Study title: Single Dose Population Pharmacokinetics

of Intravenous Posaconazole in Critically Ill Patients

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Single dose population pharmacokinetics of intravenous posaconazole in critically ill patients

Research Protocol
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Contents

1. INTRODUCTION

Treatment of fungal infections remains a significant challenge to clinicians, particularly for patients requiring intensive care unit (ICU) management where the incidence of invasive fungal infections and associated mortality rate are distinctly high[1]. Response to antifungal therapy is generally sub-optimal despite the emergence of extended spectrum novel anti-fungals like the echinocandins and triazoles. Although the relative incidence of invasive fungal infection is low, and hence therapeutic anti-fungal dosing is relatively less frequent, prophylactic use of oral/systemic antifungal agents has become a very common indication due to the increasing use immunosuppressants during critical care, cancer chemotherapy and organ transplantation [2,3]. This has led to a wide systemic exposure to antifungal drugs in considerable number of patients. In parallel, such widespread use increases the risk of emergence of resistant fungi, unless adequate exposure is defined and ensured during clinical use of the drugs. Unfortunately, it has been a challenge to explicitly describe the dose-exposure-response relationships in all target patient populations, especially for new antimicrobials prior to their wide clinical application.

Posaconazole is a new extended spectrum triazole active against a range of yeasts and molds including *Aspergillus, Candida, Coccidioides, Cryptococcus neoformans, Fusarium*, *and Zygomycetes*[4]. It may be used for the prevention of invasive fungal infections in immunocompromised patients including febrile neutropenic patients and those receiving immunosuppressant drugs for graft-vs-host disease during stem cell transplantation[5]. It may also be used for treatment of systemic fungal infections [6].The use of posaconazole in ICU patients has been limited to stable patients to ensure reliable bioavailability from the oral formulations [7].Oral formulations have important limitation in that they cannot be used in critically ill patients who may be unable to take oral doses or bioavailability may be compromised due to erratic absorption. Recently, an intravenous (IV) formulation has been developed to address these limitations[8]. Initial pharmacokinetic (PK) investigations of the IV formulation were conducted in hematology patients [8], with further data in other patient populations still forthcoming; particularly in the critically ill where the IV formulation would probably be used most frequently.

Most of the available PK data for posaconazole is from non-critically ill patients who received the oral formulation. Although the absorption phase of the kinetics is not relevant for the IV formulation, data on the distribution, metabolism and elimination properties would still be informative of the IV kinetics. The tissue distribution of posaconazole is extensive with a very large volume of distribution owing to its high lipophilicity[9]. It is highly bound to plasma proteins (98-99%) and therefore very likely to be affected by the variable changes in plasma protein concentration in critically ill patients. The major elimination pathway of posaconazoleis through biliary excretion (about 77%) of mainly the

unchanged parent compound and the rest through renal execration of as a glucuronide conjugate [9,10]. Thus, posaconazole PK is expected to be hardly affected in patients with renal impairment including those undergoing haemodialysis[11,12]. The extent of hepatic metabolism is also limited that the influence of hepatic dysfunction on the PK of posaconazole appears minimal; existing studies have not indicated a need for dosing adjustment in hepatic impairment although monitoring plasma concentration is advocated [10,13]. Other factors such as demographic variables including age, sex and race reportedly have no clinically relevant influence on the PK of posaconazole in healthy adults [14] suggesting no need of dose titration for these covariates.

However, a number of studies have described PK variability due to altered absorption/bioavailability which can frequently result in sub-therapeutic plasma concentrations, forming strong case for therapeutic drug monitoring [15,16]. Nonetheless, it is unclear whether the observed low concentrations can also be explained, at least in part, by other factors such as disease-related PK changes or if the obvious plausibility of altered absorption has masked such investigations. Most population PK models described so far are based on one compartment models, which do not reveal if the observed variability in concentrations is due to changes in PK parameters such as volume of distribution or clearances [17]. The influence of disease state on these PK parameters has been extensively described for several antimicrobials in the critically ill patient populations [18,19]. Although data on the new IV formulation of posaconazole in this patient population is lacking, there is evidence from previous PK studies on the oral formulation that PK variability not observed in healthy study participants was observed in patients with invasive fungal infections, although it was explained primarily in relation to altered bioavailability from the oral formulation[10]. In surgical ICU patients, Störzinger*et al.*[7]observed low plasma concentration of posaconazole, which was administered via nasogastric tube. Similar findings were reported in general ICU patients[20]. Although the explanation in these reports was again the irregular absorption, the influence of other pathologic changes remains to be investigated. A PK evaluation of IV posaconazole in critically ill patients, not confounded by the absorption factor, would reveal if there is any pathophysiology-induced PK alteration. Such a study will also give insight into the dose-exposure relationships and optimal treatment regimen, although the pharmacodynamic (PD, exposure-response relation) of posaconazole is yet to be clarified.

Posaconazloe is thought to exhibit both concentration and time dependent antimicrobial activity, which can be described by the ratio of AUC/MIC[21,22]. However, PD studies are limited and inconsistent that the optimal dosing target is yet to be described[17]. Generally maintaining higher concentrations may be necessary to improve patient outcomes[6,15,17,23]. Some guideline recommendations are steady state trough concentrations greater than 0.7 mg/L may be required for prophylaxis and greater than 1mg/L for treatment of invasive fungal infections[3]. Clearly, more data

is required to accurately describe optimal plasma concentration-response relationships as there is inconsistency between studies/authors in the recommended trough concentrations [3,10,15]. However, it is also clear that the clinical efficacy is well correlated with plasma concentration [15]. It is, therefore, essential to describe the relationship between dosing regimens and subsequent exposure through a thorough PK analysis, particularly for the new IV formulations, which pharmacokinetically may behave differently from the oral formulations that have been investigated so far. Such PK analysis would provide the foundation for the design of optimal dosing regimens for ICU patients, through PK/PD based modelling and clinical trial simulations. The application of population PK models also extends to the determination of susceptibility breakpoints through analysis of dosing simulations data [24]. This would be invaluable given the limited clinical experience of posaconazole in the ICU settings and that, previous break points which correspond to the oral dosing regimens [24,25], may not be relevant to the applications of the IV formulation in ICU patients.

This prospective, observational, pharmacokinetic study of posaconazole aims to describe the population PK of posaconazole after a single IV dose administration in the critically ill. It will assess the influence of pathophysiologic changes including altered plasma protein concentrations/binding in the critically ill on the PK of posaconazole.

2. CLINICAL HYPOTHESES

- Pharmacokinetic properties of the new intravenous posaconazole formulation will be distinct as compared to the previous oral formulations
- Dose-exposure relationships from the new formulation may be different in intensive care unit patients as compared to general wards patients, due to disease-related factors
- Changes in plasma protein concentration or binding capacity in the critically ill may affect the pharmacokinetics of posaconazole

3. OBJECTIVES

- To describe the pharmacokinetics of intravenous posaconazole in critically ill patients
- To assess the influence of critical illness on the pharmacokinetics of posaconazole administered via intravenous infusion
- To assess the impact of altered plasma protein concentrations/binding in the critically ill on the pharmacokinetics of posaconazole

4. STUDY DESIGN

This is a prospective, observational, pharmacokinetic study. The study will enrol eight patients with presumed or confirmed systemic fungal infections, who are admitted to ICU. Patients aged greater than 18 years with established central venous access for drug administration and no history of allergy for triazole antifungals will be approached for enrolment if they have not taken posaconazole within two weeks of time and if they are not pregnant. A single dose of 300mg IV posaconazole will be administered to eight study participants. Serial blood samples will be collected at pre-defined time points for determination of both total and unbound plasma concentrations. Structured data collection sheets will be used to collect other clinical data. The data generated will be subject to population pharmacokinetic analysis using computer software. Monte Carlo simulations will be performed to describe dose-exposure relationships.
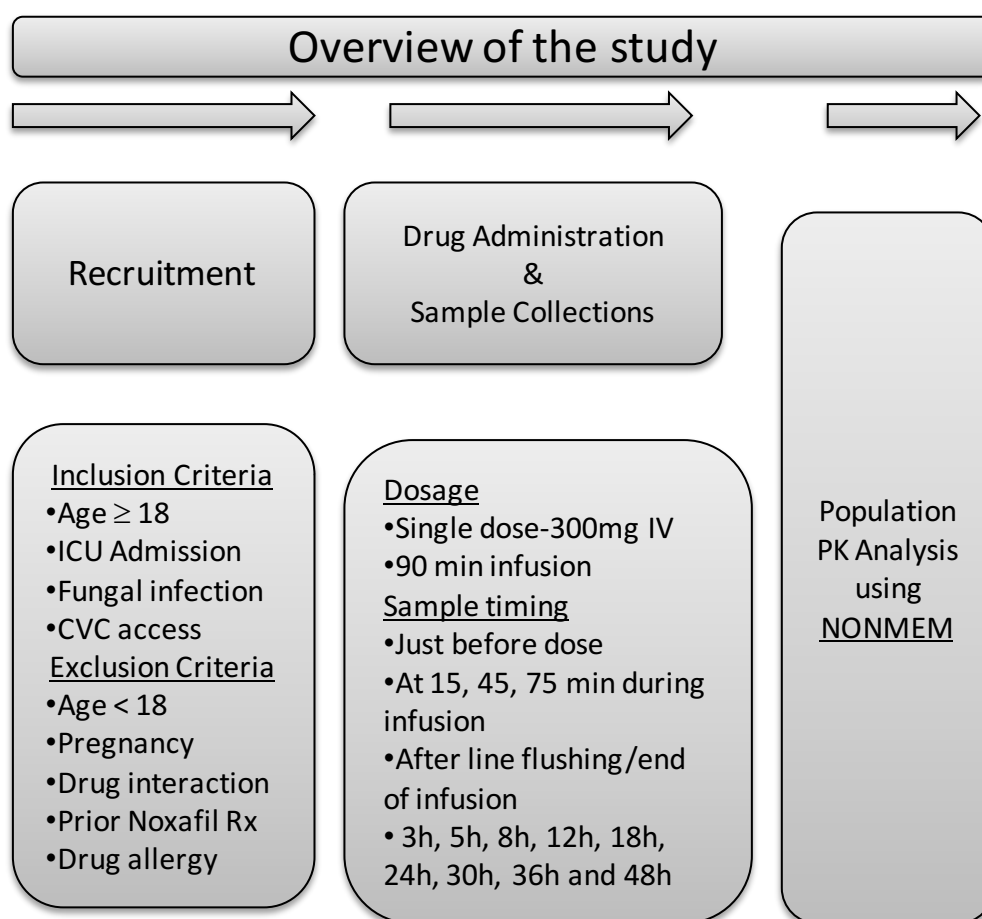

Figure 1. Study flow chart

5. STUDY PROCEDURES

5.1 Patient screening

All patients admitted to the ICU at the Royal Brisbane and Women's Hospital (RBWH) during the study period with suspected or confirmed fungal infections and receiving/requiring systemic antifungal therapy will be screened for eligibility to participate in this study based on the under listed inclusion and exclusion criteria.

Inclusion criteria

- Age ≥ 18 years
- Admission for ICU care
- The presence of suspected or confirmed fungal infection requiring systemic antifungal therapy
- Presence of central venous access for drug administration

Exclusion criteria

- Age < 18 years
- Pregnancy
- Prescription of drugs that are known to interact with posaconazole
- Oral posaconazole use within the last two week prior to enrolment
- Documented history of drug reaction to the triazole antifungal medications

A decision to prescribe an anti-fungal therapy will occur as part of the routine care by the attending clinicians. After such a decision has been made by the doctors treating the patient, the study will use the opportunity of this clinical condition that requires treatment with systemic anti-fungal medications, to investigate the pharmacokinetics of the study anti-fungal medication (a new intravenous formulation of posaconazole). Therefore, this study does not aim to initiate treatment for a suspected or proven systemic fungal infection for the study purpose, and will recruit patients only after such a decision is made by the doctors treating the patients.

The usual circumstances for the diagnosis of a suspected systemic fungal infection that requires treatment with systemic anti-fungal medications are non-specific and involve empiric assessment of the patient's clinical condition, assessment of potential risk factors as well as clinical interpretation of various diagnostic mycological and radiological investigations. Proven systemic fungal infections are those confirmed by presence of hyphae in a histological or cytological specimen with further evidence of tissue damaged seen in histological examinations, or positive culture for a clinical specimen with a clinical or radiological sign of infection at the site from which specimen was taken. Serologic tests

(mainly for *Aspergillus, Blastomyces, Candida, Coccidioides, Cryptococcus,* and *Histoplasma*) are also used to confirm fungal infections. The diagnosis of either a suspected or confirmed systemic fungal infection by the doctors treating the patient warrants treatment with systemic anti-fungal medications.

5.2 Patient enrolment

Patients that meet all the inclusion criteria and none of the exclusion criteria will be approached for informed consent. Investigators of the study will explain the procedures of the study verbally in addition to the structured patient information sheet that will be provided for the participants prior to consenting. The participants' next of kin will be approached if any of the participants are not in a position to give consent due to medical sedation or unconsciousness or severe illness. A total of 8 patients will be enrolled.

5.3 Drug administration

All patients enrolled in the study will receive the usual treatment with anti-fungal agent(s) as per the standards of practice at the study hospital. The usual care for suspected or confirmed systemic fungal infections will be at the discretion of the clinical team treating the patient and in accordance with the local guidelines and standards of practice. The typical initial empiric therapy for suspected or proven invasive fungal infections in patients at the Royal Brisbane and Women's Hospital is fluconazole. Voriconazole or amphotericin B may also considered as an alternative initial agent in immunocompromised patients if invasive aspergillosis is confirmed or if there is a high suspicion of a mould infection. In non-neutropenic patients with invasive candidiasis, fluconazole may be used if the organism is deemed susceptible. For fluconazole-resistant candidiasis in non-neutropenic patients, caspofungin is the agent most likely to be used. For suspected or proven acute invasive aspergillosis, voriconazole is first-line therapy although amphotericin B or caspofungin may also be used.

In addition to the drugs given as part of the usual care as described above, a single dose of posaconazole will be administered for the study purpose. A single dose of 300 mg intravenous posaconazole solution, diluted with 0.9% sodium chloride or 5% dextrose in water, will be administered to each study participant by slow infusion over 90 minutes through a central venous access. The drug will be infused through a 0.22 micron polyethersulfone (PES) or polyvinylidene difluoride (PVDF) filter. The magnitude of the single dose chosen for this study is in accordance with with the approved maintenance dosing regimen.

5.4 Sample collections

Serial blood samples will be collected just before and after administration of the single dose of posaconazole. The first sample will be collected immediately before commencing of the posaconazole infusion. The next three samples will be collected during drug infusion at 15 min, 45min and 75 minutes after commencing the infusion. The fifth sample will be taken at the end of line flushing (15-20min) after the 90 minutes infusion. The next samples will be taken at 3h, 5h, 8h, 12h, 18h, 24h, 30h, 36h and 48h after the commencement of drug infusion. The actual time of collection for individual samples will be recorded and used for analysis. Lithium heparin tubes will be used for sample collection. The volume of each blood samples will be 2-3ml. The plasma will be separated by centrifugation (3000 rpm for 10 minutes) and frozen under - 80°C for storage until the subsequent assay of total and unbound posaconazole concentration.

5.5 Clinical data collection

Patients' electronic and paper based medical records will be reviewed to collect clinical data including demographic characteristics, list of diagnosis, microbiological data, vital signs, and clinical haematological and chemistry data. A structured data collection sheet will be used to collect these patient specific clinical data, which will include the following:

- Physical examination including vital signs
- ICU and Hospital admission and discharge dates and times
- Acute Physiology and Chronic Health Evaluation II [APACHE II] score and risk of death at ICU admission, APACHE II diagnosis upon recruitment
- Sequential Organ Failure Assessment [SOFA] score at ICU admission and daily during ICU antibiotic course
- Presence of shock on days of sampling
- Presence of mechanical ventilation
- Serum creatinine concentrations
- Urinary creatinine clearance (if available)
- Hepatic function markers (alanine aminotransferase (ALT), aspartate aminotransferase (AST), alanine phosphatase ALP), gamma glutamyl transferase (GGT), international normalised ratio (INR), bilirubin
- Medication list on days of sampling
- Antimicrobial Data: type, dose, dosing interval, duration of infusion
- RRT data:
  - Filter type, filter size, filter age at time of sampling

- o Blood flow rates

- o Dialysate dose

- o Haematocrit

- o Pre/post dilution dose

- o Patient fluid balance on day of sampling and targeted hourly fluid removal

- o Changes made to settings during sampling interval

- o Transmembrane pressure

- Infection data:

- o Organisms isolated and sample type,

- o Minimum inhibitory concentration if available

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 Principal Investigator. All data will be collected by study research staff.

5.6 Sample assay

An LC-MS/MS method for determination of total and unbound posaconazole concentrations in human plasma will be developed, validated and used for analysis of patient samples. Previously, we have successfully developed and utilized LC-MSMS methods for the determination of unbound drug concentration using plasma protein ultrafiltration technique for sample preparation. A similar approach will be employed to develop a method for determination of unbound posaconazole concentration. Our bio-analytical laboratory has state-of-the-arts technology with highly qualified analytical chemists who have developed and validated assay methods for various antimicrobials. Therefore, it is highly likely that a validated method will be available at our laboratory when the study progresses and samples are available for analysis. However, if the need arises, samples can be analysed at Pathology Queensland, Royal Brisbane and Women's Hospital, where a validated LC-MS/MS method for posaconazole assay exists.

6. PHARMACOKINETIC ANALYSIS

Pharmacokinetic data analysis will be performed on both the total concentration and unbound plasma posaconazole concentration following the procedures described below.

6.1 Initial non-compartmental analysis

The plasma concentration-time data will be subject to non-compartmental pharmacokinetic analysis using computer software applications such as PK-Solver or WinNonlin. The linear trapezoidal rule

will be followed for computation of area under the concentration-time curve. Results will be summarized for preliminary description of the single dose PK parameters, which will be utilized as initial estimates in the subsequent population PK analysis.

6.2 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 NOMEMEM 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 statistical error models: 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.

v) Dosing Simulation: Subsequent to population PK analysis, Monte Carlo simulations will be performed using either CLSI or EUCAST MIC interpretive criteria for the presumed or confirmed etiologic organisms, or specific MICs if available.

7. STATISTICAL ANALYSIS AND SAMPLE SIZE JUSTIFICATION

All data analysis will be performed by the investigator and his research team. Power calculation is not applicable for this prospective initial pharmacokinetic investigation in ICU patients. The planed pharmacokinetic data analysis and associated statistical considerations are as described above under the study procedures. We have performed previous studies with the proposed sample size for similar antimicrobial agents and have provided clinically meaningful results.

8. STUDY DURATION

The study will be conducted over 12-18 months from date of hospital approval.

9. STUDY DRUG SUPPLY

Merck Sharpe and Dohme (MSD) (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 Principal 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.

10. FUNDING AND INDEMNITY

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 Principal Investigator and third party entities i.e. research staff at Royal Brisbane and Women's Hospital. MSD will also provide prosaconazole free of charge for study participants. Indemnity will be provided by the University of Queensland and Metro North Hospital Health Services District.

11. MONITORING AND REPORTING SAE AND SUSAR

Serious Adverse Events (SAEs) 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

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 most current Summary of Product Characteristics (SPC) or Package insert.

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 firsthand experience during the conduct of the study.

Secondly, on a day to day basis participants will be monitored for potential serious adverse reactions (ADRs) and serious unexpected suspected adverse reactions (SUSAR). 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 SUSAR. 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 visit 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 HREC and the sponsors. The SAE reports will be forwarded to the HREC in accordance with local requirements. Investigators of the study are consultant intensive care clinicians and have all the required expertise to assist and advice the HREC about reports of serious adverse events. The Principal 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.

12. ETHICAL CONSIDERATIONS

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 Human Research Ethics Committee at the Royal Brisbane and Women's Hospital for approval.Local governance approval will then be sought.

The Principal 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.

13. 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.

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

14. CONSENT

The principal investigator or the 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 a clinical trial is frequently not 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 that developed from the guidelines of the Australian NHMRC National Statement.

Where it is possible for a conscious and comprehending patient to give informed consent to take part in this study before project related activities are undertaken, the study will be explained verbally to that patient by the principle investigator or their nominated delegate. The patient will be given the opportunity to read the participant information sheet and ask any questions prior to deciding on participation in the study. Intensive care physicians are highly experienced at caring for critically ill patients and also evaluating the competence of their patients to understand their illness and consent for therapeutic interventions. If the patient is deemed competent and consents to participate, they will be given a copy of the signed and dated consent form and the participant information sheet and any other documentation discussed through the consent process.

If a potential participant lacks the capacity to give consent because of their medical condition, consent will be obtained from an authorised representative. The procedure for obtaining consent from the authorised representative will be approved by the local HREC prior to use. Authorised representatives will be given a verbal explanation of the study and the information sheet to read. They will be given opportunity to ask questions prior to deciding on participation of the participant. If the authorised representative consents to the participant's participation in the study they will be given a copy of the signed Information and consent form.

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

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