; *HR*, hazard ratio; *NFGNB*, non-fermenting Gram-negative bacilli; *RRT*, renal replacement therapy.

Figure 4. *Cox-regression 30-day survival curves for combined study population*[27]

3.4. Need for a phase III study

The rationale to proceed with the BLING III study is as follows:

1. Sepsis is a common condition with a high mortality burden.
2. Effective antibiotics and delivery methods are an essential component of therapy for patients with sepsis.
3. There is a strong microbiological basis for continuous infusion of antibiotics with time-dependent kill characteristics of which the beta-lactam antibiotic class belong to.
4. There is good evidence from human trials of better achievement of therapeutic concentrations with continuous compared with intermittent infusion.
5. Human trials have been underpowered to definitively test whether there is improved survival associated with continuous infusion.
6. The standard of care in Australia and internationally is currently intermittent infusion.
7. Continuous infusions are a viable alternative to standard intermittent infusion, which can be administered in a safe manner with no extra drug costs.
8. There is sufficient clinical equipoise and clinician uncertainty to justify the conduct of a definitive phase III study.
9. The research team and coordination centre have the expertise and track record to conduct a multi-national, multicentre RCT of global significance.

In addition, in an era of increasingly expensive therapies, administration of beta-lactam antibiotics via continuous infusion, compared with intermittent infusion, represents greater cost-efficiency in terms of workload and labour costs, while remaining cost neutral in terms of drug costs.[16,28] Similarly, there is no scientific evidence to suggest beta-lactam antibiotic administration by continuous infusion results in increased antibiotic resistance or negative sequelae compared with intermittent infusion. To this end, the potential survival and health economic advantages with using continuous beta-lactam infusion will be quantified in the proposed definitive phase III study.

3.5. Clinical significance

Regardless of the outcome, this study will provide vital evidence to answer the clinically important question of whether there is a difference in patient-centred outcomes in critically ill patients with sepsis administered beta-lactam antibiotics by continuous infusion versus intermittent infusion. If a 3.5% absolute reduction in hospital mortality is observed, then this intervention has the potential to save over 750 lives each year in Australia and New Zealand alone (based on severe sepsis incidence data).[29] This research will provide pivotal evidence on the optimal method of delivery of commonly used beta-lactam antibiotics via a phase III RCT of global relevance.

4. Study design

4.1. Aim

To conduct a multicentre randomised, controlled trial (RCT) to determine whether continuous infusion of a beta-lactam antibiotic (piperacillin-tazobactam or meropenem) results in decreased all-cause Day 90 mortality compared with intermittent beta-lactam antibiotic infusion in critically ill patients with sepsis.

4.2. Hypothesis

The BLING III Study will test the hypothesis that patients managed in the ICU with sepsis, the administration of beta-lactam antibiotics via continuous infusion decreases Day 90 mortality compared with intermittent infusion

4.3. Design

This BLING III study is a prospective, multicentre, open, phase III, RCT. Participants commenced on one of two beta-lactam antibiotics (piperacillin-tazobactam or meropenem) will be randomised to receive the beta-lactam antibiotic via either continuous infusion or intermittent infusion over 30 minutes for the treatment course for up to 14 days after randomisation while in the ICU. For participants where the beta-lactam antibiotic is subsequently changed from piperacillin-tazobactam to meropenem or vice versa for ongoing treatment of the infectious episode, the new prescription will continue to be administered in the allocated method (continuous infusion or intermittent infusion over 30 minutes).

5. Study outcomes

5.1. Primary outcome

All-cause mortality within 90 days after randomisation.

5.2. Secondary outcomes

1. Clinical cure at Day 14 post randomisation
2. New acquisition, colonisation or infection with an multi-resistant organism (MRO) or *Clostridium difficile* diarrhoea up to 14 days post randomisation
3. All-cause ICU mortality
4. All-cause hospital mortality

5.3. Tertiary outcomes

1. ICU length of stay
2. Hospital length of stay
3. Duration of mechanical ventilation in ICU up to 90 days after randomisation
4. Duration of renal replacement therapy up to 90 days after randomisation

6. Study participants

6.1. Study setting

This study will be conducted in approximately 100 ICUs worldwide, with sites anticipated in Australia, New Zealand, United Kingdom and Europe.

6.2. Inclusion criteria

1. Patient has a documented site of infection or strong suspicion of infection
2. Patient is expected to be in the ICU the day after tomorrow
3. Patient has been commenced on piperacillin-tazobactam or meropenem to treat the episode of infection
4. Giving piperacillin-tazobactam or meropenem by intermittent infusion or continuous infusion is considered equally appropriate for the patient
5. One or more organ dysfunction criteria in the previous 24 hours
    i. MAP < 60 mmHg for at least 1 hour
    ii. Vasopressors required for > 4 hours
    iii. Respiratory support using supplemental high flow nasal prongs, continuous positive airway pressure, bilevel positive airway pressure or invasive mechanical ventilation for at least 1 hour
    iv. Serum creatinine concentration > 220 µmol/L or >2.49 mg/dL

6.3. Exclusion criteria

1. Patient age is less than 18 years
2. Patient has received piperacillin-tazobactam or meropenem for more than 24 hours during current infectious episode
3. Patient is known or suspected to be pregnant
4. Patient has a known allergy to piperacillin-tazobactam, meropenem or penicillin
5. Patient is requiring renal replacement therapy at the time of randomisation, including renal replacement therapy for chronic renal failure
6. The attending physician or patient or surrogate legal decision maker is not committed to advanced life-support, including mechanical ventilation, dialysis and vasopressor administration, for at least the next 48 hours
7. Patient's death is deemed imminent and inevitable
8. Patient has previously been enrolled in BLING III

7. Study interventions

7.1. Randomisation

Randomisation will be achieved using a minimisation algorithm via a password-protected, encrypted web-based interface. Randomisation will be stratified according to participating site. Following successful randomisation, each patient will be assigned a unique 'patient study number' and be assigned an administration method of either continuous infusion or intermittent infusion over 30 minutes. The clinician prescribed beta-lactam antibiotic (piperacillin-tazobactam or meropenem) will be administered via the study allocated method as per the below study treatment regimen.

7.2. Study treatment regimen

The administration method of beta-lactam antibiotic, either piperacillin-tazobactam or meropenem, will be randomised to either continuous infusion or intermittent infusion over 30 minutes. The choice of beta-lactam antibiotic and the dose and dosing interval (i.e. the dose the patient will receive in 24 hours) will be determined by the treating physician. The administration of beta-lactam antibiotic therapy will be commenced prior to randomisation. The amount of beta-lactam antibiotic prescribed (dose) should reflect the patient body size and estimated drug clearance as per standard prescribing practices. The dose of beta-lactam antibiotic the patient receives will be the same regardless of administration method allocation. Commencement of the allocated administration method should be as early as possible in the treatment course.

During the study period, the treating physician can modify the beta-lactam antibiotic dose in response to clinical changes of the patient. If following randomisation, the treating physician decides to change from piperacillin-tazobactam to meropenem or vice versa, the new prescription will continue to be administered in the allocated method (continuous or intermittent infusion over 30 minutes).

The beta-lactam antibiotic (piperacillin-tazobactam or meropenem) will continue to be administered according to the allocated study administration method until either: 1) the beta-lactam antibiotic is ceased by the treating physician, 2) the patient is discharged from ICU (including death), or 3) 14 days after randomisation, whichever is sooner. If the patient is readmitted to ICU (with ongoing beta-lactam antibiotic treatment) or the beta-lactam antibiotic is recommenced prior to Day 14 the study assigned administration method needs to be followed. After Day 14, the study assigned administration method does not need to be followed and the patient can receive the beta-lactam antibiotic via the standard administration method used at site.

If the patient is still prescribed the beta-lactam antibiotic (piperacillin-tazobactam or meropenem) following ICU discharge, the standard administration method at the site will be used. For patients who require a change in administration method, the next scheduled intermittent infusion or commencement of continuous infusion should occur at a time equivalent to half the intended intermittent dosing interval ($t_{50\%}$) for the beta-lactam antibiotic.

Therapeutic drug monitoring of the beta-lactam antibiotic (piperacillin-tazobactam or meropenem) administered according to the study allocated method is not permitted during study participation due to impact on the intervention.

7.2.1. Continuous infusion

Patients randomised to receive the beta-lactam antibiotic via continuous infusion will receive the prescribed dose over 24 hours following an initial bolus dose by intermittent infusion over 30 minutes. Participants previously on an intermittent dosing regimen that have been randomised into the continuous infusion arm, or following an initial bolus dose, will commence the continuous infusion at a time equivalent to half the intended intermittent dosing interval ($t_{50\%}$) for the beta-lactam antibiotic, e.g. $t_{50\%}$ = 4 hours if the intended intermittent dosing interval is 8 hours (**Figure 5**).

If the beta-lactam antibiotic is changed from piperacillin-tazobactam to meropenem or vice versa, and the allocated method of administration is continuous infusion, then a bolus dose of the new beta-lactam antibiotic will be given and the continuous infusion commenced at a time equivalent to half the intended intermittent dosing interval.

7.2.2. Intermittent infusion

Patients randomised to receive the beta-lactam antibiotic via intermittent infusion over 30 minutes will receive the prescribed dose at the scheduled intermittent dosing intervals. Participants previously on a continuous infusion dosing regimen that have been randomised into the intermittent infusion arm will have the continuous infusion ceased and receive the next scheduled dose by intermittent infusion over 30 minutes. The intermittent infusion should be given at the prescribed dosing interval. If the patient has previously been receiving a continuous infusion, then the continuous infusion should be stopped and the first intermittent infusion dose given immediately.

If the beta-lactam antibiotic is changed from piperacillin-tazobactam to meropenem or vice versa, and the allocated method of administration is intermittent infusion, then the new beta-lactam antibiotic will commence at the next dosing interval.

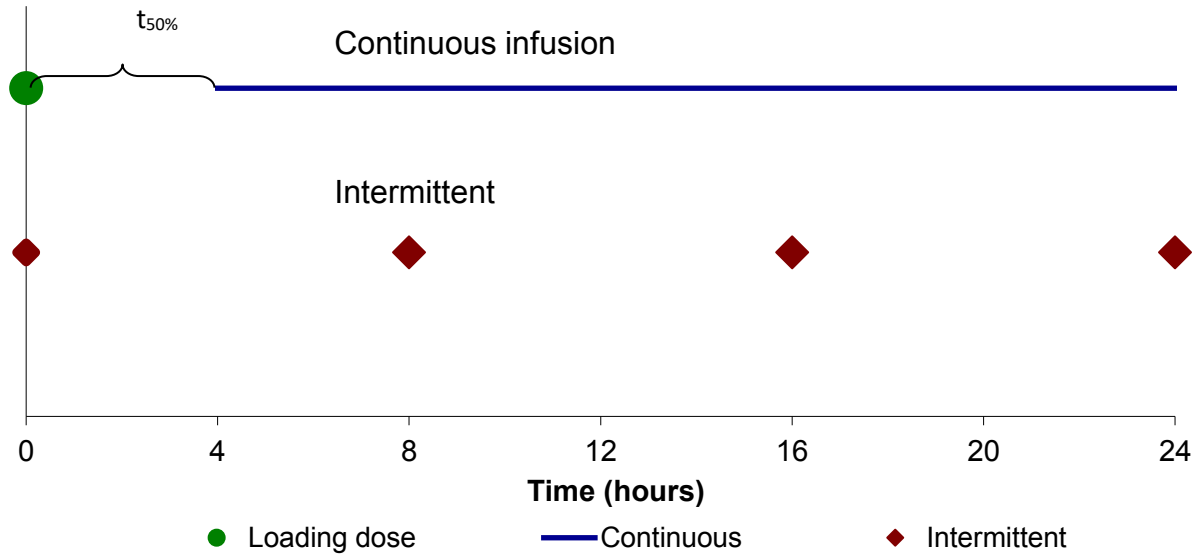


Figure 5. *Commencement of randomised study assigned administration method following the last intermittent infusion (i.e. bolus dose) for a beta-lactam antibiotic prescribed at an 8 hourly interval*

7.3. Premature cessation of study assigned administration method

Following randomisation, every effort should be made to ensure patients continue to receive the beta-lactam antibiotic (piperacillin-tazobactam or meropenem) via the allocated study administration method as described in the protocol.

Study administration method may be stopped in the following circumstances:

1. Request to stop the study assigned administration method by the patient or their substitute decision maker/person responsible. The patient or their substitute decision maker/person responsible may request the study administration method be stopped if they decide to do so, at any time, without needing to give a reason.
   Consent to continue data collection and to continue follow up, in particular, to determine vital status as 90 days, will be sought.
2. Adverse or serious adverse reaction to the beta-lactam antibiotic or to the study assigned administration method.

Appropriate ongoing treatment will be determined by the treating physician, including whether the beta-lactam antibiotic and/or study assigned administration method should be immediately ceased.

The patient will remain in the study and the data collection and follow-up schedule will continue unchanged.

7.4. Concomitant care

Other aspects of patient management will be unaffected by study procedures. The treating clinicians will be free to provide whatever care is deemed appropriate and necessary.

7.5. Blinding

This is an unblinded study: study assigned administration method will be known to the treating clinicians. Ascertainment bias will be mitigated through blinded randomisation.

7.6. Safety considerations

There is no added discomfort or additional invasive procedures arising from participating in the study. The previous BLING I and BLING II trials demonstrated that beta-lactam antibiotics can be administered via continuous or intermittent infusion safely in a trial setting. For patients randomised to receive the beta-lactam antibiotic via continuous infusion the administration of a bolus dose and timing for commencement of the infusion (half the intended intermittent dosing interval) is designed to ensure adequate plasma levels of beta-lactam antibiotic are reached.

7.6.1. Precautions and adverse reactions

Piperacillin-tazobactam and meropenem are registered products with the Therapeutic Goods Administration (Australia), Medsafe (New Zealand) and the European Medicines Authority (United Kingdom and Europe). The treating clinician must be aware of the precautions and potential adverse reactions for piperacillin-tazobactam and meropenem detailed in Product Information relevant to their geographic location. Patients will be monitored for the known side effects of intravenous therapy with piperacillin-tazobactam and meropenem.

8. Study assessments

Study participants will be followed-up to 90 days post-randomisation, or to death, whichever is sooner.

8.1. Screening

Patients will be screened and evaluated to assess eligibility for the study. A screening log will be kept to monitor recruitment and report the size of the patient population from which eligible patients have been recruited.

8.2. Randomisation

The patient's demographics will be entered into a web based randomisation system. Each eligibility criterion will be answered with a Yes / No response and only patients meeting all criteria will proceed to randomisation.

8.3. Baseline

Patient characteristics (age, sex, estimated/actual weight and height), admission diagnosis and clinical information will be collected to assess baseline balance between each treatment group. Details on the site or sites of presumed or known infection will be obtained. Clinical information will allow calculation of the Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores that classify illness severity in ICU patients.[30,31]

8.4. Intensive care unit admission

Daily clinical information and laboratory data will be recorded whilst the patient is in ICU for up to 90 days post randomisation to document response to treatment and to monitor safety and compliance with the study protocol.

8.5. Definition of clinical cure

Clinical cure will be defined as the completion of the beta-lactam antibiotic treatment course (on or prior to Day 14) without recommencement of antibiotic therapy within 48 hours of cessation. For the purposes of evaluating clinical cure, change of antibiotic therapy (i.e. either escalation or de-escalation) for the same indication for which the beta-lactam antibiotic was commenced is considered part of the antibiotic treatment course.

Participants discharged from hospital within 14 days following randomisation will be considered to meet the definition of clinical cure. However, if a participant is readmitted within 14 days of randomisation then the participant will be assessed against the definition of clinical cure as above, using information available at readmission.

Participants who decease while receiving the antibiotic treatment course or where antibiotic therapy is ceased in the setting of death being deemed imminent and inevitable, will be assessed as not meeting the criteria for clinical cure.

8.6. Definition of new MRO and *Clostridium difficile* diarrhoea

New acquisition of colonisation or infection with an MRO will be defined as newly identified Methicillin-resistant Staphylococcus aureus (MRSA), Vancomycin-resistant Enterococci (VRE), Extended-spectrum beta-lactamase (ESBL) or Carbapenem-resistant Enterobacteriaceae (CRE) or multidrug-resistant Pseudomonas on any routine swabs (e.g. nose, perineum or wounds) or clinically indicated specimens (e.g. blood, urine or endotracheal aspirates) taken between Day 1 and Day 14 (inclusive). Multidrug-resistant Pseudomonas will be defined as a Pseudomonas species resistant to three or more of the following antibiotics: ceftazidime, ciprofloxacin, meropenem, gentamicin or piperacillin-tazobactam. *Clostridium difficile* diarrhoea will be defined as a stool sample sent to the laboratory and testing as *Clostridium difficile* toxin positive between Day 1 and Day 14 (inclusive).

8.7. Follow up at Day 90

Follow-up for the primary outcome will be until death or 90 days after randomisation, whichever is sooner. At Day 90, vital status, length of stay in the ICU, length of stay in hospital, date and cause of death (if appropriate) will be recorded.

8.8. Schedule of assessments

Task	Screening	Randomisation	Baseline	Day 1 to 90	Day 90 follow-up
Assess ability to gain consent & follow-up	X				
Assess eligibility to enter study	X				
Demographics & eligibility checklist		X			
Record date and time of randomisation		X			
Administer study treatment			X		
Patient characteristics (estimated/actual weight and height)			X		
ICU admission diagnosis			X		
Baseline APACHE II (severity of illness) score components			X		
Site or sites of presumed or known infection			X		
Baseline SOFA scores			X		
Planned 24-hour dose and dosing interval of the beta-lactam antibiotic at randomisation			X		
Microbiological confirmation of infection			X		
Assess for concurrent antibiotic use up to Day 14				X	
Assessment for clinical cure: Day 14				X	
Colonisation with an MRO or *C. difficile* at 14 days after randomisation				X	
All beta-lactam antibiotic doses				X	
Reason for cessation of beta-lactam antibiotic				X	
Consent		X			
Duration of mechanical ventilation				X	
Duration of RRT				X	
Date of ICU discharge up to Day 90				X	
Vital status at ICU discharge				X	
Date of hospital discharge up to Day 90				X	
Vital status at hospital discharge				X	
Vital status at Day 90 (including date and cause of death if deceased)					X
Adverse reactions			X		
Protocol violations			X		

9. Safety monitoring and reporting

It is recognised that the patient population in the ICU will experience a number of aberrations in laboratory values, signs and symptoms due to the severity of the underlying disease and the impact of standard treatments in the ICU. These will not necessarily constitute adverse events unless they are considered to be related to study treatment or in the site Principal Investigator's clinical judgement are not recognised events consistent with the patient's underlying disease and expected clinical course.

In this study, reporting of adverse events will be restricted to events that are considered to be related to study assigned administration method (possibly, probably or definitely). Events collected as study outcomes will not be reported as adverse events.

9.1. Adverse events

Any adverse events thought to be related to study assigned administration method will be reported within 7 days of discovery. The site Principal Investigator will be responsible for determining the causal relationship as either possible, probable or definitely related. Notification will be by completing an adverse event form on the web based data management system. The central and regional coordinating centres will automatically receive an alert email when an adverse event form is completed on the web based data management system.

All adverse events will be reviewed by staff at the coordinating centres and recorded in a central safety database and will be reported to the independent Data and Safety Monitoring Committee (DSMC) on a regular basis. The central coordinating centre will be responsible for ensuring regional coordinating centres and relevant participating sites are informed of adverse events.

9.1.1. Serious adverse events

Serious adverse events (SAEs) are defined as any untoward medical occurrence that meets one or more of the following criteria:

1. Results in death
2. Is life-threatening
3. Requires inpatient hospitalisation or prolongation of existing hospitalisation
4. Results in persistent or significant disability/incapacity
5. Is a congenital anomaly/birth defect

The classification of an SAE is not related to the assessment of the severity of the adverse event. An event that is mild in severity may be classified as an SAE based on the above criteria. Given that critically ill patients are likely to meet any of the above listed criteria in the course of their ICU admission, only SAEs that are thought to be related to the study assigned administration method will be reported.

SAEs should be reported within 24 hours of participating site study staff becoming aware of the occurrence by completing an adverse event form on the web based data management system. A member of the regional or central coordinating centres will be available 24 hours a day for out of 'business hours' queries regarding SAE reporting.

9.1.2. Suspected unexpected serious adverse reactions

A suspected unexpected serious adverse reaction (SUSAR) is an Serious Adverse Drug Reaction (SADR) which is considered *unexpected*. An SADR whose nature, severity, specificity, or outcome is not consistent with the term or description used in the product information, should be considered unexpected. These will also be reported within 24 hours of participating site study staff becoming aware of the occurrence by completing an adverse event form on the web based data management system.

9.1.3. Reporting SAEs and SUSARs

The minimum information to report will include:

1. Patient initials and study number
2. Nature of the event
3. Commencement and cessation of the event
4. Outcome of the event
5. The principal or co-investigator's opinion of the relationship between study treatment and the event (possibly, probably or definitely related)
6. Whether treatment was required for the event and what treatment was administered

The regional coordinating centre staff will be responsible for following-up all SAEs, and SUSARs to ensure all details are available. The central coordinating centre is responsible for alerting other participating sites to the reported SAE, or SUSAR and reporting to the regulatory authorities within required timeframes.

The central coordinating centre is responsible for ensuring that the local or lead HREC) or Institutional Review Board (IRB) and/or Research Governance Officer are informed of all SAE, and SUSAR events that occur, in accordance with local requirements. Copies of any reporting and correspondence to and from the local HREC / IRB or research governance office should also be sent to the regional coordinating centre.

9.2. Data and Safety Monitoring Committee

A DSMC independent from the coordinating centre and investigators will perform an ongoing review of study outcomes and overall study conduct. The DSMC will review study progress, including loss to follow up, study withdrawal, mortality and all adverse reactions at predetermined intervals during the study or as deemed appropriate by the DSMC. The primary responsibility of the DSMC is to review interim analyses of outcome data and to recommend to the Study Management Committee whether the study needs to be changed or terminated based on these analyses.

Full details of the DSMC procedures and processes are documented in the DSMC charter.

9.3. Study termination

The study may be terminated at any time at the request of the study Management Committee in consultation with the DSMC, or a regulatory authority, with proper and timely notification of all parties concerned. The local or lead HREC / IRB will be informed promptly and the coordinating centre or the investigator will supply reason(s) for the termination or suspension, as specified by the applicable regulatory requirements.

Otherwise, the study will be considered terminated when the specified number of patients have been enrolled (see "Section 16: Proposed project timeline" for further details) and upon completion of all patient treatments and evaluations.

10. Ethics and dissemination

10.1. Ethical principles

The study will be conducted in accordance with ethical principles consistent with the Declaration of Helsinki[32] and all relevant national and local guidelines on the ethical conduct of research.[33-35].

10.2. Human Research Ethics Committee

The protocol for this project will be reviewed by the relevant HREC / IRB for each participating site. In jurisdictions where single ethical review of multicentre trials is in place, one Principal Investigator (known as the coordinating investigator) will take responsibility for applying to a lead HREC / IRB on behalf of investigators covered by that committee. Each site Principal Investigator will then be responsible for applying for local research governance approval at their site (as required).

Documentation of the approval of the protocol and the consent documents will be provided to the regional coordinating centre before the study may begin at any site. The regional coordinating centre will assist with this process by preparing a standard application form and template consent documents. The content and format of the standard information statements and consent forms will be adapted if necessary to comply with local HREC / IRB guidelines and requirements.

During the trial, any amendment or modification to the study protocol should be notified to the HREC / IRB by the Principal Investigator and approved by the HREC / IRB before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the HREC / IRB should be informed as soon as possible thereafter.

Each site Principal Investigator will be responsible for informing the central coordinating centre of any event likely to affect the safety of patients or the continued conduct of the clinical trial. The HREC / IRB will be notified in accordance with local requirements.

The central coordinating centre will be responsible for producing progress reports, adverse event reports, and any other required documentation to the HREC / IRB in accordance with their guidelines. Copies of all HREC / IRB and research governance office correspondence, including approved local site consent documents, will be held by the central or regional coordinating centre and the relevant participating sites.

10.3. Informed consent procedures

This study involves the random assignment of the administration method, either continuous infusion or intermittent infusion, for two beta-lactam antibiotics (piperacillin-tazobactam or meropenem) in the treatment of sepsis in patients requiring intensive care. Piperacillin-tazobactam and meropenem are both commonly used in clinical practice for a wide range of infections and are not experimental products. All study related assessments are part of standard care of ICU patients requiring antimicrobial therapy, with the exception of follow up of patient status following discharge from hospital.

The Australian NHMRC National Statement on the Ethical Conduct in Human Research,[33] the New Zealand Code of Health and Disability Consumers' Rights[34] and New Zealand Guidelines on Ethics in Health Research,[35] acknowledge that research involving patients who are heavily dependent on medical care, such as the patients in this study, is necessary to assess and improve the efficacy and safety of interventions used in their treatment.

The site Principal Investigators, or their nominated delegate, at each site is responsible for obtaining written informed consent in accordance with relevant HREC / IRB approval and any regulatory requirements. The informed consent procedure will involve a verbal explanation of the study and the provision of a written information sheet. There will be adequate time given to consider participation in the study and opportunity to ask questions. A copy of the information sheet and the signed and dated consent form will be supplied to the person providing written consent, as well as any other documentation discussed through the consent process. A copy of the information sheet and signed and dated consent form will be placed in the patient's medical record at site and the original will remain in the trial site file.

Where possible, written informed consent from any conscious and comprehending patient prior to their enrolment in the study will be obtained. Obtaining written and informed consent directly from patients in the ICU prior to enrolment in a clinical trial is frequently not possible as the patient is often unconscious, sedated, intubated and too ill to understand information relating to clinical trial participation. Additionally, antimicrobial therapy is usually a matter of clinical urgency and a treatment that must be carried out without delay to avoid adverse consequences for the patient that include the escalation of infection, worsening of organ dysfunction and at the extreme, may contribute to an increased risk of death. Where regulations allow, written consent may be obtained from a person other than the participant, and may include a legally recognised substitute decision maker or consultee.

All interaction between research staff and potential or actual participants and their relatives will take into consideration the stress or emotional factors associated with critical illness and ensure that the dependency of potential participants and their relatives on medical personnel providing treatment does not compromise the freedom of a decision to participate. Consenting to participation will be voluntary and participants or their legally recognised substitute decision maker will be free to withdraw from participation at any time without giving reasons.

In addition to the above, the following will apply to the consent process in the relevant country or region.

10.3.1. Australian context

A hierarchy for obtaining consent has been developed based on the Australian NHMRC National Statement on the Ethical Conduct of Human Research (Chapter 4.4: People highly dependent on medical care who may be unable to give consent)[33] and the ANZICS Clinical Trials Group Ethics Handbook for Researchers.[36] Under the circumstances discussed above, the approach to obtaining consent in Australia in this study will follow this hierarchy:

a) Consent from patient PRIOR to randomisation

Patients who are conscious and comprehending will be approached to give informed consent to take part in this study before project related activities are undertaken. Intensive care physicians are highly

experienced at caring for critically ill patients and also evaluating the competence of their patients to understand their illness and consent for therapeutic interventions.

b) Consent from 'substitute decision maker' PRIOR to randomisation

If a potential participant lacks the capacity to give consent due to their medical condition, whenever possible, consent will be obtained from a legally recognised substitute decision maker. Obtaining consent from the substitute decision maker will be approved by the relevant HREC / IRB and be in accordance with all applicable laws.

c) Inclusion without prior consent with option to continue or withdraw

Where it is not possible or practicable for the patient or the substitute decision maker to provide consent prior to randomisation, subject to approval by the relevant HREC / IRB and all applicable laws, the patient will be enrolled into the study without prior consent and as soon as possible and appropriate, the patient or substitute decision maker will be informed of the patient's participation in the study. At this stage, the patient or substitute decision maker will be given the option to consent to continuing in the study or to withdraw from the study. If they request withdrawal of the study assigned administration method, then it will be stopped. Permission to use study-related data and permission to collect and use outcome data will be sought.

d) Deceased patients

For patients enrolled in the study under the process explained in 10.3.1c above, where the patient dies before consent has been obtained, permission to use study related information will be sought from the relevant HREC / IRB.

e) Where informed consent cannot be obtained from the patient or substitute decision maker

In circumstance that a patient never regains competency following enrolment into the trial under the process explained in 10.3.1c above and there are no substitute decision makers available, an approach will be made to the relevant HREC / IRB to request that re-identifiable study data may be retained and used.

10.3.2. New Zealand context

In New Zealand, the approach used will be consistent with section 7.4 of the Health and Disability Code,[34] which outlines the framework for providing treatment to patients who are unable to consent for themselves.

The specific approach will be:

1. To consider whether the study assigned administration method and study participation is in the best interest of each individual patient, and
2. As soon as it is practical and reasonable, to seek the advice of persons interested in the patient's welfare to establish that study participation is consistent with the patient's wishes.

All participants who recover sufficiently will be given the opportunity to provide informed written consent for ongoing study participation and for the use of data collected for the study

10.3.3. United Kingdom context (specifically England and Wales)

If sites from Scotland or Northern Island participate, then local regulations will be adhered to in relation to persons legally capable of providing consent on behalf of the patient.

In England and Wales, there will be a hierarchy for obtaining written informed consent and/or a declaration from a consultee in the following order of priority:

a) Consent from patient PRIOR to randomisation

Patients who are conscious and comprehending will be approached to give informed consent to take part in this study before project related activities are undertaken. Intensive care physicians are highly experienced at caring for critically ill patients and also evaluating the competence of their patients to understand their illness and consent for therapeutic interventions.

b) Declaration from 'personal consultee' or 'nominated consultee' PRIOR to randomisation

If a potential participant lacks the capacity to give consent due to their medical condition, then the advice of a consultee on whether the adult lacking capacity would wish to be included in the research study will be sought. The consultee will be provided with information about the study and asked to give an opinion as to whether the patient would object to taking part in the study and to sign a declaration.
A 'personal consultee' is a person who cares for the adult lacking capacity or is interested in the person's welfare (but not for remuneration or in a professional capacity). If a personal consultee is not available or unwilling to give advice, then a 'nominated consultee' (a professional who is independent of the study) can do so.

c) Inclusion without prior consent or declaration with option to continue or withdraw

Where it is not possible or practicable for the patient to provide consent or a consultee to provide a declaration prior to randomisation, subject to approval by the relevant HREC / IRB and all applicable laws, the patient will be enrolled into the study without prior consent or declaration and as soon as possible and appropriate, the patient or consultee will be informed of the patient's participation in the study.
A consultee will be consulted as soon as possible to seek advice on the participant's likely views and feelings. As soon as possible and appropriate to approach the patient, they will be given the option to consent to continuing in the study or to withdraw from the study. If they request withdrawal of the study assigned administration method, then it will be stopped. Permission to use study-related data and permission to collect and use outcome data will be sought.
For patients enrolled in the study without prior written consent, who either die or never regain capacity, assent from the personal or nominated consultee will constitute permission to use study related information.

10.3.4. Other contexts

In sites from other regions than those specifically mentioned above, local regulations will be adhered to in relation to persons legally capable of providing consent on behalf of the patient.

We will abide by the regulations of state or country jurisdiction as approved by the relevant regulatory authority.

10.4. Confidentiality and privacy

All patient data pertaining to the study will be stored in a computer database maintaining confidentiality in accordance with local legislation regarding privacy and use of health data. When archiving or processing data pertaining to the investigator and/or to study participants, the coordinating centre will take all appropriate measures to safeguard and prevent access to this data by any unauthorised third party.

The site Principal Investigator will maintain the confidentiality of all study documentation and take measures to prevent accidental or premature destruction of these documents. The site Principal Investigator will retain the study documents for the minimum period required by local regulations after the completion or discontinuation of the study: at least 15 years in Australia and New Zealand, and 20 years in Belgium. The site Principal Investigator must notify the central coordinating centre prior to destroying any study documents following study completion or discontinuation. If the site Principal Investigator's situation is such that archiving can no longer be ensured by him/her, the site Principal Investigator will inform the central coordinating centre and the relevant records will be transferred to a mutually agreed designee.

If any site Principal Investigator retires, relocates, or otherwise withdraws from conducting the study, the responsibility for maintaining records may be transferred to the central coordinating centre, or other site Principal Investigator. The central coordinating centre must be notified of and agree to the change. All associated documentation must also be updated.

11. Data collection and management

Data management will be provided by The George Institute for Global Health, Australia. The principle means of data collection and data processing will be electronic via a password protected website (electronic Case Report Form - eCRF). All computerised forms will be electronically signed by the authorised study staff and all changes made following the electronic signing will have an electronic audit trail with a signature and date.

While in hospital, study participants will have relevant study data extracted from that routinely collected in the ICU clinical chart, medical record and available hospital databases. For study participants who have been discharged from hospital, they (or a nominated carer) will be contacted by a member of the research team at each site via telephone 90 days post randomisation to determine vital status.

A comprehensive guide to data collection with definitions and rationale will be provided together with a paper version of the case report form (CRF). Paper documents will be stored in secure locked cabinets with access limited to authorised persons.

A comprehensive guide to accessing the data entry forms on the website and entering all follow-up data will be provided in the Data Completion Manual and Operations Manual. All of these documents will also be available in PDF format for printing from the study website as required to assist the research coordinator to ensure high-quality data collection and data entry.

11.1. Record retention

All paper study records, including consent documentation, paper CRFs (if used) and electronic records will be kept following the completion of the study: 15 years in Australia and New Zealand, and 20 years in Belgium, and otherwise as per local regulations in other jurisdictions.

12. Quality control and quality assurance monitoring

12.1. Responsibilities of the investigator

The site Principal Investigator agrees to perform the clinical trial in accordance with this clinical trial protocol, ICH guideline for Good Clinical Practice[37] and all applicable regulatory requirements. The site Principal Investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by the central or regional coordinating centre.

The site Principal Investigator agrees to provide reliable data and all information requested by the clinical trial protocol in an accurate, legible and timely manner according to the instructions provided. The site Principal Investigator agrees to allow representatives of the central or regional coordinating centre (or national coordinator for European sites) to have direct access to source documents.

12.2. Responsibilities of the central coordinating centre

The central coordinating centre, The George Institute for Global Health, is responsible for taking all reasonable steps to ensure the proper conduct of the clinical trial protocol.

12.2.1. Site initiation

Prior to initiation of the study at each participating site, the central or regional coordinating centre will be responsible for providing adequate training to the site Principal Investigator and study personnel. The training will cover all aspects of the study protocol and procedures and will include practical training on the use of the web-based randomisation system, electronic CRF website and study materials. The site initiation visit will be conducted by teleconference, videoconference or face-to-face meeting at the participating site. Written and electronic materials will be supplied for study staff and for the education of clinical ICU staff at each participating site.

12.2.2. Monitoring during the study

A study monitor from the central or regional coordinating centre (or the national coordinator for European sites) will visit each participating study site on several occasions during the recruitment phase, in accordance with the Monitoring Plan. This will ensure that the study is conducted according to the protocol, Good Clinical Practice guidelines and relevant regional regulatory requirements. The main duty of the study monitor is to help the investigator and the coordinating centre maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the trial.

The site Principal Investigator and study personnel will assist the monitoring staff by providing all appropriate documentation and being available to discuss the study. These monitoring visits will include, but will not be limited to, review of the following aspects:

1. Adherence to the protocol including consistency with inclusion and exclusion criteria
2. The completeness and accuracy of the CRFs and source documentation
3. Patient recruitment

4. Adverse event documentation and reporting
5. Study assigned administration method
6. Compliance with the study assigned administration method
7. Compliance with regulations

The central coordinating centre team will conduct regular remote monitoring on the web-based database by applying validation and consistency rules and with regular data cleaning to ensure the integrity of the study data.

12.2.3. Site close out

At completion of the trial, a final monitoring and close out visit will be conducted by the study monitor in accordance with the Monitoring Plan. Secure facilities for the storage of study data for 15 years in Australia and New Zealand, and 20 years in Belgium, or otherwise as required by local regulations, will also be confirmed at this visit.

12.3. Source document requirements

According to the International Conference on Harmonisation guidelines for Good Clinical Practice[37], the monitoring team will check source documents to confirm the existence of the participant and the integrity of the study data. Source documents include the original documents related to the trial, to medical treatment and to the history of the subject. Adequate and accurate source documents allow the investigator and the site monitor to verify the reliability and authenticity of data recorded on the electronic CRFs and ultimately to validate that the clinical study was carried out in accordance with the protocol.

12.4. Management of protocol deviations

A protocol deviation is an unanticipated or unintentional departure from the expected conduct of an approved study that is not consistent with the current research protocol or consent document. A protocol deviation may be an omission, addition or change in any procedure described in the protocol.

The site investigator should not implement any deviation from or changes to the protocol without agreement by the study management committee and documented approval from the HREC / IRB of the amendment, except where necessary to eliminate an immediate hazard(s) to trial participants. In the event of an emergency intended to eliminate an apparent immediate hazard to participants the investigator may implement or omit any medical procedure as deemed appropriate.

Substantive deviations from the protocol must be documented and promptly reported to the study management committee and the HREC / IRB (if applicable). The report should summarise the event and action taken.

12.5. Direct access to data and documents

The study may be audited by government regulatory authorities, local HREC / IRBs or qualified representatives of The George Institute for Global Health as permitted by regulations. Therefore, access to medical records, other source documents, such as ICU charts and other study related files, must be made available at all study sites for monitoring and audit purposes during the course of the study and after its completion.

Participants will not be identified by name, and confidentiality of information in medical records will be preserved. The confidentiality of the participant will be maintained unless disclosure is required by regulations.

13. Statistical methods

13.1. Power calculation and sample size

The sample size for this study is based on data derived from the BLING II study and a subsequent individual patient meta-analysis,[26,27] referenced to 90-day mortality in patients with sepsis in an international setting.[4,29] A sample size of 7,000 (3,500 in each group) is required to achieve 90% power to detect an absolute risk reduction of 3.5% (i.e. a 12.7% relative risk reduction) in 90-day mortality in the intervention group from baseline mortality of 27.5%, with a significance level (alpha) of 0.05. From the calculated sample size (6,558) an estimated 5% loss to follow-up (345) was added with rounding up to 7,000.

13.2. Statistical analysis plan

The effectiveness of the intervention will be evaluated by an analysis of all randomised participants according to their allocated treatment group, irrespective of compliance. Initial range and logic tests will be performed and discrepancies corrected with the original site and data source where applicable. The coordinating centre will undertake analysis of results, including interim reporting to the DSMC.

The primary outcome (all-cause mortality within 90 days after randomisation) as well as the secondary outcomes will be analysed using either log-binomial or logistic regression. The main intervention effect will be estimated as the relative risk or odds ratio of death and its 95% CI with the control arm used as the reference. Time-to-death will be described using Kaplan-Meier plots with differences in survival estimated using a Cox proportional hazard model. Tertiary outcomes will be analysed both as number of days alive and free of outcome (e.g., days alive and free of mechanical ventilation) and as time from randomisation to resolution or discharge (e.g. time to cessation of mechanical ventilation). A two-sided *p*-value <0.05 will be considered evidence of a significant difference in the study outcome.

All statistical analyses will be conducted in accordance with a detailed pre-specified statistical analysis plan.[38]

13.3. Interim analysis

In order to address safety concerns, at least one formal interim analysis will be conducted when 3,500 patients (50% of planned recruitment) have completed 90-day follow-up.

The purpose of this interim analysis is to assess safety and efficacy according to a pre-specified DSMC Charter.

13.4. Pre-specified subgroup analyses

1. Patients with or without lung infection
2. Beta-lactam administered, either piperacillin-tazobactam or meropenem

14. Pre-specified sub-studies

14.1. Minimum inhibitory concentration distribution for identified infective organism

In participants with an identified infective organism, outcomes will be examined across the distribution of minimum inhibitory concentration values.

14.2. Pharmacokinetic-pharmacodynamic sub-study

A pharmacokinetic-pharmacodynamic (PK-PD) evaluation in up to 600 patients will be conducted at sites able to support collection and storage of blood samples. The relationship of beta-lactam antibiotic blood concentrations with the method of administration and with study outcomes will be determined. Further details will be provided in the PK-PD sub-study protocol.

14.3. Health economics analysis

A cost-effectiveness analysis at 90 days following randomisation will be conducted as a nested cohort in Australian, New Zealand and other potential regional sites. Cost data will be derived from health care utilisation to Day 90, estimated through standard per diem ICU and hospital costs. The analysis will be conducted from a health care payer perspective, comparing health care utilisation costs and quality-adjusted life years gained (measured by the EQ-5D-5L) between treatment arms. Where feasible, the cost-effectiveness analysis will be conducted in other country-specific regions. Depending on the outcome from the primary trial, several further analyses are planned including a longer-term cohort study and a modelled economic evaluation. The BLING III cost-effectiveness analysis will be informed by a separate Statistical Analysis Plan.

Additional follow up at Day 90 for the purpose of economic evaluation will be conducted for Australian, New Zealand and sites from participating regions only. Follow up at Day 90 will include recording readmission to hospital and ICU within 90 days and will assess quality of life and functional capacity using the European Quality of Life 5 Dimensions 5 Level (EQ-5D-5L) questionnaire (if not deceased).[39] The consent document used at participating sites will detail the inclusion of a quality of life questionnaire at Day 90.

Additional schedule of assessments:

Task	Day 90 follow-up
Date of ICU readmission/s & discharge up to Day 90	X
Date of hospital readmission/s & discharge up to Day 90	X
Quality of Life assessment (EQ-5D-5L)	X

15. Publications and reports

The study will be conducted in the name of the 'BLING III Study Investigators'. Central project coordination and data management will be provided by The George Institute for Global Health, Sydney, Australia.

Authorship of publications arising from the study will be consistent with current ANZICS Clinical Trials Group policies with full credit assigned to all collaborating Institutions, investigators and research coordinators. Responsibility for the content of manuscripts will rest with the writing committee, and,

where listed, the chair of the writing committee will be listed first with subsequent members listed alphabetically.

It is expected that findings will be disseminated via publication in high-quality peer reviewed journals in the medical or critical care literature. Study findings will also be presented at regional, national, and international intensive care conferences.

Funding bodies will be acknowledged in all publications.

15.1. Public access

The protocol and statistical analysis plan will be made public prior to data analysis of the principal study. The participant level dataset will be made available at a time approved by the Management Committee.

16. Proposed project timeline

The study was initially estimated to be conducted over a five-year period (January 2017 to December 2021). However, due to the significant impact on study recruitment from the SARS-CoV-2 (COVID-19) pandemic, it is estimated that the intended sample size of 7,000 will be reached by September 2022. In order to ensure maximal recruitment into the PK-PD sub-study, recruitment at sites participating in the PK-PD sub-study will continue beyond the intended sample size until 600 patients are recruited into the PK-PD sub-study or for a period of 6 months following recruitment of the 7,000th participant, whichever occurs first. Analysis, write-up and dissemination of results will occur over a subsequent 6-month period, allowing for 90-day data to be obtained for all participants.

17. References

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