COVER Page

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

BLING III Study

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

BLING III SAP Manuscript

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Title

Statistical analysis plan for the BLING III study: a phase 3 multicentre randomised controlled trial of continuous versus intermittent β-lactam antibiotic infusion in critically ill patients with sepsis

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Abstract

Background: The β-lactam Infusion Group (BLING) III study is a prospective, multicentre, open, phase 3 randomised controlled trial comparing continuous infusion with intermittent infusion of β-lactam antibiotics in 7000 critically ill patients with sepsis.

Objective: To describe a statistical analysis plan for the BLING III study.

Methods: The statistical analysis plan was designed by the trial statistician and chief investigators and approved by the BLING III management committee before the completion of data collection. Statistical analyses for primary, secondary and tertiary outcomes and planned subgroup analyses are described in detail. Interim analysis by the Data Safety and Monitoring Committee (DSMC) has been conducted in accordance with a pre-specified DSMC charter.

Results and conclusions: The statistical analysis plan for the BLING III study is published before completion of data collection and unblinding to minimise analysis bias and facilitate public access and transparent analysis and reporting of study findings.

Trial Registration: ClinicalTrials.gov Registry NCT03213990.

The aim of the β-lactam Infusion Group (BLING) III study is to determine whether continuous infusion of a β-lactam antibiotic (piperacillin-tazobactam or meropenem) results in decreased all-cause Day 90 mortality compared with intermittent β-lactam antibiotic infusion in 7000 critically ill patients with sepsis. The study protocol has been previously published.[1] This paper describes the pre-specified statistical analysis plan finalised by the trial statistician (LB) and chief investigators and approved by the BLING III management committee before the completion of patient enrolment and database lock.

Study design

The BLING III study is a prospective, multicentre, open label, phase 3, randomised controlled trial that is being conducted in 95 intensive care units (ICUs) in Australia, Belgium, France, Malaysia, New Zealand, the United Kingdom and Sweden. Eligible patients who are treated with either piperacillin-tazobactam or meropenem for a documented infection or strong suspicion of infection are randomly assigned to receive the β-lactam antibiotic by either intermittent or continuous infusion in the ICU up to a maximum of 14 days. Dose and selection of the β-lactam antibiotic is at clinician discretion and independent of group allocation. Day 1 is defined as the date of randomisation. Primary, secondary and tertiary outcomes are described in Table 1.

Participants

Patients in the ICU being treated with either piperacillin-tazobactam or meropenem for a documented infection or strong suspicion of infection, who are expected to stay in the ICU beyond the following calendar day and who meet one or more organ dysfunction criteria will be eligible for enrolment. Inclusion and exclusion criteria are summarised in Table 2.

Participants are randomised using a minimisation algorithm with stratification by site via a password-protected, secure web-based interface.

Sample size

A sample size of 6558 (3279 per group) is required to provide 90% power to detect an absolute risk reduction of 3.5% in 90-day mortality in the continuous infusion group from baseline mortality of 27.5% with an alpha of 0.05.[1,2] After adjusting for up to 5% of patients lost to follow-up (345) and rounding up, the target sample size is 7000 (3500 per group).

Interim analysis

One interim analysis occurred when 3500 patients (50% of planned recruitment) had completed 90-day follow-up. An independent Data Safety Monitoring Committee (DSMC) is responsible for the safety assessment of the trial during its conduct, including the interim analysis. The DSMC charter is available in Appendix 1.

Multiplicity adjustments

All tests are to be two-sided with a nominal level of α set at 5%. Analyses of the primary outcome (all-cause mortality at 90 days) will be unadjusted for multiplicity; however, the family-wise error rate will be controlled across secondary outcomes (one family) and tertiary outcomes (one family) using a Holm-Bonferroni correction.[3] No other multiplicity adjustment will be applied.

Data sets analysed

Analyses will be conducted on an Intention to Treat (ITT) analysis data set. The ITT data set will include all randomised study participants regardless of their compliance with the rules of

the study and excluding data for which consent is either not obtained, data are not approved for use by the relevant human research ethics committee or institutional review board, or where consent is withdrawn. The ITT data set will be used for the analyses of all primary, secondary and tertiary outcomes. All safety-related analyses will be based on a per protocol analysis of participants who received one or more doses of the β-lactam antibiotic in the assigned treatment group. Participants who did not receive at least one dose of assigned treatment will be excluded from the safety analysis.

The flow of patients through the trial will be displayed in a CONSORT (CONsolidated Standards of Reporting Trials) diagram (Figure 1).[4] The report will include the number of screened patients who met study inclusion criteria, the number of patients who were included and reasons for exclusion of non-included patients.

Data validation

The study database is maintained at The George Institute for Global Health. All data queries and corrections will be conducted by The George Institute for Global Health in a blinded manner and before database lock. Data received by The George Institute for Global Health statistician will be examined for missing values and outliers. Measures of central tendency and dispersion for continuous study parameters will be portrayed along with box and whisker plots. Extreme or unexpected values will be examined individually for authenticity and data discrepancies addressed where appropriate. Additional audit and statistical checks will be performed as necessary.

Patient characteristics and baseline comparisons

Description of the baseline characteristics will be presented by treatment group. Discrete variables will be summarised by frequencies and percentages. Percentages will be calculated according to the number of patients for whom data are available. Continuous variables will be summarised using mean and standard deviation (SD), and median and interquartile range (IQR). Baseline measures for all patients will be presented as shown in Tables 3-6.

Treatments and protocol deviations

For each day between Day 1 and Day 16, noting randomised treatment continues to a maximum of 14 days, we will report the number and proportion of patients receiving β-lactam antibiotics, as well as the dose administered summarised as the mean, SD and median (IQR) (Table 7). This will be done by treatment group and separately for piperacillin-tazobactam and meropenem. Assigned treatment will be summarised using the following variables: (1) time on β-lactam antibiotic treatment defined as the number of days between the first and last day of piperacillin-tazobactam and/or meropenem administration (up to Day 16), and (2) cumulative dose of β-lactam antibiotic (piperacillin-tazobactam and/or meropenem) received (mg) up to Day 16. Time on study treatment and cumulative dose will be summarised using mean, SD and median (IQR) with differences between treatment groups tested using a linear model with a random site effect. Other administered antibiotics (regardless of route) will be reported as the number and percentage of patients receiving at least one dose in the 24 hours prior to randomisation up to Day 16. Protocol deviations will be summarised as the number of deviations by type. All protocol deviations will be listed together with a description of the deviation.

Analysis of the primary efficacy endpoint

The primary aim of this study is to compare the effect of continuous versus intermittent infusion of piperacillin-tazobactam or meropenem on all-cause mortality up to Day 90.

Main analysis

The primary endpoint is the proportion of patients who have died up to and including Day 90 after randomisation. To account for stratification by site and to maximise power,[5] the main analysis will be performed using logistic regression with treatment allocation as a fixed effect and site as a random effect.[6] The effect of the intervention will be presented as the odds ratio (OR) of death and its 95% confidence interval (CI). Crude proportions by treatment arm will also be reported with an unadjusted OR and 95% CI and a chi-square test *P* value (Table 8). For ease of interpretation, risk difference and 95% CI will also be presented. The adjusted OR and 95% CI will be converted to an adjusted risk difference and 95% CI using the Hummel and Wiseman method described by Reeve.[7]

Adjusted analyses

Adjusted analyses will be performed by adding the following covariates to the main logistic regression model: sex, Acute Physiology and Chronic Health Evaluation (APACHE) II score at randomisation (as a continuous variable), source of admission (admitted from the operating theatre following emergency or elective surgery vs. other) and type of β-lactam antibiotic administered (piperacillin-tazobactam or meropenem). The adjusted treatment effect will be reported as the adjusted OR and 95% CI. If more than 3% of observations are lost after adding covariates, multiple imputations will be used as described in the "*Treatment of missing data*" section.

Subgroup analyses

Five pre-specified subgroup analyses will be carried out irrespective of whether there is a significant treatment effect on the primary outcome. Subgroups are defined as follows: (1) presence vs. absence of pulmonary infection at baseline, (2) type of β-lactam antibiotic administered (piperacillin-tazobactam or meropenem), (3) age (< 65 years vs. ≥ 65 years), (4) sex (male vs. female) and (5) low vs. high severity of illness (defined by APACHE II score < 25 or ≥ 25). Patients with pulmonary infection are hypothesised to have a greater primary outcome benefit associated with continuous infusion (compared to intermittent infusion) than patients without pulmonary infection.[8]

The analysis for each subgroup will be performed by adding the subgroup variable, as well as its interaction with the intervention as a fixed effect to the main logistic regression model. Within each subgroup, summary measures will include raw counts and percentages within each treatment arm, as well as the OR for treatment effect with a 95% CI. The results will be displayed on a forest plot including the *P* value for heterogeneity corresponding to the interaction term between the intervention and the subgroup variable.

Treatment of missing data

If more than 3.5% of patients from the ITT population are excluded from the analysis of all-cause mortality at Day 90 due to missing data, a sensitivity analysis will be performed using "worst-best" and "best-worst" case scenarios. In the "worst-best" scenario, the "worst" outcome (i.e. dead at Day 90) will be assigned to all patients missing the outcome in one treatment group, and the "best" outcome (i.e. alive at Day 90) will be assigned to all patients missing the outcome in the other treatment group. The "best-worst" scenario corresponds to the reverse assignment of outcomes. If these two extreme scenarios lead to the same conclusions, no further imputation of missing data will be performed. In case of inconsistent

conclusions (i.e. where one scenario leads to a statistically significant difference and not the other or where the two are significant, but in different directions), we will further explore the impact of missing data by performing multiple imputations using fully conditional specification.[9] The imputation model will include all-cause mortality at Day 90, the randomised treatment arm, study site and all baseline covariates (Table 3). Binary variables (e.g. all-cause mortality at Day 90) will be imputed using an ordinal logistic regression model, categorical variables using a discriminant function method and continuous variables using linear regression. One hundred sets of imputed data will be created and analysed using the methods described in the main analysis and adjusted analyses sections. OR estimates from the 100 imputed analyses will be combined to obtain a pooled OR and 95% CI. The same 100 imputed datasets will be used for all analyses described in the "*Main analysis*" and "*Adjusted analyses*" sections.

Survival analysis

We will perform a survival analysis of time to death. The analysis will be censored at Day 90 or at the time when the patient was last known to be alive, whichever occurs earlier. A Kaplan-Meier plot will be used to describe survival rates and derive median and IQR of time to death. Differences in survival will be tested using a Cox model with a random site effect using a shared-parameter frailty model.[10]

Secondary efficacy outcomes

Secondary efficacy endpoints are all binary (yes/no) variables and include: (1) clinical cure at Day 14 post-randomisation, (2) new acquisition, colonisation or infection with a multi-resistant organism or *Clostridium difficile* diarrhoea up to 14 days post-randomisation, (3) all-cause ICU mortality, and (4) all-cause hospital mortality. All four outcomes will be analysed

using the same approach as the analysis of 90-day mortality using a random-effects logistic regression model, however, no adjusted or subgroup analyses will be applied.

Tertiary efficacy outcomes

Tertiary efficacy outcomes include: (1) ICU length of stay, (2) hospital length of stay, (3) duration of mechanical ventilation in ICU up to 90 days after randomisation, and (4) duration of renal replacement therapy in ICU up to 90 days after randomisation. ICU length of stay and hospital length of stay will be censored at Day 90.

Analysis of duration

All four outcomes will be analysed as the number of days alive and free of the outcome (e.g. days alive and free of mechanical ventilation or days alive and outside of ICU). Days requiring mechanical ventilation and renal replacement therapy are recorded for the period of ICU admission from randomisation up to Day 90, including readmissions to the ICU during this period. Days alive and free of outcome will be calculated between randomisation and Day 90 with values ranging from 0-90 days. They will be summarised using means, SD, median, IQR, minimum and maximum and compared between treatment groups using linear regression with a fixed effect of the treatment group and a random effect of site. In addition, duration of ICU stay, hospital stay, mechanical ventilation and renal replacement therapy will be reported for all participants and separately for survivors and non-survivors; however, no formal tests will be applied.

Analysis of time to discharge

Time to discharge alive from index ICU admission and time to discharge alive from index hospital admission will be summarised using cumulative incidence functions treating

mortality as a competing risk. Medians and IQRs of time to discharge will be obtained from the cumulative incidence functions. The effect of the intervention will be estimated as the hazard ratio and its 95% CI obtained from a Cox model of the cause-specific hazard, which estimates the risk of discharge in subjects who are still alive and have not yet been discharged.[11] To model potential within-site correlations due to stratification, we will use a shared-parameter frailty Cox model with a fixed effect of treatment and a random site effect.[10] The proportional hazard assumption will be assessed by visually inspecting a plot of log(-log(survival)) versus log(time).

Safety outcomes

Adverse events, serious adverse events and suspected unexpected serious adverse reactions will be summarised as the number and proportion of patients experiencing at least one event using a per protocol analysis. The total number of events will be reported and tabulated by category of event. Proportions of patients with adverse events will be compared between treatment arms using Fisher's exact test, both overall and by body system (Table 9). A listing of all adverse drug reactions will be reported. Causes (proximate and underlying) and places of death (by Day 90) will be categorised and the distribution compared between the two treatment arms using Fisher's exact test (Table 10).

Proposed figures

The proposed figures are summarised in Table 11.

Future analyses

It is intended that there will be additional exploratory and region-specific health economic analyses that are conducted and reported separately to the main results of the study. These

additional analyses include, but are not limited to, a planned nested cohort health economic analysis, a pharmacokinetic-pharmacodynamic sub-study evaluation and exploratory analyses based on geographic, clinical and mechanistic factors of interest, such as compliance with randomised treatment, type of pathogenic organism, site of infection and country or region.

Current status

The study commenced recruitment in March 2018 and reached the study mid-point (3500th patient recruited) in April 2020. Recruitment was estimated to be completed by June 2021, however, final recruitment projections are dependent on the impact of the SARS-CoV-2 (COVID-19) pandemic with 4500 participants recruited as of November 2020.

COVID-19 pandemic contingency

Due to the significant impact on study recruitment from the COVID-19 pandemic and uncertain future impact on recruitment, revised power and effect size calculations have been performed as a pandemic contingency measure. Assuming 5% of patients lost to follow-up, the detectable difference for stopping the trial at 5000, 5500, 6000, 6500 and 7000 participants at various baseline mortality rates are detailed in Figures 2 and 3 for 80% and 90% power, respectively, with an alpha of 0.05. While the intent is to reach a sample size of 7000, the BLING III management committee will continue to monitor the situation and, if required, make an earlier stopping decision on the basis of estimated achievable recruitment and power considerations.

Conclusion

The BLING III study will provide robust and reliable evidence of whether administration of piperacillin-tazobactam or meropenem by continuous infusion will result in improved

outcomes for critically ill patients with sepsis compared with intermittent infusion. This statistical analysis plan is published prior to completion of data collection to minimise analysis bias and facilitate public access and transparent analysis and reporting of study results.

Acknowledgements

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Competing interests

Laurent Billot, Menino Cotta, Joshua Davis, Simon Finfer, Naomi Hammond, Serena Knowles, Shay McGuinness, John Myburgh, Sandra Peake, Dorrilyn Rajbhandari, Andrew Rhodes, Charudatt Shirwadkar, Therese Starr and Joel Dulhunty declare no competing interests. Jeffrey Lipman has served as a board member for the Bayer ESICM and MSD Antibacterials Advisory Boards and given lectures with honoraria from Pfizer and MSD. Stephen Brett has received a speaker's fee and attended an Advisory Board from Orion Pharma. Jan De Waele has attended Advisory Boards, acted as a consultant to, or given lectures with honoraria from Accelerate, Bayer Healthcare, Grifols, MSD and Pfizer. David

Paterson has received research grants from AstraZeneca and has attended Advisory Boards, acted as a consultant to, or given lectures with honoraria from Three Rivers Pharmaceuticals, Merck, AstraZeneca, SanofiAventis, Pfizer, Johnson & Johnson, Shionogi, Sumitomo and Leo Pharmaceuticals. Jason Roberts has served as a consultant for MSD, Bayer, Astellas, bioMerieux and Accelerate Diagnostics and has received research grants from MSD, The Medicines Company, Pfizer, Astellas and Cardeas Pharma. Claire Roger has received speaker's fees from Pfizer and MSD. Colman Taylor owns a company, Health Technology Analysts, which provides consulting services to pharmaceutical companies, medical device companies and the Australian Government.

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Table 1. Primary, secondary and tertiary study outcomes

Primary outcome
• All-cause mortality within 90 days after randomisation
Secondary outcomes
• Clinical cure at Day 14 post randomisation[1]
• New acquisition, colonisation or infection with an MRO or *Clostridium difficile* diarrhoea up to 14 days post randomisation
• All-cause ICU mortality
• All-cause hospital mortality
Tertiary outcomes
• ICU length of stay
• Hospital length of stay
• Duration of mechanical ventilation in ICU up to 90 days after randomisation
• Duration of renal replacement therapy up to 90 days after randomisation

[1]Clinical cure is defined as the completion of the β-lactam antibiotic treatment course on or before Day 14, without recommencement of antibiotic therapy within 48 hours of cessation for the same infectious episode.

ICU = intensive care unit. MRO = multi-resistant organism.

Table 2. Inclusion and exclusion criteria for the BLING III study

Inclusion criteria:

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

Exclusion criteria:

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

ICU = intensive care unit. MAP = mean arterial pressure.

Table 3. Baseline characteristics

Characteristic	Continuous Infusion (n = XXXX)	Intermittent Infusion (n = XXXX)
Age (years)	Mean ± SD or median (IQR)	Mean ± SD or median (IQR)
Sex, female	n (%)	n (%)
Weight (kg)	Mean ± SD or median (IQR)	Mean ± SD or median (IQR)
Height (cm)	Mean ± SD or median (IQR)	Mean ± SD or median (IQR)
Source of ICU admission		
Accident and Emergency Department	n (%)	n (%)
Hospital floor (i.e. wards)	n (%)	n (%)
Transfer from another ICU	n (%)	n (%)
Transfer from another hospital	n (%)	n (%)
From OT following EMERGENCY surgery	n (%)	n (%)
From OT following ELECTIVE surgery	n (%)	n (%)
Time since ICU admission (hours)	Mean ± SD or median (IQR)	Mean ± SD or median (IQR)
APACHE II score	Mean ± SD or median (IQR)	Mean ± SD or median (IQR)
Lowest PaO_2/FiO_2 ratio in the 24 hours prior to randomisation	Mean ± SD or median (IQR)	Mean ± SD or median (IQR)
Highest creatinine (μmol/L)	Mean ± SD or median (IQR)	Mean ± SD or median (IQR)
Highest bilirubin (μmol/L)	Mean ± SD or median (IQR)	Mean ± SD or median (IQR)
Lowest platelet count ($x10^9$/L)	Mean ± SD or median (IQR)	Mean ± SD or median (IQR)
Lowest MAP in 24 hours prior to randomisation (mmHg)	Mean ± SD or median (IQR)	Mean ± SD or median (IQR)
Worst Glasgow Coma Score (non-sedated)	Mean ± SD or median (IQR)	Mean ± SD or median (IQR)

Receiving inotropes/vasopressors in the 24 hours prior to randomisation	n (%)	n (%)
Receiving antibiotics in the 24 hours prior to randomisation[1]	n (%)	n (%)

[1]Other than piperacillin-tazobactam or meropenem.

APACHE = Acute Physiology and Chronic Health Evaluation. ICU = intensive care unit. IQR = interquartile range. MAP = mean arterial pressure. OT = operating theatre. SD = standard deviation.

Table 4. Acute Physiology and Chronic Health Evaluation (APACHE) III diagnosis

Diagnosis	Continuous Infusion (n = XXXX)	Intermittent Infusion (n = XXXX)
Non-operative diagnoses	n (%)	n (%)
Cardiovascular	n (%)	n (%)
Respiratory	n (%)	n (%)
Gastrointestinal	n (%)	n (%)
Neurological	n (%)	n (%)
Sepsis	n (%)	n (%)
Trauma	n (%)	n (%)
Metabolic	n (%)	n (%)
Haematological	n (%)	n (%)
Renal/genitourinary	n (%)	n (%)
Musculoskeletal/skin	n (%)	n (%)
Other	n (%)	n (%)
Operative diagnoses	n (%)	n (%)
Cardiovascular	n (%)	n (%)
Respiratory	n (%)	n (%)
Gastrointestinal	n (%)	n (%)
Neurological	n (%)	n (%)
Trauma	n (%)	n (%)
Metabolic	n (%)	n (%)
Haematological	n (%)	n (%)
Renal/genitourinary	n (%)	n (%)
Gynaecological	n (%)	n (%)
Musculoskeletal/skin	n (%)	n (%)

Table 5. Primary site of infection

Primary site of infection	Continuous Infusion (n = XXXX)	Intermittent Infusion (n = XXXX)
Pulmonary	n (%)	n (%)
Intra-abdominal	n (%)	n (%)
Blood	n (%)	n (%)
Skin	n (%)	n (%)
Urinary	n (%)	n (%)
Intravenous catheter	n (%)	n (%)
Central nervous system	n (%)	n (%)
Gut	n (%)	n (%)
Endocarditis	n (%)	n (%)
Other	n (%)	n (%)

Table 6. Infective organisms identified

Organism	Continuous Infusion (n = XXXX)	Intermittent Infusion (n = XXXX)
Gram positive bacteria	n (%)	n (%)
Methicillin-Sensitive Staphylococcus aureus	n (%)	n (%)
Methicillin Resistant Staphylococcus aureus	n (%)	n (%)
Streptococcus pneumoniae (or Pneumococcus)	n (%)	n (%)
Beta-haemolytic Streptococci (Group A, B or C)	n (%)	n (%)
Viridans Group Streptococci	n (%)	n (%)
Enterococcus	n (%)	n (%)
Coagulase negative staphylococci	n (%)	n (%)
Nocardia species	n (%)	n (%)
Gram negative bacteria	n (%)	n (%)
Pseudomonas species	n (%)	n (%)
Burkholderia species	n (%)	n (%)
Haemophilus species	n (%)	n (%)
Acinetobacter species	n (%)	n (%)
Klebsiella species	n (%)	n (%)
Enterobacter species	n (%)	n (%)
Escherichia species	n (%)	n (%)
Serratia species	n (%)	n (%)
Bacteroides species	n (%)	n (%)
Neisseria meningitidis (or Meningococcus)	n (%)	n (%)
Neisseria gonorrhoease (or Gonococcus)	n (%)	n (%)
Campylobacter species	n (%)	n (%)
Citrobacter species	n (%)	n (%)
Proteus species	n (%)	n (%)
Stenotrophamonas species	n (%)	n (%)

Other	n (%)	n (%)
Mycobacterium tuberculosis	n (%)	n (%)
Mixed anaerobes	n (%)	n (%)
Other	n (%)	n (%)

As there may be more than 1 infective organism per participant, percentages may not add up to 100%.

Table 7. β-lactam antibiotic administration details

Administration details	**Continuous Infusion** (n = XXXX)		**Intermittent Infusion** (n = XXXX)		**Significance** (*P* value)
	Antibiotic administered	Dose prepared (grams)[1]	Antibiotic administered	Dose prepared (grams)[1]	
β-lactam antibiotic prior to randomisation					
Piperacillin-tazobactam	n (%)	Mean ± SD Median (IQR)	n (%)	Mean ± SD Median (IQR)	
Meropenem	n (%)	Mean ± SD Median (IQR)	n (%)	Mean ± SD Median (IQR)	
β-lactam antibiotic prescribed for eligibility					
Piperacillin-tazobactam	n (%)	Mean ± SD Median (IQR)	n (%)	Mean ± SD Median (IQR)	
Meropenem	n (%)	Mean ± SD Median (IQR)	n (%)	Mean ± SD Median (IQR)	
Cumulative dose of antibiotics received (grams)[2]					
Piperacillin-tazobactam		Mean ± SD Median (IQR)		Mean ± SD Median (IQR)	0.XXX
Meropenem		Mean ± SD Median (IQR)		Mean ± SD Median (IQR)	0.XXX

Time on study	Mean ± SD	Mean ± SD	0.XXX
treatment (days)[3]	Median (IQR)	Median (IQR)	
Piperacillin-	Mean ± SD	Mean ± SD	
tazobactam	Median (IQR)	Median (IQR)	
Meropenem	Mean ± SD	Mean ± SD	
	Median (IQR)	Median (IQR)	

[1]For β-lactam antibiotics prior to randomisation, all doses administered are reported. For the "eligibility prescription", the dose prescription at the time of randomisation is reported. For the antibiotic surveillance period (Days 1-16), the 24-hour dose administered in both treatment groups is reported by antibiotic.

[2]Cumulative dose of β-lactam antibiotic (piperacillin-tazobactam and/or meropenem) received (mg) up to Day 16.

[3]Time on study treatment defined as the number of days between the first and last day of piperacillin-tazobactam and/or meropenem administration (up to Day 16).

IQR = interquartile range. SD = standard deviation.

Table 8. Reporting of primary, secondary and tertiary outcomes

Outcome	Raw estimates		Model estimates	
	Continuous Infusion (n = XXXX)	**Intermittent Infusion** (n = XXXX)	**OR or mean difference (95% CI)**	**Significance** (*P* value)
Primary outcome:				
All-cause mortality at Day 90	n (%)	n (%)	XX.X (XX.X to XX.X)	0.XXX
Secondary outcomes:				
Clinical cure at Day 14	n (%)	n (%)	XX.X (XX.X to XX.X)	0.XXX
New acquisition, colonisation or infection with an MRO or *Clostridium difficile*	n (%)	n (%)	XX.X (XX.X to XX.X)	0.XXX
All-cause ICU mortality	n (%)	n (%)	XX.X (XX.X to XX.X)	0.XXX
All-cause hospital mortality	n (%)	n (%)	XX.X (XX.X to XX.X)	0.XXX
Tertiary outcomes:				
ICU length of stay	Mean ± SD Median (IQR)	Mean ± SD Median (IQR)	XX.X (XX.X to XX.X)	0.XXX
Hospital length of stay	Mean ± SD Median (IQR)	Mean ± SD Median (IQR)	XX.X (XX.X to XX.X)	0.XXX
Duration of MV in ICU up to Day 90	Mean ± SD Median (IQR)	Mean ± SD Median (IQR)	XX.X (XX.X to XX.X)	0.XXX

Duration of RRT in ICU up to Day 90	Mean ± SD Median (IQR)	Mean ± SD Median (IQR)	XX.X (XX.X to XX.X)	0.XXX

CI = confidence interval. ICU = intensive care unit. IQR = interquartile range. MRO = multi-resistant organism. MV = mechanical ventilation. Q = quartile. RR = relative risk. RRT = renal replacement therapy. SD = standard deviation.

Table 9. Summary of adverse events and protocol deviations

	Continuous Infusion (n = XXXX)	**Intermittent Infusion** (n = XXXX)	**Significance** (*P* value)
Any adverse event	n_{EVT} n_{PT} (%)	n_{EVT} n_{PT} (%)	0.XXX
Any serious adverse event	n_{EVT} n_{PT} (%)	n_{EVT} n_{PT} (%)	0.XXX
Resulted in death	n_{EVT} n_{PT} (%)	n_{EVT} n_{PT} (%)	
Life-threatening	n_{EVT} n_{PT} (%)	n_{EVT} n_{PT} (%)	
Required new or prolonged hospitalisation	n_{EVT} n_{PT} (%)	n_{EVT} n_{PT} (%)	
Resulted in persistent or significant disability	n_{EVT} n_{PT} (%)	n_{EVT} n_{PT} (%)	
Was a congenital anomaly or birth defect	n_{EVT} n_{PT} (%)	n_{EVT} n_{PT} (%)	
Any SUSAR	n_{EVT} n_{PT} (%)	n_{EVT} n_{PT} (%)	0.XXX
Any protocol deviation	n_{EVT} n_{PT} (%)	n_{EVT} n_{PT} (%)	0.XXX
Randomisation of ineligible patient	n_{EVT} n_{PT} (%)	n_{EVT} n_{PT} (%)	
Follow-up assessment not done correctly	n_{EVT} n_{PT} (%)	n_{EVT} n_{PT} (%)	
Other	n_{EVT} n_{PT} (%)	n_{EVT} n_{PT} (%)	

n_{EVT} = total number of events. n_{PT} = number of patients experiencing at least one event. SUSAR = suspected unexpected serious adverse reaction.

Table 10: Cause and place of death

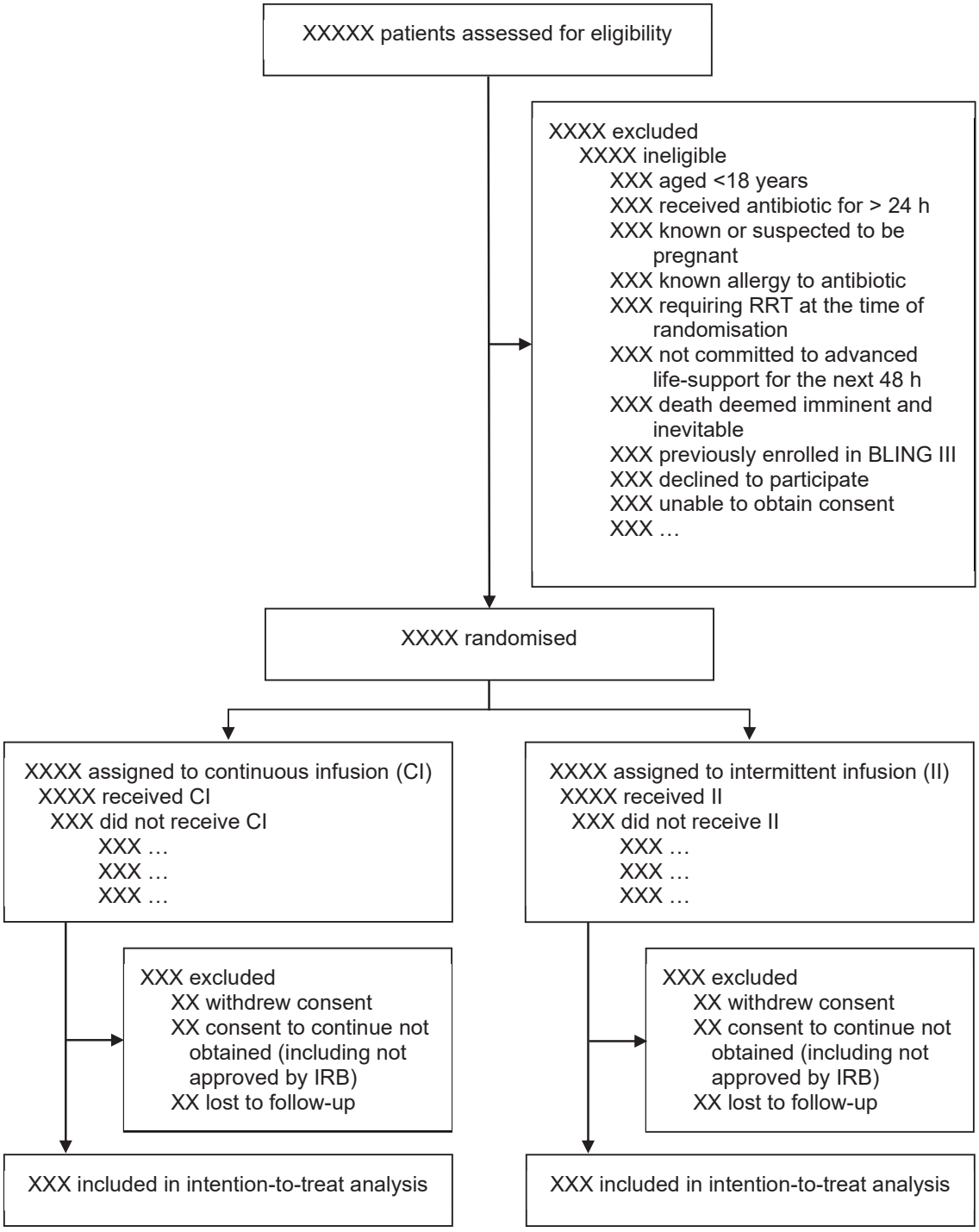
Cause/place of death	Continuous Infusion (n = XXXX)	Intermittent Infusion (n = XXXX)	Significance (*P* value)
Place of death			0.XXX
ICU	n (%)	n (%)	
Ward	n (%)	n (%)	
Home	n (%)	n (%)	
Other	n (%)	n (%)	
Proximate cause of death			0.XXX
Cause 1	n (%)	n (%)	
Cause 2	n (%)	n (%)	
…	n (%)	n (%)	
Cause k	n (%)	n (%)	
Underlying cause of death			
Cause 1	n (%)	n (%)	
Cause 2	n (%)	n (%)	
…	n (%)	n (%)	
Cause k	n (%)	n (%)	

Each participant can have only one proximate cause of death, but up to six underlying causes of death. Fisher's exact test is used to test the differences in distribution of places/causes of death between the two treatment arms.

Table 11. Proposed figures

Figure 1. CONSORT flow diagram
Figure 2. Bar chart of daily subject disposition Bar chart showing, for each day between Days 1-90, the proportion of patients in each arm who fall into one of the following 5 categories: (1) alive and in ICU, (2) discharged from ICU, but still in hospital, (3) discharged from hospital, (4) dead, and (5) with unknown status. The figure will consist of two (one plot per arm) stacked bar charts with one bar per day and, within each bar, the proportion of patients in each category (summing to 100%).
Figure 3. Longitudinal mean plot of the daily dose of antibiotics The figure will report mean daily dose by treatment arm with 95% CI for Days 1-16. Raw means will be displayed on the graph as numbers near each dot and denominators will be included below the x-axis.
Figure 4. Cumulative incidence function of time to death The figure will show the number at risk every 10 days, display median and IQRs, as well as results from the Cox model (hazard ratio, 95% CI and *P* value).
Figure 5. Cumulative incidence function of time to alive discharge from index ICU admission The figure will show the number at risk every 10 days, display median and IQRs as well as results from the Cox model (hazard ratio, 95% CI and *P* value).
Figure 6. Cumulative incidence function of time to alive discharge from index hospital admission The figure will show the number at risk every 10 days, display median and IQRs as well as results from the Cox model (hazard ratio, 95% CI and *P* value).
Figure 7: Forest plot for subgroup analysis of mortality at Day 90

CI = confidence interval. ICU = intensive care unit. IQR = interquartile range.



CI = continuous infusion. II = intermittent infusion. IRB = institutional review board. RRT = renal replacement therapy.

Figure 1. CONSORT (CONsolidated Standards of Reporting Trials) flow diagram

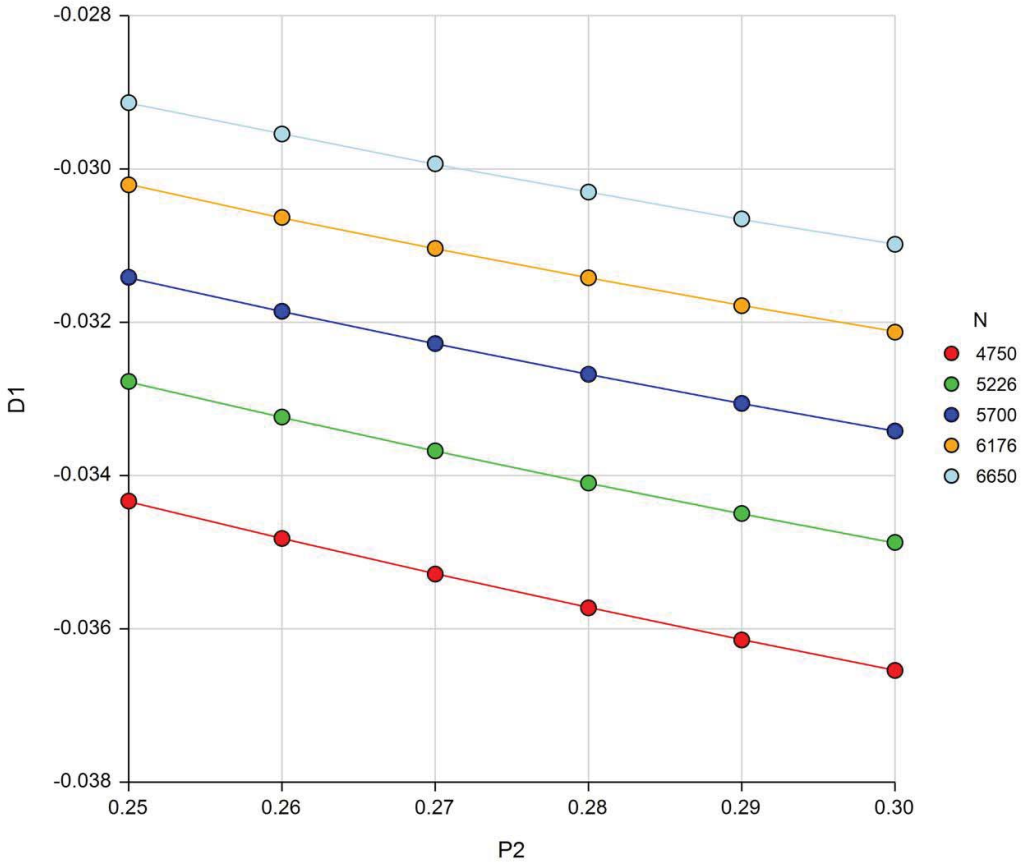


Figure 2. Detectable difference (D1) by baseline mortality in the control group (P2) for various sample sizes (N) with 80% power

Footnote: Sample sizes refer to 5000, 5500, 6000, 6500 and 7000, respectively, after adjusting for 5% loss to follow-up.

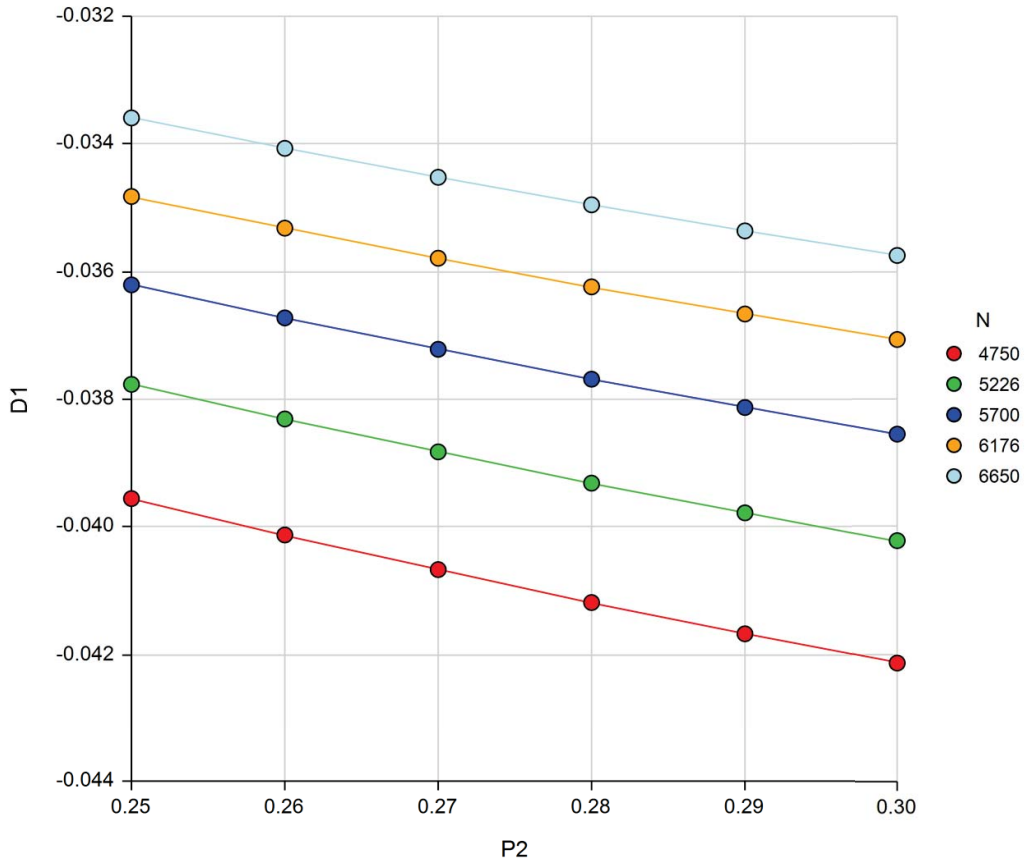


Figure 3. Detectable difference (D1) by baseline mortality in the control group (P2) for various sample sizes (N) with 90% power

Footnote: Sample sizes refer to 5000, 5500, 6000, 6500 and 7000, respectively, after adjusting for 5% loss to follow-up.

The George Institute for Global Health

BLING III

BLING III study
DATA SAFETY MONITORING COMMITTEE CHARTER

Full Title	A phase III randomised controlled trial of continuous beta-lactam infusion compared with intermittent beta-lactam dosing in critically ill patients
Short Title	The Beta-Lactam InfusioN Group (BLING) III study
Acronym	BLING III
Protocol No.	TGI-CCT254643
Version No.	5.0
Protocol Date	21 June 2018
ClinicalTrials.gov Identifier	NCT03213990

Table of Contents

BLING III study
DATA SAFETY MONITORING COMMITTEE CHARTER

1. INTRODUCTION

Title	A phase III randomised controlled trial of continuous beta-lactam infusion compared with intermittent beta-lactam dosing in critically ill patients
Short title	The Beta-Lactam InfusioN Group (BLING) III study
Design	Prospective, multicentre, open, phase III, randomised controlled trial (RCT)
Primary outcome	All-cause mortality within 90 days after randomisation
Secondary outcomes	1. Clinical cure at Day 14 post randomisation 2. New acquisition, colonisation or infection with a multi-resistant organism or *Clostridium difficile* diarrhoea up to 14 days post randomisation 3. All-cause ICU mortality 4. All-cause hospital mortality
Tertiary outcomes	1. ICU length of stay 2. Hospital length of stay 3. Duration of mechanical ventilation in ICU up to 90 days after randomisation 4. Duration of renal replacement therapy up to 90 days after randomisation
Intervention	The administration of beta-lactam antibiotic will be randomised to either continuous infusion or intermittent infusion over 30 minutes for the treatment course for up to 14 days after randomisation while the patient is in the ICU. The choice of beta-lactam antibiotic, either piperacillin-tazobactam or meropenem, and the dose and dosing interval (i.e. the dose the patient will receive in 24 hours) will be determined by the treating physician prior to randomisation.
Sample size	7,000 patients
Inclusion criteria	1. Patient has a documented site of infection or strong suspicion of infection 2. Patient is expected to be in the ICU the day after tomorrow 3. Patient has been commenced on piperacillin-tazobactam or meropenem to treat the episode of infection 4. Giving piperacillin-tazobactam or meropenem by intermittent infusion or continuous infusion is considered equally appropriate for the patient 5. One or more organ dysfunction criteria in the previous 24 hours i. MAP < 60 mmHg for at least 1 hour ii. Vasopressors required for > 4 hours iii. Respiratory support using supplemental high flow nasal prongs, continuous positive airway pressure, bilevel positive airway pressure or invasive mechanical ventilation for at least 1 hour iv. Serum creatinine concentration > 220 µmol/L or >2.49 mg/dL
Exclusion criteria	1. Patient age is less than 18 years 2. Patient has received piperacillin-tazobactam or meropenem for more than 24 hours during current infectious episode 3. Patient is known or suspected to be pregnant

4. Patient has a known allergy to piperacillin-tazobactam, meropenem or penicillin
5. Patient is requiring renal replacement therapy at the time of randomisation, including renal replacement therapy for chronic renal failure
6. The attending physician or patient or surrogate legal decision maker is not committed to advanced life-support, including mechanical ventilation, dialysis and vasopressor administration, for at least the next 48 hours
7. Patient's death is deemed imminent and inevitable
8. Patient has previously been enrolled in BLING III

2. OBJECTIVES OF THE DATA SAFETY MONITORING COMMITTEE

The objectives for the Data Safety Monitoring Committee (DSMC) will be to:

- review the research protocols, and plans for data and safety monitoring
- review data monitoring reports provided by the study statistician
- review the progress of the study and monitor adherence to the protocol, participant recruitment, outcomes, data quality, complications, and other issues related to participant safety
- monitor the assumptions underlying sample size calculations for the study and alert the investigators if they see substantial departures as the data accumulate
- ensure the confidentiality of the study data and the results of monitoring

The DSMC will consist of individuals with appropriate experience in critical care, statistics, clinical trials and DSMC responsibilities (e.g. prior DSMC experience). The committee will be supported by an unblinded statistician at The George Institute for Global Health. The independent DSMC will review safety data on an ongoing basis and may recommend the BLING III Study Management Committee to stop or amend the study based on safety findings.

3. MEMBERS OF THE DMC

The DSMC includes experts in clinical intensive care medicine, infectious diseases, clinical trials, and statistics. The names of the DSMC members and the consultants to the DSMC, their voting rights, affiliations, and contact information are listed in Appendix 1.

The DSMC may call upon other experts to attend DSMC meetings to provide information and/or advice regarding unanticipated findings or issues. These individuals are not considered DSMC members and cannot vote in DSMC meetings.

4. RESPONSIBILITIES OF THE DSMC CHAIRPERSON AND MEMEBERS

The DSMC serves as an independent expert advisory group for the BLING III Study. The DSMC is responsible for determining its operational procedures and acting in accordance with its approved DSMC charter. If changes to the charter are required, amendments will be prepared and agreed to by the DSMC and the BLING III Study Management Committee.

Throughout its tenure, the DSMC will undertake BLING III Study data reviews while maintaining the scientific integrity of the trial.

Following each DSMC meeting, the DSMC will provide the BLING III Study Management Committee with a written DSMC Meeting Report summarising their recommendations, which will not reveal any details of unblinded data.

4.1 DSMC Chairperson: The BLING III Study Management Committee have appointed Prof J Duncan Young as the chairperson of the DSMC. The chairperson will:

- sign off on the DSMC charter (and any subsequent amendments), indicating the agreement of the DSMC to conduct its operations in accordance with the charter
- ensure that DSMC meetings are scheduled
- work with the Statistics Group to ensure that the Data Monitoring Report, consisting of unblinded data listings and summaries, is received by the DSMC members within the given timeframes
- chair the DSMC meetings
- act as the contact between the DSMC and the BLING III Study Management Committee by discussing the issues and representing the views of the DSMC without jeopardising the integrity of the data
- sign the DSMC meeting minutes and the DSMC Meeting Report summarising the conclusions and recommendations of the DSMC from each meeting

- inform the BLING III Study Management Committee Chairperson of the need for additional DSMC meetings and identified issues, proposed meeting date(s), and specifications for data review
- ensure that the DSMC meeting minutes and other documentation are maintained appropriately

The DSMC Chairperson will receive administrative support from the Statistics Group as required.

4.2 DSMC Members: Each member is responsible for maintaining strict confidentiality of the study data. Members will not share any study data or information about the study with any individual external to the DSMC. The DSMC chair may contact the unblinded statistician in the Statistics Group (see below) directly with questions regarding the operational details associated with the data analyses and summary tables.

Each member will review the Data Monitoring Report thoroughly prior to each DSMC meeting. A member who believes he or she may have a potential intellectual or financial conflict of interest during the course of review of the data must inform the chairperson of the DSMC. In such cases, the DSMC meeting minutes must document the disclosure of the potential conflict of interest and the outcome of the discussion, e.g. abstention of member from voting.

5. RESPONSIBILITIES OF STATISTICS GROUP

The Statistics Group is based at The George Institute for Global Health, Australia. Their names, roles in the project, and contact information are included in Appendix 2. The Statistics Group will have primary responsibility for:

- ensuring that the Data Monitoring Report provided to the DSMC is complete and accurate
- storing copies of the Data Monitoring Reports until after the completion of the BLING III Study
- if requested, after database lock, sending to the BLING III Study Management Committee a copy of each Data Monitoring Report along with any other applicable documentation
- performing additional analyses that are requested by the DSMC, which may have the potential to unblind individuals to the results of the study. All such additional analyses will be similarly archived and made available at study termination

In addition, the Statistics Group will assist the DSMC chairperson with the following responsibilities:

- oversee the preparation of the Data Monitoring Report, ensuring that it includes the required unblinded data listings and summaries, and that it is received by the DSMC members within the given timeframes
- record and finalise minutes of closed sessions meetings with the DSMC, review and help finalise other meeting minutes prepared by the BLING III Study team
- ensure that the DSMC meeting minutes and other documentation are maintained appropriately

6. RESPONSIBILITIES OF THE BLING III STUDY MANAGEMENT COMMITTEE

The BLING III Study Management Committee is responsible for:

- constituting the DSMC
- appointing the DSMC chairperson
- agreeing to the DSMC charter
- coordinating resources and procedures to support DSMC operations
- providing the DSMC with relevant information regarding the beta-lactam antibiotic method of administration and conduct of the clinical trial including protocol amendments
- communicating the DSMC recommendations
- communicating to the DSMC the action taken based on DSMC recommendations
- reviewing unblinded information from the DSMC in the event that the DSMC recommends to stop the trial prior to scheduled closure

The names of the BLING III Study Management Committee, their roles, and contact information are included in Appendix 3.

7. RESPONSIBILITIES OF THE BLING III STUDY PROJECT MANAGER

The BLING III Study Project Manager or delegate is responsible for:

- ensuring that the DSMC charter is signed by all members of the DSMC
- scheduling DSMC meetings
- making the appropriate DSMC meeting arrangements
- recording minutes for the open session of the DSMC meeting and obtaining approval for these from the Chair of the DSMC before circulating to all those who attended

8. DSMC MEETINGS

An initial meeting of the DSMC will be held prior to receipt of any safety or efficacy data from the BLING III Study. The purpose of the meeting will be to:

- familiarize DSMC members with the BLING III Study, and the therapeutic area
- review and approve the content and format of the Data Monitoring Reports
- develop more specific operational guidelines, i.e. frequency of meetings, logistics of meetings
- review the DSMC charter and complete the procedural sections of the DSMC charter

Subsequent meetings will be scheduled at regular intervals as determined by the DSMC. DSMC members are expected to participate in each meeting. Meetings may be held in person, by videoconference or teleconference. On occasion, the DSMC may require consultants with additional expertise in the review of safety or efficacy data. These consultants will be bound by the same confidentiality requirements as regular DSMC members. The BLING III Study Management Committee Chairperson or their nominated delegate must agree to the objectives and the presence of additional participants at DSMC meetings. This information must also be documented in the DSMC meeting minutes and the DSMC Meeting Report.

The DSMC may deem it necessary to hold additional, unscheduled, meetings. The DSMC chairperson will ensure that the request for additional analyses and meetings are consistent with the objectives of the DSMC as outlined in the charter. The DSMC chairperson must inform the BLING III Study Management Committee Chairperson of the issues, proposed meeting date(s), and specifications for data review and obtain agreement.

Meeting format

The DSMC meeting will begin with an open session followed by a closed session. BLING III Study team members may present pertinent study information to the DSMC members during the open session. Investigators or experts serving as ad hoc advisors may be requested to attend an open session of the meeting. The closed session will be limited to the DSMC members, consultants to the DSMC if needed, and designated staff from the Statistics Group for presentation of the unblinded data. An executive session can be called with DSMC members only if required. BLING III Study team members and Management Committee members are excluded from participating in any closed or executive session of the DSMC.

Meeting reports

DSMC meeting minutes and the DSMC Meeting Report (Appendix 4) summarising the conclusions and recommendations of the DSMC will be drafted after each meeting. The DSMC Chairperson will oversee the finalisation of the DSMC meeting minutes and the DSMC Meeting Report and sign both documents. The DSMC meeting minutes should include important considerations that led to the DSMC recommendations. The DSMC meeting minutes will not be sent to the BLING III Study Management Committee until after the completion of the study and database lock. The DSMC Meeting Report, which will be sent to the BLING III Study Management Committee, will include DSMC conclusions and recommendations without revealing unblinded data. The Chair of the Management Committee will provide the report to the Project Manager for HREC reporting and sending to participating investigators.

Meeting schedule

To ensure ongoing safety surveillance the DSMC will review data, the two arms with assignment not revealed, periodically. The review will be based upon the best available data.

9. PREPARATION AND DISTRIBUTION OF DATA FOR DSMC REVIEW

The BLING III study database is held and maintained by The George Institute for Global Health. Likewise, the randomisation codes have been prepared and are held by The George Institute for Global Health. The preparation of DSMC reports will be done on the basis that only the independent Statistics Group and the DSMC will have access to unblinded data.

The unblinded statistician will obtain unblinded data extracts one month prior to the planned DSMC meeting. The data will be saved in an access-restricted folder. The unblinded statistician is the only person who has the access to both the study data and the randomisation code.

The preparation of the Data Monitoring Reports will be done to an agreed standard analysis and reporting format developed by the independent Statistics Group with the support of the project statistician at The George Institute and under the direction of the DSMC. The format will be signed off by the BLING III Study Management Committee.

The independent Statistics Group will send DSMC members Data Monitoring Reports at least 5 working days prior to scheduled meetings in a password-encrypted PDF file.

10. GUIDELINES FOR REGULAR MONITORING OF SAFETY AND EFFICACY

The first DSMC review will be conducted when 3500 patients (half of planned recruitment) have completed 90 day follow-up. The DSMC will also respond to specific requests made by the BLING III Study Management Committee.

At the conclusion of each regular review the DSMC will recommend to the BLING III Study Management Committee in the DSMC Meeting Report one of the following:

1. To continue the BLING III Study unchanged
2. To discontinue the BLING III Study
3. To modify the BLING III Study
4. To request additional expert review after which a recommendation will be made
5. To request additional analyses of the Statistics Group after which a recommendation will be made

The DSMC will base the primary review on the entire randomised trial population although additional analyses of subgroups may be done as requested by the DSMC.

A recommendation to discontinue the BLING III Study prematurely will be based upon there being clear evidence that the agent provides protection or causes harm for an important clinical outcome. The final recommendation to the BLING III Study Management Committee will remain at the discretion of the DSMC, but will be based upon agreed standards for the interpretation of interim analyses in clinical trials. The BLING III Study Management Committee will subsequently have the responsibility of evaluating and implementing as they consider appropriate the recommendations provided by the DSMC.

A recommendation to modify the BLING III Study will be accompanied by the maximum possible information that the DSMC can provide to the BLING III Study Management Committee without affecting the integrity of the trial. Once again, the BLING III Study Management Committee will have

the responsibility of evaluating and implementing the recommendations as they consider appropriate.

If additional expert opinion is to be sought or additional analyses are required prior to making a recommendation, the DSMC will work to schedule another meeting at the earliest possible opportunity.

11. STOPPING RULES

The DSMC will monitor safety data on an ongoing basis.

The analyses will be performed by an independent statistician from The George Institute for Global Health, who is not involved in managing the trial. If deemed appropriate the DSMC can recommend the Management Committee of the BLING III Study should:

- adjust the duration of follow-up;
- terminate the study early if there is clear and substantial evidence of benefit;
- terminate the study early if the data suggests the risk of adverse events substantially outweighs the potential benefits
- terminate the study early for futility

The DSMC will reveal the unblinded results to the BLING III Study Management Committee if, taking into account both statistical and clinical issues and exercising their best clinical and statistical judgement, the unblinded results provide sufficient evidence that the trial treatment is on balance beneficial or harmful for all, or for a particular category of patients. Stopping rules will be based on the following:

- a responsibility to inform investigators if at any time the randomised comparisons provided evidence “beyond reasonable doubt” of a difference between randomised groups in total (all cause) mortality
- OR evidence that is likely to lead many clinicians conversant with the available evidence to change their practice with regard to the choice to use or not to use continuous infusions of beta-lactam
- a three standard deviation difference in mortality would constitute such evidence, unless the DSMC should itself decide in the circumstances of the trial that other evidence constitutes evidence beyond reasonable doubt

- additionally, while the primary focus of the committee should be on all-cause mortality, this would not preclude the committee recommending termination of the study (or some modification to its design) if there emerged evidence of an important difference in some other major outcome (such as clinical cure at Day 14 or new acquisition, colonisation or infection with a multi-resistant organism or *Clostridium difficile* diarrhoea).

12. MAINTENANCE OF DOCUMENTATION

The DSMC chairperson with the support of the Statistical Group and Project Manager will compile and maintain the following documents:

- copy of the charter (and all amendments to the charter) and associated attachments and addenda
- a copy of the Investigator's Brochure (if applicable)
- protocols and protocol amendments for the BLING III Study
- curriculum vitae for each DSMC member
- copies of the Data Monitoring Reports provided to the DSMC members
- minutes of each DSMC meeting, including conclusions or recommendations concerning the conduct or evaluation of the trial and any important considerations that led to the conclusions/recommendations
- DSMC reports provided to the BLING III Study Management Committee containing conclusions or recommendations without reference to unblinded data
- copies of key correspondence related to this DSMC

Upon completion of the trial and closure of the relevant clinical database(s), the documents will be forwarded to the BLING III Study Management Committee for archiving.

13. LINES OF COMMUNICATION

All communication from the DSMC will be by the DSMC chairperson to the BLING III Study Management Committee chairperson. The BLING III Study Management Committee chairperson will then further disseminate information to the BLING III Study Management Committee. The DSMC Chairperson will send to the BLING III Study Management Committee Chairperson a DSMC Meeting Report within 5 working days of each meeting, containing the committees' recommendation, thereby documenting that the DSMC has reviewed the data. The report will divulge no details of DSMC discussions and especially no information regarding unblinded data. The BLING III Study Management Committee

chairperson will inform the DSMC chairperson of any decisions about changes to the conduct of the trial within 5 days of receipt of the DSMC Meeting Report.

14. CONFIDENTIALITY

All materials and information are strictly confidential and may not be discussed or disclosed with anyone external to the DSMC unless specifically authorised in this charter.

15. APPENDIX

Appendix 1: DSMC Members and Non-Voting Consultants to DSMC

Chairperson	**Voting Rights**			
Name: Prof J Duncan Young	Yes	X	No	
Position and Affiliation: Professor of Intensive Care Medicine, University of Oxford Phone: +44 1865 572451 E-mail address: duncan.young@nda.ox.ac.uk				

Members				
Name: Professor John Marshall	Yes	X	No	
Position and Affiliation: Director of Research, Critical Care Medicine, St Michael's Hospital, Canada Phone: E-mail address: MarshallJ@smh.ca				
Name: Professor Tom Van der Poll	Yes	X	No	
Position and Affiliation: Professor of Medicine | Chair, Department of Medicine Phone: +31-20-5665910 E-mail address: t.vanderpoll@amsterdamumc.nl				

Consultants to DSMC: will be amended if appointed by DSMC.

Name:

Position and Affiliation:

Appendix 2: Statistics Group Members

Study statistician- Blinded

Name: A/Prof Laurent Billot

Phone: +61 2 8052 4581 Fax: N/A

E-mail address: lbillot@georgeinstitute.org

Statistician reporting to DSMC - Unblinded

Name: Mr Qiang Li

Phone: +61 2 8052 4516 Fax: N/A

E-mail address: qli@georgeinstitute.org

Other unblinded statistician or programmer - To Be Assigned

Name

Phone: Fax: N/A

E-mail address:

Appendix 3: BLING III Study Management Committee Members

Chair	Prof Jeffrey Lipman
Members of the Management Committee	Prof Stephen Brett
	Dr Menino Cotta
	A/Prof Joshua Davis
	Prof Jan de Waele
	Dr Joel Dulhunty
	Prof Simon Finfer
	Dr Naomi Hammond
	Dr Serena Knowles
	Dr Shay McGuinness
	Prof John Myburgh
	Prof David Paterson
	Prof Sandra Peake
	Ms Dorrilyn Rajbhandari
	Prof Andrew Rhodes
	Prof Jason Roberts
	Dr Claire Roger
	Dr Charudatt Shirwadkar
	Ms Therese Starr
	Dr Colman Taylor

Appendix 4: Proforma for DSMC Meeting Report

To: BLING III Study Management Committee Chairperson

Meeting Date:

Protocol:

Meeting Attendees:

The DSMC charged with the review of safety and efficacy data for the BLING III Study, reviewed Data Monitoring Report number <<insert>> dated <<insert>>.

Summary of discussions in open session of the meeting:

As a result, the DSMC recommendation/course of action is:

☐ To continue trial unmodified until next scheduled meeting.

☐ To continue trial unmodified, and plan an additional meeting.
The following date is proposed for the additional meeting: [insert dd/Mon/yyyy] (to be confirmed with BLING III Study Management Committee Chairperson).

☐ To continue trial unmodified, and request additional expert review/analyses.

Describe and provide timelines of additional review:

☐ To continue trial and amend protocol(s) as described:

[Describe sections below and list protocol(s) to be amended]

☐ To set up a meeting with the BLING III Study Management Committee to discuss concerns of safety and/or efficacy within the clinical trial as outlined below.

Additional Comments:

☐ To pause patient recruitment for reasons outlined below:

Additional Comments:

Chairperson, Data Monitoring Committee for BLING III Study

Date (Day Month Year)

Appendix 5: DSMC Charter Signature Sheet

I have read and approve this Charter:

Name (print) _____

Signature _____

Date of Signature (dd/mmm/yyyy)_____