IRB & DSRB APPLICATION FORM

OFFICIAL USE ONLY	
Doc Name : IRB & DSRB Application Form	
Doc Number : 205-001	
Doc Version : 4.0 (F)	**Date : 19 Jan 2007**

I. Basic Information

Protocol Title:

Management Of Severe sepsis in Asia's Intensive Care unitS – the MOSAICS study

Protocol Number (if available) and Current Version Date (if available):

Text Field

Study Team Members:

Note: *For a Multi-centre study within NHG, please appoint a Site PI for each NHG Institution in addition to the Principal Investigator. All investigators who have a responsibility for the consent process or direct data collection for this study should be listed below. Multiple copies of this page may be submitted as necessary. Additional copies of this page can downloaded at www.b2bresearch.nhg.com.sg*

Title	Full Name	Study Role	Institution/Department
Dr	Augustine Tee	Principal Investigator	Changi General Hospital / Respiratory Medicine
Dr	Tham Huae Min	Collaborator	Changi General Hospital / Anaesthesia and Surgical Intensive Care
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Study Sponsor:

If Other/Pharmaceutical Company, please specify name: Text Field

Note: *If this Study is initiated by Industry / commercial entities, please attach Annex D.*

Nature of Project:	Phase of Clinical Trial:
Clinical research	NAD

Research May Involve:

- ☐ Pregnant Women, Foetuses or Neonates *(Attach Annex F)*
- ☐ Children (Age < 21 yrs) *(Attach Annex G)*
- ☐ Prisoners *(Attach Annex H)*
- ☐ Outpatients
- ☒ Inpatients
- ☐ Healthy Volunteers
- ☒ Cognitively Impaired Persons – Please specify type: Encephalopathic or sedated critically ill intensive care patients

Research Participants Will Be:

- ☐ Paid - $_____
- ☒ Not paid
- ☒ Not charged for trial procedures

Has this proposal been rejected by any IRB / DSRB?

☒ No ☐ Yes If yes, please provide details for the rejection: _____

Study Site details:

☐ Single-Centre Study ☒ Multi-Centre Study:- No. of local sites: 10 No. of overseas sites: _____

This Application is submitted to:

SingHealth: ☒ SGH ☐ NHC ☐ NCC ☒ CGH ☐ SERI ☐ KKH ☐ NDC ☐ NNI ☐ SHP

NHG DSRB: ☐ Domain-A ☒ Domain-B ☐ Domain-C ☐ Domain-D

Is this a US FDA IND / IDE study?

☒ No ☐ Yes ☐ IND Study. Please provide the IND number: _____

☐ IDE Study. Please provide the IDE number: _____

Protocol Administrators

NHG Only: *Protocol Administrators are persons who are responsible for administrative matters related to the Study. They can be the Study Coordinators, Research Nurses or Clinical Research Associates, and need not be part of the Study Team. While the Principal Investigator remains the primary contact person, the DSRB may contact the Protocol Administrators for clarification of administrative matters related to the Study. You may list up to 3 Protocol Administrators. This section is optional but PI's are encouraged to nominate at least one Protocol Administrator.*

Full Name:
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Institution:
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Position Held:
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Signature:

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Date:
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II. Declaration of the Principal Investigator

***Information for NHG DSRB Only** – For a Multi-centre study within NHG, the PI and each NHG Site PI must sign this page. Please submit multiple copies of this page. Additional copies of this page can downloaded at www.b2bresearch.nhg.com.sg*

The information provided in this form is correct.

a. I will not initiate this study until I receive written notification of IRB/ DSRB approval and regulatory authority approval (if applicable).

b. I will not initiate any change in protocol without prior written approval from IRB/ DSRB except when it is necessary to reduce or eliminate immediate risk to the Study Participant. Thereafter, I will submit the proposed amendment to the IRB/ DSRB and other relevant authority for approval.

c. I will promptly report any unexpected or serious adverse events, unanticipated problems or incidents that may occur in the course of this study.

d. I will maintain all relevant documents and recognize that the IRB/ DSRB staff and regulatory authorities may inspect these records.

e. I understand that failure to comply with all applicable regulations, institutional and IRB/ DSRB policies and requirements may result in the suspension or termination of this study.

f. I declare that there are no conflicting interests for any of the research personnel participating in this research study. ***(Important: Should you or any of the research personnel have any conflicting interest in this research study, please complete Annex B – Conflict of Interest Declaration Form for each individual having the conflict)***

Remarks (if any):
Text Field

_____		_____	
Principal Investigator's Signature		*Date*	
Full Name:	Dr Augustine Tee		
Institution:	Changi General Hospital	*Position Held:*	Consultant
Department:	Respiratory Medicine	*Email address:*	augustine_tee@cgh.com.sg
Telephone:	Text Field	*Fax:*	Text Field
Mailing Address:	Text Field		

**All fields must be completed.*

III. Study Team Members' Endorsements

All investigators who have a responsibility for consent process or direct data collection for this study should be listed below. Multiple copies of this form may be submitted as necessary. All collaborators/co–investigators need not sign on the same form. Additional copies of this page can downloaded at www.b2bresearch.nhg.com.sg Note: For SingHealth Institutions: Co-investigators need not sign.

Full Name:	Dr Tham Huae Min	*Study Role:*	Collaborator
Institution:	Changi General Hospital	*Department:*	Anaesthesia and Surgical Intensive Care
Position Held:	Registrar	*Email address:*	huae_min_tham@cgh.com.sg
Telephone:	Text Field	*Fax:*	Text Field
Signature:		*Date:*	Text Field

Full Name:	Text Field	*Study Role:*	Choose from list
Institution:	Text Field	*Department:*	Text Field
Position Held:	Text Field	*Email address:*	Text Field
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Signature:		*Date:*	Text Field

Full Name:	Text Field	*Study Role:*	Choose from list
Institution:	Text Field	*Department:*	Text Field
Position Held:	Text Field	*Email address:*	Text Field
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Signature:		*Date:*	Text Field

Full Name:	Text Field	*Study Role:*	Choose from list
Institution:	Text Field	*Department:*	Text Field
Position Held:	Text Field	*Email address:*	Text Field
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Institution:	Text Field	*Department:*	Text Field
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Full Name:	Text Field	*Study Role:*	Choose from list
Institution:	Text Field	*Department:*	Text Field
Position Held:	Text Field	*Email address:*	Text Field
Telephone:	Text Field	*Fax:*	Text Field
Signature:		*Date:*	Text Field

IV. Comments of Department Representative

**The Department Representative can be the Head / Chief / Research Head of the PI's Department. Should the Head or Chief be the PI or Co-Investigator, then their reporting officer should complete this Section. It is assumed that all Departments involved concur with the PI's Department Representative. The validity of this assumption rests solely on the PI. Should views differ, multiple declarations by the other Department Representatives may be submitted. Additional copies of this page can downloaded at www.b2bresearch.nhg.com.sg*

1. Significance:	
Does the study address an important problem? Will the study affect concepts and methods that drive the field?	Yes / No
2. Approach:	
Is the conceptual framework adequately developed? Are the design, methods and analyses adequately developed and appropriate?	Yes / No
3. Innovation:	
Does the study challenge existing paradigms? Does it employ novel concepts, approaches and methods?	Yes / No
4. Principal Investigator:	
Is the Principal Investigator appropriately trained to conduct this study? Does the Principal Investigator have evidence of commitment (e.g. previous track record)?	Yes / No
5. Environment:	
Is the Principal Investigator's environment suited to conduct the study? Is there an adequate patient pool and are there adequate resources?	Yes / No
6. Budget:	
Are the projected costs appropriate (i.e. accurate)? Is the overall budget reasonable for the significance of the study?	Yes / No
7. Time:	
Does the Principal Investigator have adequate resources and time to conduct and complete the study?	Yes / No

Comments:

I acknowledge that this research is in keeping with standards set by the Principal Investigator's Department.

_____

_____

Department Representative's Signature
Date

Full Name:
Text Field

Position Held:
Text Field

Institution:
Text Field

Department:
Text Field

V. Declaration of the Institution Representative*

** The Institution Representative has been determined by your institution as the authority that declares whether your research is in keeping with the institution's research objectives, reputation and standards. The role of the Institution Representative is not to evaluate the scientific or ethical aspects of your study, although they may offer their comments.*

For a multi-centre study, a copy this section must be completed by each institution. Additional copies of this page can downloaded at www.b2bresearch.nhg.com.sg

***Note:** For SingHealth Institutions, this section may be left blank.*

Comments:

I acknowledge that this research is in keeping with standards set by my Institution

_____

_____

Institution Representative's Signature
Date

Full Name:
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Position Held:
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Institution:
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Department:
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VI. Abstract of Research Proposal

In no more than 300 words, describe concisely the specific aims, hypotheses, methodology and approach of the application, indicating where appropriate the application's importance to science or medicine. The abstract must be self-contained so that it can serve as a succinct and accurate description of the application when separated from it. Please use lay terms. If this not possible, the technical and medical terms should be explained in simple language.

Severe sepsis is a prevalent, costly and frequently fatal condition. The Surviving Sepsis Campaign guidelines were first released in 2004 in an attempt to improve outcomes in severe sepsis. The Surviving Sepsis Campaign and the Institute for Healthcare Improvement recommended a 6-hour resuscitation bundle including various aspects of Rivers' early goal directed therapy, early blood cultures and antibiotics. A 24-hour management bundle was also recommended, which includes the administration or consideration of low-dose steroids and human recombinant activated protein C (rhAPC), glucose control, and guidelines on ventilatory support.

This is a multicentre Asian study, involving more than 10 countries, that will collect data from all consecutive patients who are admitted to the study ICUs in the month of July in 2009. Singapore is one of the participating countries - the ICUs involved are the medical and surgical ICUs of National University Hospital, Alexandra Hospital, Tan Tock Seng Hospital, Singapore General Hospital and Changi General Hospital (10 ICUs in total).

The primary objective of the study is to evaluate the compliance of Asian ICUs to the Surviving Sepsis Campaign's recommended resuscitation bundle within 6 hours of the onset of severe sepsis and management bundle within 24 hours of the onset of severe sepsis. . Standardised online case report forms will be used for data collection. This is a quality audit, i.e. an observational study - no additional investigations or change in management practices are required.

VII. Research Details

Organize details of the research proposal under the following headings (in no more than 7 pages).

1. Specific Aims

State concisely and realistically what the research described in this application is intended to accomplish and/or what hypothesis is to be tested.

Primary objective:

To document the compliance of Singapore's (Asia's) ICUs to the recommendations within the Surviving Sepsis Campaign resuscitation and management bundles.

Secondary objectives:

a. To document the epidemiology and outcomes of severe sepsis in Singapore's (Asia's) ICUs.
b. To document ventilation practices in Singapore's (Asia's) ICUs.
c. To evaluate if compliance of Singapore's (Asia's) ICUs to the recommendations within the Surviving Sepsis Campaign resuscitation and management bundles may lead to improved outcomes.

2. Introduction

Briefly describe the background to the current proposal, critically evaluate existing knowledge and specifically identify the gaps that the project is intended to fill.

Severe sepsis is a prevalent, costly and frequently fatal condition [1]. In fact, mortality rates continue to rise in the United States [2, 3]. The Surviving Sepsis Campaign guidelines were first released in 2004 in an attempt to improve outcomes in severe sepsis [4]. The Surviving Sepsis Campaign and the Institute for Healthcare Improvement recommended a 6-hour resuscitation bundle including various aspects of Rivers' early goal directed therapy [5], early blood cultures and antibiotics [6]. A

24-hour management bundle was also recommended, which includes the administration or consideration of low-dose steroids [7] and human recombinant activated protein C (rhAPC) [8], glucose control [9, 10], and guidelines on ventilatory support [11]. Several single as well as multicentre studies have shown that compliance with these recommendations can lead to a survival benefit [12-17].

However, many questions remain unanswered. Adherence to guidelines is often poor for various reasons [18], and whether Asian ICUs and emergency departments follow the Surviving Sepsis Campaign bundles is unknown. Outcomes of severe sepsis differ between races [19], and predominantly Western recommendations may not be readily applicable to Asians. Recent papers have questioned the purported benefits of the recommended interventions [20-23], and the revised Surviving Sepsis Campaign guidelines released in 2008 have toned down the recommendations for steroids and rhAPC [24].

The proposed study hopes to evaluate the management of severe sepsis in Asian ICUs given the above uncertainties.

State concisely the importance of the research described in this application by relating the specific aims to the long term objectives.
This study is driven by the need for our own data on severe sepsis since the medical literature from the rest of the world may not be directly applicable to Asia.

Relevant references (please submit copies of at least two relevant papers)
1. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med. 2001;29(7):1303-1310.
2. Dombrovskiy VY, Martin AA, Sunderram J, Paz HL. Facing the challenge: decreasing case fatality rates in severe sepsis despite increasing hospitalizations. Crit Care Med. 2005;33(11):2555-2562.
3. Dombrovskiy VY, Martin AA, Sunderram J, Paz HL. Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: a trend analysis from 1993 to 2003. Crit Care Med. 2007;35(5):1244-1250.
4. Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Crit Care Med. 2004;32(3):858-873.
5. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001;345(19):1368-1377.
6. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006;34(6):1589-1596.
7. Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA. 2002;288(7):862-871.
8. Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med. 2001;344(10):699-709.
9. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. N Engl J Med. 2001;345(19):1359-1367.
10. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. N Engl J Med. 2006;354(5):449-461.
11. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med. 2000;342(18):1301-1308.
12. Gao F, Melody T, Daniels DF, Giles S, Fox S. The impact of compliance with 6-hour and 24-hour sepsis bundles on hospital mortality in patients with severe sepsis: a prospective

observational study. Crit Care. 2005;9(6):R764-770.
13. Trzeciak S, Dellinger RP, Abate NL, et al. Translating research to clinical practice: a 1-year experience with implementing early goal-directed therapy for septic shock in the emergency department. Chest. 2006;129(2):225-232.
14. Micek ST, Roubinian N, Heuring T, et al. Before-after study of a standardized hospital order set for the management of septic shock. Crit Care Med. 2006;34(11):2707-2713.
15. Kortgen A, Niederprum P, Bauer M. Implementation of an evidence-based "standard operating procedure" and outcome in septic shock. Crit Care Med. 2006;34(4):943-949.
16. Nguyen HB, Corbett SW, Steele R, et al. Implementation of a bundle of quality indicators for the early management of severe sepsis and septic shock is associated with decreased mortality. Crit Care Med. 2007;35(4):1105-1112.
17. Ferrer R, Artigas A, Levy MM, et al. Improvement in process of care and outcome after a multicenter severe sepsis educational program in Spain. JAMA. 2008;299(19):2294-2303.
18. Cinel I, Dellinger RP. Guidelines for severe infections: are they useful? Curr Opin Crit Care. 2006;12(5):483-488.
19. Barnato AE, Alexander SL, Linde-Zwirble WT, Angus DC. Racial variation in the incidence, care, and outcomes of severe sepsis: analysis of population, patient, and hospital characteristics. Am J Respir Crit Care Med. 2008;177(3):279-284.
20. Wachter RM, Flanders SA, Fee C, Pronovost PJ. Public reporting of antibiotic timing in patients with pneumonia: lessons from a flawed performance measure. Ann Intern Med. 2008;149(1):29-32.
21. Sprung CL, Annane D, Keh D, et al. Hydrocortisone therapy for patients with septic shock. N Engl J Med. 2008;358(2):111-124.
22. Eichacker PQ, Natanson C, Danner RL. Surviving sepsis--practice guidelines, marketing campaigns, and Eli Lilly. N Engl J Med. 2006;355(16):1640-1642.
23. Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med. 2008;358(2):125-139.
24. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med. 2008;36(1):296-327.

3. Preliminary Studies / Progress Reports

Provide an account of the Principal Investigator's preliminary studies (if any) pertinent to the application.
The 10 ICUs involved have recently completed a one-day national multicentre survey on sedation practices.

4. Methodology

Discuss in detail the experimental design and procedures to be used to accomplish the specific aims of the project.
Data will be collected on the how each ICU manages severe sepsis, specifically, does each ICU follow the Surviving Sepsis Campaign's recommended resuscitation bundle (within 6 hours of the onset of severe sepsis) and management bundle (within 24 hours of the onset of severe sepsis)?

TIME ZERO
To do this, time zero must first be defined: this is the onset of severe sepsis, which is determined according to the patient's location within the hospital when severe sepsis is diagnosed:
a. In patients diagnosed with sepsis in the emergency department, time zero is defined as the time of triage.
b. In patients who developed severe sepsis in the medical and surgical wards or other non-emergency department units, time zero is determined by searching the clinical documentation for the time of diagnosis of severe sepsis. This may include, for example, a physician's note or timed and dated orders, a timed and dated note of a nurse's discussion of severe sepsis with a physician, or timed records initiating referral to the ICU for severe sepsis.
c. If no time and date can be found by searching the chart, the default time of presentation is the time of admission to the ICU.

Although the Surviving Sepsis Campaign recommends that the components of the sepsis resuscitation bundle be achieved within 6 hours from time zero, and the components of the sepsis management bundle be achieved within 24 hours from time zero, data regarding the individual components of both bundles will be collected for 24 hours.

STANDARDISED ONLINE CASE REPORT FORMS
Standardised online case report forms will be used. The major fields in the forms are self-explanatory, and are summarized below:

SEPSIS RESUSCITATION BUNDLE
In this bundle, various targets should be achieved within 6 hours in the ideal situation. The case report forms will capture information on whether these targets were achieved:
(1) Measure lactate within 6 hours.
(2) Obtain blood cultures before antibiotics within 6 hours.
(3) Administer broad-spectrum antibiotics within 3 hours for emergency department admission; or within 1 hour for non-emergency department admission.
(4) For hypotension and / or serum lactate > or = 4 mmol/L (36 mg/dL), deliver an initial minimum of 20 mL/kg of crystalloid or equivalent within 6 hours.
(5) For septic shock, apply vasopressors within 6 hours.
(6) For septic shock and / or serum lactate > or = 4 mmol/L (36 mg/dL), achieve CVP > or = 8 mmHg within 6 hours.
(7) For septic shock and / or serum lactate > or = 4 mmol/L (36 mg/dL), achieve ScvO2 > or = 70% or SvO2 > or = 65% within 6 hours.

SEPSIS MANAGEMENT BUNDLE
In this bundle, various targets should be achieved within 24 hours in the ideal situation. The case report forms will capture information on whether these targets were achieved:
(1) For septic shock, have a standardised ICU policy for low dose steroids or consider low dose steroids or administer low dose steroids within 24 hours.
(2) For severe sepsis with APACHE II > or = 25 or multiple organ failure, have a standardised ICU policy for rhAPC or consider rhAPC or administer rhAPC within 24 hours.
(3) Lowest glucose value > or = 3.9 mmol/L (70 mg/dL) and highest value < 8.3 mmol/L (150 mg/dL) between 6 – 24 hours.
(4) For invasive mechanical ventilation and ALI/ARDS, delivered tidal volumes < or = 6 mL/kg of predicted body weigh within 24 hours.

In addition more detailed data are collected for each of the above-stated targets. For mechanical ventilation practices, the mode of ventilation, tidal volumes and positive end-expiratory pressure (PEEP) used, and the presence of ALI/ARDS will be recorded.

OUTCOMES
a. In-hospital mortality.
b. ICU mortality.
c. 28-day mortality.
d. Ventilator-free days in the first 28 days. This is defined as the number of days of unassisted breathing to day 28 after time zero, assuming a patient survives and remains free of invasive or noninvasive (both noninvasive positive pressure ventilation [NIV] and continuous positive airway pressure [CPAP]) assisted breathing for at least 48 consecutive hours after extubation or on a tracheostomy mask.
e. ICU length of stay.
f. Hospital length of stay.

Describe the protocol(s) to be used. If the study is a drug trial, please include information of the study drug and any other drugs that will be used in the trial. Will placebo control be used? If so, please include completed Annex A.
As detailed above, this is a quality audit, an observational study, not a drug trial. No placebo control will be used.

Include details on sample size calculation and the means by which data will be analysed and interpreted.
a. Given the primary objective of the study, no sample size calculation is performed. The aim is to include as many Singaporean and Asian ICUs as possible.

b. The frequencies of achieving each individual target in the presence of the stated clinical scenarios listed above be described.

c. Care will be defined as compliant to the Surviving Sepsis Campaign resuscitation bundle only if ALL targets listed above are achieved. However, all 7 targets need not necessarily be considered. E.g. if the clinical scenario of septic shock and hyperlactatemia is not present, the targets for vasopressors, CVP and ScvO2 or SvO2 will not be considered.

d. Care will be defined as compliant to the Surviving Sepsis Campaign management bundle only if ALL targets listed above are achieved. However, all 4 targets need not necessarily be considered. E.g. if the clinical scenario of mechanical ventilation and ALI/ARDS is not present, the targets for delivered tidal volumes will not be considered. For the purpose of this study, because of the ongoing controversy about the absolute benefits of low-dose steroids and rhAPC, targets will be considered achieved as long as (1) there is a standardised ICU policy for these therapies, (2) there is evidence or documentation that these therapies were considered, or (3) these therapies were administered.

e. Outcomes will be compared between patients where targets were achieved versus patients where targets were not achieved.

f. Multivariable logistic regression will be performed with hospital mortality as the dependent variable and each of the 11 targets as independent variables.

g. Categorical variables will be expressed as frequencies and percentages. Continuous variables will be expressed as means, standard deviations and confidence intervals, and medians and interquartile range, as appropriate. For comparisons, Student's t test, the Mann-Whitney U test and the chi-square test will be used. All tests will be two-tailed, and a p value of < 0.05 will be considered statistically significant.

List all trial related procedures. Please also describe the study participant visits (frequency and procedures involved).For studies with multiple visits, please attach study schedule.
STANDARDISED ONLINE CASE REPORT FORMS
Observational data on the Surviving Sepsis Campaign's resuscitation and management practices will be entered into the standardised online case report forms.

QUESTIONNAIRES FOR INDIVIDUAL ICUS
Site investigators will also be asked to fill in these questionnaires before the start of the 1 month study period. These questionnaires will capture information on the nature of each participating ICU and whether each ICU has written protocols for various clinical practices.

STUDY PARTICIPANT VISITS
Not applicable. This is a quality audit of a patient's stay in the ICU, focusing primarily on the first day of management after the recognition of time zero.

If the study involves the use of study drug / device, describe how you plan to ensure that investigators are trained in the management (receipt, storage, utilization, and disposal) of the study drug/device.
No study drug / device.

Please describe how you plan to ensure that the study drug / device would be used only by investigators, and only in study participants.
No study drug / device.

If samples of body fluids or tissues are taken as part of this research, state the amount and frequency at which these samples are taken. Will these samples be stored? If so, please include completed Annex C.
No samples to be taken.

What are the anticipated benefits and risks to study participants in this research?
This being a quality audit which merely collects observational data on what is already usually done, without additional investigations or change in management, there are no potential risks to subjects.

The Hawthorne effect is a possibility, i.e. the participating ICUs may "optimise" their management practices if they realise that a study is ongoing. As such, an unintended "side effect" is that the subjects may benefit from such an improvement in management practices.

Discuss the potential difficulties and limitations of the proposed procedures and alternative approaches to achieve the aims.
This is a quality audit which merely collects observational data on what is already usually done. It does not seek to change management or mandate additional investigations. Accordingly, minimal difficulties are anticipated.

Nevertheless, the Hawthorne effect is a concern, i.e. the participating ICUs may "optimise" their management practices if they realise that a study is ongoing. To preventing this from happening, the study is designed such that only the study team, i.e. the individual representatives of each ICU, are familiar with the study objectives.

Will any part of the procedures be recorded on audiotape, film/video, or other electronic medium?
Yes *No*
If 'Yes', what is the recording medium? Explain how the recorded information will be used? How long will the recording medium be retained and how will they be disposed of?
No

5. Characteristics of Target Study Participants / Target Patient Data

If the target Study Participants include these vulnerable populations, please complete and attach the relevant Annexes to the Application Form:-

- ***Annex F:*** *Pregnant Women, Foetuses and Neonates*
- ***Annex G:*** *Children (Persons under the age of 21 years)*
- ***Annex H:*** *Prisoners*

If the study only involves the collection of tissue samples, please indicate the number of samples to be collected in lieu of recruitment numbers.

What is the number of Study Participants to be enrolled? Give a breakdown by institution for multi-center studies within Singapore.

Institution	**Total Recruitment Number**	**No of Adult Males**	**No of Adult Females**	**No of Children** (Persons under the age of 21 years)
Changi General Hospital	50	25	25	_____

Singapore General Hospital	50	25	25	_____
Alexandra Hospital	50	25	25	_____
Tan Tock Seng Hospital	50	25	25	_____
National University Hospital	50	25	25	_____
Choose from list	_____	_____	_____	_____
Choose from list	_____	_____	_____	_____
Choose from list	_____	_____	_____	_____

If there are more sites, please fill up Additional Sheet for Characteristics of Target Study Participants. Additional copies of this section can downloaded at www.b2bresearch.nhg.com.sg

Study Participants' Lower Age Limit: 21

Study Participants' Upper Age Limit: 99

Total number of Study Participants targeted for enrollment worldwide (for international studies): **2000**

Are there any recruitment restrictions based on race of the Participant?
☐ *Yes* ☒ *No*
If 'Yes', Please provide details:-
Text Field

List the Inclusion criteria

All consecutive patients with severe sepsis who are admitted to the study ICUs between 1st July 2009 at 00:00 hours (midnight) and the finish date of 31st July 2009 at 23:59 hours (11.59 pm). Patients who are already in the ICUs prior to 1st July 2009 at 00:00 hours will not be included in the study.

Definitions:

Severe sepsis is sepsis with one of the following organ dysfunctions:
a. Hypotension: Systolic blood pressure (SBP) < 90 mmHg or decrease > 40 mm Hg or mean arterial pressure (MAP) < 65 mm Hg.
b. Hyperlactatemia: Serum lactate > or = 2 mmol/L (18 mg/dL).
c. Renal: Acute increase in serum creatinine to >176.8 mmol/L (2.0 mg/dL) or urine output < 0.5 mL/kg/hour for > 2 hours.
d. Lung: Acute lung injury with PaO2/FIO2 < or = 300 mmHg.
e. Liver: Acute increase in bilirubin to > 34.2 umol/L (2 mg/dL).
f. Thrombocytopenia: Acute decrease in platelet count to < 100 000.
g. Coagulopathy: International normalized ratio (INR) > 1.5 or a partial thromboplastin time (aPTT) > 60 secs.

Septic shock is defined as sepsis-induced hypotension (definition above) despite adequate fluid resuscitation.

Acute lung injury is defined based on the American-European Consensus Conference criteria, i.e. namely the acute onset of hypoxemia [partial pressure of arterial oxygen to fraction of inspired oxygen (PaO2/FIO2) ratio < or = 300 mm Hg] and diffuse radiologic infiltrates which is not predominantly due to heart failure.

List the Exclusion criteria

a. Patients less than 21 years.
b. Patients with severe sepsis who were directly transferred to the study ICUs from another hospital or another ICU.
c. For all patients who are discharged from the ICU and readmitted to the ICU again during

the study period, only the first admission during the study period will be included.

Do the Study Participants have a dependent relationship with the researchers?
☒ *Yes* ☐ *No* ☐ *Not applicable*
If ' Yes', Please provide details:-

The subjects are critically ill ICU patients. The study team is made up of the PI, the site PIs and collaborators who are all intensivists, each of whom represents one ICU.

During the study period, the study team doctors may or may not be rostered to cover the ICUs - this is dependent on the individual departments' roster.

If the study team doctors are not scheduled to cover the ICUs during the study period, then all they do is ensure that the observational data is collected.

In any case, even if the study team doctors are scheduled to cover the ICUs during the study period, it will not change the relationship between the subjects and the doctors because the study is designed such that no additional investigations or change in management is required.

In other words, this is a quality audit which aims to document "real world" practice.

Will any vulnerable Study Participants (Pregnant Women, Foetuses & Neonates, Children (Persons under the age of 21 years), Prisoners) be recruited in this research study?
☐ *Yes* ☒ *No*
If 'Yes', please describe steps that will be taken to minimize the possibility of coercion or undue influence over the vulnerable Study Participants.
Text Field

6. Informed Consent Process and Consent Document

The PI is responsible for ensuring that all Study Participants give informed consent before enrolling into the study. Please submit a copy of the Consent Document. For guidelines on preparing a Participation Sheet and Consent Form compliant with Good Clinical Practice Guidelines please contact the IRB/DSRB Secretariat. A Consent Form template can be downloaded at www.b2bresearch.nhg.com.sg

Please describe the consent procedure. Please specify the following:-

When will consent be taken?
For waiver of informed consent.

Where will consent be taken?
For waiver of informed consent.

Who will conduct the consent process?
For waiver of informed consent.

Do you anticipate a situation where obtaining informed consent from a potential Study Subject is not possible and informed consent will be taken from the legally acceptable representative (including spouse, parent, and guardian)?
For waiver of informed consent.

Describe provisions to protect the privacy interests of Study Subjects, where "privacy interests" refer to interests of individuals to be left alone, free from intrusion and comfort with the proposed settings
For waiver of informed consent.

Besides the Consent document, will any other materials or documents be used to explain the study to potential Study Subjects? (eg. scripts, handouts, brochures, videos, logs, etc)

For waiver of informed consent.

7. Recruitment Process

Explain the process of recruitment in detail. For example, state how the list of potential Study Participants will be obtained. (e.g. whether from attending doctor who will refer potential subjects.)
The attending ICU team will make the first contact with the subjects when they are admitted to the ICUs with severe sepsis. The attending ICU team will then inform the ICU's representative, i.e. the study PI and collaborator, if they meet the inclusion criteria and not the exclusion criteria.

Will subjects be chosen from medical records? If so, how will you obtain names and NRIC numbers of Study Participants?
No, the subjects will not be chosen from medical records.

Please submit a copy of any advertisements/posters that will be used.
No advertisements or posters will be used.

8. Data And Safety Monitoring Plan (DSMP)

If the research involves more than minimal risks to Study Participants, please provide details on the Data And Safety Monitoring Plan (DSMP) of the research.

Who performs the data and safety monitoring? If there is a Data Safety Monitoring Board (DSMB), please provide the charter of the DSMB.
This study involves no risk. Nevertheless, the overall study PI Dr Jason Phua from National University Hospital will perform the data and safety monitoring.

When and what safety data is monitored?
Because this is a quality audit that merely captures observational data with no additional investigations or change in management, no significant safety issues are identified. Besides, this is a short study that will only recruit patients over a period of 1 month. Nevertheless, the overall PI Dr Jason Phua will communicate with the site PIs and the collaborators on a weekly basis for feedback and to ensure that the study is going on smoothly.

When and how is data integrity monitored?
This is a short study that will only recruit patients over a period of 1 month. As such, no interim data analysis is planned. Nevertheless, the overall study PI Dr Jason Phua will communicate with the site PIs and the collaborators on a weekly basis for feedback and to ensure that data collection is going on smoothly.

At the end of the study, the overall study PI will scrutinise the data for data integrity and will ask the site PIs and collaborators for clarification should any queries arise.

What are the criteria for suspending the research?
Because this is a short one-month quality audit that merely captures observational data with no additional investigations or change in management, no criteria are set to stop the study.

How will the outcome of data and safety monitoring be communicated to other sites? (for multi-centre studies only)
The overall study PI will communicate with the site PIs and the collaborators on a weekly basis for feedback.

At the end of the study, the overall study PI will scrutinise the data for data integrity and will communicate with the site PIs and collaborators.

9. Research Data Confidentiality

In general, to protect Study Participant's confidentiality, research data should be coded, and the links between the Participant's identifiers and the codes should be stored separately from the research data.

Will coded research data be sent to the sponsor, and no research database will be created in NHG?
☐ *Yes, If 'Yes', please skip this question and go to Section 10 – Timelines.*
☒ *No, If 'No', please answer the following questions:-*

Describe where the research data will be stored? (i.e.: network or Stand alone PC and the physical location)
An online data entry website will be designed for the purpose of this study. This website will contain data fields that are reflected in the attached study protocol.

Only each ICU's representative will have username and password access to enter data into these online forms.

At the end of the study, only the PI will have access to all the data captured online. This data will be stored in a password protected computer based in the overall study PI Dr Jason Phua's office in the Department of Medicine of NUH.

Who will have access to the research data and how will access to the research data be controlled and monitored?
As stated above, only the overall study PI will have access to all the research data captured online. This data will be stored in a password protected computer which only the overall study PI can access.

Are there any research data sharing agreements with individuals or entities outside the Institution, to release and share research data collected?
☒ *No*
☒ *Yes, If yes, please describe the agreement*
This is a multinational study. Singapore is but one of the many countries in Asia that are participating in this study. At the end of the study, Singapore's data will be analysed together with all the other countries'. Regardless, the overall study PI Dr Jason Phua will still be primarily in charge of all the Asian data because he is also the PI for the entire Asian collaboration.

Describe what will happen to the research data when the study is completed.
These data will be stored in the overall study PI's computer for 10 years, after which they will be deleted.

Are there any other measures in place to protect the confidentiality of the research data?
The online forms will not capture any patient identifiers such as names or identity card numbers. They will only capture patient index numbers which are specially created for this study. Only each ICU's representative will have a list which identifies these patients using their patient index numbers. This list is kept at the individual ICUs and is not shared online.

10. Timelines

What are the estimated start and end dates of the study?
Start Date: 1st July 2009 End Date: 30th Jun 2010

Indicate the duration of subject involvement in the research. Please also state the recruitment period.
Patients will be recruited if they are admitted with severe sepsis to the participating ICUs in the month of July 2009.

All patients should be followed up till one of the following situations, whichever is later:

a. Discharge from the current hospital admission

b. Death in the current hospital admission.
c. Till 28 days from time zero
d. Death in the 28 days from time zero.

11. Financial Aspects

Who will be responsible for research related costs? For sponsored projects, list the costs that will be borne by the sponsor. For industry sponsored clinical trials, please complete Annex D.
This is primarily an unfunded study.

Total amount of grant/fund: $ NAD

If this study has a Grant Application, please answer the following questions.

a) Has grant been awarded?
☐ *Pending approval*
☐ *Yes. If 'Yes', please submit a copy of the grant approval letter.*

b) Which grant exercise was this submitted to? (enter Grant Submission Deadline date)
Text Field

*c) For **approved grant applications** (including United States Department of Health and Human Services (DHHS) approved studies), please submit the protocol and consent document (if any) approved by the grant body.*

Are the Protocol and Consent documents approved by the grant body, identical to the information that has been submitted in this application?
☐ *Yes*
☐ *No. If 'No', please provide details of the differences:*
Text Field

Will the Study Participants receive any financial payment/incentive for participation?
☐ *Yes* ☒ *No*
If 'Yes', please elaborate.
Text Field

Who will be responsible for the payment and compensation of injury or illness arising from participation of subjects in the research project?
Not applicable. This is merely an observational study and quality audit of how ICUs currently manage severe sepsis. This study does not affect or change management.

Note:-
***NHG:** For investigator-initiated studies – Contact your OBR/CRU for more information on available NHG Clinical Trial Compensation Insurance Scheme.*
***SingHealth:** Please contact your IRB on how to word the Informed Consent Document.*

12. Application Checklist:	
Attached?	**Document**
Yes	Study Protocol *(latest version)*
Not Applicable	Approved Grant Application *(including DHHS approved Study Protocol and Sample Consent Form, if one exists)*
Not Applicable	Participant Information Sheet and Consent Form
Yes	Principal Investigator's CV (**NHG**: For PI only. **SingHealth**: For all investigators)
Not Applicable	CITI Certificate (**NHG**: For PI only. **SingHealth**: For all investigators)
Not Applicable	Investigator Brochure
Not Applicable	Survey Forms/Questionnaires / Diary Card
Not Applicable	Data Collection Form
Not Applicable	Posters for Advertisement
Not Applicable	Letter of Invitation to Patients
Not Applicable	Letter to Doctors Requesting Referral
Yes	Relevant Publications
Not Applicable	Cheque payment for Industry Sponsored Trials
Not Applicable	Participant Payment Details +
Not Applicable	Participant Compensation Details +
Not Applicable	Financial Agreement
Not Applicable	Annex A – Placebo Usage
Not Applicable	Annex B – Conflict of Interest Declaration Form
Not Applicable	Annex C – Biological Materials Storage
Not Applicable	Annex D – Industry Sponsored Studies
Yes	Annex E – Waiver of Informed Consent
Not Applicable	Annex F – Research involving Pregnant Women, Foetuses and Neonates
Not Applicable	Annex G – Research involving Children (*Persons under the age of 21 years.)*
Not Applicable	Annex H – Research involving Prisoners
Not Applicable	Any other materials/documents? Please list here:- Text Field

* For NHG PI only

+ If information is not included in the protocol / application form

~ End of Application Form ~