ROAD-RCT Protocol: Amendment 3.0 dated 28 July 2026
Summary of changes and rationale:

1. Study logo updated for consistency across study documentation.

2. Amended 7.2.1 to highlight that ID-ODS is a tool to assist the study clinician led dosing to minimise the potential of it being classified as a medical tool.

3. Updated schedule of assessments to include fidelity measures and the adverse events data collection.

4. Microbiology sampling updated to day 7 and day 14. Figure 2 updated accordingly.

5. RRT dosing exclusion criteria updated. >2 g/day meropenem and >18 g/day piperacillin/tazobactam.

6. Dosing clinician time tracking inclusion.

7. Added the sampling of blood to determine the concentration of study drug within the first 24 h and at the cessation of study drug therapy (or day 14) for the control arm. This will allow for the impact of different exposures to be evaluated and accounted for in the analysis. We anticipate that this will pose no additional risk or amend the consent process in any significant way.

8. Updated all references from UQ Centre for Clinical Research (UQCCR) to Frazer Institute, Herston.

ROAD-RCT Protocol: Amendment 2.0 dated 01 April 2026
Summary of changes and rationale:

1. Added an exclusion criterion on page 6 and section 6.3 on page 18 to include '… a prior known or likely reason that the patient would not consent if they were able to be asked'. This reflects one of the requirements for a waiver of consent.

2. Included a target tazobactam exposure (between 2 and 20 mg/L) for section 7.2.1 on page 19. We have included the tazobactam exposure range as some sites are able to perform therapeutic drug monitoring for tazobactam.

3. Amended the exclusion criterion in section 6.3 on page 17, which is also reflected in section 7.2.2 on page 21 and page 6 summary, to extend the duration of antibiotic therapy allowable prior to enrolment in the ROAD-RCT from 24 to 48 h in response to concerns from some site principal investigators regarding enrolment capacity.

4. We have included additional detail required for a waiver of consent in the specific instance where consent cannot be obtained from either the patient or substitute decision maker on page 38 in section 10.3.



Multicentre, international, investigator-initiated, open-label, randomised, parallel-group, superiority trial to compare resistance-optimised precision dosing versus standard care in critically ill patients: the ROAD-RCT Protocol

Version Number: 3.0
Date: 28 July 2026

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Not for distribution beyond intended function.

Table of Contents

1. Protocol synopsis 4

2. Administrative information 7
2.1. Chief investigator 7
2.2. Study Sponsor 7
2.3. Central trial coordinating centre (global) 7
2.4. Data and safety monitoring committee chair 7
2.5. Management structure 8
2.6. Funding 9
2.7. Role of trial sponsor and funding bodies 9
2.8. Trial registration 9
2.9. Consumer engagement/patient and public involvement 9

3. Introduction 10
3.1. Background 10
3.2. Nosocomial respiratory infections in the ICU and risk of emergence of resistance 11
3.3. Antimicrobial dose optimisation in critically ill patients 11
3.4. Preliminary data from the ROAD pilot study 12
3.5. Need for a phase IIb study 13
3.6. Clinical significance 14

4. Objective and Study design 15
4.1. Objective 15
4.2. Study Design 15
4.3. Study Intervention 15

5. Study outcomes 16
5.1. Primary outcome 16
5.2. Secondary outcomes 16

6. Study participants 17
6.1. Study setting 17
6.2. Inclusion criteria 17
6.3. Exclusion criteria 17

7. Study Procedures 18
7.1. Randomisation 18
7.2. Study treatment dosing strategy 19
7.2.1. Model-informed precision dosing (MIPD) 19
7.2.2. Microbiological studies 22
7.3. Modification or premature cessation of the allocated dosing strategy 23
7.4. Concomitant care 24
7.5. Blinding 24
7.6. Safety considerations 24
7.6.1. Precautions and adverse reactions 25
7.6.2. Safety assessment 25

8. Study assessments 25
8.1. Screening 25

8.2. Baseline data collection 25
8.3. Intensive care unit admission 26
8.4. Definition of clinical cure 26
8.5. Definitions of the secondary outcomes 28
8.6. Definition of other assessments 31
8.7. Follow up at Day 14 and Day 28 32
8.8. Schedule of assessments 33
8.9. Recruitment 35

9. Safety monitoring and reporting 36
9.1. Adverse events 36
9.1.1. Treatment emergent adverse events 36
9.1.2. Suspected unexpected serious adverse reactions (SUSAR) 37
9.1.3. Reporting TEAEs and SUSARs 37
9.2. Data and Safety Monitoring Committee (DSMC) 37
9.3. Study Termination 37

10. Ethics 38
10.1. Ethical principles 38
10.2. Human Research Ethics Committee 38
10.3. Consent and enrolment procedures 38
10.3.1. Australian context 42
10.3.2. Other contexts 43
10.4. Confidentiality and privacy 43
11. Data collection and management 44
11.1. Record retention 44
11.2. Data sharing 44

12. Quality control and quality assurance monitoring 45
12.1. Responsibilities of the site Principal investigator 45
12.2. Responsibilities of the central co-ordinating centre 45
12.2.1. Site initiation 45
12.2.2. Monitoring during the study 45
12.2.3. Site close out 46
12.3. Source document requirements 46
12.4. Management of protocol deviations 46
12.5. Direct access to data and documents 46

13. Statistical methods 47
13.1. Power calculation and sample size 47
13.2. Statistical analysis plan 47
13.3. Interim analysis 47
13.4. Pre-specified sub-group analyses 47

14. Pre-specified sub-studies 49
14.1. Health-economics sub-study 49
14.2. Precision dosing sub-study 50
14.3. Metagenomic sub-study 50
14.4. Intervention Scalability Assessment 51

15. Publications and reports 52

15.1. Public access 52

16. References 53

1. Protocol synopsis

Title	Resistant-Optimised Antimicrobial Dosing in Critically Ill Patients, a Randomised Controlled Trial
Short title	ROAD-RCT
Design	Multicentre, international, investigator-initiated, open-label, randomised, parallel-group, superiority trial
Primary outcome	Clinical cure at Day 14 following the initiation of study beta-lactam antimicrobial therapy (Day 14)
Secondary outcomes	1. Time to clinical cure 2. Clinical outcomes at Day 14 - All-cause mortality - Treatment emergent adverse events - *Clostridioides difficile* diarrhoea - Duration of mechanical ventilation - Duration of renal replacement therapy - Duration of extracorporeal membrane oxygenation - Duration of vasopressor therapy 3. Microbiological outcomes at Day 14 - Emergence of resistance to beta-lactam antimicrobials in the index microorganism from surveillance and/or clinical samples - Acquisition of (a) new beta-lactam resistant microorganism(s) in the surveillance and/or clinical samples - Detection of new antimicrobial resistance gene classes (whole genome sequencing and metagenomic evaluation) in the surveillance and/or clinical samples 4. Clinical, microbiological and health-economic outcomes at Day 28 - All-cause mortality - New episode(s) of infection caused by microorganisms that are multidrug resistant (MDR) or that have a reduced susceptibility to the study antimicrobials - Acquisition of (a) new beta-lactam resistant microorganism(s) in the surveillance samples (only if the patient is still in the - intensive care unit [ICU]) - ICU length of stay - Hospital length of stay - Duration of isolation care - ICU-free days - Hospital-free days - Quality of life (EQ-5D-5L questionnaire). - ICU readmission. - Hospital readmission. - Health economic outcomes

Other assessments	At Day 14: 1. Time to first dosing intervention 2. Pharmacokinetic/Pharmacodynamic (PK/PD) target attainment within 24 h from randomisation 3. Time to PK/PD target attainment 4. Proportion of daily PK/PD target attainment 5. Description and frequency of dosing adjustments 6. Therapeutic Drug Monitoring (TDM) results 7. Time to TDM since initial antibiotic dose 8. Proportion of erroneous samples 9. Clinical adherence to model-informed precision dosing (MIPD) recommendations 10. Scalability assessment
	Patients will be randomised to receive either resistance-optimised precision dosing or standard care dosing of piperacillin/tazobactam or meropenem. The intervention will continue for up to Day 14 or until the patient is discharged from the ICU, whichever occurs first.
Sample size	610 mechanically ventilated patients
Inclusion criteria	1. The patient is ≥ 18 years of age. 2. The patient has been admitted to the hospital for ≥ 48 h or was discharged from a hospital within the preceding seven days and is currently admitted to the ICU. 3. The patient is intubated and mechanically ventilated. 4. The patient is diagnosed with a probable or definitive respiratory infection and exhibits at least one of the following clinical features: I. New onset or worsening pulmonary symptoms or signs: increase in volume and/or purulence of respiratory secretions, worsening of hypoxaemia requiring an increase in the inspired oxygen concentration (FiO2) and/or need for acute changes in the ventilator support system to support oxygenation. II. Radiological findings deemed consistent with a respiratory infection. III. Clinical signs and symptoms of infection: fever, leucocytosis, increase in acute phase reactants such as C-reactive protein or procalcitonin. 5. The patient has been commenced on empiric or targeted treatment with piperacillin/tazobactam or meropenem for the management of a respiratory infection, with an expected duration of treatment of > 72 h. 6. Piperacillin/tazobactam or meropenem have been commenced in an ICU that participates in ROAD-RCT. 7. The patient has an appropriate arterial or venous access for blood sampling.
Exclusion criteria	1. The patient is known or suspected to be pregnant. 2. The patient has a known allergy to piperacillin/tazobactam or meropenem.

	3. The patient has a community-acquired respiratory infection or chemical pneumonitis in the context of bronchoaspiration. 4. The patient has received piperacillin/tazobactam or meropenem for more than 48 h. 5. The antimicrobial dose initiated empirically is > 18 g daily (16 g piperacillin / 2 g tazobactam) for piperacillin/tazobactam or > 4 g daily for meropenem (excluding the loading dose) for patients not receiving renal replacement therapy. 6. The antimicrobial dose initiated empirically is > 18 g daily for piperacillin/tazobactam and > 2 g daily for meropenem in patients receiving renal replacement therapy. 7. The patient's death is deemed imminent and inevitable. 8. The patient has previously been enrolled in ROAD-RCT. 9. The patient is or has been enrolled in another antimicrobial clinical trial that may interfere with the intervention as determined by the study investigators. 10. The patient has a baseline (at ICU admission or enrolment) positive rectal and/or nasopharyngeal screening swab, or is known to have been colonised within the past 6 months, with any of the following beta-lactam–resistant Gram-negative microorganism(s): carbapenem-resistant Enterobacterales, *Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR) or carbapenem-resistant *Acinetobacter baumannii* complex. 11. There is a prior known or likely reason that the patient would not consent if they were able to be asked.

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36. Dr Linna Zhang, Anaesthesiologist, The Affiliated Hospital of Xuzhou Medical University, China

2.6. Funding

This study is funded by an Australian Medical Research Future Fund (MRFF) Clinical Trials Activity project grant (Reference: 2039566) and a Queensland Health Clinical Research Fellowship (Dr Aaron Heffernan, Reference: 2023002921).

2.7. Role of trial sponsor and funding bodies

Investigators employed by the sponsor will design and initiate the study, conduct trial management activities, monitoring, reporting, data management and analysis. Results will be presented and published by the investigators. These activities will be independent of funding agencies**.**

2.8. Trial registration

This protocol will be registered on ClinicalTrials.gov and Australian New Zealand Clinical Trials Registry (ANZCTR) registries pending ethics approval.

2.9. Consumer engagement/patient and public involvement

This RCT has been developed with ongoing guidance by the Centre Research Excellence (CRE) RESPOND End User and Consumer Advisory Committee at The University of Queensland. Membership includes expert consumers with lived experience of infection, admissions to intensive care and a role as a carer of someone who has been an ICU patient. The consumer engagement leading up to this RCT has used knowledge gained from earlier phase studies that have informed this research. The CRE RESPOND End User and Consumer Advisory Group has reviewed the study documents prior to submission to the lead (Australian) Human Research Ethics Committee (HREC) and will continue to be consulted throughout the study. The Principal Consumer Investigator (Dr Julie Vermeir) will chair the consumer advisory steering committee with membership from participating sites. Dr Vermeir will have ongoing support from the CRE RESPOND End User and Consumer Advisory Group and its Terms of Reference guidance.

3. Introduction

3.1. Background

Antimicrobial resistant bacteria are a global threat. Data from 2019 has associated antimicrobial resistance with almost 5 million deaths worldwide, with a disproportionate burden among different geographical areas with a predominance in low and middle-income countries; from these, 1.27 million deaths are directly attributable to antimicrobial resistance. [1] Furthermore, and besides the obvious global clinical and epidemiological implications, antimicrobial resistance also poses a significant economic burden, with direct healthcare and lost productivity costs in the US in 2019 exceeding USD 20 billion and USD 35 billion, respectively, and an excess of AUD $18,000 per treatment episode when the patient is infected by a resistant microorganism. [2,3] Given this critical situation, the World Health Organisation (WHO) published in 2023 the new global research agenda for antimicrobial resistance in human health highlighting the research priorities in this area. Within therapy optimisation, a key priority is research into efficacious and safe antimicrobial treatment regimens for old and new antimicrobial agents that also minimise the risk of emergence of resistance. [4]

In this context, sub-optimal antimicrobial dosing and exposure is nowadays regarded as a major risk factor of beta-lactam antimicrobial emergence of resistance in Gram-negative bacilli. [5] Substantial *in vitro* microbiological data suggest that maintaining beta-lactam antimicrobial concentration above the minimum inhibitory concentration (MIC) of the bacteria may be sufficient for inhibiting bacterial growth in the initial phase of treatment but, after a certain period of antimicrobial exposure, regrowth of bacteria that are less susceptible to this agent occurs. [6,7] The theoretical explanation for this phenomenon is that high density bacterial populations contain spontaneously less susceptible bacteria (due to pre-existing mutations and/or hyperexpression of inducible endogenous resistance mechanisms) that can be selected when exposed to a sub-optimal antimicrobial concentration following the Darwinian advantage principle. [8] Therefore, the mutant prevention concentration (MPC) is defined as the drug concentration required to prevent the growth of those less susceptible bacteria that may selectively proliferate above the minimum inhibitory concentration (MIC). The mutant selection window (MSW) describes the range of antimicrobial concentrations between the MIC and MPC. Below the MIC, there is no selective pressure, and thus resistant bacteria are unlikely to overgrow (i.e., be selected). Antimicrobial exposures within the MSW promote the selection of resistant bacteria. [8]

When dynamic *in vitro* experiments are performed using simulated human dosing, the principles of antimicrobial PK/PD can be explored to define the optimal exposure that minimises emergence of resistance. For beta-lactam antimicrobials, the time that the unbound concentration is maintained above the MIC of the pathogen over a dosing interval (% $fT_{>MIC}$) has repeatedly been shown to be the PK/PD index most closely linked to bactericidal activity in *in vitro* and animal models. [9] However, significant pre-clinical data with dynamic hollow-fibre infection models with planktonic Gram-negative bacteria show that, after the first 72 h – 120 h of exposure, regrowth of resistant bacteria occurs even with 100 % $fT_{>MIC}$, and more aggressive targets of unbound trough concentration (fC_{min})/MIC ≥ 4 for intermittent dosing and unbound constant steady state concentration (fC_{ss})/MIC ≥ 6 for continuous infusion are required for supressing the regrowth of resistant Gram-negative bacteria. [6,7,10,11] The clinical implication of these findings is that, although 100% $fT_{>MIC}$ is nowadays the accepted efficacy target for treating severe infections such as sepsis with beta-lactam antimicrobials, [12-17] more stringent PK/PD targets may be needed to minimise resistance selection in infections at high risk of intra-treatment emergence of resistance. [5]

3.2. Nosocomial respiratory infections in the ICU and risk of emergence of resistance

At any given time, approximately 54 % of critically ill patients in an ICU have a suspected or proven infection, with 22 % of these infections being nosocomial. [18] Of those, respiratory infections account for 64 % of the cases and are among the most frequent complications in the ICU, with mortality rates that can be as high as 50 % in mechanically ventilated patients. [19,20] Nosocomial respiratory infections are often caused by Gram-negative bacilli including *P. aeruginosa* [19-21] and represent a typical example of high-inoculum, non-drainable infections that are at a theoretical risk of clinical failure and selection of antimicrobial resistant subpopulations when exposed to the MSW. Although limited, important clinical data support this concept. Gatti and colleagues [22] performed a systematic review and meta-analysis of observational studies in critically ill patients with confirmed Gram-negative infections, mostly nosocomial pneumonia, with a good representation of *P. aeruginosa*.

They pooled data from 21 studies, defined aggressive PK/PD target as C_{min}/MIC ≥ 4 and found that attaining this target was significantly associated with a higher clinical cure rate (n = 1873 patients, OR 1.7; 95% CI 1.2–2.5); when this analysis was performed to evaluate emergence of resistance, aggressive exposure was also associated with a lower risk of beta-lactam antimicrobials resistance development (n= 365 patients, OR 0.06; 95% CI 0.01–0.29). [22] More focused on respiratory infections, the REPROVE trial compared the efficacy of ceftazidime/avibactam 2 g/0.5 g 8-hourly as a 2 h extended infusion for the treatment of nosocomial respiratory infections, including ventilator-associated pneumonia, with labelled doses of meropenem, i.e. 1 g 8-hourlyas a short intermittent infusion. In this study, end-of-treatment emergence of resistance to meropenem, defined as ≥ 4- fold MIC increase, was 25.7 % in patients with a *P. aeruginosa* infection, occurring even in patients who achieved clinical cure. [21] In contrast, the APEKS-NP trial that compared cefiderocol (2 g 8-hourly as a 3 h extended infusion) with higher and optimised doses of meropenem (2 g 8-hourly as a 3 h extended infusion) reported lower rates of end-of-treatment emergence of resistance, that were 12.5 % for *P. aeruginosa* and 2.2 % for *Klebsiella pneumoniae*, even though resistance also emerged in patients that achieved clinical cure. [23]

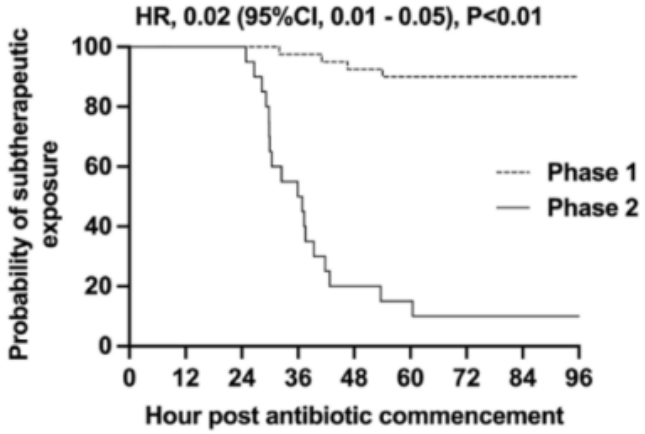
Other studies support these findings. In this line, Dhaese *et al.* [24] examined the dynamics of end-of-treatment emergence of resistance in ICU patients with confirmed infections caused by Enterobacterales and non-fermentative Gram-negative bacilli in a single-centre retrospective study. Patients received piperacillin/tazobactam or meropenem at the labelled doses by renal function (i.e. 16 g q24 h piperacillin or 3 g q24 h meropenem for preserved renal function), administered either as intermittent or continuous infusion. They reported a global 11.7 % incidence of end-of-treatment emergence of resistance, mainly in patients with respiratory infections (58 %) or intra-abdominal infections (37.5 %), with 58.3 % of cases linked to *P. aeruginosa*. This represented a 34.1 % rate of emergence of resistance for *P. aeruginosa*, 16.2 % for *Escherichia coli*, 15.4 % for *Enterobacter cloacae* and 9.1 % for *K. pneumoniae*. [24] Similarly, Tamma and colleagues [25] performed a case-control study in patients with infections caused by DTR *P. aeruginosa* treated with ceftolozane/tazobactam; even though it was a small cohort (28 patients), they reported a 50 % emergence of resistance to ceftolozane/tazobactam defined as ≥ 4- fold MIC increase. In this study, the risk factors for emergence of resistance were deep-seated infections that could not undergo source control and administration of ceftolozane/tazobactam as a short intermittent infusion. [25]

3.3. Antimicrobial dose optimisation in critically ill patients

Despite this evidence, currently there are no dosing strategies that are designed to treat the infection and reduce the risk of antimicrobial resistance emergence. Optimising antimicrobial dosing to suppress resistance could potentially benefit patients by enhancing bacterial eradication, improving clinical cure and reducing the risk of intra-treatment resistance emergence, thereby lowering the likelihood of recurrences or new infections caused by resistant microorganisms. However, achieving drug concentrations sufficient to prevent resistance emergence is particularly challenging in critically ill patients. Profound pathophysiological derangements in this population cause substantial alterations in antimicrobial pharmacokinetics compared with non-critically ill patients, significantly influencing plasma concentration-time profiles. Consequently, standard dosing regimens developed for non-critically ill patients may lead to suboptimal exposures in this vulnerable group. [26] On the other hand, higher exposures require daily doses above the standard range, which in unstable ICU patients with different degrees of organ dysfunction may increase the risk of toxicity. Therefore, dose titration must be performed with great precision to maintain drug concentrations within the MPC – toxicity window.

The use of population pharmacokinetic models developed with data from critically ill patients offers a strategy to optimise dosing titration accounting for the marked pharmacokinetic variability in this population. The clinical use of these models through dosing software combined with TDM, an approach known as MIPD, can assist in the design of dosing regimens that maximise antimicrobial efficacy, suppress the emergence of resistance and remain within toxicity thresholds for safety. Briefly, dosing software uses a population pharmacokinetic model developed in the patient population of interest to generate dosing recommendations based on clinical characteristics and the selected PK/PD target. These recommendations can then be further individualised by integrating TDM data into the software, which refines the estimation of individual pharmacokinetic parameters through Bayesian methods. Dosing software such as ID-ODS™ has proven effective for the early attainment of target exposures for various beta-lactam antimicrobials. [27-29] The DIRECT trial, a pre-post multi-centre study of antimicrobial dosing decision-making (Phase 1: clinician-guided; Phase 2: dosing software-guided) in children and adult patients with severe infections demonstrated the potential of dosing software to dramatically reduce the time to optimal antimicrobial exposure (96 h vs 36.4 h in Phase 1 and Phase 2, respectively, $p < 0.01$) for those patients not achieving efficacy targets in the first 24 h. [28]

Figure 1. Kaplan-Meier plots for probability of sub-therapeutic antimicrobial exposure from the DIRECT trial; [28] Phase 1: pre-intervention clinician-based dosing and Phase 2: intervention with MIPD.



3.4. Preliminary data from the ROAD pilot study

The ROAD pilot study was a prospective, open-label phase IIa clinical trial conducted in an Australian tertiary ICU aiming to evaluate the safety and feasibility of piperacillin/tazobactam and meropenem

resistance-optimised precision dosing. [29] Adult patients without significant baseline organ dysfunction or receiving any extracorporeal organ support that received either piperacillin/tazobactam or meropenem for a suspected or microbiologically confirmed infection were enrolled. Within 48 h from the initiation of the study antimicrobial, doses were adjusted using dosing software (ID-ODS™) in combination with TDM to achieve and maintain a fC_{min}/MIC or fC_{ss}/MIC ≥ 4 based on the European Committee on Antimicrobial Susceptibility Testing (EUCAST) *P. aeruginosa* susceptibility breakpoint of 16 mg/L and 2 mg/L for piperacillin/tazobactam and meropenem, respectively. PK/PD targets could be adjusted to achieve a fC_{min}/MIC or fC_{ss} /MIC ≥ 4 relative to a specific infecting pathogen MIC once this MIC was known. This meant that the efficacy targets for resistance suppression used in ROAD were four-times higher than the efficacy targets for clinical cure targeted in DIRECT. Twenty-five patients (14 piperacillin/tazobactam, 11 meropenem) with a mean age of 56 years were enrolled; from those, 93 % achieved the target drug exposure which occurred within a median < 1 day (interquartile interval 0.81–1.73 days) from study enrolment. In 56 % of patients, the dosing intervention was a change to a continuous infusion with 36 % of patients also receiving an increased daily dose. Median (range) maximum daily doses were 22.5 g (9 g– 27 g)/day for piperacillin/tazobactam (corresponding to 20 g piperacillin / 2.5 g tazobactam (8 g/1 g – 24 g/3 g)) and 6 g (3 g – 12 g)/day for meropenem. Five patients developed 'at risk' acute kidney injury, whilst one patient developed kidney 'failure' and one patient developed hepatotoxicity; however, none of these adverse events were assessed to be caused by the study antimicrobial and in all cases the treatment was continued by the treating physician. Emergence of resistance was identified in one patient with in a respiratory sample with *P. aeruginosa* (4 %). [29]

3.5. Need for a phase IIb study

The rationale for ROAD-RCT is as follows:

1. Nosocomial respiratory infections are frequent in mechanically ventilated critically ill patients and are associated with high mortality. They are often caused by Gram-negative bacteria with reduced antimicrobial susceptibility and/or the ability to develop beta-lactam antimicrobial intra-treatment resistance.
2. There is strong *in vitro* microbiological evidence that higher beta-lactam exposures enhance efficacy by preventing the emergence of intra-treatment resistance in Gram-negative organisms. Higher exposures may therefore be required for supressing the emergence of resistance in critically ill patients with Gram-negative infections at high-risk of intra-treatment resistance emergence.
3. The altered physiology of critically ill patients is likely to result in significant pharmacokinetic variations that may compromise the attainment and maintenance of optimal exposures for hydrophilic drugs like beta-lactam antimicrobials.
4. In the context of altered physiology, standard beta-lactam antimicrobial dosing in critically ill patients is likely to result in subtherapeutic exposures, leading to lower clinical cure rates and promoting the emergence of antimicrobial resistance. On the other hand, higher doses increase the risk of toxicity in unstable patients with varying degrees of organ failure.
5. Dosing optimisation strategies aimed at effectively suppressing the emergence of antimicrobial resistance have not been widely investigated.
6. The ROAD pilot study used MIPD and TDM to design dosing strategies aimed for PK/PD targets associated with suppression of resistance emergence. This approach facilitated early PK/PD target attainment with minimal toxicity.
7. There is sufficient clinical uncertainty about whether the intervention will result in higher clinical cure to justify the conduct of a phase IIb RCT.

3.6. Clinical significance

Currently, no beta-lactam antimicrobial strategies are designed to both optimise clinical cure and supress the emergence of resistance to beta-lactam antimicrobials in critically ill patients with severe Gram-negative infections. Regardless of outcome, this study will generate critical data on whether resistance-optimised precision dosing improves clinical cure, suppresses the emergence of resistance and is safe in critically ill patients with nosocomial respiratory infections. Beyond addressing this important clinical question, the findings will also provide effect-size estimates and safety and feasibility data, that will inform the development of a definitive phase III clinical trial, if warranted, and help guide future antimicrobial stewardship strategies in the ICU setting.

4. Objective and Study design

4.1. Objective

The ROAD-RCT hypothesises that, in critically ill patients with nosocomial respiratory infections, resistance-optimised precision dosing of beta-lactam antimicrobials improves clinical cure compared with standard care dosing. The objective of the ROAD-RCT is to conduct a randomised, superiority clinical trial evaluating whether resistance-optimised precision dosing guided by MIPD leads to higher Day 14 cure rates than standard care in mechanically ventilated critically ill patients with nosocomial respiratory infections treated with piperacillin/tazobactam or meropenem.

4.2. Study Design

ROAD-RCT is a multicentre, international, investigator-initiated, open-label, randomised, parallel-group, superiority trial. It will enrol 610 patients that will be randomised 1:1 in a parallel-group design to receive either resistance-optimised precision dosing or standard care. Mechanically ventilated critically ill patients commenced on either piperacillin/tazobactam or meropenem for the treatment of a nosocomial respiratory infection are eligible to be randomised to receive the beta-lactam antimicrobial with resistance-optimised precision dosing guided with MIPD (*intervention*) or standard care dosing (*standard care*) for up to 14 days following the initiation of beta-lactam antimicrobial therapy. For participants where the beta-lactam antimicrobial is subsequently changed from piperacillin/tazobactam to meropenem or *vice versa*, the new prescription will continue to be administered in the allocated dosing strategy (resistance-optimised dosing or standard care dosing).

4.3. Study Intervention

The study intervention includes 4 key components:

1. Dosing using MIPD is prescribed within 48 h of antibiotic commencement.
2. The recommended resistance-optimised dose is administered within 48 h of antibiotic commencement.
3. The TDM sampling is performed within 48 h of antibiotic commencement.
4. Ongoing review and optimisation of antibiotic dosing are conducted throughout the patient's stay in accordance with MIPD recommendations.

5. Study outcomes

5.1. Primary outcome

Clinical cure at Day 14 following the initiation of study beta-lactam antimicrobial therapy (Day 14)

5.2. Secondary outcomes

1. Time to clinical cure

2. Clinical outcomes at Day 14
   - i All-cause mortality
   - ii Treatment emergent adverse events
   - iii *C. difficile* diarrhoea
   - iv Duration of mechanical ventilation
   - v Duration of renal replacement therapy
   - vi Duration of extracorporeal membrane oxygenation
   - vii Duration of vasopressor therapy

3. Microbiological outcomes at Day 14
   - i Emergence of resistance to beta-lactam antimicrobials in the index microorganism from the surveillance and/or clinical samples
   - ii Acquisition of (a) new beta-lactam antimicrobials-resistant microorganism(s) in the surveillance and/or clinical samples
   - iii Detection of new antimicrobial resistance gene classes (whole genome sequencing and metagenomic evaluation) in the surveillance and/or clinical samples

4. Clinical, microbiological and health-economic outcomes at Day 28
   - i All-cause mortality
   - ii New episode(s) of infection caused by microorganisms that are MDR or that have a reduced susceptibility to the study antimicrobials
   - iii Acquisition of (a) new beta-lactam resistant microorganism(s) in the surveillance samples (only if the patient is still in the ICU)
   - iv ICU length of stay
   - v Hospital length of stay
   - vi Duration of isolation care
   - vii ICU-free days
   - viii Hospital-free days
   - ix ICU readmission
   - x Hospital readmission
   - xi Quality of life (EQ-5D-5L questionnaire)
   - xii Health economic outcomes

6. Study participants

6.1. Study setting

This study will be conducted in 15 ICUs worldwide, with sites anticipated in *Australia*: Royal Brisbane & Women's Hospital, Gold Coast University Hospital, Alfred Health, Austin Hospital, St Vincent's Hospital, The Prince Charles Hospital, Princess Alexandra Hospital; *France*: University Hospital of Nîmes and University Hospital of Nancy; *Italy*: University Health Authority of Central Friuli; *Spain*: Hospital del Mar; Clínico San Cecilio University Hospital; Hospital Clínic de Barcelona, *Malaysia*: University Malaya Medical Centre, and *China*: The Affiliated Hospital of Xuzhou Medical University.

6.2. Inclusion criteria

1. The patient is ≥ 18 years of age.
2. The patient has been admitted to the hospital for ≥ 48 h or was discharged from a hospital within the preceding seven days and is currently admitted to the ICU.
3. The patient is intubated and mechanically ventilated.
4. The patient is diagnosed with a probable or definitive respiratory infection and exhibits at least one of the following clinical features:
    I. New onset or worsening pulmonary symptoms or signs: increase in volume and/or purulence of respiratory secretions, worsening of hypoxaemia requiring an increase in the FiO_2 and/or need for acute changes in the ventilator support system to support oxygenation.
    II. Radiological findings deemed consistent with a respiratory infection.
    III. Clinical signs and symptoms of infection: fever > 38 °C, leucocytosis, increase in acute phase reactants such as C-reactive protein or procalcitonin.
5. The patient has been commenced on empiric or targeted treatment with piperacillin/tazobactam or meropenem for the management of a respiratory infection, with an expected duration of treatment of > 72 h.
6. Piperacillin/tazobactam or meropenem have been commenced in an ICU that participates in ROAD-RCT.
7. The patient has an appropriate arterial or venous access for blood sampling.

6.3. Exclusion criteria

1. The patient is known or suspected to be pregnant.
2. The patient has a known allergy to piperacillin/tazobactam or meropenem.
3. The patient has a community-acquired respiratory infection or chemical pneumonitis in the context of bronchoaspiration.
4. The patient has received piperacillin/tazobactam or meropenem for more than 48 h.
5. The antimicrobial dose initiated empirically is > 4 g daily for meropenem and > 18 g daily (16 g piperacillin / 2 g tazobactam) for piperacillin/tazobactam (excluding the loading dose) in patients who are not receiving renal replacement therapy.
6. The antimicrobial dose initiated empirically is > 18 g daily (16 g piperacillin / 2 g tazobactam) for piperacillin/tazobactam and > 2 g daily for meropenem in patients receiving renal replacement therapy (Table 1).
7. The patient's death is deemed imminent and inevitable.
8. The patient has previously been enrolled in ROAD-RCT.

9. The patient is or has been enrolled in another antimicrobial clinical trial that may interfere with the intervention as determined by the study investigators.
10. The patient has a baseline (at ICU admission or enrolment) positive rectal and/or nasopharyngeal screening swab, or is known to have been colonised within the past 6 months, with any of the following beta-lactam–resistant Gram-negative microorganism(s): carbapenem-resistant Enterobacterales, *P. aeruginosa* with DTR or carbapenem-resistant *A. baumannii* complex.
11. There is a prior known or likely reason that the patient would not consent if they were able to be asked.

(*): Renal failure and requirement for renal replacement therapy and extracorporeal membrane oxygenation are not exclusion criteria to participate in the ROAD-RCT.

Table 1: Renal Replacement Therapy simulations to inform exclusion dosing criteria **

Dosing Regimen	**Probability of Target Attainment (%)*** **
Meropenem 2 g CI	73.8
Meropenem 3 g CI	89.6
Meropenem 4 g CI	94.2
Meropenem 1 g Q8H	74.2
Meropenem 1 g Q12H	39.6
Meropenem 1 g Q24H	0.6
Meropenem 2 g Q12H	72.2
Meropenem 2 g Q24H	13.2
Piperacillin/tazobactam 9 g CI	43.4
Piperacillin/tazobactam 13.5 g CI	76.4
Piperacillin/tazobactam 18 g CI	88
Piperacillin/tazobactam 4.5 g Q24H	0
Piperacillin/tazobactam 4.5 g Q12H	5.6
Piperacillin/tazobactam 4.5 g Q8H	54.4
Piperacillin/tazobactam 4.5 g Q6H	78.2

** Determined using a high dose continuous renal replacement therapy with a dialysate rate and replacement fluid rate of 2 L/h.

*** Probability of achieving C_{min}/MIC ≥ 6 for CI or ≥ 4 for intermittent infusions assuming an MIC at the clinical breakpoint of 2 and 16 mg/L for meropenem and piperacillin/tazobactam respectively.

7. Study Procedures

7.1. Randomisation

Randomisation will be performed as soon as possible from the initiation of the study drug by the site coordinator using a password-protected, encrypted web-based interface. Following randomisation, a patient will be assigned a unique 'patient study number'. Randomisation will be stratified according to participating site. The allocation ratio will be 1:1. An independent statistician will generate the stratified randomisation list using the Stata program "ralloc". Various block sizes will be used. The list will be uploaded to a section of REDCap only visible to the trial manager.

7.2. Study treatment dosing strategy

The initial choice of beta-lactam antimicrobial, dose, infusion duration, and dosing interval will be determined by the treating physician until randomisation. Once randomised, the *intervention* arm will receive a resistance-optimised precision dosing regimen guided by MIPD, that will be commenced as early as possible from the initiation of the study drug. The *standard care* arm will receive the study antimicrobial dosed at the discretion of the treating clinicians *as per* their standard care.

During the study period, the treating physician can modify the beta-lactam antimicrobial dose in response to clinical changes of the patient or microbiology results. 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 using the allocated dosing strategy (resistance-optimised precision dosing or standard care dosing). The beta-lactam antimicrobial (piperacillin/tazobactam or meropenem) will continue to be administered according to the allocated dosing strategy until either 1) the beta-lactam antimicrobial is ceased by the treating physician, 2) the patient is discharged from ICU (including death) or 3) 14 days after the initiation of the study antimicrobial (Day 14), whichever is sooner. If the patient is readmitted to ICU while receiving the study beta-lactam antimicrobial (piperacillin/tazobactam or meropenem), or the beta-lactam antimicrobial is recommenced prior to Day 14, the allocated dosing strategy needs to be followed. After Day 14, the allocated method does not need to be followed, and the patient can receive the beta-lactam antimicrobial at the standard care dosing used at site. If the patient is still prescribed the beta-lactam antimicrobial following ICU discharge, standard care dosing at the site will be used from discharge.

7.2.1. Model-informed precision dosing (MIPD)

Patients in the *intervention* arm will receive resistance-optimised precision dosing guided by MIPD.

PK/PD targets for intermittent and continuous infusion

Precision dosing antimicrobial target exposures will aim for maximal suppression of bacterial resistance as a beta-lactam antibiotic fC_{min}/MIC ≥ 4 for patients receiving intermittent infusion or fC_{ss}/MIC ≥ 6 for patients receiving prolonged (i.e. extended or continuous) infusion. For patients receiving tazobactam at sites able to perform tazobactam concentration monitoring, the target exposure will be a fC_{ss} ≥ 2 mg/L.

Possible scenarios:

1. Where a causative pathogen has not been identified, dosing will be adjusted using MIC targets correspondent to the EUCAST clinical breakpoints *P. aeruginosa*, i.e. 2 mg/L for meropenem and 16 mg/L for piperacillin/tazobactam.

2. Once (and if) the infecting microorganism is identified, target exposures will be adjusted to unbound fC_{min}/MIC ≥ 4 or unbound fC_{ss}/MIC ≥ 6, [6,7,10,11] using the microorganism's clinical breakpoint defined by EUCAST. The rationale for the use of clinical breakpoints instead of the measured MIC is based on findings from the BLING III PK/PD sub-study. In this analysis, the strongest predictors of clinical cure in patients with confirmed Gram-negative sepsis (50 % respiratory source) were the fC_{min}/MIC or fC_{ss}/MIC index when the EUCAST clinical breakpoint or the EUCAST ECOFF for the infecting organism was used as MIC surrogate, compared with the MIC determined by broth microdilution (BMD) (unpublished data). As the full susceptibility profile of the microorganism is usually obtained after more than 72 hours of therapy, the rationale for using the clinical breakpoint is an *"empirical*

susceptibility" dosing strategy and is in accordance with usual clinical practice. [22] In the worst-case scenario, corresponding to empirical treatment or targeted treatment for *P. aeruginosa*, the target fC_{ss} concentrations would be 96 mg/L for piperacillin, 2 mg/L for tazobactam, and 12 mg/L for meropenem, which are substantially lower than the toxicity thresholds reported in the literature (see section 7.6) [30-33]. The toxicity threshold for tazobactam has not been established in the literature; however, an upper threshold of 20 mg/L has been implemented within the guidelines for the Royal Brisbane and Women's Hospital.

The therapeutic ranges by drug and infecting microorganism are detailed in the following tables:

Table 2: Therapeutic range for piperacillin. The lower limit corresponds to an unbound fC_{min} or fC_{ss}= 4 or 6 x clinical breakpoint respectively. Total C_{min} is calculated from fC_{min} assuming a piperacillin protein binding of 20 % at high concentrations, extrapolated from Wong *et al*. [34] The toxicity threshold for total C_{min} or C_{ss} is 160 mg/L, [30,31] and the fC_{min} or fC_{ss} is 128 mg/L assuming a 20 % protein binding.

Microorganism (examples)	Clinical breakpoint	Short intermittent infusion		Prolonged infusion	
		Therapeutic range for unbound C_{min}	Therapeutic range for total C_{min}	Therapeutic range for unbound C_{ss}	Therapeutic range for total C_{ss}
P. aeruginosa (and empirical)	16	64 - 128	76.8 - 160	96 - 128	115.2 - 160
Enterobacterales	8	32 - 128	38.4 - 160	48 - 128	57.6 - 160

Prolonged infusion: extended and continuous infusion

Table 3: Therapeutic range for meropenem. The lower limit corresponds to an fC_{min} or fC_{ss} = 4 or 6 x clinical breakpoint respectively. Total C_{min} is approximated to fC_{min} because meropenem protein binding is around 2 % in healthy volunteers. The toxicity threshold for total C_{min} or C_{ss} and fC_{min} or fC_{ss} is 44.5 mg/L in all cases. [30]

Microorganism (examples)	Clinical breakpoint	Short intermittent infusion		Prolonged infusion	
		Therapeutic range for unbound C_{min}	Therapeutic range for total C_{min}	Therapeutic range for unbound C_{ss}	Therapeutic range for total C_{ss}
P. aeruginosa (and empirical)	2	8 - 44.5	8 - 44.5	12 - 44.5	12 - 44.5
Enterobacterales	2	8 - 44.5	8 - 44.5	12 - 44.5	12 - 44.5

Prolonged infusion: extended and continuous infusion

Dosing software

The dosing software ID-ODS™ applies published pharmacokinetic models in combination with patient clinical characteristics and, when available, incorporates TDM data to provide precision dosing recommendations designed to maximise the likelihood of attaining an exposure target. In this context, we define MIPD as use of dosing software combined with TDM data. After randomisation, an *a priori* empirical dosing software regimen generated by ID-ODS™ based on patient clinical data and a resistance-optimised PK/PD target will be designed and commenced as early as possible and within 24 h from the initiation of the study drug. This empirical regimen will be maintained until TDM results become available. Once TDM results are available, they will be inputted into the ID-ODS™ software to refine dosing recommendations. No patient-identifiable information will be entered into ID-ODS™, and no data will be stored within any ID-ODS™ database. A senior, experienced clinical study clinician will

be available to provide additional dosing guidance to study sites as needed. The ID-ODS™ user manual is accessible online, and study clinicians involved in antimicrobial dosing will receive appropriate training for its use.

The ROAD-RCT is not assessing the accuracy of ID-ODS for achieving the target exposure; rather, ID-ODS is used as a tool to assist the expertise of the study clinician in dosing the antibiotic to achieve the target exposure. Moreover, the ROAD-RCT is assessing if achieving the target exposure to suppress antibiotic resistance emergence is associated with improved clinical outcomes.

Therapeutic drug monitoring

In the *standard care* arm, TDM is permitted if it is part of routine clinical practice at the study site and will be routinely obtained at the mid-point and end of the first dosing interval and at the completion of antibiotic therapy (or day 14, whichever is sooner) at approximately 30 min of what would have been the anticipated next dose due. No dosing alterations will occur in response to these obtained study drug concentrations. In the *intervention* arm, TDM will be used for MIPD and facilitated by the clinical team. Blood will be sampled using standard unit-based protocols from an intra-arterial line or a central venous catheter that has not been used to administer the study drug. The first TDM sampling occasion will be obtained promptly after randomisation, timed as closely as possible with the institution's TDM availability and processing schedule (e.g., if a patient is enrolled on a Saturday or Sunday and TDM is available on Monday, TDM sampling should happen on Monday morning). For the first occasion, two blood samples will be collected, ideally with one sample collected approximately half-way through the dosing interval and the other sample within 30 min of the next scheduled dose (Table 4).

Thereafter, routine TDM of meropenem and piperacillin/tazobactam will be performed daily, including on weekends (site dependent), for the duration of the study. For intermittent infusion, trough concentrations will be collected; for continuous infusion, concentrations may be measured at any time. Where possible, TDM sampling should align with routine blood sampling. At sites without daily TDM availability, sampling and assays should follow the recommended schedule as closely as possible. Samples will be immediately refrigerated or transported on ice for up to 4 h at 2 - 8 °C for analysis at Pathology Queensland or respective laboratories in Europe or Malaysia after collection following local protocols. Test samples (unbound and/or total concentrations depending on local assay) will be assayed alongside plasma calibrators and quality controls in accordance with Good Laboratory Practice. Following analysis, samples will be disposed of in accordance with the laboratory procedure. Dosing intervention clinician activity and duration of time will be averaged based on a subset of 5 patients with an external observer timing the activity.

Table 4: TDM sampling schedule

Type of administration	Sample timing	Day 1/dose change*	Days 2 to end of treatment
Intermittent infusion (includes short 30 min infusion and extended infusion)	Half-way through the dosing interval	X	
	Trough (ideally 30 min before next dose)	X	X
24 h continuous infusion	After 6 h since the initiation of the continuous infusion	X	
	At any time during the continuous infusion	X (the second sample should be separated ≥ 6 h from the first one)	X

(*): after dosing changes, two samples will be taken for the first TDM assessment.

7.2.2. Microbiological studies

Collection of clinical samples

Clinical investigations to elucidate the etiology of the respiratory infection will be performed *as per* routine clinical practice. This will include collection of samples from bronchoalveolar lavage and/or bronchoaspirate and/or endotracheal aspirate and/or sputum where appropriate, as well as blood cultures and other investigations if necessary. Collected specimens will be processed in the relevant microbiology laboratory for pathogen identification and antimicrobial susceptibility testing as per their usual clinical practice. Susceptibility testing will be carried out in each centre according to standard practice using semi-automated systems and/or E-test methodologies and/or other complementary methods such as multiplex polymerase chain reaction (PCR) or immunochromatography for beta-lactamase detection as appropriate for routine clinical practice.

Following initial microbiological evaluation, minimally invasive respiratory samples (e.g., endotracheal aspirates) should be collected every 7 days during the study antimicrobial course, at the end of therapy, and on Day 14, as outlined in Figure 2. These serial samples aim to detect intra-treatment emergence of resistance of the index organism to beta-lactam antimicrobials, and superinfection or respiratory colonisation by other MDR microorganisms. These samples will be processed, stored and disposed of in the local microbiology laboratory in accordance with routine clinical procedures.

Susceptibility testing and genotypic resistance mechanism identification the clinical samples

Phenotypic susceptibility testing
Gram negative bacterial isolates from clinical samples (i.e. blood cultures and respiratory secretion samples) will be frozen and shipped to the Frazer Institute Herston for susceptibility testing using BMD following validated protocols. In the occurrence of a polymicrobial infection, the predominant Gram-negative bacterial species should be selected as index. If several Gram-negative bacterial species and equally predominant, the species with the higher baseline MIC to the study antimicrobial should be selected. If the infection is caused by a Gram-positive microorganism, the isolates will also be frozen and shipped to the Frazer Institute Herston for consideration of susceptibility testing using BMD following validated protocols.

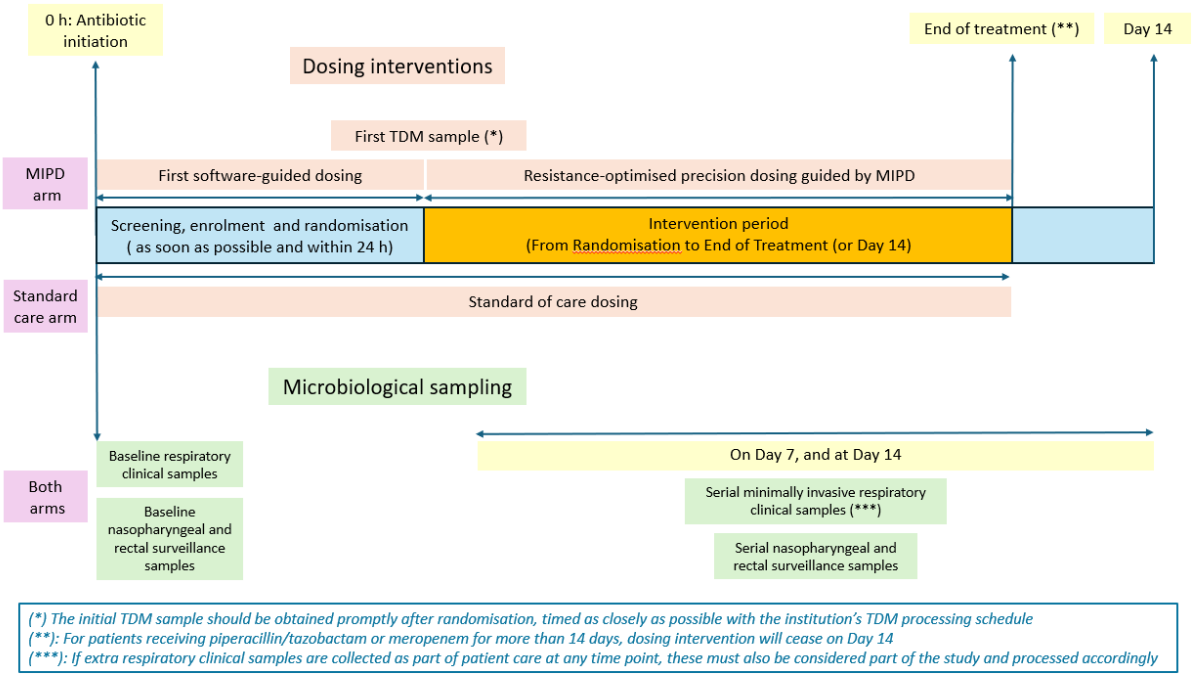
Genotypic resistance mechanism identification
In the serial isolates showing phenotypic emergence of resistance to beta-lactam antimicrobial(s), genotypic analysis via whole-genome sequencing (WGS) will be performed to compare presence or absence of genes and gene mutations, including point-mutated and known resistance genes, between the index Gram negative bacteria and subsequent resistant Gram negative bacterial isolates. These analyses will be also performed in the Frazer Institute Herston following validated methodology. Samples will be disposed of in accordance with standard laboratory policy.

Screening for colonisation by antimicrobial resistant microorganisms

Monitoring for MDR organisms including Enterobacterales resistant to 3rd generation cephalosporins, carbapenem-resistant Enterobacterales, *P. aeruginosa* with DTR, carbapenem-resistant *A. baumannii* complex, methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) will be conducted through rectal and nasopharyngeal screening swabs collected at ICU admission (following each institution's routine protocols), at randomisation, every 7 days during antimicrobial therapy, at the end of the treatment course, at Day 14, and at Day 28 (the day 28 sample is to be collected if the patient is still in the ICU or on the ward if able). Additional samples that are obtained for clinical requirements will be included in the analysis. If the antimicrobial duration is planned for ≤

7 days, an additional but optional sample may be obtained. These screening samples will be collected, stored, and disposed of in accordance with standard clinical and laboratory methods as appropriate. These screening samples will be subjected to metagenomics analysis for Australian sites only.

Figure 2: Summary of the study interventions and microbiology sampling since the initiation of the beta-lactam antimicrobial to Day 14.



7.3. Modification or premature cessation of the allocated dosing strategy

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

The allocated dosing strategy may vary or be stopped during the study period in the following circumstances:

1. The beta-lactam antimicrobial is changed by the treating physician:
    a From piperacillin/tazobactam to meropenem or *vice versa*. In this case, the new prescription will continue to be administered using the allocated dosing strategy (resistance-optimised precision dosing or standard care dosing).
    b From piperacillin/tazobactam or meropenem to another study antimicrobial. In this case, the patient will be evaluated for the clinical outcomes as specified in section 8, and data collection follow-up will be performed.

2. The patient has known toxic beta-lactam antimicrobial concentrations (meropenem total or unbound $C_{min}/C_{ss} > 44.5$ mg/L, piperacillin $C_{min}/C_{ss} > 160$ mg/L or $fC_{min}/fC_{ss} > 128$ mg/L, tazobactam $C_{min}/C_{ss} > 20$ mg/L) and manifests signs or symptoms of beta-lactam antimicrobial toxicity that are attributable to the study antimicrobial which are sufficiently severe that the treating physician deems necessary to cease the study intervention and/or the study antimicrobial. The patient will remain in the study, and the data collection and follow-up schedule will continue unchanged.

3. The patient presents a treatment emergent adverse reaction to the beta-lactam antimicrobial. Appropriate ongoing treatment will be determined by the treating physician, including whether the beta-lactam antimicrobial and/or study intervention should be immediately ceased. The patient will remain in the study, and the data collection and follow-up schedule will continue unchanged.

4. The patient or their substitute decision maker (SDM)/person responsible request to stop the study assigned dosing strategy. The patient or their SDM/person responsible may request the study dosing strategy 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, including vital status at Day 28, will be sought.

7.4. Concomitant care

Other aspects of patient management will not be affected by the study procedures. Treating physicians will be free to provide any care they consider appropriate and necessary, including the administration of other antimicrobial agents.

7.5. Blinding

The study assigned administration method will be known to the treating clinicians, participants, other care providers, outcome assessors, and the statistician preparing reports for the DSMC. The statistician leading the development of the Statistical Analysis Plan (SAP) will be blinded at least until the SAP is made publicly available. Potentially suggestive clinical outcomes will be evaluated by one blinded independent physician not responsible for the care of the patient.

7.6. Safety considerations

At the labelled doses, beta-lactam antimicrobials have a large safety margin between effective and toxic exposures. However, the incidence of toxicity at higher doses is not that well characterised and may include neurotoxicity, nephrotoxicity, haematological toxicity and hepatotoxicity.[35] Although limited, published observational data have identified potential toxicity thresholds for neurotoxicity and nephrotoxicity. For neurotoxicity, reported thresholds include: piperacillin (in combination with tazobactam) C_{min} or C_{ss} > 160 mg/L (that correspond to fC_{min} or fC_{ss} > 128 mg/L assuming a 20 % protein binding), and meropenem total or unbound C_{min} or C_{ss} > 44.5 mg/L. For nephrotoxicity, thresholds of C_{min} or C_{ss} > 452.7 mg/L for piperacillin and C_{min} or C_{ss} > 44.5 mg/L for meropenem have been reported. [30,36] A toxicity threshold for tazobactam has not been clearly defined; however, an upper limit of 20 mg/L has been set by our institution.

The ROAD pilot study has previously explored the tolerability and safety of resistance-optimised beta-lactam antimicrobial doses; in this study, median doses were 22.5 g/day for piperacillin/tazobactam (corresponding to 20 g piperacillin / 2.5 g tazobactam) and 6 g/day for meropenem, with a low incidence of adverse events. [29] Furthermore, MIPD-guided dosing, particularly when combined with TDM, may reduce concentration-related toxicity by enabling closer patient monitoring and greater control of supratherapeutic exposures, reflecting the increased oversight of adverse events associated with high antimicrobial doses and the more intensive TDM implemented in the intervention arm compared with standard therapy. Notably, the selected therapeutic ranges consider conservative published toxicity thresholds for piperacillin in combination with tazobactam and meropenem, [30,36] and a daily dose of 36 g per day of piperacillin/tazobactam (corresponding to 32 g of piperacillin and 4 g of tazobactam) and 12 g per day of meropenem will be considered as the maximum dose permitted.

Patient-acceptability was discussed with our study consumer group, with members reporting a willingness to accept potential short-term side effects for resistance-optimised precision dosing potential benefits including improved clinical cure, a reduced length of stay and suppression of emergence of resistance.

7.6.1. Precautions and adverse reactions

Piperacillin/tazobactam and meropenem are registered products with the Therapeutic Goods Administration (Australia), the European Medicines Agency (Europe), and National Pharmaceutical Regulatory Agency (Malaysia). 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 in addition to those collected in case report forms. Patients will be monitored for the known side effects of intravenous therapy with piperacillin/tazobactam and meropenem and adverse events reported accordingly.

7.6.2. Safety assessment

Safety will be assessed by clinical evaluation and the monitoring of routine clinical and laboratory parameters for critically ill patient admitted to the ICU. An independent physician will ascertain the likelihood of the beta-lactam antimicrobial contributing to toxicity if the clinical team wishes to stop the intervention. Toxicity will be monitored for up to 48 h following the cessation of the study (i.e. up to Day 16 post-randomisation).

8. Study assessments

Patients will be followed up to Day 28 post-initiation of the study beta-lactam antimicrobial or to death, whichever is sooner.

8.1. Screening

Patients admitted to the study ICUs will be screened and evaluated to assess enrolment eligibility by study clinicians and/or their representatives at the respective sites. 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. Baseline data collection

Patient baseline demographic and clinical characteristics including age, sex, estimated/actual weight and height at admission, admission diagnosis (using the Acute Physiology and Chronic Health Evaluation (APACHE) III classification), organ function, major comorbidities including immunosuppression status, microbiology data, empirical antimicrobial treatment, dose, frequency and infusion duration, concomitant antimicrobials will be collected to assess baseline balance between each treatment group. Clinical information will allow calculation, among others, of the APACHE II and Sequential Organ Failure Assessment (SOFA) scores that quantify illness severity in ICU patients. The country specific diagnosis-related group (DRG) code will be collected.

8.3. Intensive care unit admission

Daily clinical information and laboratory data will be recorded whilst the patient is in ICU and up to Day 28 to document response to treatment and to monitor safety and compliance with the study protocol.

8.4. Definition of clinical cure

Clinical cure at Day 14 will be defined as:
(i) Completion of the antimicrobial treatment course (on or prior Day 14) without recommencement of antimicrobial therapy within 48 h of cessation for the same infectious episode; and
(ii) The reason for cessation of the antimicrobial treatment is not palliative care; and
(iii) Patient survival after 48 h of completion of the antimicrobial course.

No clinical cure at Day 14 will be defined as one of the following options:

Death by any cause during antimicrobial treatment

Persistent infection:
Up to Day 14 or ICU discharge:
(i) Absence of clinical cure; and
(ii) Positive respiratory culture at the end of trial antimicrobial therapy, or by Day 14, with the same microorganism for which the study antimicrobial was initiated. This definition includes strains that developed intra-treatment resistance to the study beta-lactam antimicrobial.

Superinfection:
Up to Day 14 or ICU discharge:
(i) Absence of clinical cure; and
(ii) Positive respiratory culture at the end of trial antimicrobial therapy, or by Day 14, with a microorganism different from the one for which the study beta-lactam antimicrobial was initiated.

Other complications:
Up to Day 14 or ICU discharge:
(i) Absence of clinical cure.
(ii) Other complications of the infection that need an intervention besides antimicrobial therapy, e.g. suppurative complications like empyema that need pleural drainage.

For the purposes of evaluating clinical cure, changes of antimicrobial therapy (i.e. escalation or de-escalation) based on clinical cultures and/or patient clinical evolution will be evaluated as follows:

1. Escalation due to isolation of a microorganism resistant to the study antimicrobial in the first clinical sample.
    I. If the antimicrobial is changed from piperacillin/tazobactam to meropenem or *vice versa* in the context of directed treatment, this is not considered neither as antimicrobial escalation nor as clinical failure for the primary outcome, but as part of the antimicrobial treatment course. Clinical cure will be evaluated *as per* the abovementioned criteria.
    II. If the antimicrobial is changed to an antimicrobial different to piperacillin/tazobactam or meropenem, this is not considered neither as antimicrobial escalation nor as clinical failure for the primary outcome. Clinical cure will be evaluated *as per* the abovementioned criteria.

2. Escalation from piperacillin/tazobactam to meropenem in the context of unfavourable clinical evolution. This will be considered as antimicrobial escalation and clinical failure.

3. Escalation from piperacillin/tazobactam to meropenem in the context of development of intra-treatment resistance in subsequent clinical cultures and/or occurrence of a superinfection. This will be considered as emergence of resistance in the secondary outcome(s). Clinical cure will be evaluated *as per* the above criteria.

4. Escalation from piperacillin/tazobactam or meropenem to another antimicrobial in the context of unfavourable clinical evolution. This will be considered as antimicrobial escalation and clinical failure for the primary outcome.

5. Escalation from piperacillin/tazobactam or meropenem to another antimicrobial in the context of development of intra-treatment resistance in subsequent clinical cultures and/or occurrence of a superinfection. This will be considered as emergence of resistance in the secondary outcome(s). Clinical cure will be evaluated as per the above criteria.

Clinical outcomes will be evaluated by one blinded independent physician not responsible for the care of the patient. Participants discharged from hospital before Day 14 will be considered to meet the definition of clinical cure. However, if a participant is readmitted to the ICU before Day 14, then the participant will be assessed against the definition of clinical cure as above, using information available at readmission. Participants who die while receiving the antimicrobial treatment course or where antimicrobial therapy is ceased in the setting of death being deemed imminent and inevitable, will be assessed as not meeting the criteria for clinical cure.

8.5. Definitions of the secondary outcomes

<table>
<tr><th>Objective</th><th>Outcome measures</th></tr>
<tr><td>Time to clinical cure</td><td>Time in hours from the initiation of the trial antimicrobial to clinical cure.</td></tr>
<tr><td colspan="2"></td></tr>
<tr><td colspan="2">Clinical outcomes within Day 14</td></tr>
<tr><td>All-cause mortality</td><td>Day 14 all-cause mortality</td></tr>
<tr><td>Treatment emergent adverse effects</td><td>Up to Day 14 or ICU discharge:
Type and occurrence of adverse events, including neurotoxicity, nephrotoxicity, hepatotoxicity and haematological toxicity, occurring only during treatment with the study antimicrobial and deemed likely related to the study drug.

Neurotoxicity
(i) Abnormal electroencephalograph.
(ii) Neurotoxicity symptoms such as seizures, convulsive or non-convulsive status epilepticus and, where evaluable, worsening consciousness, tremor, agitation, bizarre behaviour, delirium, slurred or incoherent speech, drowsiness/somnolence, myoclonus, hallucinations, confusion, ataxia/loss of coordination, and disorientation.

Hepatotoxicity
The pattern of drug induced liver injury will be defined as:
- Hepatocellular when there is a ≥ 5-fold increase in the ALT or the ratio of ALT/ALP ≥5.
- Cholestatic when there is a ≥ 2-fold increase in the ALP alone or the ratio of ALT/ALP ≤ 2, and mixed when the ALT/ALP ratio is between 2 and 5.

Nephrotoxicity
As defined by the KDIGO guidelines for the definition and classification of acute kidney injury. [37]

<table>
<tr><th>Stage</th><th>Serum creatinine</th><th>Urine output</th></tr>
<tr><td>1</td><td>1.5–1.9 times baseline
OR
⩾0.3 mg/dl (⩾26.5 μmol/l) increase</td><td><0.5 ml/kg/h for 6–12 hours</td></tr>
<tr><td>2</td><td>2.0–2.9 times baseline</td><td><0.5 ml/kg/h for ⩾12 hours</td></tr>
<tr><td>3</td><td>3.0 times baseline
OR
Increase in serum creatinine to ⩾4.0 mg/dl (⩾353.6 μmol/l)
OR
Initiation of renal replacement therapy OR, In patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m^2</td><td><0.3 ml/kg/h for ⩾24 hours
OR
Anuria for ⩾12 hours</td></tr>
</table>
</td></tr>
</table>

	Haematological toxicity Decrease in neutrophil count of at least 50 % and < 500/mm^3 or in platelet of at least 50 % and < 50000/mm^3 during the whole antimicrobial course.
Clostridioides difficile diarrhoea	Up to Day 14 or ICU discharge: signs and symptoms consistent with *C. difficile* diarrhoea plus confirmatory positive testing for glutamate dehydrogenase + cytotoxin.
Duration of mechanical ventilation	Up to Day 14 or ICU discharge: Duration in days of mechanical ventilation
Duration of renal replacement therapy	Up to Day 14 or ICU discharge: Duration in days of renal replacement therapy.
Duration of extracorporeal membrane oxygenation	Up to Day 14 or ICU discharge: Duration in days of extracorporeal membrane oxygenation.
Duration of vasopressor therapy	Up to Day 14 or ICU discharge: Duration (h) of vasopressors therapy.
Microbiological outcomes within Day 14	
Microbiological cure	Up to Day 14 or ICU discharge: (i) Clinical cure, and (ii) Negative respiratory culture at the end of trial antimicrobial therapy or by Day 14.
Emergence of resistance to beta-lactam antimicrobial(s) in the index microorganism in the clinical samples and/or surveillance samples	Up to Day 14 or ICU discharge: (i) Positive respiratory or epidemiological culture of a Gram-negative microorganism which was the same microorganism in which the study antimicrobial was initiated for, and (ii) Significant phenotypic change in the MIC to any beta-lactam antimicrobial determined by BMD defined as: - A phenotypic change in the causative organism from susceptible or susceptible at high exposures to resistant as per the current EUCAST clinical breakpoints, or - A ≥ 4- fold increase in the MIC compared with the baseline MIC of the index organism. (*): in the occurrence of a polymicrobial infection, the predominant Gram-negative species should be selected as index. If several Gram-negative species and equally predominant, the species with the higher baseline MIC to the study antimicrobial should be selected.
Acquisition of new beta-lactam antimicrobials resistant microorganism(s) in the	Up to Day 14 or ICU discharge: New detection of any of the following organisms not previously detected at the ICU admission and randomisation surveillance samples: piperacillin/tazobactam–resistant Enterobacterales, 3rd and/or 4th generation cephalosporin-resistant Enterobacterales,

clinical samples and/or surveillance samples	carbapenem-resistant Enterobacterales, carbapenem-resistant *Acinetobacter baumannii* complex, DTR *Pseudomonas aeruginosa* and MRSA. Additionally, VRE. These microorganisms may be identified either from the serial surveillance samples (nasopharyngeal and rectal swabs) or from clinical specimens collected during the study period.
Detection of new antimicrobial resistance gene classes	Up to Day 14 or ICU discharge: - New detection of genes and gene mutations with WGS, including point-mutated and known resistance genes, that confer resistance to beta-lactam antimicrobials between the index and subsequent isolates. - Antimicrobial resistance gene (ARG) (and ARG classes, e.g., ESBL or carbapenemase gene) abundance and microbiota-species composition and richness (using the Shannon diversity and Bray-Curtis dissimilarity indices) determined by metagenomic sequencing of faecal samples at day 14 or ICU discharge compared to baseline.
Clinical, microbiological and health-economic outcomes at Day 28	
Day 28 all-cause mortality	All-cause mortality at Day 28.
New episode(s) of infection caused by microorganisms that are MDR or that have a reduced susceptibility to the study beta-lactam antimicrobial	This includes: - Recurrence of the respiratory infection: signs and symptoms of a new respiratory infection with a positive respiratory culture with the same microorganism to the one the study antimicrobial was initiated for. This definition includes strains that developed intra-treatment resistance to the study beta-lactam antimicrobial. - New respiratory infection: signs and symptoms of a new respiratory infection with a positive respiratory culture with a different MDR microorganism to the one the study beta-lactam antimicrobial was initiated for. - New non-respiratory infection: signs and symptoms of a new infection with a positive clinical culture (e.g. blood, urine) with a MDR microorganism or a microorganism with reduced susceptibility to the study beta-lactam antimicrobial.
Acquisition of new beta-lactam antimicrobials resistant microorganism(s) in the surveillance samples	At Day 28: New detection in the serial surveillance samples (nasopharyngeal and rectal swabs) of any of the following organisms not previously detected at the ICU admission and randomisation surveillance samples: piperacillin/tazobactam–resistant Enterobacterales, 3rd and/or 4th generation cephalosporin-resistant Enterobacterales, carbapenem-resistant Enterobacterales, carbapenem-resistant *Acinetobacter baumannii* complex, *P. aeruginosa* with DTR and MRSA. Additionally, VRE. This evaluation will only be performed if the patient is still in the ICU at Day 28.

ICU Length of stay	Total length of ICU stay (including readmissions) since the initiation of the beta-lactam antimicrobial up to Day 28.
Hospital length of stay	Total length of hospital stay (including readmissions) since the initiation of the beta-lactam antimicrobial up to Day 28.
Duration of contact isolation care	Duration of new contact isolation (days) requirements since the initiation of the beta-lactam antimicrobial up to Day 28.
ICU Free Days	Defined as: - ICU-free days = 0 if the patient dies within 28 days of ICU admission. - ICU-free days = 28 − x, where x is the number of days spent in the ICU, if the patient is discharged from the ICU before day 28. - ICU-free days = 0 if the patient remains in the ICU for 28 days or more.
Hospital Free Days	Defined as the number of days the patient is alive and not hospitalised up to Day 28. - If a patient dies during the follow-up period, their hospital-free days are typically counted as zero, regardless of how many days they were actually out of the hospital. - If a patient is hospitalised for the entire follow-up period, hospital-free days are also zero. - If a patient is discharged and survives, hospital-free days = total follow-up days − days spent in hospital.
Readmissions	ICU and hospital readmission.
Health-economic analysis	Up to Day 28: Quality-adjusted life years (QALY) will be used to conduct a cost-utility analysis, summarised by the incremental cost-effectiveness ratio between intervention and control. The economic evaluation will examine the set up and implementation cost, plus healthcare resource utilisation costs. This will also include Diagnosis Related Codes (DRG) for the relevant countries.

8.6. Definition of other assessments

MIPD intervention fidelity up to Day 14 or ICU discharge	
Time to first dosing intervention (*)	Time (h) to first MIPD dose intervention from the initiation of the study beta-lactam antimicrobial and from randomisation.
PK/PD target attainment within 24 h from randomisation (**)	Proportion of PK/PD target attainment within the first 24h post-randomisation.
Time to PK/PD target attainment (**)	Time (h) to PK/PD target attainment from the initiation of the beta-lactam antimicrobial and from randomisation.

Proportion of daily PK/PD target attainment (**)	Proportion of days where the PK/PD target is attained over the treatment period.
Description and frequency of dosing adjustments (*)	Details on the type of MIPD recommendation and number of dosing adjustments per patient required to attain the PK/PD target.
TDM results and performance up to Day 14 or ICU discharge	
TDM results (**)	Total or unbound C_{min} or C_{ss} concentrations measured in plasma for TDM along the study period
Time to TDM since initial antimicrobial dose (**)	Time (h) to TDM from the initiation of the study beta-lactam antimicrobial and from randomisation.
Proportion of erroneous samples (**)	Extent of samples for TDM that may have been lost in transit, breached stability standards, or deviations in actual vs documented sample timing resulting in a protocol deviation.
Intervention adherence up to Day 14 or ICU discharge	
Clinical adherence to MIPD recommendations (*)	Proportion of MIPD recommendations that were rejected and reason(s).
Intervention scalability assessment at the conclusion of study	
Assessment of whether the intervention can be successfully expanded for widespread real work use (*)	Using the Intervention Scalability Assessment Tool to assess the following in individual patients: • Evidence of effectiveness • Implementation costs • Intervention acceptability to end users • Fidelity and reach of the intervention

(*): only for patients the intervention group.

(**): patients in the intervention group and patients in the standard care group that receive TDM

8.7. Follow up at Day 14 and Day 28

Follow-up for the primary and majority of secondary outcomes will be until death or at Day 14, whichever is sooner. At Day 28, length of stay (LOS) in the ICU, hospital LOS, date and cause of death (if appropriate), ICU/hospital free days, duration of isolation care and quality of life via EuroQoL 5-Dimension 5-Level (EQ-5D-5L) questionnaire will be recorded.

8.8. Schedule of assessments

Table 5. Schedule of Assessments

Task	Screening	Randomisation (Day 1)	Baseline	Day 1 to 14	Day 28 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			
Documentation of information sharing/consent with patient or Substitute Decision Maker			X	X	
Administer study intervention			X		
ICU admission diagnosis			X		
Patient clinical and demographic characteristics			X		
Baseline APACHE II (severity of illness) score components, APACHE III score components, SOFA score			X		
Colonisation with an MDR microorganism at ICU admission			X		
Planned 24-hour dose and dosing interval of the beta-lactam antimicrobial at randomisation			X		
Collection of respiratory samples for microbiology			X	X	X (only if still in the ICU)
Collection of surveillance swabs			X	X	X (only if still in the ICU)
Collection of samples for metagenomics			X	X	
Microbiological confirmation of infection			X	X	
Resistance-optimised dosing recommendations with MIPD (only for intervention arm)				X	
Assess for concurrent antimicrobial use up to Day 14				X	
Assessment for clinical cure at Day 14				X	
Date and time of clinical cure assessment				X	
Date and time of death				X	X
Date and time for delirium diagnosis				X	
Liver function test values				X	
Creatinine concentration values			X	X	
Date and time for any seizures			X	X	
Haematological values			X	X	
Colonisation with an MDR microorganism up to Day 14				X	
C. difficile diarrhoea up to Day 14				X	
All beta-lactam antimicrobial doses				X	
Dosing recommendation rationale			X	X	

Dosing recommendation agreed upon by treating clinician/team				X	X	
All beta-lactam antimicrobial concentration data					X	
Duration of dosing intervention documented by study clinician				X	X	
Reason for cessation of beta-lactam antimicrobial					X	
Duration of mechanical ventilation					X	
Duration of vasopressor treatment					X	
Duration of renal replacement therapy					X	
Duration of extracorporeal membrane oxygenation					X	
Vital status at Days 14 and 28					X	X
Adverse reactions ascribed to beta-lactam antimicrobial					X	
Protocol violations					X	
Health economic assessment	ICU Length of Stay (LOS)				X	X
	Hospital LOS				X	X
	Isolative care LOS				X	X
	ICU readmission rate					X
	Hospital readmission rate					X
	Isolative care readmission rate					X
	ICU readmission LOS					X
	Hospital readmission LOS					X
	Isolative care readmission LOS					X
	EQ-5D-5L questionnaire				X	X
	Survival (including date and cause of death)					X
	Diagnosis Related Group Code (DRG)					X
Intervention Scalability Assessment	Acceptability survey for substitute decision maker		X			X
	Acceptability survey staff				X	
	Reach assessment	X			X	

8.9. Recruitment

Recruitment strategy

The study investigator(s), in collaboration with the research coordinator (s), from each site will conduct daily screening of the patients in the ICU to identify individuals who meet the study's eligibility criteria. Once a potentially eligible participant is identified, participation in the study will follow the informed consent hierarchy detailed in section 10.3.

Recruitment feasibility

For a sample size of 610 patients, we intend to recruit approximately 20 patients per month across the 14 international sites, for a total of 36 months of recruitment. Demonstrating we have the necessary ICU network and infrastructure to support highly feasible patient recruitment in ROAD RCT, sites from France and Malaysia (Investigators Roger and Hasan) and Australian site leads (J Roberts, Harris, Dhanani, Marriott, Trubiano, Udy, Mangalore) have also recruited for dosing intervention studies including BLING III RCT, [38] which recruited > 800 participants in France and Malaysia and > 2000 patients in Australia over a 3.5 years period (including COVID-19 disruptions).

9. Safety monitoring and reporting

It is recognised that patients in the ICU will experience a number of alterations 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 the study drug and dosing strategy (possibly, probably or certain). 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 dosing strategy will be reported within seven days of discovery. The site Principal Investigator will be responsible for determining the causal relationship as either possible, probable or certainly related in accordance with the World Health Organisation Causality Assessment matrix. 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. Treatment emergent adverse events

Treatment emergent adverse events (TEAEs) 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 TEAE is not related to the assessment of the severity of the adverse event. An event that is mild in severity may be classified as a TEAE 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 TEAEs that are thought to be related to the study assigned dosing and administration method will be reported.

TEAEs should be reported within 24 h of participating site study staff becoming aware of the occurrence by completing an adverse event form on the web-based data management system.

9.1.2. Suspected unexpected serious adverse reactions (SUSAR)

A SUSAR is a Serious Adverse Drug Reaction (SADR) which is considered *unexpected*. A 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 h 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 TEAEs 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 investigator of each site and an independent physician's assessment of the relationship between the study drug, the dosing strategy and the event (classified as possibly, probably, or certainly related).
6. Whether treatment was required for the event and what treatment was administered.

The regional co-ordinating centre staff will be responsible for following up all TEAEs and SUSARs to ensure all details are available. The central coordinating centre is responsible for alerting other participating sites to the reported TEAEs or SUSAR, and for 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 (DSMC)

A DSMC independent from the sponsor coordinating centre and funder 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 and upon completion of all patient treatments and evaluations.

10. Ethics

10.1. Ethical principles

The study will be conducted in accordance with ethical principles consistent with the Declaration of Helsinki [39] and all relevant national and local guidelines on the ethical conduct of research. [40]

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 demonstrating approval of the protocol, the participant information and consent forms, and other supporting materials 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, 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. Consent and enrolment procedures

This study involves the random assignment of mechanically ventilated critically ill patients to either resistance-optimised precision dosing or standard care dosing for two beta-lactam antimicrobials (piperacillin/tazobactam or meropenem) for the treatment of nosocomial respiratory infections. Piperacillin/tazobactam and meropenem are both commonly used beta-lactam antimicrobials 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 except for the

serial collection of minimally invasive microbiological clinical samples and screening samples and the Day 14 and Day 28 follow-up of patient status, that may happen following discharge from the hospital.

The Australian NHMRC National Statement on the Ethical Conduct in Human Research, [40] acknowledges 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.

This trial will determine whether resistance-optimised precision dosing of beta-lactam antimicrobials improves clinical cure compared with standard dosing in critically ill mechanically ventilated patients with nosocomial infection. A key facet of the intervention is the application of precision dosing *as soon as possible* after antimicrobial treatment has commenced; any potential benefit of the trial treatment may only be realised if administered in a *timely* fashion. Moreover, initiation of antimicrobial therapy is considered an urgent time-critical medical intervention and must not be delayed, as postponement may result in infection progression, worsening organ dysfunction, or even death. Obtaining written and informed consent directly from patients prior to enrolment in this clinical trial is therefore not possible, as they will all be receiving mechanical ventilation, and will be too unwell to understand information relating to clinical trial participation. Additionally, because trial treatment should commence without delay to maximise any potential benefits, there is unlikely to be sufficient time to obtain informed consent from a Substitute Decision Maker on behalf of the patient.

Under these circumstances, 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) [40] and the ANZICS Clinical Trials Group Ethics Handbook for Researchers. [41] As such, the approach to obtaining consent in this trial will be as follows:

1. A waiver of consent

For sites where it is legally and otherwise acceptable, a waiver of consent may be considered. A waiver of consent would be justified per section 2.3.10 of the 2025 guidelines, with each point addressed below.

2.3.10 a) *Involvement in the research carries no more than low risk:* We have established that the intervention dosing strategy is supported by literature demonstrating improved clinical cure rates. The risks of adverse events related to the dosing strategy are also unlikely to exceed that for patients receiving standard dosing given the increased monitoring of those patients receiving the intervention dosing strategy, as well as the wide therapeutic range for the included beta-lactam antibiotics. Strict adherence to ICH GCP principles ensures the highest level of protection and safety.

2.3.10 b) *The benefits from the research justify any risks of harm associated with not seeking consent* Potential harms related to not obtaining consent that include privacy and data protection concerns would remain consistent with other patients. There is an opportunity to include patient cohorts that may be traditionally hard to reach, to access participation and ensure equity in clinical trials.

2.3.10 c) *It is impracticable to obtain consent:* In this context, the patient themself would be unable to provide consent. Moreover, the critically ill nature of the patient's illness and the necessity to implement antibiotic therapy in a timely manner to improve the probability of a positive clinical outcome may limit the feasibility of obtaining consent from a stressed and concerned SDM.

2.3.10 d) *There is no known or likely reason for thinking that participants would not have consented if they had been asked:* Exclusion criteria 10 (section 6.3) precludes enrolment if it was previously known

or reasonably suspected that the patient had a reason that they would not have provided consent if they were asked to be enrolled in the ROAD-RCT.

2.3.10 e) *There is sufficient protection of their privacy;* and f) *There is an adequate plan to protect the confidentiality of data:* The patient's privacy and data confidentiality would be to the level established in sections 10.4 and 11 of this protocol.

2.3.10 f) *In case the results have significance for the participants' welfare there is, where practicable, a plan for making information arising from the research available to them:* It is unlikely that the patient's enrolment will have any lasting significance for their welfare. The dosing strategies and computing methods for the intervention dosing are currently available to clinicians. It is highly unlikely that patients would specifically benefit from the information resulting from the study being made available to them following their involvement with the study given that this is an ICU specific condition being examined.

2.3.10 g) *The possibility of commercial exploitation of derivatives of the data or tissue will not deprive the participants of any financial benefits to which they would be entitled:* It is unlikely that the specific outcomes of this research or of any samples obtained during the conduct of this research are of commercial interest. Moreover, there is no known financial entitlements for patients participating in this research nor the investigators involved.

2.3.10 h) *The waiver is not prohibited by State, federal, or international law:* The waiver of consent in this context will be consistent with state, federal, or international law for Australian and international sites.
The SDM will be provided with the ROAD-RCT information brochure and have the ability to discuss the trial enrolment with the site principal investigator or delegate as appropriate. The provision of the brochure and discussion(s) as appropriate will be documented both in the patient's medical record, and in the CRF.

2. 'Opt out' from the patient or Substitute Decision Maker (SDM)

Where it is not possible SDM to provide consent prior to randomisation, or a waiver of consent is not applicable, (subject to approval by the relevant HREC and all applicable legislation) the patient will be able to be enrolled into the trial. Following this, as soon as possible and appropriate, the patient and/or SDM will be informed of the patient's enrolment into the trial.

At this stage, the trial will be explained verbally to the patient or SDM and they will be given the brochure, providing them the option to withdraw 'opt out' from the trial. The patient or SDM will be given the opportunity to read the information sheet and ask any questions prior to deciding. The information sheet will provide information on how to withdrawal from the trial. This will also be documented in the patient's medical record.

The SDM or patient may withdraw their consent to participate in the study at any time. If they choose to withdraw from ongoing trial participation, permission to use trial-related data and to collect and use outcome data will be sought. Patients who recover sufficiently to understand the explanation of the trial and that consent was provided by the SDM will be offered the chance to withdraw from the trial. If the patient chooses to withdraw from the trial procedures, they will be asked for permission with written consent to use their trial-related data and for permission to collect and use outcome data.

3. 'Consent to continue' from the patient or Substitute Decision Maker (SDM)

Where it is not possible SDM to provide consent prior to randomisation, or a waiver of consent is not applicable, (subject to approval by the relevant HREC and all applicable legislation) the patient will be able to be enrolled into the trial. Following this, as soon as possible and appropriate, the patient or SDM will be informed of the patient's enrolment into the trial.

At this stage, the trial will be explained verbally to the patient or SDM and they will be given the brochure, providing them the option to consent to continue participating with the trial. The patient or SDM will be given the opportunity to read the information sheet and consent form and ask any questions prior to deciding. The information sheet will provide information on how to withdrawal from the trial, or alternatively, if the SDM or patient consents to continue, they will be given a copy of the signed and dated consent form, the information sheet, and any other documentation discussed during the consent process. This will also be documented in the patient's medical record.

Verbal Consent

In circumstances where an identified SDM is unable to be physically present at the participating site to provide written consent, verbal consent may be obtained. The trial will be explained verbally to the SDM by the Principal Investigator or their nominated delegate(s) as per the phone script and verbal consent form, over the telephone or online video conference call. The SDM will be given the opportunity to ask any questions prior to deciding on the patient's ongoing participation in the trial.

If the SDM consents for the patient to participate or continue participating, a record of the verbal consent conversation will be made, signed and dated by the principal investigator or their nominated delegate(s), as well as a witness. The information sheet will be provided via post or email to ensure the SDM has the trial information and site contact details. Patients or the SDM may withdraw their consent to continue to participate in the trial at any time.

Deceased patients

The patients enrolled in this trial will be critically ill and unfortunately the sickest patients may die from their critical illness before informed consent is obtained, in situations where a waiver of consent is not able to be considered. In these cases, obtaining consent from a SDM may add considerably to the distress that the death of a loved one naturally causes. All efforts will be taken by the Principal Investigator or their nominated delegate(s) to obtain consent from the patient or SDM following enrolment into the trial.

4. Consent from a substitute-decision maker prior to randomisation:

Finally, at sites where neither a waiver or consent to continue model of consent is either incongruent with cultural/other values, or is inconsistent with local legislation, consent will be obtained from a legally recognised SDM. The procedure for obtaining consent from an SDM must be in accordance with the ICH Good Clinical Practice and site regulatory requirements and approved prior to use. Once a SDM has been identified, the trial will be explained verbally to the SDM by the Principal Investigator or their nominated delegate(s). Because study treatment needs to begin as soon as possible, the SDM will be given a brochure which has been developed in partnership with consumer representatives, which provides a summary of the treatment they are being asked to agree to on behalf of the patient. SDM will be given the opportunity to read the brochure and ask any questions and provided with the Information Sheet and Consent Form.

If the SDM consents for the patient to participate, written consent will be obtained, and they will be given a copy of the signed and dated consent form, the information sheet, and any other documentation discussed during the consent process. The SDM will be given the opportunity to read

the extended participant information sheet and ask any questions. Patients or SDM's may withdraw consent to participate in the study at any time.

Additional Ethics Considerations
All interaction between research staff and potential or actual participants and their SDM will take into consideration the stress or emotional factors associated with critical illness and ensure that the dependency of potential participants on medical personnel providing treatment does not compromise the freedom of a decision to participate. Consenting to participate will be voluntary and participants or their legally authorised representative, or SDM or consultee will be free to withdraw from participation at any time without giving reasons. The study patient, when able, may also withdraw consent at any time until follow up cessation. Permission to use study-related data and permission to collect and analyse outcome data will be sought from either the study patient, or the consenting SDM at the time of the request to withdraw from the study.

10.3.1. Australian context

Participants enrolled into this trial, by virtue of the fact that they will be receiving invasive mechanical ventilation, will require emergency care in the ICU. These are people who are necessarily highly dependent on medical care and will be unable to give consent. Given this context, we have considered the ethical issues relevant to people highly dependent on medical care who may be unable to give consent.

In particular, this research will involve people who require emergency care, intensive care, and the care of unconscious people. The research has been designed to ensure compliance with the National Statement on Ethical Conduct in Human Research 2025, published by the National Health and Medical Research Council of Australia and we refer below to the specific sections of the National Statement on Ethical Conduct in Human Research 2025, referred to as the National Statement.

The ROAD-RCT proposal underwent rigorous peer review and received funding in the MRFF 2023 Clinical Trials Activity scheme (APP 2039566). If the hypothesis of our trial is confirmed, this will realise a 12% absolute increase in the rate of clinical cure in mechanically ventilated ICU patients with nosocomial respiratory tract infection. As such, we submit that it is likely that this trial will lead to increased understanding about, or improvements in, the care of this population (section 4.4.1 (a)).

As previously outlined, the study antimicrobials are some of the most widely prescribed antibiotics in Australian hospitals, with known and very low risk safety profiles. The low risk profile and frequency with which these agents are currently used in usual practice in Australian hospital, combined with the potential for the intervention to improve clinical cure, provides a justification that the low risk and burden of the proposed research, is offset by the potential benefits (section 4.4.1 (c)). Furthermore, although the study intervention is expected to result in higher than usual daily antimicrobial doses, the MIPD-guided dosing strategy and particularly the daily monitoring of plasma concentrations are likely to facilitate the early identification and mitigation of toxicity through closer oversight in the intervention group and more precise control of plasma concentrations (e.g. the intervention group will receive more tailored dosing, and greater scrutiny of measured drug concentrations, as compared to standard care).

In relation to the burden of trial participation, most trial data are routinely collected for clinical purposes and will be obtained from the medical records; data that are collected as part of follow-up beyond hospital discharge have been carefully considered so that follow-up is not unduly burdensome for participants (section 4.4.1 (c)).

The trial will involve people who are unconscious, encompassing emergency care research, and intensive care research. As both arms of the trial represent differing dosing strategies for drugs that are already very commonly used in this patient population, the research is designed to be therapeutic and to improve treatments for patients with nosocomial infection, meeting the requirements of section 4.4.8 of the National Statement.

As the trial requires the intervention to be administered as soon as practical after commencing antimicrobial therapy in order for the maximal potential benefits of the treatment to be realised, rapid enrolment into the trial is of paramount importance, and thus the trial meets the requirements of section 4.4.6 of the National Statement. Under these circumstances there will be insufficient time to obtain informed consent and a waiver of consent for enrolment into the trial and administration of the trial interventions is required.

The trial participants will require heavy sedation that will impair their ability to understand and communicate their preferences. Therefore, as prior consent is not possible as noted above and in accordance with section 4.4.7, 4.4.9 and 4.4.14 of the National Statement, we will follow the process outlined above to seek consent as soon as practical, in accordance local legal requirements in each jurisdiction.

With regards to section 4.4.13, we submit that the trial is of minimal risk to trial participants as it involves use of pharmaceuticals that are already commonly used in this population. The risks to trial participants are also minimised by limiting data collection to information that is already available as part of routine clinical care (section 4.4.13(b)). The project involves medications that are commonly used in clinical practice and does not involve any significant moral or cultural sensitivities to the community (section 4.4.13 (c)).

As detailed above, based upon prior research and the preliminary data collected by our team, there is a reasonable possibility of benefit of the trial intervention over standard care (section 4.4.13(d)). Given that the trial imposes minimal risks and burdens above standard care in this population, and there is a reasonable expectation of potential benefits (section 4.4.13(e)), inclusion of participants is not contrary to their own interests (section 4.4.13(f)).

10.3.2. Other contexts

In sites from other countries/regions, 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 an online 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 co-ordinating 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. 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 co-ordinating 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 Frazer Institute Herston, Australia. The principle means of data collection and data processing will be electronic via a password protected website (electronic Case Report Form – eCRF). The eCRF will be hosted via the secure REDCap platform hosted on the University of Queensland server. 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 at Day 28 to determine vital status and to provide the questionnaire data (EQ-5D-5L).

A comprehensive guide to data collection with definitions and rationale will be provided together with a paper version of the 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 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 otherwise as per local regulations in other jurisdictions.

11.2. Data sharing

The study database will contain non-identifiable information from all study participants. There is no plan to share this data. However, this information may be made available to other researchers on request to the Study Management Committee, pending appropriate ethics and other regulatory approvals as required. No identifiable information will be made available to other researchers who request access to the study database. Details regarding what information will be shared, when, by what mechanism, with whom and for what types of analyses will be decided by the Study Management Committee and will adhere to all local privacy regulations within each participating country.

12. Quality control and quality assurance monitoring

12.1. Responsibilities of the site Principal investigator

The site Principal Investigator agrees to perform the clinical trial in accordance with this clinical trial protocol, ICH guideline for Good Clinical Practice [42] 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 co-ordinating centre

The central coordinating centre 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, the eCRF website, the dosing software ID-ODS™ and the study materials among other topics. The site initiation visit will be conducted by teleconference, videoconference or face-to-face meetings 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 regional coordinator for Europe) will visit (or videoconference) each participating study site 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(s) 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. Correct information sharing and consent processes following the informed consent hierarchy detailed in the section 10.3.
2. Adherence to the protocol including consistency with inclusion and exclusion criteria.
3. The completeness and accuracy of the eCRFs and source documentation.

4. Patient recruitment and issues relating to patient recruitment. To optimise study recruitment, senior leadership from the research coordinators and clinical staff will be included in the study recruitment monitoring to facilitate feedback to the study coordinators.
5. Adverse event documentation and reporting.
6. Study assigned dosing strategy.
7. Compliance with the study assigned dosing strategy.
8. 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 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, [42] 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. A protocol deviation may be an omission, addition or change in any procedure described in the protocol such as the use of a dosing regimen not recommended by the study investigator after study enrolment.

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 other qualified personnel 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 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 proposed sample size of 610 patients will provide 80 % power to detect an increase in clinical cure rate from 56 % (standard care dosing) to 67 % (resistance-optimised precision group), assuming a 5 % loss to follow-up and a two-sided significance level of 5 %. Justification for this effect size is based on data from the BLING III RCT, which reported an overall clinical cure rate of 55.7 % in the continuous infusion group, a rate likely to reflect that of the standard care group in the ROAD-RCT, [38] and the BLING PK/PD sub-analysis, which found higher cure rates (67 %) among patients with confirmed Gram-negative bacterial infections who achieved antimicrobial exposures above usual clinical cure targets of 100 % $fT_{>MIC}$. With respect to anticipated loss to follow-up, only 0.7 % of patients had missing 90-day mortality data in the BLING III RCT, supporting the assumption that a 5 % sample size inflation is conservative and appropriate.

13.2. Statistical analysis plan

All statistical analyses will be conducted in accordance with a detailed pre-specified statistical analysis plan (SAP), which will be uploaded to the trials registry before the statistician who leads the development of the SAP is unblinded.

The main analysis of the primary outcome (clinical cure at Day 14) will be a chi-square test comparing patients according to their allocated dosing strategy group. A two-sided p-value < 0.05 will be considered evidence of a statistically significant difference. The difference in cure rates will be reported with a 95% confidence interval. Missing data will not be imputed.

13.3. Interim analysis

To help the DSMC assess safety and futility, interim analyses will be conducted just prior to their meetings. There are no formal stopping rules for the effectiveness of the intervention.

13.4. Pre-specified sub-group analyses

1. **Patients with a confirmed Gram-negative respiratory infection**

   Hypothesis: A resistance-optimised precision dosing approach may improve clinical outcomes and prevent emergence of resistance in patients with confirmed Gram-negative respiratory infections.

   Methods: Primary and secondary outcomes will be compared between patients receiving resistance-optimised precision dosing versus standard care in the subgroup of patients with confirmed Gram-negative respiratory infection.

2. Patients with a confirmed non-fermentative Gram-negative bacilli respiratory infection

Hypothesis: The effect of resistance-optimised precision dosing approach on clinical outcomes and prevention of emergence of resistance may be more marked in patients with infections caused by non-fermentative Gram-negative bacilli due to their more efficient and varied mechanisms of developing intra-treatment resistance to these antimicrobials when exposed to concentrations in the MSW.

Methods: Primary and secondary outcomes will be compared between patients receiving resistance-optimised precision dosing versus standard care in the subgroup of patients with confirmed non-fermentative Gram-negative bacilli infections.

3. Patients that have completed at least 5 days of antimicrobial therapy with the study drug

Hypothesis: The effect of resistance-optimised precision dosing approach on clinical outcomes and prevention of emergence of resistance may be better quantified in those patients that have completed at least 5 days of treatment with the study antimicrobial.

Methods: Primary and secondary outcomes will be compared between patients receiving resistance-optimised precision dosing versus standard care in the subgroup of patients that have received at least 5 days of the study antimicrobial.

4. Patients treated with piperacillin/tazobactam and patients treated with meropenem

Hypothesis: The effect of resistance-optimised precision dosing approach on clinical outcomes and prevention of emergence of resistance may be different due to an antibiotic class effect, given the differential mechanisms by which Gram-negative bacteria develop intra-treatment resistance to these antimicrobials.

Methods: Primary and secondary outcomes will be compared between patients receiving resistance-optimised precision dosing versus standard care in the subgroup of patients treated with piperacillin/tazobactam and in the subgroup of patients treated with meropenem.

5. Patients in the intervention arm versus patients in the standard care arm who do not receive TDM as part of their clinical care

Hypothesis: The effect of resistance-optimised precision dosing on clinical outcomes and prevention of emergence of resistance may be diminished when compared with patients that receive TDM as part of their clinical care.

Methods: Primary and secondary outcomes will be compared between patients receiving resistance-optimised precision dosing with MIPD dosing and those in the standard arm who do not receive TDM as part of their clinical care.

6. Patients that receive a pre-randomisation initial loading dose versus patients that do not receive a pre-randomisation initial loading dose

Hypothesis: Even though one of the exclusion criteria is the prescription of a pre-randomisation empirical daily dose exceeding 4 g for meropenem or 18 g for piperacillin/tazobactam (16 g piperacillin and 2 g tazobactam), patients may still receive an initial pre-randomisation loading dose

that is not accounted for in this daily limit. This pre-randomisation loading dose may independently influence clinical cure rates and the prevention of resistance emergence.

Methods: Primary and secondary outcomes will be compared between patients who receive an initial loading dose and those who do not as part of their pre-randomisation clinical care, while controlling for allocation to the resistance-optimised precision dosing versus standard care arms.

14. Pre-specified sub-studies

14.1. Health-economics sub-study

The ROAD-RCT health-economics sub-study will be conducted in accordance with the Health Economics Analysis Plan (HEAP). [43,46] The economic evaluation will be conducted to assess the costs and outcomes of the intervention relative the standard of care. This will be through a nested cohort in Australia; with the inclusion of international sites should they opt in. The primary outcome for the evaluation is the QALY. The secondary outcomes will include the ICU LOS, hospital LOS, isolative care LOS and readmission rates to ICU, isolative care and hospital. The primary evaluation will be a cost-utility analysis. Health-related quality of life and functional capacity will be collected using the health condition-generic EQ-5D-5L instrument. [47] The consent document used at participating sites will detail the EQ-5D-5L questionnaire at baseline. The value set for each individual participant will be converted into utility weights using population-specific algorithms (as per trial sites), which will be used to generate their QALYs. The EQ-5D-5L will be collected at baseline, 7 days post-cessation of treatment (or day 14 post enrolment) and at 28 days post enrolment. A bottom-up costing approach will be adopted to measure and value specific resources (costs) associated with set-up and implementation of the intervention (including the ID-ODS™ software, TDM, time required for training pharmacists, and staff time involved in the intervention) and the cost of healthcare resource utilisation. The cost of healthcare resource utilisation will include medications, pathology/radiology tests, costs associated with treating adverse outcomes, cost of ICU, isolative care and hospital stay plus any re-admission, derived from the LOS using the Independent Health and Aged Care Pricing Authority (IHACPA) national weighted activity unit (NWAU) calculators and the National Hospital Cost Data Collection. [48-50] The cost of healthcare utilisation to Day 28, will be estimated through standard per diem ICU and hospital costs. The cost of healthcare utilisation per day in isolative care will be estimated as the cost per day in ICU plus the additional cost from isolative care materials, extra cleaning and disinfection, and extra staff workload due to isolative care. [51] All costs will be adjusted to 2029 USD values, following the guidelines of the Campbell and Cochrane Economics Methods Group (CCEGM) and the Evidence for Policy and Practice Information and Coordinating Centre (EPPI-Centre). [52,53]

The summary of the cost-utility analysis result will be presented as an incremental cost-effectiveness ratio (ICER) from a healthcare system perspective.

Where the ICER = $\frac{Cost\ of\ the\ Intervention - Cost\ of\ the\ Standard\ of\ Care}{QALY\ of\ the\ Intervention - QALY\ of\ the\ Standard\ of\ Care}$

A willingness-to-pay (WTP) threshold of 0.5 times the GDP per capita per QALY will be applied so that ICER below the WTP threshold will be considered cost-effective. [54] Joint uncertainty of costs and outcomes at 28 days post recruitment will be explored by non-parametric bootstrapping resampling (10,000) of patients' costs and QALYs. One-way sensitivity analyses to ascertain how changes in key parameters could affect the ICER will be explored. For example, a one-way sensitivity analysis of the QALY will be performed by excluding dead patients from the recruited sample. Exploratory analysis to explore contribution of baseline variables including co-morbidities and socio-demographic factors, to

the total costs and QALYs will be examined using regression models. A detailed pre-specified health-economics analysis plan will be developed by the lead head-economics researcher and uploaded to the trial's registry.

14.2. Precision dosing sub-study

The ROAD-RCT Precision Dosing sub-study will evaluate the adherence to the components of Precision Dosing, including the dosing software and TDM, in the attainment of the PK/PD target in the intervention group and in those patients in the standard care group that receive TDM as part of usual care. This will include:

1. Completion of site questionnaires describing standard of care every six months across the duration of the study
2. Proportion of participants in whom dosing software-based MIPD dosing is prescribed within 24 h of randomisation.
3. Proportion of participants in whom the recommended resistance-optimised dose is administered within 24 h of randomisation
4. Proportion of participants in whom MIPD dose adjustments based on TDM are performed within 72 hours of randomisation.
5. Proportion of participants in whom ongoing review and optimisation of antibiotic dosing are conducted throughout the patient's stay in accordance with MIPD recommendations.
6. Time from initiation of antibiotic and time to randomisation
7. Description and frequency of dosing adjustments
8. Attrition rates of participants

In addition, the study will examine the association between beta-lactam plasma concentrations and clinical outcomes and emergence of resistance considering the susceptibility of the pathogens. A detailed pre-specified precision dosing analysis plan will be developed by the lead precision dosing researchers and uploaded to the trial's registry.

14.3. Metagenomic sub-study

The ROAD-RCT metagenomic sub-study will be conducted in some Australian sites in accordance with the Metagenomic Analysis Plan (MAP). Faecal samples will be collected at baseline and at Day 14. Metagenomic sequencing will determine antimicrobial resistance genes (ARG) (and ARG classes, e.g. ESBL or carbapenemase genes) abundance and microbiota-species composition and richness (using the Shannon diversity index, and Bray-Curtis dissimilarity index). Relative abundance of bacterial species/genera and ARGs will be calculated as fragments per kilobase million (FPKM), allowing for variation in both sample sequencing depth and reference length. The relationship between dosing strategy (i.e. resistance-optimised precision dosing vs standard dosing) and metagenomic indicators will be determined. A detailed pre-specified metagenomics analysis plan will be developed by the lead metagenomics researchers and uploaded to the trial's registry.

14.4. Intervention Scalability Assessment

An Intervention Scalability Assessment (ISAT) [55-57] will be undertaken to assess scalability to a larger clinical trial and/or implementation to reach a greater proportion of the eligible population while retaining effectiveness. Measures as a part of this assessment will include:

Acceptability
Acceptability is defined as the perception of both the SDM that provided consent, and of clinical teams providing care, that they are comfortable, engaged with, confident with the intervention. [44]
Acceptability will be investigated by describing:

1. Acceptability survey:

    a. Completion of the Acceptability of the Intervention survey by the SDM when providing informed consent
    b. Completion of the Acceptability of the Intervention survey by clinical team members providing care at Day 14

2. Acceptability assessments:

    a. The proportion of registered patients who progress to randomisation with written informed consent.
    b. Qualitative interviews with at least two clinical team members from each site when the study has reached recruitment. These interviews will be conducted via Microsoft Teams on the University of Queensland platform. Staff will be asked to provide an understanding of the study, their profession and role within the broader clinical team, what they perceive as enablers and barriers to readiness for uptake, implementation infrastructure in clinical care. All interviews will be transcribed verbatim in a non-identifiable format. The results will be analysed used the Framework Method. [45]

Findings will be explored to assess any variation according to participant characteristics and/or site-level characteristics.

Reach
Reach is defined as the number and representativeness of individuals that participate in the study. Reach will be investigated by describing participant characteristics including age, gender, socioeconomic status. [46] Findings will be explored to assess any variation according to participant characteristics and/or site-level characteristics.

These assessments, and the 14.1 Health Economics Sub-study, 14.2 Precision Dosing sub-study and 14.3 meta-genomic sub-study will be used to conduct the validated ISAT at the end of the study.

15. Publications and reports

The study will be conducted in the name of the 'ROADRCT Investigators'. Authorship of publications arising from the study will be consistent with standard authorship guidelines 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 the study protocol and the study findings will be disseminated via publication in high-quality peer reviewed journals in the medical literature. Study findings will also be presented at regional, national, and international intensive care conferences. Funding bodies will be acknowledged in all publications. The study consumer group in conjunction with investigators will communicate trial results to participants, healthcare professionals, the public, and other relevant groups by producing a plain language summary in the trial registry.

15.1. Public access

The protocol, statistical analysis plan and sub-studies analysis plans will be made public prior to the main data analysis. The participant level dataset will be made available at a time approved by the Study Management Committee.

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