PILOT STUDY: EFFICACY OF ENHANCED MODEL PREDICTIVE CONTROL (eMPC) IN INSULIN THERAPY IN THE CRITICALLY ILL

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Field of Study: Anaesthesiology

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ABSTRACT

Background: Hyperglycaemia, in patients with diabetes or stress-induced, is known to be associated with poor outcome. The main cause of hyperglycaemia in the critically ills is due to the release of counter-regulatory stress hormones, and pro-inflammatory cytokines. Insulin therapy has been shown to improve patient outcome. However, blood sugar management is a challenging. The eMPC(Enhanced Model Predictive Control) algorithm is a computer-based decision support system to help with blood glucose management. The eMPC algorithm has been successfully tested in several clinical trials involving more than 200 patients. We thus aim to undertake a prospective, randomized, open-label, single center study to investigate the effectiveness of the algorithm in local adult intensive care patients with sepsis. This is a pilot study to determine the appropriate design of the study.

Methods: Patients are to be randomized into 2 groups. One group of patients receiving the convention insulin therapy via Insulin Sliding Scale, another group receives insulin therapy delivered via the eMPC algorithm based machine. The study endpoint is to compare the effectiveness of each intervention, with glucose within targeted range of 5.5mmol/l to 8.9mmol/l.

Results: A total of 14 patients have been recruited. We see a higher mean percentage of blood glucose within targeted range in eMPC group, 54.2%, compared to the insulin sliding scale group, 37.5% ($p<0.05$) . There was no significant difference in the number of times blood glucose testing is done, and insulin dosage for both groups ($p>0.05$).

Conclusion: The eMPC model is effective in maintaining blood glucose level in critically ill patients in intensive care patients.

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LIST OF SYMBOLS AND ABBREVIATIONS

eMPC	Enhanced Model Predictive Control
ICU	Intensive Care Unit
UMMC	University Malaya Medical Centre
IL-6	Interleukin-6
n	Number
cm	Centimeter
kg	Kilogram
BMI	Body Mass Index
APACHE II Score	Acute Physiology And Chronic Health Evaluation II Score
TWC	Total White Cell Count
CRP	C-Reactive Protein
SD	Standard Deviation
IQR	Inter-quartile Range

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CHAPTER 1: INTRODUCTION

Hyperglycaemia, whether occurring in patients with known diabetes or as a result of undue stress is known to be associated with poor outcome, such as prolonged hospitalization, increased rates of infection and in-hospital death. The main cause of hyperglycaemia, in the critically ill, is the release of counter-regulatory stress hormones (catecholamines, cortisol, glucagon, growth hormone) and pro-inflammatory cytokines that interfere with insulin signaling cascade at the post receptor level. Insulin therapy has been characterized as an important treatment option to substantially improve outcome in medical and surgical intensive care patients.

However, blood sugar management is a challenging, complex and time consuming task that requires a lot of vigilance and experience. The commonly used method is a preset or predetermined protocol for manual intravenous insulin therapy, which is the Insulin Sliding Scales, which may differ between centers. Often, the required dosage of insulin is estimated rather than determined based on objective measurements and criteria. As a result, estimations of the requirement may only be made based on assumptions, and this can lead to potential lethal consequences under certain circumstances.

The eMPC (Enhanced Model Predictive Control) is a computer-based decision support system which helps to achieve safe and reliable blood glucose control in the desired range. Information on intravenous fluid infusion, parenteral and enteral nutrition, is automatically integrated into the calculations. The automated algorithm may help to overcome some of the limitations, by integrating various data to aid in the decision making process. The eMPC algorithm has been successfully tested in several clinical trials, which involves more than 200 patients.

The aim of this study is to investigate the effectiveness of the algorithm, in local adult intensive care patients with hyperglycaemia and sepsis. This study is a prospective, randomized, open-label, single-centre study.

This is a pilot study, to determine the appropriate sample size, duration, equipments, potential problems and issues pertaining to this study before starting a large scale quantitative study.

CHAPTER 2: LITERATURE REVIEW

Hyperglycaemia is common in acutely ill patients, including those treated in intensive care units.(van den Berghe et al., 2001) The occurrence of hyperglycaemia, is associated with increased morbidity and mortality in a variety of group of patients.(Van den Berghe, Wilmer, Hermans, et al., 2006) The main cause of hyperglycaemia, in the critically ill, is the release of counter-regulatory stress hormones (catecholamines, cortisol, glucagon, growth hormone) and pro-inflammatory cytokines that interfere with insulin signaling cascade at the post receptor level.(McCowen, Malhotra, & Bistrian, 2001) Insulin therapy has been characterized as an important treatment option to substantially improve outcome in medical and surgical intensive care patients. (Van den Berghe, Wilmer, Milants, et al., 2006)

Sepsis is a systemic, deleterious host response to infection leading to severe sepsis with organ dysfunction and septic shock. Sepsis is a major healthcare problem, affecting millions of people worldwide. (Angus et al., 2001) In the Surviving Sepsis Campaign Guideline, glucose control is part of the supportive therapy in the care bundle. (Vassalos & Rooney, 2013)

Blood glucose management continues to be a challenge in intensive care patients, where this particular group of patient is critically ill. Insulin can be delivered via subcutaneous or intravenous route. Conventional methods of intermittent administration of subcutaneous insulin in this group of patient may not be suitable due to altered pharmacokinetics. Hence, continuous intravenous insulin therapy is used to control blood glucose level in the critically ill patient. The Insulin Sliding Scale or Insulin Infusion Protocol is a preset and

predetermined protocol which acts as a guide to the amount of insulin which is required to be delivered to patient. The protocol may vary between hospitals or institutions.

Management of blood glucose control requires extensive nursing efforts, including frequent point-of-care testing of blood glucose level monitoring and implementation of complex Insulin Infusion Protocols. (Goldberg et al., 2004) When insulin is required, the rate of infusion is selected based on a table with regards to the current blood glucose level. The interval of blood glucose monitoring is based mainly on clinical judgement, by correlating with the rate of changes in the blood glucose level and insulin requirement. An example of an Insulin Sliding Scale/Insulin Infusion Protocol from the Intensive Care Unit of University Malaya is shown in the table below (Table 2.1) :

Table 2.1 : Insulin Sliding Scale

Scale	8 unit	12 unit	16unit	20unit
0-5	0	0	0	0
5.1-10	1	2	4	6
10.1-15	2	4	8	12
15.1-20	4	6	12	18
20.1-25	6	8	16	24
25.1-30	8	12	20	30
>30	Inform Doctor	Inform Doctor	Inform Doctor	Inform Doctor

The implementation of the insulin sliding scales requires vigilant physicians and nurses. The Intensive Care Unit is fast paced, and is often a stressful environment to work in. It is not uncommon to have nursing staff experiencing burnouts. (Guntupalli, Wachtel, Mallampalli, & Surani, 2014). In this situation, medical errors can occur and may lead to lethal consequences.

The eMPC algorithm is used in the B Braun SpaceGlucose (Figure 2.1) . The Space GlucoseControl system is an integrated computer-based decision support system that comprises three parts: a control unit; the computer algorithm (eMPC) used to calculate

insulin dosing ; and the insulin and nutrition infusion pumps. The eMPC algorithm has been successfully tested in several clinical trials, which involves more than 200 patients. (trials on eMPC) The trials are mainly done in healthcare institutions in Europe. There are no local data available at the time of writing. (NICE, 2014)

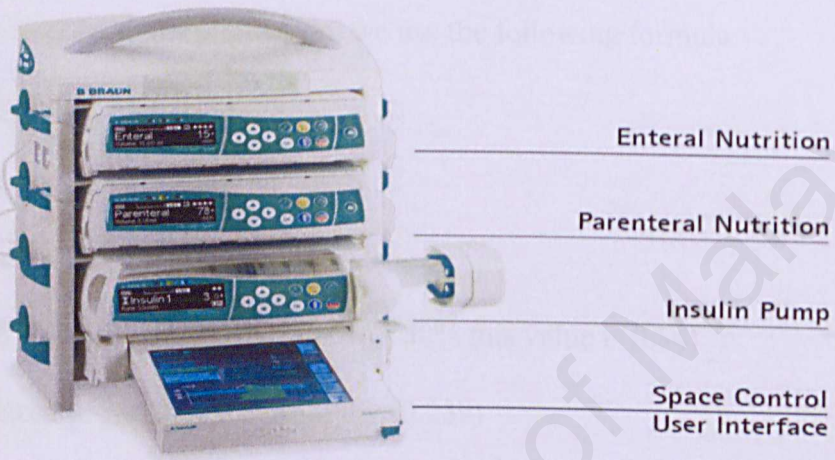

Figure 2.2 B Braun Space GlucoseControl

CHAPTER 3: METHOD/ METHODOLOGY

3.1 SAMPLE SIZE

To determine sample size for this study we use power study. To prove the sample size adequacy for a study this is a very useful and frequently used tool in medical research. The prevalence of severe sepsis patients in PPUM Malaysia is 25.9 percent (Malaysian Registry of Intensive Care, 2015). Since our population size is unknown, to obtain an appropriate sample size from this population, we use the following formula.

$$n = \frac{(Z_{1-\beta})^2 [p(1-p)]}{d^2}$$

Where,

n = required sample size

$Z_{1-\beta}$ = Z value at power 1-β (at power 80% this value is 0.84)

p = referred prevalence for the study (0.259)

d = margin of error (ideal value is 0.05 for estimated proportions in the range of 20%-80%) (Gorstein et al., 2007)

Considering 80% power of test, 5% marginal error and 25.9% prevalence rate, the formula gave us a sample size of 54.17. Finally we use 60 samples for the study, with 30 patients in each arm.

3.2 STUDY DESIGN

This study is a prospective, randomized, open label single-center study. The primary objective is to determine the efficacy of the eMPC algorithm. Secondary objectives were to determine the safety and correlations with inflammatory markers in regards to glucose control.

The study is conducted in accordance with the guidelines proposed in the Declaration of Helsinki, and was approved by the University Malaya Medical Center (UMMC) Medical Ethics Committee.

Insulin is prepared in the same manner for both groups; in standard 50ml syringe, with 50units of Actrapid (Novo Nordisk) in 50 ml of normal saline. The insulin infusion is connected to a central venous catheter. Undiluted arterial blood for measurement of blood glucose is drawn manually from an arterial line which is available for routine monitoring procedure in ICU. Blood glucose level is analyzed via a standard point-of-care testing device available in ICU. The target blood glucose range for both groups has been set to 5.5mmol/l -8.9mmol/l.

Patients will be randomized into two groups. One group of patients will be randomized into a group with the eMPC algorithm device for blood glucose management. Upon commencement of the insulin therapy, at 0^{th} hour, baseline blood glucose will be measured and recorded, with the insulin infusion commenced at a rate calculated by the algorithm. Based on the eMPC algorithm prediction, the device calculates the time interval to the next blood glucose measurement and gives and audio-visual alarm to alert nursing staff when it is due. The nurse then measures and enters the current blood glucose values, and the system suggests an appropriate insulin dose and time to next measurement. Advised insulin dose rate has to be confirmed by the nurse at the interface, and is then set automatically at the

pump. Time interval for blood sampling ranges from 30minutes to 4 hours depending on computer calculations. If patient is started on enteral or parenteral nutrition, the data is also entered into the device and adjustments will be made according to the algorithm of the device. All trial related activities and data will be carried out until the completion of 5days. After 5 days, insulin therapy in this group will still be provided if required, via the conventional method, which is the Insulin Sliding Scale.

Another group of patients will be randomized into a group with blood glucose management via the conventional method- Insulin Sliding Scale (Table 2.1). Upon commencement of insulin therapy, at 0^{th} hour, the baseline of blood glucose level will be measured and the rate of insulin infusion therapy will be determined by the insulin sliding scale, which will be selected (8unit/12unit/16unit/20unit) by the medical practitioner in charge. At 1^{st} hour of insulin infusion therapy, blood glucose level will be measured, and the nurse in charge will manually adjust the rate of infusion, in accordance to the insulin sliding scale table. Blood glucose will continue to be monitored every hour until stable and then at intervals of 2-4 hours (when there is no rate change in 2 consecutive hours), and adjustment of the insulin infusion rate will be made manually in accordance to the insulin sliding scale selected. If blood glucose is still not within the target, a different scale may be chosen. All trial related activities and data will be carried out until the completion of 5 days. After days, insulin therapy in this group will still be provided if required via the same method (Insulin Sliding Scale).

During the ICU stay, blood samples would also be taken from the patient and sent for IL6 levels, Full Blood Count (FBC) and C-Reactive Protein (CRP). The blood sample would be taken from the arterial line, on Day 1, Day 3 and Day 5 of admission.

3.3 PATIENT ELIGIBILITY AND RECRUITMENT

From April 2016 until November 2016, adult patients admitted to the ICU with severe sepsis or septic shock (Table 3.1), with expected admission of more than 5 days, blood glucose level of 8.9mmol/l or more, or already on insulin therapy are recruited for this study. The exclusion criteria for this are patients with Diabetic Ketoacidosis and Hyperosmolar Hyperglycaemic Syndrome or with a known allergy to insulin.

Informed consent is obtained from patients who are conscious and has the capacity to provide consent or from surrogate or legal guardian prior to inclusion.

Table 3.1:	Definition of Sepsis
Sepsis	Presence (Probable or Documented) of infection together with systemic manifestation of infection
Severe Sepsis	**Sepsis with sepsis induced organ dysfunction or tissue hypoperfusion**
Septic Shock	**Sepsis induced hypotension persisting despite adequate fluid resuscitation**
Septic Induced Hypotension	SBP< 90mmHg or MAP< 70mmHg or SBP decrease >40mmHg or less than 2 standard deviations below normal for age in the absence of other causes of hypotension

3.4 RANDOMIZATION

Randomization was done by using a web based randomizer http://www.graphpad.com/quickcalcs/randMenu/ on 18th March 2016@1500H where the total number is separated in 2 groups and each group containing 30 samples. The numbers are randomized and printed according to the web based randomizer at the aforementioned date and time. Generated numbers are then saved for further reference. The numbers are then placed in envelopes labelled 1 to 60, and each patient will receive an envelope upon successful recruitment to determine which group the patient has been randomised into.

3.5 DATA ANALYSIS

Statistical analysis of the data collected is done via IBM SPSS Data 24 software package.

CHAPTER 4: RESULTS

4.1 PATIENT DEMOGRAPHICS

A total of 14 patients have been recruited for this study. The patient demographic characteristics are listed in Table 4.1.1. From the demographic breakdown, the average age of the patients 64 years old, and half of those recruited are obese.

Table 4.1.1: Patient Demographics (n= 14) Table 4.1.1	
Male	8 (42.9%)
Female	6 (57.1%)
Age (Years)	64.07 ± 11.5
Ethnic: Malay Chinese Indian	 6 (42.9%) 5 (35.7%) 3 (21.5%)
Height (cm)	166.7 ± 7.4
Weight (kg)	80.59± 17.48
BMI (kg/m2)	28.8 ± 5.9
Obese (BMI ≥ 30)	7 (50%)

Of all the recruited patients, 10 of the patients have background history of diabetes mellitus, with 6 on oral hypoglycaemic agents and 4 on insulin therapy, other medical characteristics of the patients are listed in Table 4.1.2.

Table 4.1.2: Patient Medical Characteristics (n=14)	
Diabetes Mellitus	10 (71.4%)
Diabetes Mellitus: On Oral Hypoglycaemic Agents (OHA) On Insulin	 6 (60%) 4 (40%)
Hypertension	12 (85.7%)
Dyslipidaemia	7 (50%)
Coronary Artery Disease	3 (21.4%)
Chronic Kidney Disease	6 (42.9%)

From the collected data, we see an average APACHE II score of 20.43, most patients develop acute kidney injury as part of the organ dysfunction in severe sepsis. Half of the patients have been started on steroid therapy on admission for severe sepsis. Other characteristics are listed in Table 4.1.3.

Table 4.1.3: Patient Admission Characteristics (n=14)	
APACHE II Score	20.43 ± 5.747
Severe sepsis with:	
Acute Kidney Injury	11 (78.6%)
Coagulopathy or Thrombocytopenia	9 (64.3%)
Liver Impairment	5 (35.7%)
Hospital Acquired Pneumonia (HAP)	5 (35.7%)
Ventilator Associated Pneumonia (VAP)	1 (7.1%)
Steroid Therapy	7 (50%)

4.2 RESULTS

The main aim of this study is to look at the effectiveness of the eMPC model compared to the conventional insulin sliding scales. The main parameter for measurement of effectives is the mean percentage of time the blood glucose is within range. The target blood glucose range is 5.5mmol/l to 8.9mmol/l. To compare between the two groups, the Independent Sample T-Test is done, where the mean amount of time within range for the eMPC group is 54.21% (Figure 4.2.2) (Table4.2.1), compared to the conventional insulin sliding scale group 37.5% (Figure 4.2.3) (Table 4.2.1), and the result has shown statistical significance difference between the group ($p<0.05$). It is thus shown that the eMPC is more effective in controlling blood glucose level. The number of times blood sugar is checked with a point-of-care testing device for the eMPC group is also slightly more, 50.6 times, compared to the insulin sliding group 43.5 times, but by running the Mann-Whitney –U test, this has shown no statistical significance or difference ($p>0.05$). Hence, this means that the usage of the eMPC does not increase the amount of blood sugar testing as compared to the conventional method, in which would be related to cost and workload. The mean insulin dosing, on average at units per hour, that the patients receive when on insulin therapy, the eMPC group receives 2.154units per hour compared to the insulin sliding scale 2.584 units per hour, in which there is no statistical difference ($p>0.05$). (Table 4.2.1) There were no adverse events reported throughout the study period.

Table 4.2.1 :Results

Variables	Insulin Sliding Scale	eMPC	P value
Mean percentage of time within range	37.5%	54.21%	0.019*
Mean number of testing	43.5	50.6	0.518**
Mean insulin dosing (unit/hour)	2.584	2.545	0.615*

*Independent T-Test **Mann-Whitney U Test

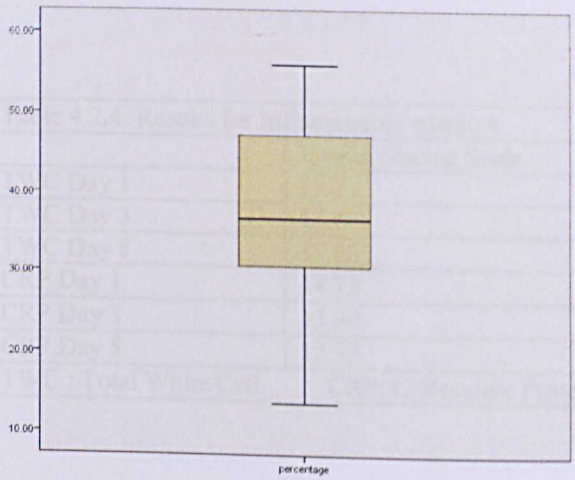

Figure 4.2.2

Stem and Leaf plot for percentage of time within range achieved for Insulin Sliding Scale group.

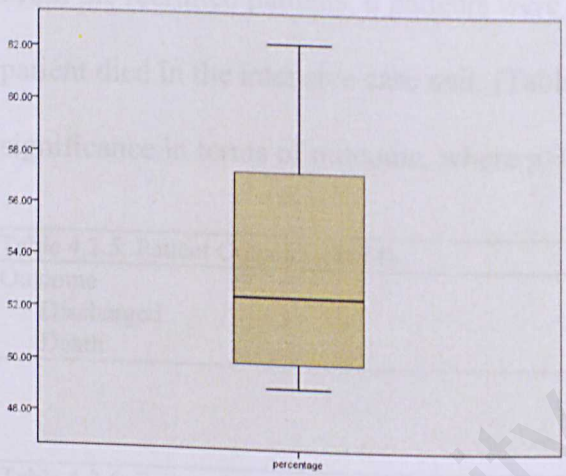

Figure 4.2.3

Stem and Leaf plot for percentage of time within range achieved for eMPC group.

The secondary outcome of this study is the inflammatory markers, and their correlation with glucose control. We aim to look at total white cell counts, C-reactive protein and IL-6 levels. IL-6 is not done for this pilot study, as one test kit for IL-6 requires a total number of 32 patients to run. The results are shown in the Table 4.2.4. In both groups we see a reduction in total white cell count (TWC) and C-reactive protein from Day 1 to Day5. However, comparatively, there is no statistical significance in the reduction of inflammatory markers (total white cell count and c-reactive protein) for both groups, where $p>0.05$ (Table 4.2.4).

Table 4.2.4: Results for Inflammatory markers			
	Insulin Sliding Scale	eMPC	P value
TWC Day 1	19.71	16.34	0.298
TWC Day 3	17.87	18.16	0.724
TWC Day 5	17.06	15.76	0.724
CRP Day 1	14.73	14.32	0.898
CRP Day 3	13.30	15.22	0.733
CRP Day 5	12.35	9.36	0.724
TWC : Total White Cell CRP: C-Reactive Protein			

From the recruited patients, 6 patients were discharged from the intensive care unit, 8 patient died in the intensive care unit. (Table 4.2.5). Both groups did not show statistical significance in terms of outcome, where $p>0.05$ (Table 4.2.6).

Table 4.2.5: Patient Outcome (n=14)	
Outcome	
Discharged	6 (42.8%)
Death	8 (57.2%)

Table 4.2.6: Patient Outcome by group			
Variables	Insulin Sliding Scale	eMPC	P value
Discharged From ICU	3	3	0.679
Died	6	2	0.373

CHAPTER 5: DISCUSSION

From this pilot study, we see that the eMPC model is an effective method for blood glucose control, as shown in studies done previously in other centers. The safety profile of the usage is also ascertained, as there were no adverse outcomes reported.

In this pilot study, we see that the recruited patients from an older population (WHO, 2013), with multiple co-mobidities. The average APACHE II score of the patients is 20, with a predicted mortality of 30-40%. These patients are all admitted with severe sepsis or septic shock, with multi-organ failure.

During the initial screening process of all admissions to the intensive care unit for the eligibility to be recruited into the study, patients may present with normal blood glucose level or hypoglycaemia. The patients fulfill the criteria for severe sepsis or septic shock, often, with multiorgan failure. However, the blood glucose is normal or hypoglycaemic at the initial screening process. It was noted that blood glucose may rise several days later during the admission. This may reflect the severity of the disease. (Van Cromphaut, Vanhorebeek, & Van den Berghe, 2008)

We chose specifically, this targeted group of patient to study regarding sepsis and blood glucose control because patients with severe sepsis and septic shock are major healthcare problem, affecting millions of people. (Vassalos & Rooney, 2013) Severe sepsis and septic shock is associated with increased mortality and healthcare costs. (Angus et al., 2001). Blood glucose control in this group of patients can be difficult due to multiple confounding factors, and is a dynamic process throughout the course of the septic insult.

In the pathophysiology of sepsis, pro-inflammatory cytokines are known to play a significant role, which leads to organ failure via humoral mediator network activation and

vascular endothelial damage. (Gustot, 2011) High blood IL-6 level was correlated with hyperglycemia and with difficulties in glucose control in septic patient, and hypercytokinaemia might be involved in the development of hyperglycemia in sepsis, and thereby might affect the success of glucose control. (Nakamura et al., 2012) Hence, it would be consequential to see the control of blood glucose in relations to inflammatory markers and patient outcomes.

For a qualitative study, to see the correlation with glucose control and inflammatory markers, we would need a multicentre study, with a larger study population to see a significant impact. Further funding would be required, cost for equipments, consumables, test kits for inflammatory markers, staff training need to be taken into consideration. The duration of the study would need to be a longer period. Adequate training of the equipment must be done thoroughly as to ensure the confidence of the user during the usage of the equipments. A few key individuals must be indentified for feedbacks, troubleshooting and queries regarding the equipments and study. Collection of data would also need to be streamlined, and patients would need to be followed up for a certain period of time (30 days and one year) to see the outcome after discharge from the intensive care.

CHAPTER 6: CONCLUSION

The eMPC model is an effective method for blood glucose control, as shown in studies done previously in other centers. The amount of testing done for blood glucose level is not significantly higher in the eMPC group of patients compared to the group with conventional insulin sliding scale, and hence this would not mean that there will not be additional costs for blood glucose testings. The mean insulin usage is similar in both groups. The safety profile of the usage is also ascertained, as there were no adverse outcomes reported.

A larger, multicentre trial would need to be undertaken to show the correlation with efficacy of blood glucose control and outcomes of septic patients.

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APPENDIX A

UNIVERSITY OF MALAYA MEDICAL CENTRE
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(Formerly known as Medical Ethics Committee)
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NAME OF ETHICS COMMITTEE/IRB Medical Research Ethics Committee, University Malaya Medical Center	**MREC ID NO**: 20158-1588
ADDRESS : LEMBAH PANTAI, 59100 KUALA LUMPUR, MALAYSIA	**NMRR.ID** : NMRR-15-2332-27127
PROTOCOL NO(if applicable) :	
TITLE: Efficacy of enhanced Model Predictive Control (eMPC) in Insulin Therapy in the Critically Ill	
PRINCIPAL INVESTIGATOR : Dr Cheng Yee Shin	**SPONSOR** -

The following item [√] hae been received and reviewed in connection with the above study to conducted by the above investigator.

[√]	Application to Conduct Research Project(form)	Ver.No :	Ver.Date : 24-08-2015
[√]	Study Protocol	Ver.No :	Ver.Date :
[√]	Patient Information Sheet	Ver.No : 1	Ver.Date : 13-09-2015
[√]	Consent Form	Ver.No :	Ver.Date :
[ ]	Questionnaire	Ver.No :	Ver.Date :
[√]	Investigator's CV / GCP (Dr Cheng Yee Shin,VINEYA RAI HAKUMAT RAI, FOO LI LIAN, CHAW SOOK HUI, GRACIE ONG SIOK YAN,)	Ver.No :	Ver.Date :
[ ]	Insurance certificate	Ver.No :	Ver.Date :
[√]	Other documents		
	1) CRF	Ver.No : 1	Ver.Date : 24-08-2015
	2) Patient Consent Forms	Ver.No : 1	Ver.Date : 24-08-2015
	3) Appendices (Tables for Methodology Section)	Ver.No : 1	Ver.Date : 24-08-2015

and the decision is [√]

[√] Approved (Full Board)
[ ] Approved (Expedited)
[ ] Rejected(reasons specified below or in accompanying letter)

Comments:

The Investigators are required to:

1) *follow instructions, guidelines and requirements of the Medical Research Ethics Committee.*
2) *report any protocol deviations/violations to Medical Research Ethics Committee.*
3) *provide annual and closure report to the Medical Research Ethics Committee.*
4) *comply with International Conference on Harmonization – Guidelines for Good Clinical Practice (ICH-GCP) and Declaration of Helsinki.*
5) *obtain a permission from the Director of UMMC to start research that involves recruitment of UMMC patient.*
6) *ensure that if the research is sponsored, the usage of consumable items and laboratory tests from UMMC services are not charged in the patient's hospital bills but are borne by research grant.*
7) *note that he/she can appeal to the Chairman of Medical Research Ethics Committee for studies that are rejected.*
8) *note that Medical Research Ethics Committee may audit the approved study.*
9) *ensure that the study does not take precedence over the safety of subjects.*

Date of meeting : 17-02-2016
Date of approval : 17-02-2016

This is a computer generated letter. No signature required.

APPENDIX B

MEDICAL ETHICS COMMITTEE
UNIVERSITY MALAYA MEDICAL CENTRE

PATIENT INFORMATION SHEET (For Patient or Family Member)

Please create Version No. and Version Date for this document:

Version No.: 1.2

Version Date: 20.01.2016

Attention to the investigator: Please fill in simple layman language as you would speak to research subjects.

Please read the following information carefully, do not hesitate to discuss any questions you may have with your Doctor/Investigator

1. **Study Title:**
   Efficacy of enhanced Model Predictive Control (eMPC) in Insulin Therapy in the Critically Ill

2. **Introduction (Scientific basis of the study)**
   Sepsis is a potentially life-threatening complication of an infection. Sepsis occurs when chemicals are released into the body to fight the infection, which will trigger inflammatory response in the body. Sepsis can lead to severe sepsis, in which certain organs in the body are affected causing dysfunction, or septic shock, in which the blood pressure is persistently low. Severe sepsis and septic shock are major healthcare problems, affecting millions of people around the world each year, killing one in four (often more) and increasing in incidence.

   High blood glucose/sugar level (Hyperglycaemia) is a common complication arising from sepsis. Insulin is a naturally occurring hormone produced by the body to control the blood glucose in the body. When sepsis occurs, insulin is required to be given via injection to control the blood glucose level. Persistent high blood glucose level is associated with increased complications and death.

   You or your family member is being chosen to participate in a research study looking at the control of blood sugar level in a critically ill patient requiring intensive care. This is a clinical study. We chose you/him/her to participate in this study because you/he/she is at least 18 years old, and has severe infection requiring Intensive Care Unit (ICU) care for more than 5days.

3. **What is the purpose of this study?**

   In this study, we are investigating the efficacy of the enhanced Model Predictive Control (eMPC) algorithm in controlling the blood sugar level. This is an automated machine which helps to deliver insulin to keep the patient's blood sugar level within a targeted range. We are comparing the usage of this automated machine, to the conventional machine which requires manual adjustment to deliver the insulin.

4. **What are the procedures to be carried out?**
   Your/Patient's blood sugar level will be checked before to admitting to ICU. And subsequently checked every hour or every 4 hours, in which a small amount(1 drop) of blood is taken from a monitoring port

inserted into the artery (blood vessel). The Insulin is either delivered with the conventional machine or automated machine, connected to an intravenous line (an injection port inserted into the veins).

The duration of participation is 5days. Upon completion of 5 days, if you/the patient still requires insulin during the stay in the hospital, it will still be provided via the conventional method.

5. **How long will the patient be involved in this study?**
The duration of this study is 5 days.

6. **Who should not enter the study (exclusion criteria)?**
You/The patient who are less than 18 years old, or with known allergy to Insulin, Diabetic Ketoacidosis and Hyperosmolar Hyperglycaemic Syndrome should not enter the study.

7. **How many patients/research subjects will be recruited into this study?**
A total of 60 patients will be recruited for this study.

8. **Who will have access to the subjects medical records or research data?**
The study doctor may need to look at health records for more information. This includes things like past medical history and test results. He/She may also need to speak with you or the patients' doctors for more medical information. This health information collected as part of this study will be kept private. The information gathered will be used only for the purpose of the research study. By signing the consent form you give permission to the study staff to look at health records only if it is needed for the research study. The only other people who can look at the information are the Health Research Ethics Board. All information will be kept a minimum of 10 years per the Research Ethics Board.

9. **Will the records/data be kept confidential?**
Personal records from this study will be kept confidential. Any information about the patient from this study will not be identified by name, only by initials and a coded number. Any report published as a result of this study will not identify the patient by name.

10. **What will be the benefits of the study to the subject?**

Taking part in this study will probably not directly benefit the patients' care in hospital.

11. **What are the possible drawbacks (side effects, etc.)?**

This study does not cause additional risks to the participants.

12. **Is the investigatory product derived from a source that may be cultural sensitive, eg: bovine or porcine? (if applicable)**

Not applicable.

13. **What payments or reimbursement will research subjects receive?**

There will be no payment or reimbursements given.

14. **Can I refuse to take part in the study?**

If consent is given for a patient to be entered into the study, the patient may withdraw or be withdrawn from the study at any given time and this will no was affect the quality of care the patient receives. Removal of the patient's data from the study is optional as well. However, the investigator may remove

the patient from the study without prior notice or permission.

15. **Who should I contact if I have additional questions during the course of the study?**

Doctor's name: Cheng Yee Shin Phone no.: 0128382996

Doctor's name: Foo Li Lian Phone no.: 0129889011

BK-MIS-1116-E03

APPENDIX C

CRF 1 **ELIGIBILITY** Version 1.0, 3-8-15

Patient ID:

A: Inclusion Criteria (Must be "Yes" to all)	**Yes**	**No**
1. Patient is more than 18 years of age		
2. Patient has Severe Sepsis or Septic Shock Severe Sepsis ☐ Septic Shock ☐		
3. Expected ICU admission more than 72 hours		
4. Blood glucose more than 8.9mmol/l or already on insulin therapy		

Note:

Severe Sepsis	Sepsis with sepsis induced organ dysfunction or tissue hypoperfusion
Septic Shock	Sepsis induced hypotension persisting despite adequate fluid resuscitation SBP< 90mmHg or MAP< 70mmHg or SBP decrease >40mmHg or less than 2 standard deviations below normal for age in the absence of other causes of hypotension

B. Exclusion Criteria (Must be "No" to all)	**Yes**	**No**
1. Know Allergy to Insulin		
2 DKA or HHS		

Eligibility Confirmation

Date of Birth (day/month/year)

Age (years) (month)

Patient is eligible (i.e. ALL Inclusion criteria met and No exclusion criteria) Yes NO

Date and Time written informed consent taken (day/month/year)

(Hour/Minutes)

Name of Authorized Person Completing this CRF

Date of Completing (day/month/year)

CRF 2 **Patient Demographics** Version 1.0, 3-8-15

Patient ID:

A. Patient Demographics

1. Patient Ethnicity
   - ☐ Malay
   - ☐ Chinese
   - ☐ Indian
   - ☐ Others _____

2. Gender
   - ☐ Male
   - ☐ Female

3. Height ____ cm

4. Weight ____ kg

5. BMI ____ kg/m2

6. Age ____ Years

B. Medical History

	NO	YES	
1. Diabetes			→Years of Diagnosis
2. Hypertension			
3. Dyslipidaemia			
4. COPD			
5. Asthma			
6. Coromary Artery Disease			
7. Cardiac Arrhythmia			
8. Congestive Cardiac Failure			
9. Prior Stroke			
10. Prior TIA			
11. ESRF (On Dialysis)			
12. CKD			

☐ OHA
☐ Insulin
List of Medications:
(i)
(ii)
(iii)
(iv)
(v)

C. Admission Particulars:

1. Date of Hospital Admission ____/____/____ (day/month/year)
2. Date of ICU Admission ____/____/____ (day/month/year)
3. Time of ICU Admission ____ (24 Hour format)
4. Date of ICU Discharge ____/____/____ (day/month/year)
5. Date of Hospital Discharge ____/____/____ (day/month/year)

6. Discipline
   - ☐ Medical
   - ☐ Surgical
   - ☐ Others _____

Name of Authorized Person Completing this CRF _____

Date of Completing ____/____/____ (day/month/year)

CRF3 **ICU Admission** Version 1.0, 3-8-15

Patient ID:

1. APACHE II SCORE (CRF7)

2. Diagnosis Septic Shock/Severe Sepsis Secondary to

3. Diagnostic Category

	Yes	No
1 Infection		
2 Cardiovascular		
3 Genitourinary		
4 Gastrointestinal		
5 Neurologic		

6 Others: _____

4. Problem List

	Yes	No
1 Acute Kidney Injury		
2 Coagulopathy/Throbocytopenia		
3 Liver Impairment		
4 HAP		
5 VAP		
6 Sacral Sore		

7 Others: (i)_____
(ii)_____
(iii)_____
(iv)_____

8 CPR ☐ NO ☐ Yes If **Yes**,Hypothermia Therapy→ ☐ NO ☐ Yes

5. Inotropic Support

Name of Inotrope	Dose	Start Date(DD/MM/YY)	Stop Date(DD/MM/YY)

6. Fluid Regime

	Type	Total Volume	Type	Total Volume
Day 1				
Day 2				
Day3				
Day4				
Day5				

7. Nutrition

	Type	Total Volume	Type	Total Volume
Day 1				
Day 2				
Day3				
Day4				
Day5				

(E) Denotes Enteral*
(P) Denotes Parenteral*

Name of Authorized Person Completing this CRF

Date of Completing (day/month/year)

CRF4 **Concomitant Medications** Version 1.0, 3-8-15

Patient ID:

1. Is the participant taken any concomitant medications at screening ?					☐ No	☐ Yes, Complete below	
Medication (Record Generic or trade name)	Reason for use (Medical History diagnosis or other reason,	Dose and units	Frequency	Route	Start Date (DD/MMM/YYYY)	Stop Date (DD//MMM/YYY)	Or tick if ongoing at Screening Visit
1					___/___/____	___/___/____	
2					___/___/____	___/___/____	
3					___/___/____	___/___/____	
4					___/___/____	___/___/____	
5					___/___/____	___/___/____	
6					___/___/____	___/___/____	
7					___/___/____	___/___/____	
8					___/___/____	___/___/____	
9					___/___/____	___/___/____	
10					___/___/____	___/___/____	

2. Is the patient started on steroids?

☐ No	
☐ Yes	→ Type _____ → Route_____ → Dose _____ → Start Date_____/_____/_____ → Stop Date_____/_____/_____

Name of Authorized Person Completing this CRF

Date of Completing (day/month/year)

CRF5 **Baseline and Investigation** Version 1.0, 3-8-15

Patient ID:

1.Vital Signs

SBP	mmHg	
DBP	mmHg	
MAP	mmHg	

Heart Rate	/min	
Respiratory Rate	/min	
Temperature	°C	

2. Baseline Glucose mmol/l **3. HbA1C**

4. FBC

	Day 0		*Day 3*
Hb		Hb	
TWC		TWC	
Platelet		Platelet	

5.ABG

pH	
pO2	
pCO2	
HCO3	
BE	
Lactate	

6.Renal Profile

Na	
K	
Cl	
Urea	
Creatinine	

7.LFT

T.Bil	
D.Bil	
ALP	
AST	
ALT	

8. Inflammatory Markers

i) CRP
ii)ESR
iii)Fibrinogen

Day0	Date	Day3	Date

iv) IL-6

Day 1	Date	Day3	Date	Day5	Date

iv) Procalcitonin ☐ No ☐ Yes If Yes→ (Value)

Name of Authorized Person Completing this CRF

Date of Completing (day/month/year)

CRF6 **Outcome** Version 1.0, 3-8-15

Patient ID:

1. Completion of study

☐ No
☐ Yes

2. Withdrawal from Study

☐ No
☐ Yes

If Yes, Reason:_____

3. Outcome

☐ Alive
☐ Discharged to ward
☐ Discharged to Home
☐ Unknown
☐ Died, Cause of Death _____

4.Ventilation Duration

Total Days ☐

☐ Invasive

Total Days ☐

☐ Non-Invasive

Total Days ☐

Name of Authorized Person Completing this CRF

Date of Completing ☐☐☐☐☐ (day/month/year)

Patient ID:

APACHE II Scoring System

A Acute Physiology Points:

Physiologic variable	High Abnormal Range					Low Abnormal Range			
	+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature (rectal, °C)	≥41	39-40.9		38.5-38.9	36- 38.4	34-35.9	32 -33.9	30 -31.9	≤29.9
Mean Arterial Pressure (mm Hg)	≥160	130 155	110-129		70-109		50-69		≤49
Heart rate (ventricular response)	≥ 180	140-179	110-139		70-109		55-69	40-54	≤39
Respiratory rate (non-ventilated or ventilated)	≥50	35-49		25-34	12-24	10-11	6-9		≤5
Oxygenation: $AaDO_2$ or PaO_2 (mmHg) a. FIO_2 ≥0.5 record only AaDO b. FIO_2 <0.5 record only PaO_2	≥500	350-499	200-349		<200 PO_2 >70	PO_2 61-70		PO_2 55-60	PO_2 <55
Arterial pH	≥7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	<7.15
Serum sodium (mMol/L)	≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110
Serum potassium (mMol/L)	≥7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		<2.5
Serum creatinine (mg/100 mL) (double point score for acute renal failure.)	≥3.5	2-3.4	1.5-1.9		0.6-1.4		<0.6		
Hematocrit (%)	≥60		50-59.9	46-49.9	30-45.9		20-29.9		<20
White Blood Count	≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1
Glasgow Coma Score (GCS) Score = 15 minus actual GCS									
Total Acute Physiology Score									
Serum HCO_3 (venus, mMol/L) (not preferred, use if no ABGs)	≥52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	<15

B AGE POINTS:

Assign points to age as follows:

Age (yrs)	Points
≤ 44	0
45 – 54	2
56 – 64	3
65 – 74	5
≤ 75	6

C CHRONIC HEALTH POINTS:

If the patient has a history of severe organ insufficiency or is immunocompromised, assign points as follows:

a. nonoperative or emergency post-operative patients: **5 points**
b. elective postoperative patients: **2 points**

Definitions: Organ insufficiency or immunocompromised state evident prior to this hospital admission and conforming to the following criteria:
LIVER: Biopsy proven cirrhosis and documented portal hypertension; episodes of past upper GI bleeding attributed to portal hypertension; or prior episodes of hepatic failure/encephalopathy/coma.
CARDIOVASCULAR: New York Heart Association Class IV.
RESPIRATORY: Chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction, ie, unable to climb stairs or perform household duties; or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (>40 mm Hg), or respirator dependency.
RENAL: Receiving chronic dialysis.
IMMUNOCOMPROMISED: Patient has received therapy that suppresses resistance to infection, eg, immunosuppression, chemotherapy, radiation, long term or recent high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection (eg, leukemia, lymphoma, AIDS)

APACHE II SCORE

Sum of A + B + C

A APS Points	_____
B Age Points	_____
C Chronic Health Points	_____
TOTAL APACHE II	_____

Name of Authorized Person Completing this CRF

Date of Completing (day/month/year)