

# A protocol for a multicentre randomised controlled trial of continuous beta-lactam infusion compared with intermittent beta-lactam dosing in critically ill patients with severe sepsis: the BLING II study

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Beta-lactam antibiotics are commonly used for treatment of life-threatening infections in critically ill patients with severe sepsis.<sup>1,2</sup> The rationale for administration of beta-lactams via continuous infusion is well recognised.<sup>3-5</sup> Despite this, standard practice in most intensive care units is intermittent bolus dosing.<sup>1,6</sup> As a class of agents, beta-lactams are known as time-dependent antibiotics because they have their greatest effect when the antibiotic concentration remains above a critical level (equivalent to four times the minimum inhibitory concentration [MIC] of the pathogen) for the duration of the course.<sup>3</sup> Continuous infusion has been shown to be superior to bolus administration in animal immunodeficient and in-vitro models of infection, and to more consistently achieve time-dependent pharmacokinetic and pharmacodynamic end points in human studies.<sup>3,7</sup> Two meta-analyses of the human trials, respectively conducted up to 2004 and 2007, failed to demonstrate the superiority of continuous infusion over intermittent administration in terms of clinical cure and survival, although the included studies were primarily conducted in non-critically ill patients, were unblinded and, in most cases, employed higher doses in the intermittent treatment arm.<sup>8,9</sup>

As a precursor to a well designed, large, prospective study on the efficacy of continuous administration of beta-lactam antibiotics in ICU patients, we conducted a multicentre, randomised controlled trial powered for a pharmacokinetic end point in 60 patients across five ICUs.<sup>10</sup> That study showed the feasibility of randomly allocated patients started on one of three beta-lactam antibiotics for severe sepsis, and of preparing and administering blinded medications in a clinical setting. We confirmed the adequacy of blinding and pharmacokinetic separation between treatment arms. The purpose of this Beta-lactam Infusion Group (BLING) II study is to conduct a Phase IIB trial to confirm clinical end point separation between continuous infusion and intermittent bolus dosing, and to estimate the survival benefit before a potential Phase III trial. The study is endorsed by the Australian and New Zealand Intensive Care

## ABSTRACT

**Background and rationale:** Beta-lactam antibiotics are largely administered by bolus dosing, despite displaying time-dependent pharmacokinetics and pharmacodynamics and there being a strong rationale for continuous administration. The randomised controlled trials conducted to date comparing the mode of beta-lactam administration have been inconclusive and limited by non-equivalent dosing, unblinded administration and small sample sizes.

**Objective:** A multicentre, randomised controlled trial (the Beta-lactam Infusion Group [BLING] II study) is currently under way, comparing continuous infusion to standard bolus administration of beta-lactam antibiotics in critically ill patients, independent of dose.

**Design, settings, participants and interventions:** BLING II is a Phase IIB, double-blinded, randomised controlled trial recruiting 420 intensive care unit patients with severe sepsis to receive one of three beta-lactam study antibiotics (ticarcillin–clavulanate, piperacillin–tazobactam or meropenem) by either continuous infusion or intermittent bolus administration.

**Main outcome measures:** The primary outcome is ICU-free days at Day 28. Secondary outcomes include 90-day survival, clinical cure 14 days after study antibiotic cessation, organ failure-free days at Day 14 and duration of bacteraemia.

**Results and conclusions:** The study started in July 2012 and will provide clinical evidence as to whether continuous infusion of beta-lactam antibiotics is superior to intermittent bolus administration in critically ill patients with severe sepsis. A Phase III study powered for a survival end point may be justified, based on the results of our study.

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**Table 1. Primary and secondary study outcomes**

## Primary outcome

- Intensive care unit-free days up to Day 28 after randomisation

## Secondary outcomes

- Survival at Day 90 after randomisation
- Clinical cure at 14 days after cessation of the study drug
- Number of days free of cardiovascular, respiratory and renal organ failure at Day 14 after randomisation
- Duration of bacteraemia in patients with culture-positive bloodstream infection at baseline.

Society Clinical Trials Group (ANZICS-CTG) and the Australasian Society for Infectious Diseases Clinical Research Network. This article describes the BLING II study protocol. The BLING II study has been registered with the Australian New Zealand Clinical Trials Registry (ACTRN12612000138886).

**Study design and outcomes**

The BLING II study is a prospective, multicentre, concealed, randomised, Phase IIB controlled trial. Participants started on any one of three beta-lactam study antibiotics (ticarcillin–clavulanate, piperacillin–tazobactam or meropenem) will be randomly allocated to receive the prescribed antibiotic by either continuous infusion (intervention arm) or

intermittent bolus administration (control arm). The total 24-hour dose is determined by the treating clinician and will be used irrespective of treatment arm allocation. For participants where the study drug is subsequently switched to flucloxacillin or escalated to meropenem within 14 days of randomisation, administration of the new antibiotic will continue via the allocated treatment arm.

Primary and secondary outcomes are summarised in Table 1. ICU-free days at Day 28 will be determined from the date of randomisation (Day 1). The number of non-ICU days after ICU discharge, and excluding days of ICU readmission, will be counted for each day a participant is alive up to Day 28. Study participants will be followed up until death or Day 90, whichever is earlier. For participants discharged alive from hospital, a phone call will be made at 90 days to determine survival status.

Clinical cure at a test-of-cure date will be rated according to whether there is disappearance of all signs and symptoms related to infection (Table 2). The test-of-cure date will be 14 days following cessation of the study drug or, if study drug administration continues for more than 2 weeks, 14 days from cessation of blinded administration. Clinical cure will be assessed by a blinded treating doctor if the participant is still in the ICU, or by blinded review of the patient record if the participant has been discharged from the ICU. The number of days free of cardiovascular, respiratory and renal organ failure at Day 14 will be determined from the next calendar day from when a patient last required vasopressors, had a  $P_{aO_2}/F_{iO_2} < 300$  or required invasive mechanical ventilation, or had a serum creatinine concentration  $> 170 \mu\text{mol/L}$ , or required renal replacement therapy.<sup>13,14</sup>

Duration of bacteraemia will be defined as the number of days from the initial blood culture to the day of a culture-negative result 48 hours after collection. Participants will have a first blood culture before study drug commencement by venepuncture as per standard practice of care. Repeat blood cultures will be collected via an arterial line for each calendar day a patient receives blinded study medications until there is no growth of the initial pathogen in the blood culture 48 hours after collection. Additional pathogens or contaminant organisms identified on subsequent blood cultures will not be used to inform repeat blood cultures or the duration of bacteraemia.

**Participants and study sites**

The study will enrol patients from participating study centres who are admitted to the ICU and who satisfy the protocol-defined inclusion and exclusion criteria (Table 3 and Table 4). A total of 420 participants will be recruited from up to 28 ICUs in Australia, New Zealand and Hong Kong. Centres will be selected on the basis of size, clinical

**Table 2. Definition of clinical cure at test-of-cure date**

Clinical response will be assessed as follows:

- Resolution: disappearance of all signs and symptoms related to the infection
- Improvement: marked or moderate reduction in the severity and/or number of signs and symptoms of infection
- Failure: insufficient reduction of the signs and symptoms of infection to qualify as improvement, including death or indeterminate (no evaluation possible, for any reason).<sup>11</sup>

For participants discharged from the ICU prior to the test-of-cure date, clinical response will be evaluated by review of the patient record for the test-of-cure date (midnight to midnight) as follows:

- Resolution: absence of any SIRS criteria attributable to infection
- Improvement: only one SIRS criterion, at any time point, that is attributable to infection
- Failure: two or more SIRS criteria met concurrently and attributable to infection.<sup>12</sup>

If the subject has a separate episode of infection on the test-of-cure date, clinical response will be rated for any day (midnight to midnight) in the preceding 7 days. The best clinical response during this period will be recorded. Clinical cure is defined as follows:

- Resolution: absence of any SIRS criteria attributable to infection
- All other findings (ie, improvement and failure).

ICU = intensive care unit. SIRS = systemic inflammatory response syndrome.

**Table 3. Inclusion criteria for the Beta-lactam Infusion Group (BLING) II study**

- Severe sepsis; confirmed or suspected infection meeting one or more of the following organ dysfunction entry criteria in the previous 24 hours:
  - cardiovascular: arterial SBP  $\leq$  90 mmHg or MAP  $\leq$  70 mmHg for  $\geq$  1 hour, despite adequate fluid resuscitation or adequate intravascular volume status and/or need for vasopressors,<sup>15</sup> to achieve SBP or MAP target (specified by treating physician) for > 1 hour
  - renal: acute kidney injury with serum creatinine > 1.5 times the hospital admission creatinine, or urine output < 0.5 mL/kg/hour for 6 hours (excluding loss of kidney function or end-stage kidney disease<sup>16</sup>)
  - respiratory: PaO<sub>2</sub>/FiO<sub>2</sub>  $\leq$  200
  - haematological: platelet count < 80 × 10<sup>9</sup>/L or > 50% decrease in platelet count from highest recorded value within preceding 3 days
  - metabolic acidosis: pH < 7.3, base deficit > 5 mmol/L or venous or arterial plasma lactate level > 1.5 times upper limit of normal for reporting laboratory.
- Ticarcillin–clavulanate, meropenem or piperacillin–tazobactam used to treat the infectious episode.
- Treating doctor is uncertain if administration of chosen antibiotic by bolus administration or infusion is superior.
- At assessment of eligibility, treating doctor expects patient to need treatment in ICU beyond next calendar day.

SBP = systolic blood pressure. MAP = mean arterial pressure. ICU = intensive care unit.

**Table 4. Exclusion criteria for the Beta-lactam Infusion Group (BLING) II study**

- Receipt of a potential study medication for more than 24 hours before randomisation
- Age less than 18 years
- Allergy or potential allergy to the study medications
- Pregnancy
- No central venous catheter access with three or more lumens
- Receiving palliative or supportive treatment only, at the time of assessment for eligibility
- Treating doctor not committed to provision of advanced life-support, including any of mechanical ventilation, dialysis and vasopressor administration for at least the next 48 hours
- Death is deemed imminent and inevitable
- Patient has an underlying process likely to result in death before 90 days of follow-up
- Consent not gained for study participation, and entry under a waiver-of-consent not approved by the jurisdictional human research ethics committee.

research capacity, their ability to prepare blinded study medications, and expressions of interest via the ANZICS-CTG. Screening will occur for all patients admitted to the ICU who meet sepsis criteria.<sup>12</sup>

## Study treatments

Study drug concealment will occur by double-dummy administration via labelled syringes and infusion bags that are identical, regardless of treatment arm allocation (Figure 1). Participants randomly allocated to the intervention arm will receive the study antibiotic by continuous infusion, and placebo intermittent boluses containing 0.9% sodium chloride or water for injection. Participants randomly allocated to the intermittent bolus arm will receive the study antibiotic as intermittent boluses and a placebo (0.9% sodium chloride) continuous infusion. The treating doctor will choose the dose and dosing interval of the antibiotic. Participants randomly allocated to the intervention will receive an equivalent 24-hour dose, administered by continuous infusion. The participants, treating clinical team, study investigators and research staff involved in data collection will be blinded to the treatment allocation.

The storage and administration of study medications will be in keeping with the stability of the study antibiotics at room temperature and refrigerated at 2–8°C. Piperacillin–tazobactam, ticarcillin–clavulanate and flucloxacillin have sufficient stability at room temperature to be administered by infusion over 24 hours (with the 24-hour dose compounded in 0.9% sodium chloride to a total volume of 250 mL);<sup>17–20</sup> meropenem requires administration over 8 hours (with the 8-hour dose compounded in 0.9% sodium chloride to a total volume of 100 mL).<sup>21,22</sup> Prepared study medications that are not immediately administered will be refrigerated and administered within 72 hours as per the stability profile of all study antibiotics at 2–8°C.

To ensure adequate plasma antibiotic concentrations are achieved from the start of blinded administration, the continuous infusion will start at a time equivalent to half the scheduled bolus dosing interval ( $t_{1/2}$ ) after at least one open-label bolus dose (Figure 2). Bolus study medications will subsequently start at the scheduled bolus-dosing interval.

Blinded study drug administration will continue until the decision to cease the antibiotic, patient withdrawal from the study, ICU discharge, ICU death, or Day 14, whichever occurs first. Only one study drug will be administered in a blinded fashion at any one time. For participants restarting open-label treatment, standard bolus dosing will commence between  $t_{1/2}$  and a full ( $t_1$ ) dosing interval from the last blinded bolus dose, depending on the timing of cessation of the blinded infusion (Figure 3).

## Randomisation and allocation concealment

The Queensland Clinical Trials and Biostatistics Centre (QCTBC) will perform block randomisation with stratification by participating institution, and 1:1 allocation to treatment arm. An unblinded staff member involved in preparation of

**Table 5. Variables recorded in the study case report form**

## Admission details

- Patient characteristics (age, sex)
- Inclusion criteria and consent details
- Date and time of ICU admission
- ICU admission diagnosis
- Admission APACHE II score and immunocompromised status
- Site or sites of presumed or known infection
- Date of randomisation

## Medication details

- Study antibiotic and prescribed 24-hour dose
- Date and time of study antibiotic commencement and cessation, including commencement and cessation of blinded treatment
- Concurrent antimicrobial use

## Microbiological details

- Initial pathogenic organism identified
- Daily blood cultures until no growth at 48 hours postcollection
- Subsequent pathogenic organisms identified (if any)

## Augmented renal clearance details

- Patient height and weight
- 8-hour creatinine clearance measured on the first day of study drug administration

## Organ failure details

- Daily SOFA score (excluding CNS score) up to Day 15 of study drug administration or ICU discharge (whichever is sooner)
- Last day of receiving invasive mechanical ventilation and renal replacement therapy

## Completion and outcome details

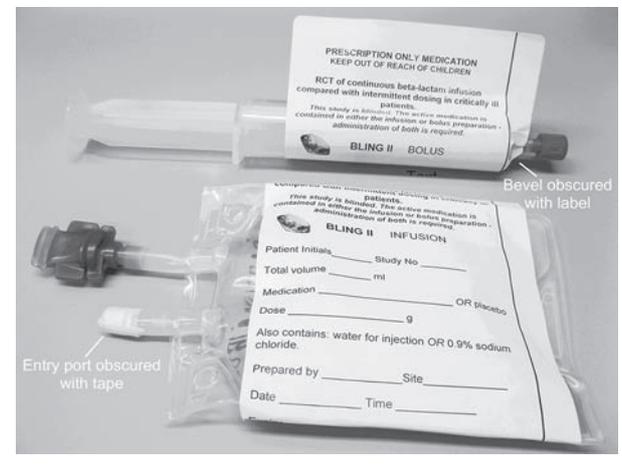
- Reason for cessation of blinding of study drug
- Clinical cure at test-of-cure date
- Date, time and vital status at ICU discharge
- Readmission to the ICU before Day 28
- Vital status at hospital discharge
- 90-day survival (including date of death if dead)
- Adverse events and protocol violation details

ICU = intensive care unit. APACHE = Acute Physiology and Chronic Health Evaluation. SOFA = sequential organ failure assessment. CNS = central nervous system.

study medications will obtain the allocation status for each participant at the time of study enrolment by opening a consecutively labelled sealed opaque envelope.

**Data collection and management**

Data collection will be conducted by trained staff at each study site and data will be entered into a web-based clinical trial database system (OpenClinica, LLC). Information to be collected via the case report form is outlined in Table 5. Personnel trained by the George Institute for Global Health will conduct monitoring for the study. Three site visits by study monitors will occur over the length of the study, with 100% data monitoring of the first two participants, and 100% monitoring of participant consent and 10%–20% of

**Figure 1. Continuous and intermittent blinded study medications**

study outcomes at subsequent visits. The QCTBC will develop and manage the trial database, and will conduct the data analyses.

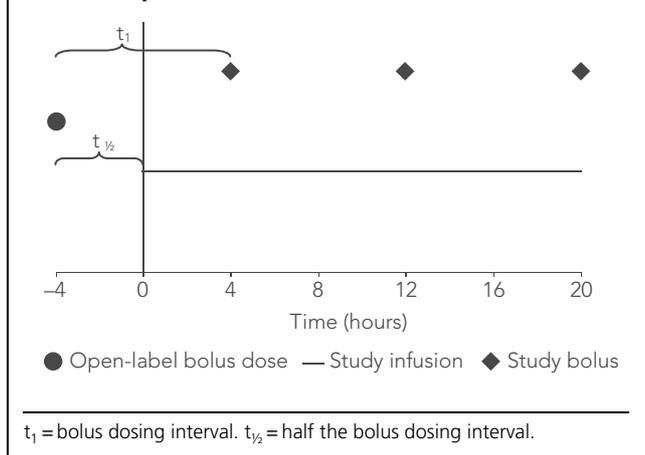
**Study preparation and logistics**

The trial coordination centre comprises the project management team (JL, JMD, JAR and TS) at the Burns, Trauma and Critical Care Research Centre, Brisbane. The study management committee provides oversight of the scientific integrity and conduct of the study (personnel are listed in the Appendix). Site initiation and training will be conducted by JMD and TS via web conferencing and site visits. Study medications will be predominantly prepared by trained staff on site at participating centres. In New South Wales, where NSW Health policy requires preparation of continuous infusions immediately before administration, on-site medication preparation will occur immediately before each administration until delivery of compounded study medications by Baxter Australia. A video on preparing study medications for the BLING II study was developed to assist in site training.

**Ethical issues**

The study has received ethics approval from the Royal Brisbane and Women's Hospital human research ethics committee (HREC) (HREC/12/QRBWH/26), with additional jurisdictional HREC approval to be obtained as per study site requirements. As of January 2013, HREC approval has been obtained in seven jurisdictions, including provision for entry into the study under a waiver of consent (delayed consent) if the subject is not able to provide initial consent and all

**Figure 2. Start of blinded study drug administration after an open-label bolus dose**



avenues to seek consent from the person responsible have been exhausted. For participants enrolled under this provision, consent to continue with study participation will be obtained from the subject or person responsible as soon as practicable after study enrolment.

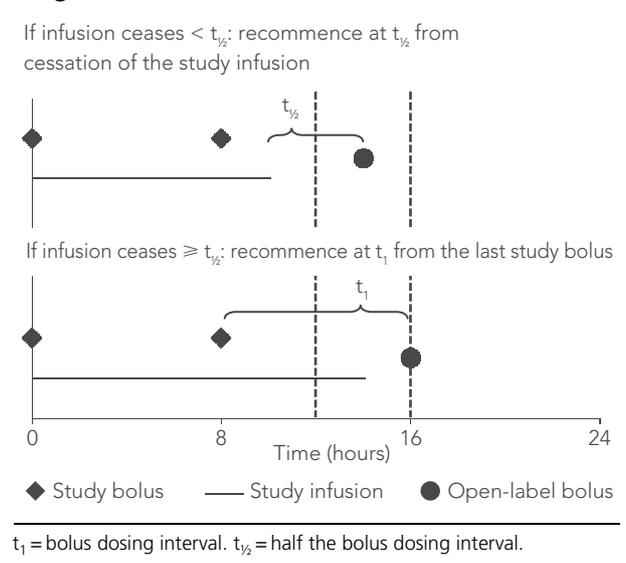
### Sample size and power

Sample size calculations were based on pilot data and estimates from a cohort of patients with severe sepsis.<sup>10,15</sup> A sample size of 420 (210 in each group) is required to detect a difference of 3 days in the number of ICU-free days between the treatment arms (from a control group estimate of 14 ICU-free days), with 90% power and a significance level of 0.05 using a Mann–Whitney *U* test. In a sample of 420, a 5% absolute increase in 90-day survival from a baseline of 60% achieves 19% power using a two-sided log-rank test. Power of 88% is achieved to detect a 15% increase in the proportion of patients who achieve clinical cure (from a baseline proportion of 50% in the control group). An increase of 1.5 days in the number of days free of cardiovascular, respiratory and renal organ failure at Day 14 (from a control group estimate of 8 days) achieves 91% power using a Mann–Whitney *U* test.

### Statistical analysis

The efficacy and safety of the intervention will be evaluated by an intention-to-treat analysis of all eligible participants who are randomly allocated, irrespective of whether study drug is started or the duration of study drug administration. A planned per-protocol analysis will evaluate primary and secondary end points in eligible participants who received a minimum of 3 days of randomised treatment. A Mann–

**Figure 3. Recommencement of the open-label bolus administration following cessation of blinded study drug**



Whitney *U* test will be used to evaluate the primary outcome. Survival at 90 days will be analysed by Kaplan–Meier survival analysis. Clinical cure will be analysed by logistic regression analysis, with treatment group as the only covariate and the odds ratio and 95% confidence interval reported with reference to the control arm. Organ failure-free days to Day 14 and duration of bacteraemia in patients with a positive blood culture will be analysed by a Mann–Whitney *U* test. A two-sided *P* value  $< 0.05$  will be considered evidence of a significant difference in the study outcomes.

### Subgroup analysis

An exploratory subgroup analysis for the outcomes of interest will occur for patients hypothesised to have the greatest benefit from continuous infusion. The subgroups of interest are patients with:

- gram-negative bloodstream infection
- augmented renal clearance (as defined by a measured creatinine clearance  $> 130 \text{ mL/min/1.73m}^2$ )<sup>23</sup>
- immunocompromised status (as defined in the Acute Physiology and Chronic Health Evaluation II severity of disease classification system<sup>24</sup>).

Duration of bacteraemia is expected to be applicable to 36%–58% of the study sample (75 or more in each group), based on previous reports of bacteraemia prevalence in an Australian cohort of patients with sepsis.<sup>15,25</sup> A conservative estimate of 25% of the study sample (53 in each group) is anticipated to meet the definition of augmented renal clearance.<sup>26</sup> Immunocompromised status is estimated at 7% of the study sample (14 in each group).<sup>27</sup>

## Data and safety monitoring

A data monitoring committee (DMC) has been established comprising three members with combined expertise in intensive care, infectious diseases, clinical trials and biostatistics. The DMC will review recruitment statistics, safety data, survival outcomes and duration of treatment blinding by blinded treatment group at the study midpoint. The trial coordination centre will report adverse events linked with study treatment to the DMC on a quarterly basis. Sites will report all adverse events in which study participation was a contributing factor to the trial coordination centre. All serious adverse events will be reported to the Royal Brisbane and Women's Hospital HREC and as per institutional and jurisdictional HREC requirements.

## Funding

The study is funded by the National Health and Medical Research Council (APP1022460) with a supplementary grant from the Royal Brisbane and Women's Hospital Foundation. An unrestricted grant from Baxter Australia will contribute to funding of compounding of blinded study medication for NSW sites. Funding bodies have no input into the design, management or reporting of the trial.

## Current status

The study started recruitment on 2 July 2012, with eight sites recruiting participants from January 2013. It is estimated that recruitment will be completed by June 2014. The BLING II recruitment tracker is accessible online (see Appendix).

## Summary

This study will provide vital evidence to answer the clinically important question of whether administration of beta-lactam antibiotics by continuous infusion will result in improved outcomes for patients with severe sepsis. The potential significance of this research is that it may lead to a simple and cheap intervention to improve ICU-free days and provide strong support as to whether the intervention can improve survival for patients with severe sepsis. It is anticipated that this study will determine whether a large Phase III study looking at survival end points with the use of continuous infusions is warranted.

## Competing interests

Joel Dulhunty, Jason Roberts, Rinaldo Bellomo, Charudatt Shirwadkar, Glenn Eastwood, Therese Starr and Andrew Udy declare no competing interests. Jason Roberts has been a consultant for AstraZeneca, Pfizer, Gilead and Janssen-Cilag. Steven Webb has attended advisory boards and been a consultant to Janssen-Cilag and AstraZeneca. Charles Gomersall has been a consultant for

Janssen-Cilag and Pfizer. John Myburgh has received travel and speaker fees for research projects from Fresenius Kabi. David Paterson has received research grants from AstraZeneca and has attended advisory boards, been a consultant to, or given lectures with honoraria from Three Rivers Pharmaceuticals, MSD, AstraZeneca, Sanofi, Pfizer, Johnson and Johnson and Leo Pharma. Sanjoy Paul has been a consultant and speaker for Novartis and Amylin Pharmaceuticals and has received grants for clinical studies from Amylin Pharmaceuticals, Sanofi, MSD, Novo Nordisk and Pfizer. Jeffrey Lipman has received research grants from AstraZeneca and has attended advisory boards, been a consultant to, or given lectures with honoraria from AstraZeneca, Janssen-Cilag, MSD, Pfizer and Wyeth.

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## Appendix

## Beta-lactam Infusion Group (BLING) II study management committee

Jeffrey Lipman (Chair) (Royal Brisbane and Women's Hospital), Rinaldo Bellomo (Austin Hospital), Joshua Davis (John Hunter Hospital), Joel Dulhunty (Royal Brisbane and Women's Hospital), Glenn Eastwood (Austin Hospital), Charles Gomersall (Prince of Wales Hospital), John Myburgh (St George Hospital), David Paterson (Royal Brisbane and Women's Hospital), Jason Roberts (Royal Brisbane and Women's Hospital), Charudatt Shirwadkar (Blacktown Hospital), Therese Starr (Royal Brisbane and Women's Hospital) and Steven Webb (Royal Perth Hospital).

## BLING II data monitoring committee

Marin Kollef (Chair) (Division of Pulmonary and Critical Care Medicine, Barnes-Jewish Hospital, and School of Medicine, Washington University, United States), John Turnidge (SA Pathology, University of Adelaide and University of South Australia) and Sanjoy Paul (Queensland Clinical Trials and Biostatistics Centre, University of Queensland).

## Online resources

The BLING II recruitment tracker and training video on preparing study medications are accessible at <http://www.som.uq.edu.au/research/research-centres/burns-trauma-critical-care-research-centre/our-research/multi-centre-clinical-trials.aspx>