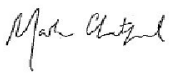
Investigator-Driven Randomised Controlled Trial of Cefiderocol versus Standard Therapy for Healthcare-Associated and Hospital-Acquired Gram-negative Bloodstream Infection (the GAME CHANGER trial): Statistical Analysis Plan

Version 1.0, Dated 5 Feb 2024

The preparation of this document has been led by the trial biostatistician, who will remain blinded until this document has been fully signed and uploaded to: https://clinicaltrials.gov/study/NCT03869437.

The analysis plan has been approved by the following:

Position	Name	Signature	Date
Principal Investigator	Prof David Paterson		5 Feb 2024
Investigator	Dr Patrick Harris		5 Feb 2024
Trial biostatistician	Mr Mark Chatfield		5 Feb 2024

1. Introduction

This document describes the planned presentations and analyses of the data from the GAME CHANGER trial. The study is an open-label randomised controlled non-inferiority trial, comparing cefiderocol vs. standard of care therapy for bloodstream infections caused by Gram-negative organisms that are hospital- or healthcare-associated. The study is an international, multi-centre hospital-based study with sites in Australia, Thailand, Malaysia, Singapore, Taiwan and Turkey. The purpose of this study is to determine whether cefiderocol (a new antibiotic with efficacy against multi-resistant gram-negative bacteria) is as effective as antibiotics that are currently used as standard of care.

The trial protocol was published in *Trials* in 2021 (Wright H, Harris PNA, Chatfield MD, Lye D, Henderson A, Harris-Brown T, Donaldson A, Paterson DL. Investigator-Driven Randomised Controlled Trial of Cefiderocol versus Standard Therapy for Healthcare-Associated and Hospital-Acquired Gram-negative Bloodstream Infection: Study protocol (the GAME CHANGER trial): study protocol for an open-label, randomised controlled trial. Trials. 2021 Dec 7;22(1):889. doi: 10.1186/s13063-021-05870-w ; https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-021-05870-w)

The outcomes of the trial have been carefully reviewed and revised. This document details all of the revised trial outcomes*, all the ways we plan to present and analyse these outcomes, as well as report other data from the trial. (*Note: Day 14 mortality remains the primary outcome)

2. Main analysis population

The main analysis population will include all patients randomised except where:

a) No aerobic Gram-negative bacilli (GNB) grew from a patient's index blood culture
b) Post randomisation, patients did not receive at least one dose of Cefiderocol (if randomised to Cefiderocol) or an agent with activity against GNB if randomised to SOC, or
c) Patients withdrew consent prior to Day 14

Patients who are not included in the main analysis population will not contribute any information to any table/analysis.

Note. Patients that were randomised but ineligible for the following reasons will be included in the main analysis population:

- Patient actually enrolled >48h since index blood culture collection
- Patients with a significant Gram-positive pathogen grown from index blood culture collection in a polymicrobial infection alongside a GNB (e.g. *Staphylococcus aureus* plus *Klebsiella pneumoniae*); [note: while polymicrobial infection was an exclusion criteria at the time of initial screening, in some rare cases the second organism only became apparent in the post randomisation period]

3. Carbapenem-resistant (CR) subset

Hypothesis: Cefiderocol is superior to standard of care treatment for a subset of patients with bloodstream infection caused by carbapenem-resistant (CR) organisms.

The CR subset is defined as patients in the main analysis population with a GNB grown from the index blood culture with:

- Carbapenem non-susceptibility will be defined as any isolate of any species testing resistant (R) or susceptible increased exposure (I) to meropenem or imipenem (or ertapenem for Enterobacterales) according to results of broth microdilution performed at the central study laboratory (UQCCR) using EUCAST clinical breakpoint criteria.
- If an organism is not received by UQCCR or is non-viable on sub-culture, susceptibility will be defined as recorded by the site laboratory using locally approved clinical breakpoints and test methodology. Carbapenem non-susceptibilty will be defined as any isolate reported as "R" or "I" to meropenem or imipenem (or ertapenem in Enterobacterales).
- Species with intrinsic resistance to carbapenems (i.e., *Stenotrophomonas maltophilia*, *Chryseobacterium indologenes, Aeromonas* spp (except *A. caviae*) or *Elizabethkingia* spp.) will be categorised as CR, regardless of any carbapenem susceptibility result.

4. Study Hypothesis and Objectives

The main study hypothesis is that cefiderocol is non-inferior to standard of care (SOC) treatment for gram-negative bloodstream infection that is healthcare-associated or hospital-acquired.

4.1 Primary Study Objective

To compare 14-day mortality from day of randomisation of each regimen (cefiderocol versus SOC). If the primary objective meets the criteria for non-inferiority (with a margin of 10% for the difference in proportions), superiority will be examined.

4.2. Secondary Study Objectives

To compare clinical, microbiological, functional and safety outcomes between arms (see section 5).

5. Outcome definitions and presentations

In what follows, the day of randomisation will be considered to be "Day 1".

5.1 Mortality outcomes

5.1.1 Primary outcome

14-day mortality

5.1.2 Secondary outcomes 1a and 1b: 1a) 30-day mortality ; 1b) 90-day mortality

If a date of death is recorded on or before our calculation of Day 14, the patient will be classed as dead, otherwise considered to be alive. Similar for Day 30. Where possible this rule will also be applied for Day 90 vital status. If the Day 90 follow-up actually occurred on day 85 to 89 and the patient was alive we will assume the patient was alive at day 90.

Table: Mortality results for main analysis population and the CR subset

	Cefiderocol n (%)	SOC n (%)	RD (95% CI), % Cef. – SOC	RR (95% CI) Cef./SOC
All	*N=X*	*N=X*		
Day 14	X (X.X)	X (X.X)	X.X (X.X to X.X)	X.XX (X.XX to X.XX)
Day 30	X (X.X)	X (X.X)	X.X (X.X to X.X)	X.XX (X.XX to X.XX)
Day 90	X (X.X)	X (X.X)	X.X (X.X to X.X)	X.XX (X.XX to X.XX)
CR subset	*N=X*	*N=X*		
Day 14	X (X)	X (X)	X (X to X)	X.X (X.X to X.X)
Day 30	X (X)	X (X)	X (X to X)	X.X (X.X to X.X)
Day 90	X (X)	X (X)	X (X to X)	X.X (X.X to X.X)

*RD Risk difference, RR Risk ratio

5.2 Other outcomes

5.2.1 Secondary outcome 2: Clinical and microbiological failure at day 14, defined as composite of:

1) Death
2) Still in hospital and clinical failure, as defined by
   a) If baseline SOFA ≥3, D14 SOFA not improved by ≥30%
   b) If baseline SOFA <3, D14 SOFA worse
3) Microbiological failure (GNB Growth in blood of same species as index GNB from days 3-14)

The SOFA score we will calculate is a slight modification of the original SOFA score. It will be used for ICU and non-ICU patients. The sole modification is that the respiratory component will be scored as in the modified SOFA:

- 0 (if SaO2/FiO2 >400)
- 1 (if SaO2/FiO2 315-400)
- 2 (if SaO2/FiO2 235-314)
- 3 (if SaO2/FiO2 150-234)
- 4 (if SaO2/FiO2 <150)

Missing data issues

- Cardiovascular components: If dose of vasoactive agents required = Unknown, score as if "Dopamine ≤5 or dobutamine (any dose)."
- Where key data is missing for "Day 1", available data for that patient as soon after will be imputed.
- Where key data is missing for "Day 14", available data for that patient as soon before will be imputed.
- If data is still missing, patients will be assumed to have the best data, i.e. score low.

5.2.2 Secondary outcome 3: Microbiological failure days 3 to 90 post randomisation. Defined as growth in blood cultures of the same GNB as the index blood culture(s), from day 3 up to day 90

5.2.3 Secondary outcome 4: Colonisation or infection with methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), carbapenem-resistant Gram-negative bacilli

or *Candida* bloodstream infection. Defined as the presence of MRSA, VRE or carbapenem-resistant Gram-negative bacilli (of a different species from primary BSI organism) on culture +/- molecular test of clinical samples or screening swabs, or *Candida* species grown in blood cultures from day 3 up to day 90.

5.2.4 Secondary outcome 5: *Clostridioides difficile* infection days 3 to 90 post randomisation.

Defined as presence of a compatible clinical illness with a positive laboratory stool test for *C. difficile* (as per local diagnostic protocol / method)

5.2.5 Secondary outcome 6: Improvement in functional status at day 30 post randomisation

compared to baseline. Functional status will be measured according to a score ranging from 0 (dead) to 7 (out of hospital, healthy, able to complete daily activities). This score is based on the Functional Bloodstream Infection Score (FBIS) [McNamara et al. Clin Microbiol Infect. 2020 Feb;26(2):257.e1-257].

5.2.6 Secondary outcome 7: Time to hospital discharge.

Defined as to the day of first discharge alive (e.g. Day 2 is the day after randomisation). However, if a patient dies in the 3 days following first hospital discharge, we will consider that patient as not having a discharge alive.

5.2.7 Secondary outcome 8 (safety): Treatment emergent SAEs.

Defined as a serious adverse event possibly, probably or definitely related to the randomized drug treatment.

Table: Secondary efficacy outcomes.

	Cefiderocol (N=X)	SOC (N=X)	Cef. - SOC
	n (%)	n (%)	RD (95% CI), %
Clinical or microbiologic failure, Day 14, including: - Death - Other clinical failure D14 - Microbiological failure D3-14	X (X.X) X (X.X) X (X.X) X (X.X)	X (X.X) X (X.X) X (X.X) X (X.X)	X.X (X.X to X.X)
Microbiological failure D3-90	X (X.X)	X (X.X)	X.X (X.X to X.X)
Identification of MRO or *Candida* BSI, D3-90	X (X.X)	X (X.X)	X.X (X.X to X.X)
C. difficile infection, D3-90	X (X.X)	X (X.X)	X.X (X.X to X.X)
FBIS, D30			
0 - Dead	X (X.X)	X (X.X)	
1 - Palliative care	X (X.X)	X (X.X)	
2 – Long-Term ventilator unit	X (X.X)	X (X.X)	
3 – Hospitalized; ICU	X (X.X)	X (X.X)	
4 – Hospitalized; not ICU	X (X.X)	X (X.X)	
5 - Out of hospital, significant disability	X (X.X)	X (X.X)	
6 - Out of hospital, moderate signs of disease	X (X.X)	X (X.X)	
7 - Out of hospital, basically healthy	X (X.X)	X (X.X)	
Change in FBIS from D1-30			
Deteriorated	X (X.X)	X (X.X)	
Unchanged	X (X.X)	X (X.X)	
Improved	X (X.X)	X (X.X)	X.X (X.X to X.X)
	Median (Q1, Q3)	Median (Q1, Q3)	sHR*
Day of first discharge alive	X (X, X)	X (X, X)	X.XX (X.XX to X.XX)

N = number of patients. FBIS = Functional Bloodstream Infection Score. *sHR = subhazard ratio for the “hazard” of alive discharge from hospital (treating death is a competing risk, and excluding discharges where the patient died in the following 3 days).

Table: Secondary efficacy outcomes for the CR subset.

	Cefiderocol (N=X)	SOC (N=X)	Cef. - SOC
	n (%)	n (%)	RD (95% CI), %
Clinical or microbiologic failure, Day 14, including: - Death - Other clinical failure D14 - Microbiological failure D3-14	X (X) X (X) X (X) X (X)	X (X) X (X) X (X) X (X)	X (X to X)
Microbiological failure D3-90	X (X)	X (X)	X (X to X)
FBIS, D30			
0 - Dead	X (X)	X (X)	
1 - Palliative care	X (X)	X (X)	
2 – Long-Term ventilator unit	X (X)	X (X)	
3 – Hospitalized; ICU	X (X)	X (X)	
4 – Hospitalized; not ICU	X (X)	X (X)	
5 - Out of hospital, significant disability	X (X)	X (X)	
6 - Out of hospital, moderate signs of disease	X (X)	X (X)	
7 - Out of hospital, basically healthy	X (X)	X (X)	
Change in FBIS from D1-30			
Deteriorated	X (X)	X (X)	
Unchanged	X (X)	X (X)	
Improved	X (X)	X (X)	X (X to X)
	Median (Q1, Q3)	Median (Q1, Q3)	sHR
Day of first discharge alive	X (X, X)	X (X, X)	X.X (X.X to X.X)

Table: Detail for MRO outcome, Days 3-90.

	Cefiderocol (N=X)	SOC (N=X)
Blood		
CR GNB (not index)	X (X.X)	X (X.X)
Candida	X (X.X)	X (X.X)
VRE	X (X.X)	X (X.X)
MRSA	X (X.X)	X (X.X)
Other cultures		
CR GNB (not index)	X (X.X)	X (X.X)
VRE	X (X.X)	X (X.X)
MRSA	X (X.X)	X (X.X)

Values are number of patients (percent). Note. Candida from other (non-blood) cultures not considered an MRO. CR definition the same as that for the CR subset.

Table: Descriptive list of treatment emergent SAEs (Day 1 to the last dose plus 5 days).
To include: Patient ID, Cef./SOC, in CR subset or not, Day, possibly/probably/definitely related to "study drug", SAE

6. Subgroup analyses

An analysis of the primary outcome for the following subgroups of the main analysis population:

1. Urinary tract infection (UTI) vs non-UTI as source of bloodstream infection
2. *Acinetobacter* spp*. vs*. non- *Acinetobacter* spp*.* as species identified from index blood culture [includes if present as component of polymicrobial infection]
3. Charlson co-morbidity score ≥4 vs <4 at baseline

Table: Subgroup analyses of Day 14 mortality (primary outcome).

	Cefiderocol n/N (%)	SOC n/N (%)	RD (95% CI), % Cef. – SOC	RR (95% CI) Cef./SOC
Urinary tract infection				*Interaction p = 0.XX*
Yes	X/X (X.X)	X/X (X.X)	X.X (X.X to X.X)	X.XX (X.XX to X.XX)
No	X/X (X.X)	X/X (X.X)	X.X (X.X to X.X)	X.XX (X.XX to X.XX)
Acinetobacter spp.				*Interaction p = 0.XX*
Yes	X/X (X.X)	X/X (X.X)	X.X (X.X to X.X)	X.XX (X.XX to X.XX)
No	X/X (X.X)	X/X (X.X)	X.X (X.X to X.X)	X.XX (X.XX to X.XX)
Charlson				*Interaction p = 0.XX*
≥4	X/X (X.X)	X/X (X.X)	X.X (X.X to X.X)	X.XX (X.XX to X.XX)
<4	X/X (X.X)	X/X (X.X)	X.X (X.X to X.X)	X.XX (X.XX to X.XX)

Interaction p-value from logistic regression model (with arm, subgroup, and the arm × subgroup interaction as the only fixed effects).

These subgroup analyses are based on prior literature, where we hypothesise that:

–> Cefiderocol superior if UTI (might get lower RR in UTI subgroup compared with non-UTI subgroup) [APEKS-UTI trial]

–> Cefiderocol inferior if *Acinetobacter spp.* (might get higher RR in *Acinetobacter spp.* subgroup compared with non- *Acinetobacter spp.* subgroup) [CREDIBLE-CR Trial]

–> Cefiderocol inferior if Charlson ≥4 (might get higher RR in Charlson ≥4 subgroup compared with non- Charlson <4 subgroup)

7. General analysis

Using Stata version 18, effect sizes with two-sided 95% confidence intervals (CIs) will be derived for:

- Binary outcomes: 2×2 tables generated and outcomes compared using the `cs` command
- Cumulative incidence function of alive discharge: analysed using `stcrreg` (competing-risk regression with death considered a competing risk)

These 95% CIs will not be adjusted for multiplicity.

8. Additional Figures and Tables

The following figures and tables will be produced.

8.1 Figures

Figure: Screening, Randomization and Analysis of Study Participants (CONSORT Flow Diagram)

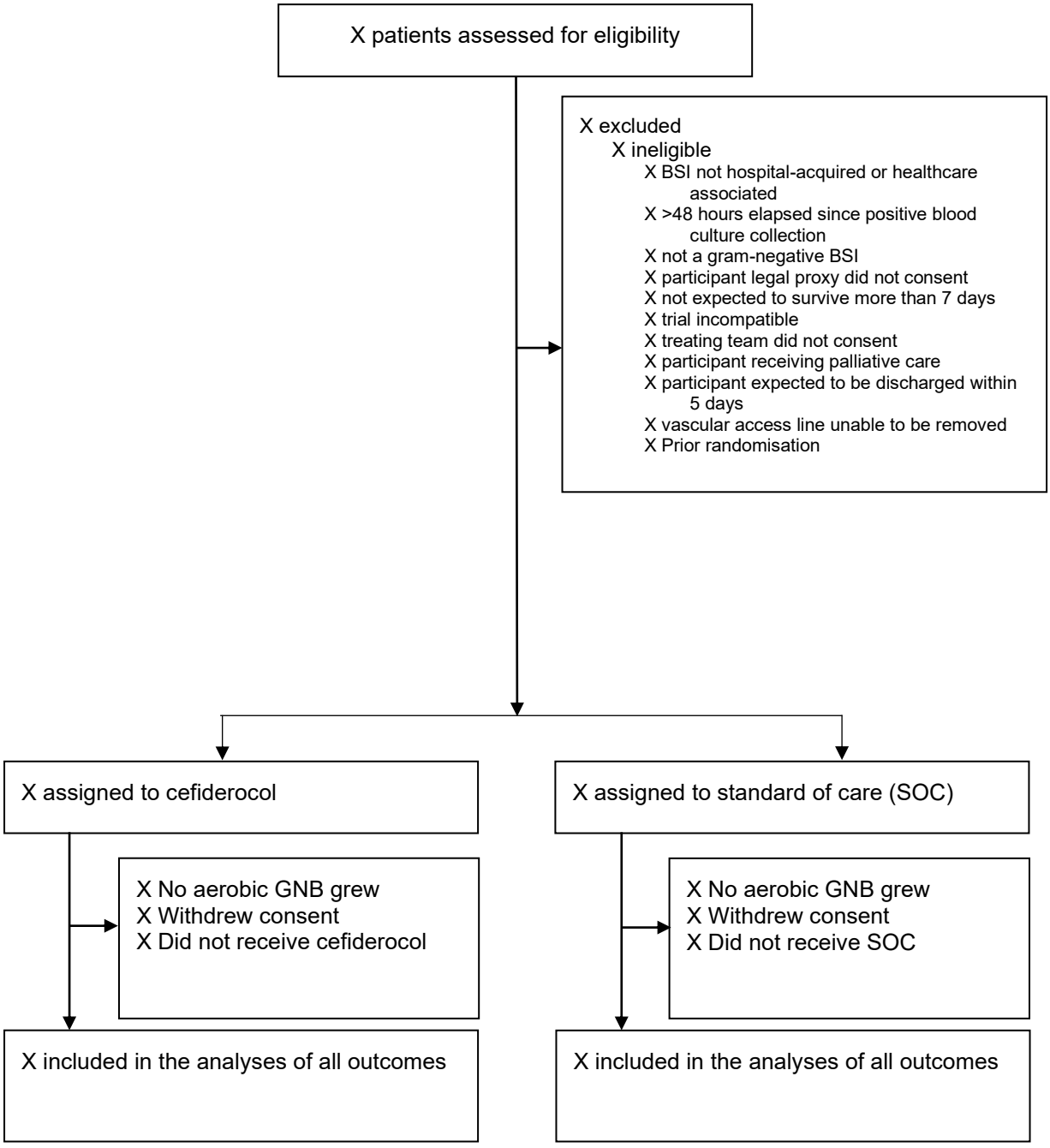


Figure: Kaplan-Meier plot of survival from D1 to D90.

Repeated for CR subset.

Figure: Kaplan-Meier-like plot showing cumulative incidence of patients surviving to hospital discharge, D1 to D90.

Repeated for CR subset.

8.2 Additional Tables

Table: Baseline characteristics of the main analysis population

Characteristic	**Cefiderocol** (N = X)	**Standard of Care** (N = X)
Age, mean (SD), y	X (X)	X (X)
Female sex, No. (%)	X (X)	X (X)
Body Mass Index, median (IQR)	X (X-X)	X (X-X)
Country, No. (%)		
Australia	X (X)	X (X)
Malaysia	X (X)	X (X)
Singapore	X (X)	X (X)
Taiwan	X (X)	X (X)
Thailand	X (X)	X (X)
Turkey	X (X)	X (X)
Functional Bloodstream Infection Score, No. (%)		
2: Long-term ventilator unit	X (X)	X (X)
3: Hospitalized; ICU	X (X)	X (X)
4: Hospitalized; non-ICU	X (X)	X (X)
5: Out of hospital, significant disability	X (X)	X (X)
6: Out of hospital, moderate signs of disease	X (X)	X (X)
7: Out of hospital, basically healthy	X (X)	X (X)
Charlson Comorbidity Score, median (IQR)	X (X-X)	X (X-X)
Comorbidity, No. (%)		
Congestive heart failure	X (X)	X (X)
Chronic pulmonary disease	X (X)	X (X)
Diabetes mellitus	X (X)	X (X)
Moderate or severe renal disease	X (X)	X (X)
Moderate or severe liver disease	X (X)	X (X)
Solid tumor	X (X)	X (X)
Hematologic malignancy	X (X)	X (X)
AIDS	X (X)	X (X)
Immunosuppressed, No. (%)	X (X)	X (X)
Neutropenia, No. (%)	X (X)	X (X)
Acquisition site, No. (%)		
Healthcare-associated	X (X)	X (X)
Hospital-acquired	X (X)	X (X)

For hospital-acquired BSI, days from hospital admission to date of index blood culture collection, median (IQR)	X (X-X)	X (X-X)
Surgery within 14 days of index blood culture, No. (%)	X (X)	X (X)
ICU at randomisation (%)	X (X)	X (X)
On mechanical ventilation at randomisation, No. (%)	X (X)	X (X)
On inotropic support at randomisation, No. (%)	X (X)	X (X)
Baseline SOFA score, median (IQR)	X (X-X)	X (X-X)
Presumed source of bacteremia, No. (%)		
Urinary tract infection	X (X)	X (X)
Intra-abdominal infection	X (X)	X (X)
Line-related infection	X (X)	X (X)
Pneumonia	X (X)	X (X)
Skin and soft tissue infection	X (X)	X (X)
Other	X (X)	X (X)
Unknown	X (X)	X (X)
Monomicrobial bacteremia, No (%)	X (X)	X (X)
Organisms in index blood culture, No (% patients)		
Escherichia coli	X (X)	X (X)
Klebsiella pneumoniae	X (X)	X (X)
Enterobacter spp.	X (X)	X (X)
Miscellaneous Enterobacterales	X (X)	X (X)
Pseudomonas aeruginosa	X (X)	X (X)
Acinetobacter spp.	X (X)	X (X)
Stenotrophomonas maltophilia	X (X)	X (X)
Miscellaneous non-fermenter	X (X)	X (X)
Other	X (X)	X (X)
Antimicrobial resistance category, No. (% patients)		
3GC non-susceptible Enterobacterales Carbapenem non-susceptible Enterobacterales Cefiderocol non-susceptible Enterobacterales Carb non-susceptible *Acinetobacter* spp. Cefiderocol non-susceptible *Acinetobacter* spp. Carb non-susceptible *Pseudomonas* spp. Cefiderocol non-susceptible *Pseudomonas* spp. Carbapenem non-susceptible organism	X (X) X (X) X (X) X (X) X (X) X (X) X (X) X (X)	X (X) X (X) X (X) X (X) X (X) X (X) X (X) X (X)

Abbreviations: SD, standard deviation; IQR, interquartile-range; ICU, intensive care unit; AIDS, acquired immunodeficiency syndrome; BSI, bloodstream infection; MDR, multidrug-resistant; XDR, extensively drug-resistant; 3GC, third generation cephalosporin.

Repeat above table just for CR subset with different section describing resistance types:

1. KPC or OXA-48-like producing Enterobacterales
2. MBL producing Enterobacterales
3. CR-*Acinetobacter* spp.
4. CR-*Pseudomonas* spp
5. *Stenotrophomonas maltophilia*
6. *Aeromonas* spp.
7. Miscellaneous non-fermenters

Table: Denominators and number missing for each characteristic.

Repeat above table just for CR subset.

Table: Summary of change in antibiotic therapy due to lack of susceptibility in vitro, clinical failure, or adverse event related to initial treatment regimen

	Cefiderocol (N=X)	SOC (N=X)
Requirement to change therapy days 1-5	X (X.X)	X (X.X)
In vitro resistance to randomised therapy	X (X.X)	X (X.X)
Change due to perceived clinical failure	X (X.X)	X (X.X)
Change due to adverse drug event	X (X.X)	X (X.X)

Repeat above table just for CR subset.

Table: Summary (by group) of antibiotics

	Cefiderocol (N=X)	SOC (N=X)
Empirical regimen		
Expanded spectrum cephalosporin ^	X (X)	X (X)
Carbapenem	X (X)	X (X)
Piperacillin-tazobactam	X (X)	X (X)
Ceftazidime-avibactam	X (X)	X (X)
Fluoroquinolone	X (X)	X (X)
Combination therapy	X (X)	X (X)
No antibiotics	X (X)	X (X)
Others*	X (X)	X (X)
Appropriateness of empirical regimen		
Empirical treatment appropriate #	X (X)	X (X)
Antimicrobial therapy from the time of randomisation		
Cefiderocol monotherapy	X (X)	X (X)
Cefiderocol + 2nd agent (<3 days)	X (X)	X (X)
Cefiderocol + 2nd agent (≥ 3 days)		
Expanded spectrum cephalosporin^	X (X)	X (X)
Carbapenem	X (X)	X (X)
Piperacillin-tazobactam	X (X)	X (X)
Ceftazidime-avibactam	X (X)	X (X)
Fluoroquinolone	X (X)	X (X)
Combination therapy (two or more antimicrobials administered for ≥ 3 days)	X (X)	X (X)
Others*	X (X)	X (X)
Time from index BC to randomisation (h), Median (IQR)	X (X, X)	X (X, X)
0-12h 12-24h 24-36h 36-48h	X (X) X (X) X (X) X (X)	X (X) X (X) X (X) X (X)

48-60h >60h	X (X) X (X)	X (X) X (X)
Total duration of randomised treatment (days)†, Median (IQR)	X (X, X)	X (X, X)

* list :
# in vitro susceptibility to at least one agent commenced within 24h of initial blood culture collection
^ ceftriaxone/ceftazidime/cefepime/cefoperazone
† Note duration of treatment measurement truncated at 14 days

Repeat above table just for CR subset.

Table: Antimicrobial treatment in the CR subset in the first 5 days post randomisation

Antimicrobial treatment of CR-GNB infections in the first 5 days		Cef. (N=X)	SOC (N=X)
a)	In vitro effective empirical to cefiderocol	X (X)	X (X)
b)	In vitro effective empirical to polymyxin in combination	X (X)	X (X)
c)	In vitro effective empirical to others	X (X)	X (X)
d)	Ineffective empirical to cefiderocol	X (X)	X (X)
e)	Ineffective empirical to ceftazidime-avibactam monotherapy	X (X)	X (X)
f)	Ineffective empirical to ceftazidime-avibactam in combination	X (X)	X (X)
g)	Ineffective empirical to polymyxin in combination	X (X)	X (X)
h)	Ineffective empirical to polymyxin monotherapy	X (X)	X (X)
i)	Ineffective empirical to others	X (X)	X (X)
j)	No empirical therapy to cefiderocol	X (X)	X (X)
k)	No empirical therapy to ceftazidime-avibactam monotherapy	X (X)	X (X)
l)	No empirical therapy to polymyxin in combination	X (X)	X (X)
m)	No empirical therapy to others	X (X)	X (X)

8.3 Other information

8.3.1 Additional or "Rescue" therapy will be described. This includes:

- the use of cefiderocol in the SOC arm
- the addition of other agents with activity against Gram-negative pathogens (defined by the same antibiotic given for ≥3 calendar days) in the cefiderocol arm

8.3.2 Cefiderocol resistance. A descriptive analysis will be provided for:

- Outcomes of patients in the cefiderocol arm whose index blood culture isolate tested resistant/intermediate to cefiderocol
- Outcomes of patients in the cefiderocol arm whose follow up blood cultures showed resistance to cefiderocol

8.3.3 Patients that withdrew consent: The reason for withdrawal of consent will be documented, if details are known. Any microbiologic failure or SAEs in patients who withdrew consent will be noted.

9. Protocol violations

All protocol violations occurring post randomisation will be listed and tabulated by Study Subject ID and study centre.

10. Treatment emergent SAEs

All treatment emergent SAEs will be listed by Study Subject ID and study arm.

11. Data Export and Archive

The study database has been developed using the electronic data capture platform REDCap®, which is under the licensed and maintenance by The University of Queensland. All centralised monitoring and quality control of the database is performed by the Study Management Team following standard operating procedures. All analyses performed, the Clinical Study Report(s) and the final data set will be archived together according to standard operating procedures and the guidelines of The University of Queensland.

12. Data Validation

Data received is continuously centrally monitored by the Study Management Team including examining for missing values and outliers. Query generation and resolutions are all performed via central monitoring, along with remote source data verification measures being routinely performed as outlined within the study's monitoring plan. Extreme or unexpected values will be examined individually for authenticity and data discrepancies addressed where appropriate. Additional audit and statistical checks are performed as necessary.