Burns Trauma and Critical Care Research Centre,

The University of Queensland, Australia

A prospective pharmacokinetic evaluation of the plasma and cerebrospinal fluid concentrations of a single dose ceftolozane/tazobactam in infected critically ill patients with an indwelling external ventricular drain

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CLINICAL STUDY PROTOCOL

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A prospective pharmacokinetic evaluation of the plasma and cerebrospinal fluid concentrations of a single dose ceftolozane/tazobactam in infected critically ill patients with an indwelling external ventricular drain

Version 2.0 21/03/2017

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AIC	Akaike Information Criterion
BBB	Blood-brain-barrier
BIC	Bayesian Information Criterion
BTCCRC	Burns Trauma and Critical Care Research Centre
CRF	Case report form
CSF	Cerebrospinal fluid
EVD	External ventricular drain
HPLC	High performance liquid chromatography
HREC	Human Research Ethics Committee
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICU	Intensive care unit
LC-MS	Liquid chromatography–mass spectrometry
LOQ	Limit of quantification
MDR	Multi-drug-resistant
MIC	Minimum inhibitory concentration
MS	Mass spectrometry
MSC	Management Systems Certification
PD	Pharmacodynamic
PK	Pharmacokinetic
PK/PD	Pharmacokinetic/pharmacodynamic
RBWH	Royal Brisbane and Women's Hospital
SAE	Serious Adverse Event
SDM	Substitute decision maker
SOFA	Sepsis-related Organ Failure Assessment
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
UQCCR	The University of Queensland Centre for Clinical Research

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1. GENERAL INFORMATION

1.1 Title:

A prospective pharmacokinetic evaluation of the plasma and cerebrospinal fluid concentrations of a single dose ceftolozane/tazobactam in infected critically ill patients with an indwelling external ventricular drain

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1.3 Investigators:

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Royal Brisbane and Women's Hospital – Ms Janine Stuart

2. BACKGROUND INFORMATION

2.1 Rationale for the study

Although relatively less frequent, Gram-negative nosocomial meningitis and ventriculitis are observed in critical care settings, often associated with brain trauma, brain surgery, spinal fluid shunt after brain surgery, spinal abnormalities or severe urinary tract infections with bacteraemia [1]. Gram-negative meningitis is particularly challenging for treatment, when reduced susceptibility of some of the common etiologic bacteria is encountered (e.g. *Acinetobacter baumannii*, *Pseudomonas aeruginosa, Enterobacter aerogenes*) [1, 2]. Furthermore, the presence of the blood-brain-barrier (BBB) has meant that the choice of systemic antibiotics is very restricted due to the limited ability of many antibiotics to achieve adequate concentrations in the cerebrospinal fluid (CSF). The poor CSF penetration may also contribute to an accelerated rate of the emergence of resistant pathogens in some patients/units. A significant proportion of Gram-negative bacilli clinical isolates (from patients with meningitis) are resistant to broad spectrum antibiotics such as the third or later generation cephalosporins [2]. With the wide spread use of these antibiotics, the incidence of resistant nosocomial infections has increased. Thus, there is an acute need for novel antibiotics that can achieve adequate concentrations in the CSF, while exhibiting an excellent spectrum of activity.

Ceftolozane/tazobactam is an emerging newly available antibiotic that has a broad spectrum of activity, and could be potentially useful in the treatment of Gram-negative meningitis. As compared to other commonly used beta-lactam antibiotics, it exhibits superior antibacterial activity against difficult-to-treat Gram-negative organisms, such as *Pseudomonas aeruginosa* and Enterobacteriaceae spp [3]. It is relatively stable against various resistance mechanisms encountered by other beta-lactams, and may be useful in the treatment of multi-drug-resistant (MDR) infections [3-5]. However, data relating to CSF penetration is limited. In the critically ill, achieving adequate antibiotic exposure, especially against the high MIC of some Gram-negatives (e.g. *Pseudomonas*), is difficult even in plasma, let alone in CSF for which a distribution barrier (i.e. BBB) exists. Thus, it is prudent to investigate the CSF pharmacokinetics of this new drug before it is used ‘off-label’ by clinicians without supportive data.

This study will describe the plasma and CSF pharmacokinetics of a 3g dose of ceftolozane/tazobactam in critically ill patients with an indwelling external ventricular drain (EVD). We will use a population pharmacokinetics approach to determine if altered dosing or alternative modes of administration, such as prolonged infusion, should be considered to improve plasma exposure. Given that direct administration into the CSF (e.g. intra-ventricular route) is not only invasive but also may risk neurotoxicity, pharmacokinetic studies should explore the extent of drug distribution into CSF with systemic administration. There is no clinical data on the CSF penetration of ceftolozane/tazobactam in critically ill patients at the moment, and as such, this is a highly valuable study.

2.2 Study feasibility

The intensive care unit (ICU) at the Royal Brisbane and Women's Hospital (RBWH) is a 30-bed tertiary-level ICU that serves as a major referral centre for neurosurgical patients. A significant proportion of these neurosurgical patients have EVDs *in situ* as part of their routine clinical care in the ICU. As such, the prospective pharmacokinetic (PK) study describing both the plasma and CSF PK of a single dose of ceftolozane/tazobactam in ten critically ill patients with indwelling EVD aged ≥ 18 years is highly feasible. The Burns, Trauma and Critical Care Research Centre (BTCCRC), UQCCR, The University of Queensland, which has extensive experience in antibiotic PK studies and is affiliated with RBWH, will oversee the overall project management.

3. STUDY OBJECTIVE & HYPOTHESIS

3.1 Objective

The objective of the study is to describe the pharmacokinetics of a single dose of ceftolozane/tazobactam in the plasma and CSF in critically ill patients with an indwelling EVD.

3.2 Hypothesis

1. The plasma PK of cefolozane/tazobactam may be altered in critically ill patients with an indwelling EVD.
2. The distribution of ceftolozane/tazobactam into the CSF may be impaired by the BBB.

4. STUDY DESIGN

4.1 The Study

This is an open-label, single-dose PK study that will describe both the plasma and CSF PK of a single dose of ceftolozane/tazobactam in ten critically ill patients with indwelling EVD aged ≥ 18 years.

5. ASSESSMENT OF ENDPOINTS

5.1. Primary endpoints

The primary endpoint will be the development of a population PK model as well as dosing simulations that are likely to achieve pharmacokinetic/pharmacodynamic (PK/PD) targets of ceftolozane/tazobactam based on presumed or confirmed etiologic bacterial pathogens.

6. SELECTION OF PARTICIPANTS

6.1 Inclusion criteria

Patients treated in the ICU are eligible for inclusion in the study if **ALL** of the following criteria are met:

- Age ≥ 18 years

- The presence of an indwelling external ventricular drain (EVD) or requiring EVD insertion due to obstructive hydrocephalus/subarachnoid haemorrhage

6.2 Exclusion criteria

Patients are excluded from the study if **ONE OR MORE** of the following criteria are met:

- Known or suspected allergy to penicillins and cephalosporins
- Pregnancy
- Receiving renal replacement therapy
- Glomerular filtration rate less than 10 mL/min
- Receiving piperacillin/tazobactam or having received piperacillin/tazobactam in the past 7 days before enrolment

7. ASSESSMENT OF PARTICIPANTS

7.1 Study Procedures

Study Protocol (**Figure 1**)

Patient enrolment:

All patients admitted to the ICU at RBWH during the study period will be screened for eligibility to participate in this study based on the under listed inclusion and exclusion criteria. Clinical staff in the ICU will identify potential patients that may be suitable for inclusion into the study. The clinical research team will further assess patients suitable for participation. As patients will not be in a position to give consent due to medical sedation or unconsciousness or severe illness, the patient's authorised representative (termed 'substitute decision maker') will be approached for informed consent. Investigators will explain the procedures of the study verbally in addition to the structured Person Responsible Information Sheet and Consent Form that will be provided to the substitute decision maker (SDM) prior to consenting. Following their enrolment and participation in the study, a Participant Information Sheet and Consent Form will be provided to the patient, seeking their consent for continued participation in the study. A total of ten patients will be enrolled.

Enrolment Log:

An enrolment log will be used to record patient recruitment to the study. This will be maintained by the research staff.

Study drug:

Ceftolozane sulfate/tazobactam sodium (Zerbaxa) is a white to yellow powder for solution. Each vial contains 1000 mg of ceftolozane (as ceftolozane sulfate) and 500mg tazobactam (as tazobactam sodium). Each vial contains the following inactive ingredients: sodium chloride, arginine and anhydrous citric acid.

Merck Sharp and Dohme (Australia) Pty Limited shall make available sufficient quantities of Study drug free of charge to carry out the study. The sponsor (University of Queensland) and the Chief Investigator shall be responsible for the maintenance of appropriate records and assure appropriate supply, handling, storage, distribution and usage of the Study Drug in accordance with the Protocol. The supplied Study Drug will not be used for any other purpose other than stated in the protocol. There will be no cost to the study participants.

Drug administration:

Each vial of ceftolozane/tazobactam will be reconstituted with 10 mL of sterile water for injection or 0.9% Sodium Chloride for injection (normal saline) and gently shaken to dissolve. For preparation of the specified dose: the entire contents of each reconstituted vial will be withdrawn and added to an infusion bag containing 100 mL of 0.9% Sodium Chloride for Injection (normal saline) or 5% Glucose Injection. The study participants will receive a single dose of 3g ceftolozane/tazobactam (2g ceftolozane + 1g tazobactam, i.e. two vials) via intravenous infusion over 1 hour. Ceftolozane/tazobactam is to be infused through a dedicated peripheral line, or through a dedicated lumen of a central venous catheter or peripherally inserted central catheter line. No other medications or fluids are to be infused through the lumen dedicated to study drug during study drug administration. The line will be flushed at the conclusion of the infusion. The dose will be administered while the EVD is in place.

Sample collection:

Blood sample collection

Arterial blood samples (2 to 3 mL for each sample) will be collected on 12 occasions (i.e. prior to dose administration, and serially at 15 min, 45 min, 75 min (after 15 min line flushing), 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 24 hours).

CSF sample collection

CSF samples (0.5 to 1 mL) will be simultaneously collected from the EVD on 6 occasions (prior to dose administration, at 2 hours, 4 hours, 6 hours, 8 hours, 24 hours). The drip chamber of the EVD system will be emptied about 30 minutes before the first CSF sample collection and after each sample collection. In addition, the entire volume of the CSF drainage during the eight hours of sampling will be recorded and collected. The actual time of collection for individual samples will be recorded and used in the analysis. All samples will be coded and stored in the ICU Research Laboratory and will be analysed at the BTCCRC laboratory located on the RBWH campus. Sample handling procedures as per Attachments - Appendix A.

Urine sample collection

Total volume of urine produced over the 24-hour sampling period will be collected. A 1mL aliquot will be kept to analyse the amount of drug cleared into urine over the dosing interval and the rest will be used to measure the patient's urinary creatinine clearance.

Clinical Data Collection:

A structured data collection sheet will be used to collect patient specific clinical data exclusively from electronic and paper based patient medical records, including:

- Admission details
- Demographic data - initials, date of birth, gender, race, medical history, height, weight
- Physical examination including vital signs
- Acute Physiology and Chronic Health Evaluation II [APACHE II] and APACHE III score and risk of death at ICU admission
- Sequential Organ Failure Assessment [SOFA] score at ICU admission
- Presence of shock on day of sampling
- Presence of mechanical ventilation on day of sampling
- Concurrent medications on day of sampling
- Diagnosis/es
- Patient co-morbidities
- Clinical hematological and biochemical data on day of sampling including: total white cell count, neutrophil count, platelet count, serum creatine concentration, hepatic function markers (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alanine phosphatase [ALP], gamma glutamyl transferase [GGT], international normalised ratio [INR], bilirubin).

All case report forms and other data (including, without limitation, written, printed, graphic, video and audio material, and information contained in any computer database or computer readable form) created or developed in connection with the Study will be owned by the Chief Investigator. All data will be collected by study research staff.

Sample assay:

After sampling, all samples will be stored at -80^{o}C until assayed. The concentrations of ceftolozane and tazobactam in the biological samples will be determined by chromatographic methods (HPLC and LC-MS/MS) that are validated and conducted in accordance with the Food and Drug Administration's guidance for industry on bioanalysis. The limit of quantification (LOQ) of the assay methods will be $\leq$0.1 mg/L for both ceftolozane and tazobactam. The validated concentrations will be submitted for population pharmacokinetic analysis and dosing simulation with PK/PD analysis.

Population Pharmacokinetic Analysis:

NONMEM software (version 7.3, GloboMax LLC, Hanover, MD) will be used for population PK analysis. A stepwise approach will be following in the model building process: (i) determination of the structural base model; (ii) selection of the best fit statistical error model (iii) development of covariate model, (iv) and finally model evaluation.

(i) Determination of the structural base model: Different structural models based on one, two or three compartment will be fitted to the concentration-time data using NONMEM subroutines. Both linear and/or Michaelis–Menten kinetics will be assessed for elimination and distribution of the drug. Also linear and/or non-linear binding to plasma proteins will be considered.

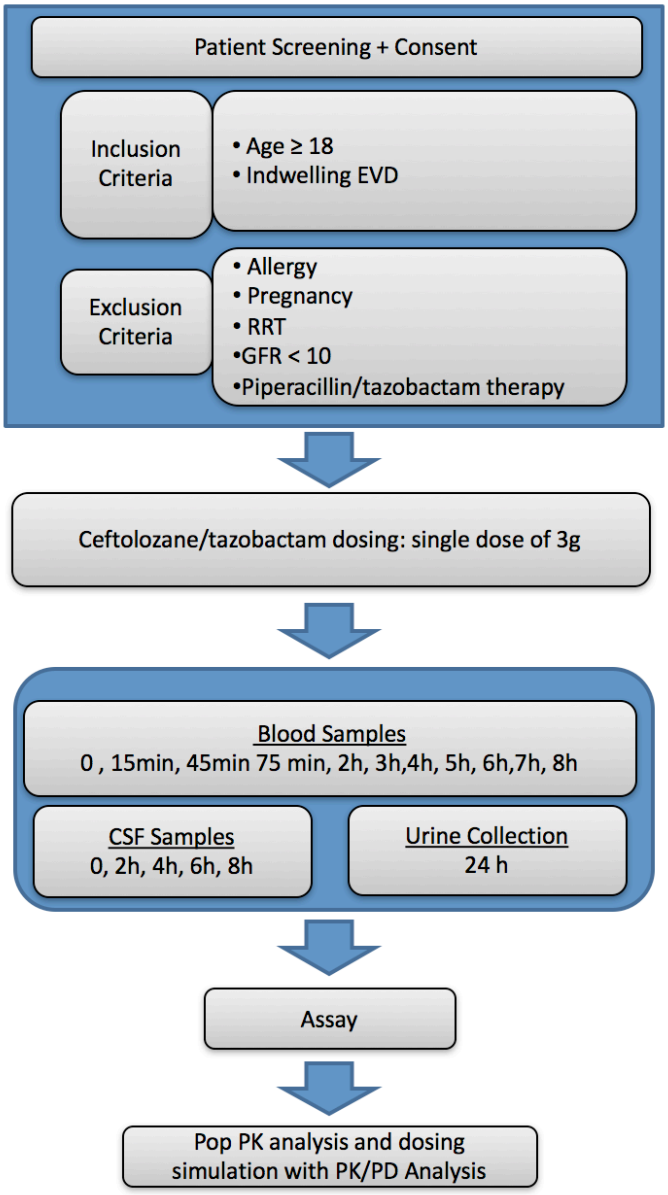
ii) Selection of the best fit statistical error model: Inter-individual variability will be assumed to follow a log-normal distribution. For the residual error model additive, proportional and a combination of additive and proportional models will be tested.

(iii) Development of covariate model: Available clinical covariates will be assessed for biological plausibility and subsequently evaluated in the covariate analysis. Selected covariates will be tested on the structural model parameters (volume(s) of distribution and clearance). Standard covariate evaluation algorithms will be followed through forward addition and backward elimination or a combination of forward addition and backward elimination in a stepwise fashion.

(iv) Model evaluation: Diagnostic plots and statistical examination through objective function values will be used for comparison of models. Diagnostic plots will include scatter plot of residuals versus predicted values, scatter plot of observed values versus predicted values and scatter plot of weighted residuals versus explanatory variables. Objective functions will include log-likelihood ratio test for nested model. A decrease in objective function value by greater than 3.84 (which corresponds to $p < 0.05$ based on chi-square test) will be considered statistically significant. Other objective function values also, Akaike Information Criterion (AIC) or Bayesian Information Criterion (BIC) will be examined. Finally, the stability of the final model will be assessed by the nonparametric bootstrapping method.

Dosing Simulations with PK/PD analysis: Subsequent to population PK analysis, Monte Carlo simulations for drug concentrations in plasma will be performed using reported minimum inhibitory concentrations (MICs) of the presumed or confirmed etiologic bacterial organisms, or specific bacterial MICs if determined.

Figure 1: Study protocol



8. DURATION OF PARTICIPATION

The duration of study for each patient will be 24 hours following administration of a single dose of ceftolozane/tazobactam.

9. STUDY TERMINATION

The study may be terminated at any time at the request the Chief Investigator, or a regulatory authority, with proper and timely notification of all parties concerned. The Independent Ethics Committee will be informed promptly and the investigator will supply reason(s) for the termination or suspension, as

specified by the applicable regulatory requirements. Otherwise, the study is considered terminated upon completion of all patient treatments and evaluations.

10. ASSESSMENT OF SAFETY

10.1 Study Safety Reporting

10.1.1 Serious Adverse Event

All patients will be monitored for potential development of Serious Adverse Events (SAEs) which are defined as any untoward medical occurrence that meets one or more of the following criteria:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect; or
- Is an important medical event which may require intervention to prevent one of the previously listed outcomes?

10.1.2 Suspected Unexpected Serious Adverse Reaction

Suspected Unexpected Serious Adverse Reaction (SUSAR) is any SAE, the nature, severity or frequency of which is not consistent with information in the most current Summary of Product Characteristics (SPC) or Package insert. Any adverse event, SAE or SUSAR will be recorded in the study CRF and managed in the ICU in line with best clinical practice according to the patient symptoms.

10.2 Safety Monitoring of Study Participants

Monitoring the safety of study participant and the progress of the study will be made at two levels. Firstly, the ICU research management forum at the study site, which is attended by all intensive care specialists, will be used for a comprehensive appraisal of the study protocol including assessment of risk to study participants. Monthly meetings of this forum will be used to evaluate the progress of the conduct of the study based on first-hand experience during the conduct of the study.

Secondly, on a day to day basis participants will be monitored for potential SAEs and SUSARs. This monitoring will be done by nursing staff, doctors treating the patient and the research team. The clinical staff at the study site (nurses and doctors) will be aware when a patient is enrolled in the study and will be requested to remain vigilant for any ADRs or SUSARs. Nurses look after the patients in the ICU 24 hours per day (one nurse for one patient) and this provides a constant monitoring of the patients. In addition doctors will examine the patient multiple times per day. Further to these, the clinical pharmacists and research team will provide additional reviews of the patient. Following these reviews, investigators of the study will report any ADRs or SUSARs related to the study drug both to

the RBWH Human Research Ethics Committee (HREC) and the sponsors. The SAE reports will be forwarded to the HREC in accordance with local requirements. The Chief Investigator of the study is a consultant pharmacist and has the required expertise to assist and advice the HREC about reports of serious adverse events.

The Chief Investigator will forward to MSC Global Safety Group (fax number: +1-215-993-1220) any SAE and SUSAR information within 2 business days of learning of the information. The SAE reports will be forwarded to the Independent Ethics Committee in accordance with local requirements.

The Chief Investigator agrees to perform the study in accordance with this study protocol, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and the applicable regulatory requirements. The Chief Investigator is required to ensure compliance with all procedures required by the study protocol.

10.3 Management of Safety Risks

There are risks to participants involved with the conduction of this study: mainly an increased risk of developing or worsening CNS infection related to CSF sampling via the EVD. Patients undergo routine CSF sampling once per day as part of standard care and surveillance. For this study, the EVD will be accessed 6 times, however, investigators will incorporate routine sampling into the study to reduce sampling times over the 24 hour period. So in effect, the EVD will be accessed an additional 4 times. Two samples will be divided into two aliquots with one going to the local laboratory for routine evaluation and the other aliquot being used for the study analysis. This increased risk will be minimised by strict adherence to RBWH ICU guidelines/protocol for safe and effective CSF sampling from an EVD. The person sampling CSF from the EVD will be a research nurse specially trained as per these guidelines/protocol. Although there is added risk associated with more frequent CSF sampling via the EVD, this is justified given that more frequent sampling will greatly improve the accuracy in describing the exposure of ceftolozane/tazobactam in the CSF.

11. ETHICAL CONSIDERATIONS

11.1 Ethical Principles

This study is to be performed in accordance with the ethical principles of the Declaration of Helsinki and all relevant national and local guidelines on the ethical conduct of research. Prior to commencement, the study protocol will be presented to the HREC at the RBWH for approval. Local governance approval will then be sought. The Chief Investigator will be responsible for submitting progress reports, adverse event reports and any other required documentation to the HREC in accordance with their guidelines. Copies of all HREC and research governance correspondence will be kept with the study investigator files.

11.2 Confidentiality and Privacy

Patients enrolled will be allocated a unique study number. The Research Coordinator will compile an enrolment log including the patient's name, date of birth, hospital identification number, unique study number and date and time of enrolment. Subsequent data will be identified by the unique study number only. The enrolment log and study data will be kept separately. All patient details and study data will be kept in a locked office at the study site. No identifying data will be entered into the electronic data base.

All study data will be entered into a secure computer maintaining confidentiality in accordance with local legislation on privacy and use of health data. When archiving or processing data pertaining to the investigator/and or patients, the coordinating centre will take all appropriate measures to safeguard and prevent access to this data by any unauthorised party.

The Chief Investigator will maintain the confidentiality of all study documentation, and take measures to prevent accidental or premature destruction of these documents. The Chief Investigator will retain the study documents at least fifteen years after the completion or discontinuation of the study. The Chief Investigator will be notified prior to the destruction of any study essential documents following the study completion or discontinuation. If the Chief Investigator's personal situation is such that archiving can no longer be ensured by him/her, the investigator shall inform the sponsor, MSD and the local HREC of these changes in circumstances and the relevant records shall be transferred to a mutually agreed designee.

11.3 Participant Consent

The Chief Investigator or their nominated delegate will obtain written informed consent from any conscious and comprehending patient, prior to enrolment in the study. Obtaining written and informed consent directly from patients in the ICU prior to enrolment in the study will not be possible because these patients are often unconscious, sedated, intubated and too ill to understand information relating to study participation. Under these circumstances, the approach to obtaining consent in this study will be based on the guidelines of the Australian National Health and Medical Research Council (NHMRC) National Statement (i.e. consent will be obtained from their SDM). The procedure for obtaining consent from the patient's SDM will be approved by the local HREC prior to use. SDMs will be given a verbal explanation of the study and the Person Responsible Information Sheet and Consent Form to read. They will be given opportunity to ask questions prior to deciding on participation of the participant. If the SDM consents to the participant's participation in the study they will be given a copy of the signed Person Responsible Information Sheet and Consent Form. Following their enrolment and participation in the study, a Participant Information Sheet and Consent Form will also be provided to the participant, seeking their consent to continued participation in the study. If the partipant consents to

their continued participation in the study, they will be given a copy of the signed Participant Information Sheet and Consent Form.

All interaction between research staff and potential or actual participants and their SDMs will take into consideration the stress or emotional factors associated with critical illness and ensure that the dependency of potential participants and their SDMs on medical personnel providing treatment does not compromise the freedom of decision making to participate.

12. FINANCING AND INSURANCE

12.1 Funding and Indemnity

All costs related to ethics preparation, patient enrolment, data collection and sample collection assaying will be incurred by The University of Queensland.

MSD has provided The University of Queensland (Sponsor) with funding in support of this study. The University of Queensland will contract with the Intensive Care Services Research Office at the Royal Brisbane and Women's Hospital to conduct the study within the ICU. These payments are for services provided by the Chief Investigator and third party entities i.e. research staff at Royal Brisbane and Women's Hospital. Indemnity will be provided by the University of Queensland and Metro North Hospital Health Services District.

13. PROJECT TIMELINE

Date	Project Milestone
February 2017	CRF and Patient information and consent documents
March 2017	Ethics application to Independent Ethics Committee
April 2017 to February 2019	Patient recruitment
March to April 2019	Database lock, data analysis and initial results

14. REFERENCES

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15. APPENDICES

Appendix A: Sample Collection, Handling and Storage

Plasma Samples

- Blood (1 to 2 mL) will be collected into a 3 ml Lithium Heparin tube, with or without separator gel (acceptable alternate anticoagulants to be announced).
- Blood samples should be kept chilled on ice or in the fridge until centrifugation (within 6 hours).
- Blood samples should be centrifuged at 3000 rpm for 10 minutes to separate plasma.
- Plasma (approximately 1 mL) should be transferred into a labelled cryovial and stored at -80°C until analysis.

CSF samples

CSF will be collected in lithium heparin tubes and centrifuged (3000 rpm for 10 minutes) to separate out any red cells that may be present. The samples will be aliquoted and frozen at ¯80°C until recruitment is complete.

- CSF (0.5 to 1 mL) will be transferred to a labelled cryovial prior after sampling via the EVD.
- CSF samples will then be chilled on ice or in the fridge until stored at -80°C prior to analysis.