CRITICAL CARE AND RESUSCITATION

Online Appendix

This appendix was part of the submitted manuscript and has been peer reviewed.
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Appendix to: Billot L, Lipman J, Brett SJ, et al; BLING III Investigators. 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 *Crit Care Resusc* 2021; 23: 273-84. https://doi.org/10.51893/2021.3.OA4

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, informed consent documents 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:

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)_____