The Normoglycemia in Intensive Care Evaluation (NICE) (ISRCTN04968275) and Survival Using Glucose Algorithm Regulation (SUGAR) Study: Development, design and conduct of an international multi-center, open label, randomized controlled trial of two target ranges for glycemic control in intensive care unit patients

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Trial Summary

Title
Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation Study

Acronym:
NICE - SUGAR Study

Scientific Title:
A multi-center, open label randomized stratified controlled trial of the effects of blood glucose management on 90-day all-cause mortality in a heterogeneous population of intensive care unit (ICU) patients.

Disease under study:
Hyperglycemia in intensive care unit patients

Participants
4500 patients recruited from up to 23 ICUs in Australia and New Zealand and up to 16 ICUs in Canada who are expected to require treatment in the ICU that extends beyond the calendar day following the day of admission to the ICU

Interventions
Participants will be randomized to one of two target ranges for blood glucose.
Lower range - blood glucose between 81-108 mg/dL (4.5 - 6.0 mmol/L),
Higher range - blood glucose less than 180 mg/dL (10.0 mmol/L) with insulin being infused if blood glucose exceeds 180 mg/dL (10.0 mmol/L) and adjusted when needed to maintain blood glucose between 144-180 mg/dL (8.0 – 10.0 mmol/L).
Blood glucose management is guided by a study specific web-based treatment algorithm

Primary outcome: 90-day all-cause mortality

Key secondary outcomes:
ICU and hospital mortality and length of stay
Degree and duration of organ dysfunction
Extended Glasgow outcome score at 90 days and 6 months in patients with traumatic brain injury

Projected completion date for recruitment: December 2006

Sources of funding:
Australian National Health and Medical Research Council
New Zealand Health Research Council
Vancouver General Hospital Foundation
Canadian Intensive Care Foundation
Canadian Diabetes Association

Background and rationale

Hyperglycemia is a common finding in patients who are acutely ill. The incidence of hyperglycemia in critically ill patients has been documented to be as low as 20% and as high as 90% reflecting the diverse definitions adopted by various investigators. [1-3] Associations between hyperglycemia and adverse clinical outcomes have been reported in many observational studies. A single center retrospective unadjusted analysis of 1826 intensive care unit (ICU) admissions found that hospital mortality increased progressively as mean glucose concentrations increased; mortality was 9.6% in patients with glucose concentrations between 80-99 mg/dL (4.5-5.5 mmol/L) and 42.5% in those with concentrations greater than 300 mg/dL (16.5 mmol/L).[4] In a cohort of 1886 consecutive hospital admissions, newly-discovered hyperglycemia was associated with a hospital mortality rate of 16% compared to 3% among patients known to have diabetes and 1.7% in patients with normoglycemia.[1] After adjustment for confounding factors, stress hyperglycemia was associated with an 18 fold increase in mortality. These observational studies make important contributions to our understanding of the relationship between glucose homeostasis and clinical outcomes; however, they are not designed to test whether intensive glycemic control improves important clinical outcomes in critically ill patients.

Van den Berghe and colleagues conducted a randomized controlled trial to determine the effect of intensive insulin therapy compared to conventional management in a surgical ICU in Leuven, Belgium. Mechanically ventilated surgical patients were randomly assigned to intensive insulin therapy (treated

with insulin to maintain blood glucose between 80-110 mg/dL [4.4-6.1 mmol/L]) or conventional insulin therapy (treated with insulin when necessary to maintain blood glucose between 180-200 mg/dL [10-11.1 mmol/L]).[2] The planned recruitment was 2500 patients but the trial was stopped at a fourth interim analysis after 1548 patients were recruited. A significant reduction in hospital mortality was found in the intensive insulin group (7.2% vs. 10.9%, P=0.01). After adjustment for interim analyses, the median estimate of the reduction in mortality was 32% (95% confidence interval of 2 – 55%; P<0.04). Fewer patients receiving intensive insulin therapy had blood stream infections, acute renal failure requiring dialysis and critical illness polyneuropathy. Patients receiving intensive insulin therapy also had fewer blood transfusions and a shorter duration of hospital stay. The reduced mortality was limited to patients who stayed in the ICU for more than five days.

Although these findings are compelling, there are several issues to consider before advocating the use of intensive insulin therapy in ICU patients worldwide. Concerns related to the study participants and setting have been raised. In particular, the population was narrowly defined (primarily male cardiac surgery patients) and the illness severity (measured by the APACHE II score[5]) was lower than that found in most ICUs. In addition, concerns have also been raised about the amount of intravenous glucose administered to Van den Berghe's patients. Patients in both arms of the study received 200 – 300 g of intravenous glucose per day amounting to, which is many times more than usual in Australia, Canada and New Zealand. In an observational study,

Dhingra and colleagues noted that Canadian critical care physicians administer an average of only 30 grams of intravenous glucose per day.[6]

Also in a prospective observational study, Mitchell et al found that Australian and New Zealand practitioners administer on average only 2.2 g of IV glucose per day. (Mitchell – unpublished data) In the control group of Van den Berghe's study, ICU mortality was higher than anticipated from the reported APACHE II scores, for example cardiac surgical patients in the conventional group had a 5.1% mortality compared to 1.0% for cardiac surgical patients admitted to Australasian ICUs (ANZICS Adult Patient Database – unpublished data). This difference in mortality may be explained by differences in case-mix and severity of illness, but may also indicate that the administration of high dose intravenous glucose without correction by intensive insulin treatment increased mortality in the control group. In the ICU community, significant uncertainty remains regarding the benefits of intensive glycemic control in heterogeneous critically ill patients, especially among patients who stay in the ICU less than five days, and among those not administered large amounts of intravenous glucose. Finally, intensive insulin therapy is not without risk. Even in Van den Berghe's carefully controlled trial, one in twenty patients assigned intensive insulin therapy suffered severe hypoglycemia (blood glucose less that 40mg/dL [2.2mmmol/L]). A recent attempt to replicate Van den Berghe's trial in another RCT in England resulted in 42% of patients assigned intensive insulin therapy suffering severe hypoglycemia,[7] this raises serious safety concerns about disseminating the intervention outside the research setting.

Despite these concerns, given the prevalence of hyperglycemia in critically ill patients, the potential for adverse health consequences, and the emerging evidence that intensive insulin therapy may result in improved outcomes, there is a pressing need to rigorously test the effectiveness of this intervention in a multi-center, multi-national randomized controlled trial (RCT). Such a trial is now underway in Australia, Canada and New Zealand.

Pre-trial activities

Pre-trial activities included:

- Self administered questionnaires regarding attitudes to hyperglycemia and the treatment of hyperglycemia in Canadian, Australian and New Zealand ICUs.
- Prospective observational studies of actual management of blood glucose in Canadian, Australian and New Zealand ICUs.
- Pilot Randomised Controlled Trials (RCTs).

Self-administered surveys and prospective observational studies:

In 2003, a self-administered survey and prospective cohort study on current management of hyperglycemia in ICUs active in the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG) found that only four (12%) of 33 ICU directors surveyed reported using intensive insulin therapy in all their patients. Amongst 939 consecutive admissions to 29 ICUs, 92% of patients had a blood glucose concentration greater than 110 mg/dL (6.1mmol/L) at least once during their ICU stay. A target range for blood glucose was documented for only 32% of patient-days; the range was

consistent with intensive insulin therapy (80-110 mg/dL, 4.4 – 6.1 mmol/L) on only 3.6% of patient-days. The commonest target range was 108-180 mg/dL (6-10 mmol/L). The median (IQR) highest blood glucose during ICU stay was 178mg/dL (141, 227) (9.9 mmol/L [7.8, 12.6]) and the median (IQR) amount of intravenous dextrose administered during the first 24 hours of ICU admission was 1.1g (0, 30). Intravenous insulin was given to 287 patients (31.1%) to control blood glucose during their ICU stay. The median blood glucose concentration that triggered administration of intravenous insulin was 207 mg/dL (169, 252) (11.5 mmol/L [9.4, 14]) with no differences between ICUs (Table 1). [8]

The beliefs and attitudes of Canadian ICU clinicians about glycemic control, were studied using a self-administered survey of 317 ICU nurses and physicians in five university-affiliated multidisciplinary ICUs. For both non-diabetic and diabetic patients, the clinically important threshold for hyperglycemia was 180mg/dL (10 mmol/L); however, nurses had a significantly higher threshold than physicians (p=0.02). Avoidance of hyperglycemia was judged most important for diabetic patients (87.7%), patients with acute brain injury (84.5%), patients with a recent seizure (74.4%), patients with advanced liver disease (64.0%), and for patients with acute myocardial infarction (64.0%). Physicians expressed more concern than nurses about avoiding hyperglycemia in patients with acute myocardial infarction (p=0.0004). ICU clinicians (46.1%) raised concerns about the accuracy of glucometer measurements in critically ill patients. The authors concluded that attention to these beliefs and attitudes could enhance the

success of future clinical, educational and research efforts to modify clinician behaviour and achieve better glycemic control in the ICU setting.[9]

In Canada, in a prospective cohort study of 403 patients admitted to a multidisciplinary university-affiliated ICU, the mean (SD) admission blood glucose concentration was 157 +/- 74 mg/dL (8.7 +/- 4.1 mmol/L) with 50% of the population having a blood glucose concentration greater than 141 mg/dL (7.8 mmol/L). The mean (SD) blood glucose concentration for the entire cohort over 28 days was 146 +/- 5 mg/dL (8.1 +/- 2.1 mmol/L). Of the total cohort, 60.2% received insulin at some point during their ICU stay. Despite a steady decrease in glucose concentration over time, the average daily insulin dose remained constant at a mean (SD) of 4.0 +/- 2.9 units/hour. This is a daily average of 96 units/day to maintain a mean (SD) glucose concentration of 150 +/- 41.4 mg/dL (8.3 +/- 2.3 mmol/L). Over 60% of the cohort had insulin started within the first two days in the ICU and the mean (SD) glucose concentration at the start of insulin therapy was 225 +/- 67 mg/dL (12.5 +/- 3.7 mmol/L) (Table 1).[10]

Table 1: Surveys of blood glucose (BG) management in intensive care units (ICUs) prior to commencing the NICE-SUGAR trial. [8;10]

	Mitchell *et al*, 2005	Chittock *et al*, 2005
Setting	29 ICUs, Australia and New Zealand	1 Canadian ICU
Sample size	939	403
ICU patient-days observed	3790	11284
BG on ICU admission (mg/dL)	130 (105, 168)[a]	157 ± 74[b]
Patients (%) receiving insulin during ICU admission	287 (30.6%)	242 (60.2%)
BG that triggered insulin administration (mg/dL)	207 (169, 252)[a]	225 ± 67[b]
BG >110 mg/dL during admission	861 (91.7%)	403(100%)

[a] Median (interquartile range)
[b] Mean ± SD

These data indicate that in the Australian, Canadian and New Zealand ICUs studied, patients are not administered large amounts of intravenous glucose and intensive insulin therapy is not widely practiced. In Canada, 180 mg/dL (10mmol/L) was considered the clinically important glycemic threshold at which insulin therapy would be administered, in Australian and New Zealand the most commonly targeted range for blood glucose was 110-180 mg/dL (6-10mmol/L).

Pilot randomized controlled trials (RCTs)

Three pilot RCTs were conducted during the development of the current trial.

The Lowering Of Glucose In Critical Care (LOGIC) pilot was a randomized feasibility trial. Twenty adult ICU patients were randomized to control (target glucose 144-216mg/dL [8.0-12.0 mmol/L]) or intervention (target glucose 90 – 126mg/dL [5.0-7.0 mmol/L]) using intravenous insulin infusions and pre-tested algorithms. Although the lower target group had more glucose measurements performed, glucose values were within the target range a similar proportion of time in both groups (42.4% in the intervention group and 38.7% in control group). A blood glucose concentration of less than 45mg/dL (2.5 mmol/L) was recorded 9 times in 7 patients (6 in the 90 – 126mg/dL [5.0-7.0 mmol/L] range).[11]

In the Survival Using Glucose Algorithm Regulation (SUGAR) pilot RCT, 68 patients were randomly assigned to have their blood glucose maintained between 72-126 mg/dL (4.0-7.0 mmol/L) or 162-198 mg/dL (9.0-11.0 mmol/L). Hypoglycemic events (glucose less than 40mg/dL [2.2 mmol/L]) occurred in 7 (10.2%) patients in the 72-126 mg/dL (4.0-7.0 mmol/L) group and 1 (1.4%) patient in the 162-198 mg/dL (9.0-11.0 mmol/L) group (0.39% and 0.04% of all measurements in each group respectively).[12]

The Intensive Insulin Therapy in General Intensive Care Patients Trial enrolled 70 patients in Canberra, Australia.[13] Patients were randomly assigned to receive either intensive or conventional insulin therapy (blood glucose target 80-110 mg/dL [4.4–6.1 mmol/L] or 180-200 mg/dL [10.0–11.1 mmol/L] respectively). Of the 3044 blood glucose samples in the intensive group, 0.23% had a glucose concentration of less than 40 mg/dL (2.2

mmol/L). None of the 2917 blood glucose samples taken in the conventional insulin group had a blood glucose concentration less than 40 mg/dL (2.2 mmol/L). [13]

Whilst there were no significant differences in mortality in any of the three pilot RCTs, these trials demonstrated the feasibility of conducting a large RCT in Australia, Canada and New Zealand.

The Normoglycemia in Intensive Care Evaluation (NICE) and Survival Using Glucose Algorithm Regulation (SUGAR) Study

Study design

The Normoglycemia in Intensive Care Evaluation (NICE) and Survival Using Glucose Algorithm Regulation (SUGAR) study is a multi-center, open label, randomized stratified controlled trial of the effects of blood glucose management on 90-day all-cause mortality in 4500 patients recruited from up to 23 ICUs in Australia and New Zealand and up to 16 ICUs in Canada. An intensive insulin regimen, designed to maintain blood glucose between 81-108 mg/dL (4.5 - 6.0 mmol/L), is being compared with an insulin regimen maintaining blood glucose less than 180 mg/dL (10.0 mmol/L) with insulin being infused if blood glucose exceeds 180 mg/dL (10.0 mmol/L) and adjusted when needed to maintain blood glucose between 144-180 mg/dL (8.0 – 10.0 mmol/L).

Study population

In this large effectiveness trial, we will include a wide spectrum of critically ill adults as a means of maximizing the generalizability of our results. Consequently, we will recruit participants from centers across two continents. Eligibility criteria are as simple as possible (Table 2). Whilst seeking to include a broad population of patients, we are excluding patients likely to be exposed to the trial intervention for less than 24 hours, as we consider that such short duration exposure to intensive insulin therapy may seriously limit the ability of this intervention to alter the primary outcome.

Table 2: Eligibility criteria for the NICE/SUGAR study

Patients are eligible for inclusion in the study if the following criteria are met: 1. At time of the patient's admission to the ICU the treating ICU specialist expects the patient will require treatment in the ICU that extends beyond the calendar day following the day of admission. 2. Patient has an arterial line in situ or placement of an arterial line is imminent (within the next hour) as part of routine ICU management.
Patients are excluded from the study if one or more of the following criteria are present: 1. Age less than18 years. 2. Imminent death (cardiac standstill or brain death anticipated in less than 24 hours) and the treating clinicians are not committed to full supportive care. This is confirmed by a documented treatment-limitation order that exceeds a "not-for-resuscitation" order. 3. Patients admitted to the ICU for treatment of diabetic ketoacidosis or hyperosmolar state. 4. Patients expected to be eating before the end of the day following the day of admission to the ICU. 5. Patients who have previously suffered hypoglycemia without documented full neurological recovery.

6. Patients thought to be at abnormally high risk of suffering hypoglycemia (e.g. known insulin secreting tumor or history of unexplained or recurrent hypoglycemia or fulminant hepatic failure)
7. Patient has previously been enrolled in the study.
8. Patient cannot provide prior informed consent and there is documented evidence that the patient has no legal surrogate decision maker and it appears unlikely that the patient will regain consciousness or sufficient ability to provide delayed informed consent.
9. Patient has been in the study ICU or another ICU for 24 hours or more for this admission.

Randomized treatment allocation

Randomization of patients occurs via a secure, password-protected, encrypted website and is available 24 hours a day. The centralized system based at The George Institute for International Health (the trial coordinating center) was developed from the system used successfully in the 6997-patient SAFE study. [14] The web-based system enables absolute concealment of the randomization schedule and automatically records treatment allocation which facilitates analysis of study outcomes on an intention-to-treat basis. A minimization algorithm stratifies treatment allocation by type of critical illness (medical vs. surgical) and by continent (Canada vs. Australia and New Zealand).

Figure 1 – NICE – SUGAR website. Registered users menu

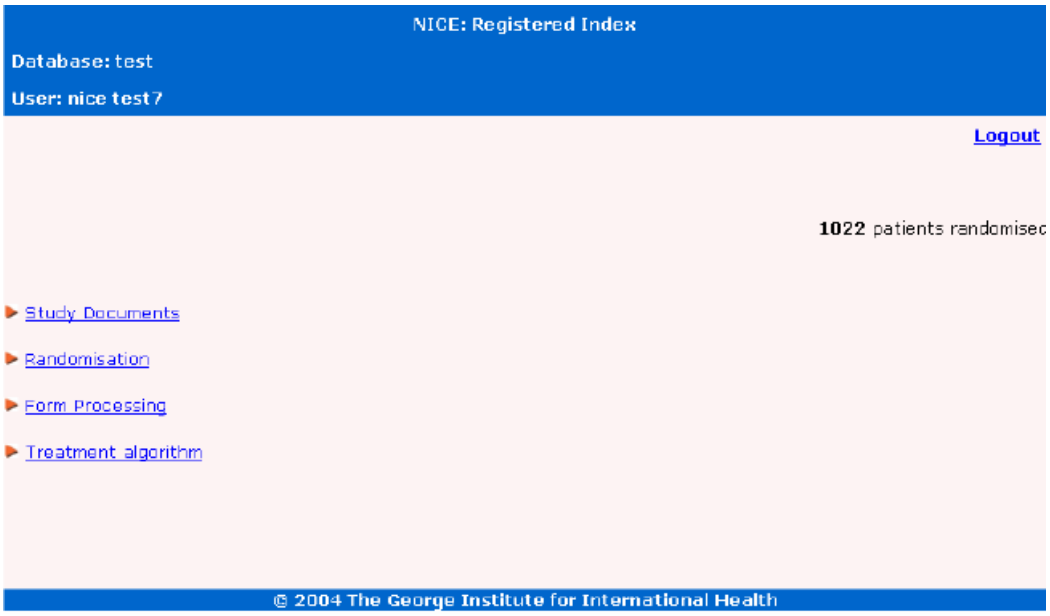


Figure 2 – NICE – SUGAR website. Randomization form

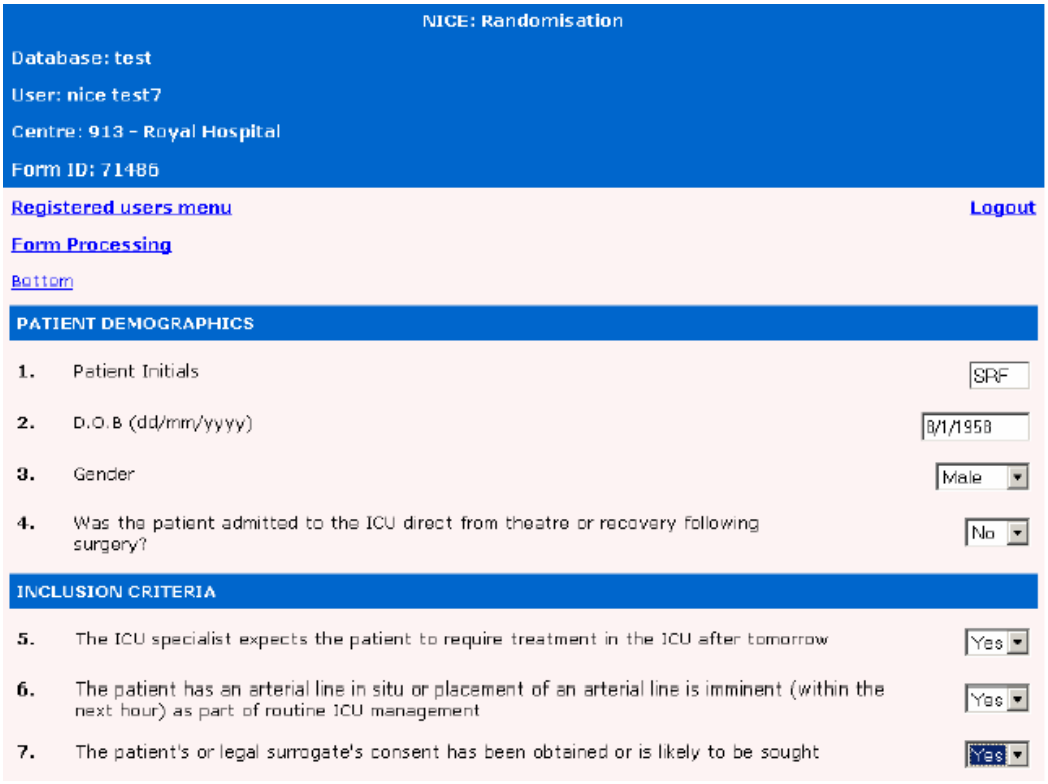


Figure 3. NICE – SUGAR website. Randomization warning form alerting staff to possible duplicate randomization

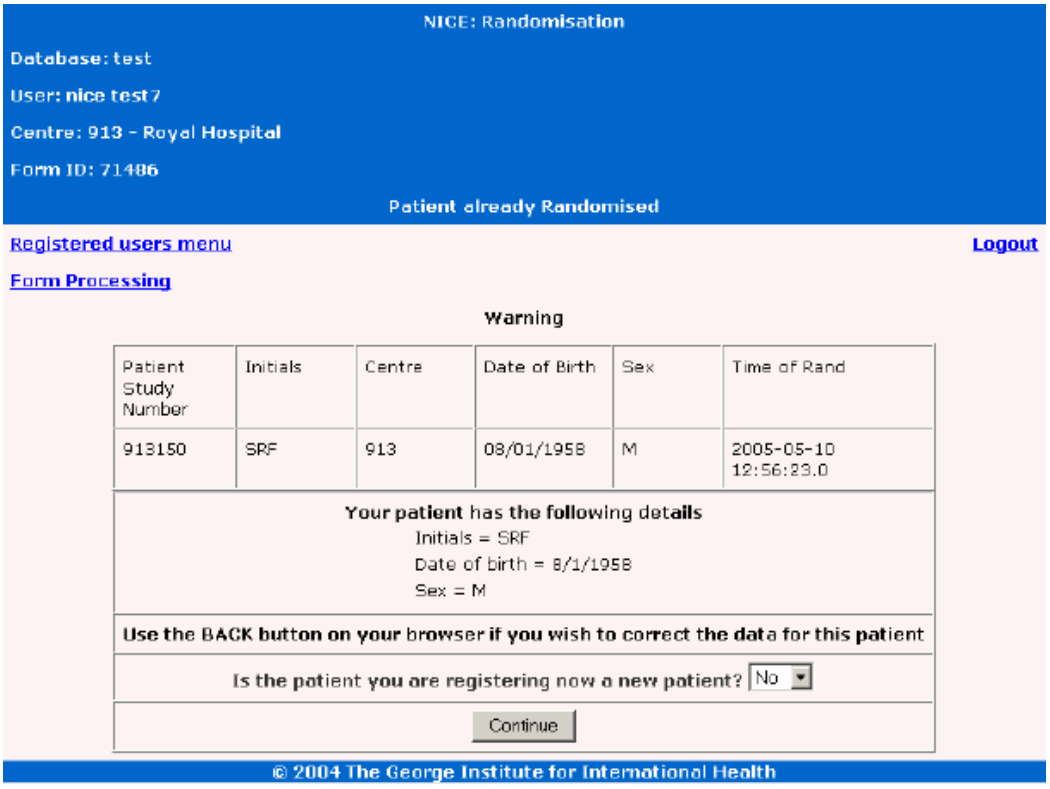
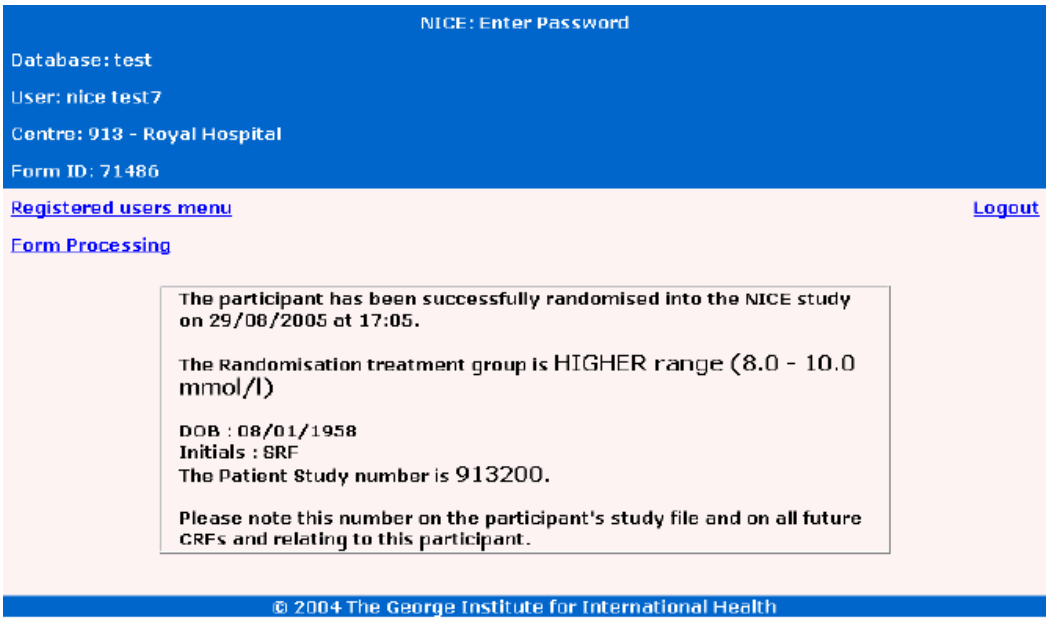


Figure 4. NICE – SUGAR website. Notification of successful randomization



Minimizing sources of bias

This will be an open-labeled RCT. After extensive discussions with members of the ANZICS and Canadian Critical Care Trials Groups, the study management and executive committees determined that double blinding of the treatment strategies was not practical in a large scale trial targeting different blood glucose concentration ranges. The pilot RCTs had shown that the safe conduct of such RCTs required extremely careful, hour by hour, monitoring of blood glucose concentration. To blind clinical staff in the participating centers, glycemic control would have to be monitored and managed by a research team separate from the clinical ICU team. This was not only impractical with the trial resources, but would also introduce an element of artificial care that would limit the generalizability of the trial result. Accordingly, we have taken a number of precautions to minimize potential biases resulting from the inability to blind the treatment strategies at the bedside: 1) the use of 90 day mortality as the primary endpoint. Mortality is a robust clinically relevant outcome that is exceedingly difficult to influence through measurement or ascertainment bias and 2) having the insulin administration carefully guided and monitored using centralized computer algorithms based upon pre-established guidelines. A related concern is whether the inability to blind the treatment strategies from the ICU team will result in a differential treatment of patients based on their allocation to one or other target range; this is especially pertinent in regard to the provision of nutrition. Consequently we have protocolized feeding regimens and will collect detailed information related to nutritional support in all patients.

Despite the lack of blinding, we expect the results of this definitive trial to have a major impact on practice. The medical literature has many examples of well conducted open-labeled clinical trials which have provided important estimates of treatment effects and have significantly affected clinical practice; examples from the critical care literature include the Transfusion Requirements in Critical Care Trial and recent pulmonary artery catheter trials.[15-17]

A screening log will be maintained at each center to record the number of patients screened, number not randomized and the diagnosis and reason for exclusion (ineligible or eligible but not enrolled). In doing so, we will comment on referral patterns into the trial.

Data collection and management

As appropriate to a large simple effectiveness study, data collection has been kept a minimum and is a simple as possible.[18] Data collected at baseline allow comparison of participant characteristics in each of the study groups. Baseline data include age, sex, source of admission, diagnostic category, APACHE II score, presence of sepsis, trauma and traumatic brain injury, presence and degree of organ dysfunction, diagnosis of diabetes mellitus, and use of concomitant therapies such as mechanical ventilation, renal replacement therapy and corticosteroids.

Data collected on a daily basis while the participants are in the ICU allows characterization of the presence and degree of organ dysfunction, use of

concomitant therapies, and details of all enteral and parenteral nutrition delivered.

Data for each patient are entered electronically into the structured reporting forms accessed via the study's secure website. Data checks and queries for out-of-range, missing and inconsistent information are raised in real time. Data are collated centrally at the coordinating center. Unless consent for ongoing data collection is withdrawn by the patient or their legal surrogate decision maker, all study participants are followed until death or 90-days post-randomization. Participants who have suffered a traumatic brain injury are followed until six months post-randomization.

Study treatments

Each patient is randomly assigned on a one-to-one basis to one of two blood glucose concentration targets: either 81-108 mg/dL (4.5 - 6.0 mmol/L) (the lower range) or less than 180 mg/dL (10.0 mmol/L) with insulin being infused if blood glucose exceeds 180 mg/dL (10.0 mmol/L), and titrated when needed to maintain the blood glucose concentration between 144 and 180 mg/dL (8 - 10 mmol/L) (the higher range). The lower range was chosen from Van den Berghe's original study (rounded to appropriate SI units), the higher range was chosen by consensus based on the common target range in use in Australian and New Zealand ICUs. [8]

A continuous intravenous infusion of insulin is commenced if required as determined by the patient's treatment allocation. In the first instance, adjustments to the insulin dose are made based on the measurement of whole blood glucose in undiluted arterial blood performed at hourly intervals.

The frequency of blood glucose measurement may be reduced to two-hourly and then four-hourly once the insulin infusion rate, blood glucose concentration and caloric intake are sufficiently stable. Blood samples are obtained from arterial or central venous lines wherever possible and the use of capillary samples is discouraged. Blood glucose concentration measurements may be performed using a calibrated glucometers, an arterial blood gas machine with a glucose electrode or other calibrated point-of-care measurement system. All glucometer measurements of less than 72 mg/dL (4.0mmol/L) are checked against a calibrated laboratory measurement.

A study treatment algorithm guides management of glycemic control in study participants. The algorithm was developed from clinical protocols used in routine clinical practice by members of the management committee and from the protocol used in the Canberra pilot study.[13] The algorithm, which is accessed via the study's secure website, was developed to standardize insulin therapy at participating centers, provide a real time record of blood glucose and insulin doses in study patients and to independently record the incidence of severe hypoglycemia (blood glucose of 40mg/dL [2.2 mmol/L] or less). Clinical staff (both doctors and nurses) in the participating ICUs received formal training in the use of the algorithm. The study algorithm recommends insulin infusion rates based on the current blood glucose measurement, the previous blood glucose measurement and the current insulin infusion rate. In addition, the algorithm may recommend a doctor review the patient and recommend the administration of glucose for the

treatment of actual or impending hypoglycemia. The algorithm also encourages clinician discretion to ensure the safe and effective use of insulin.

Figure 5. NICE – SUGAR website. Treatment algorithm front screen

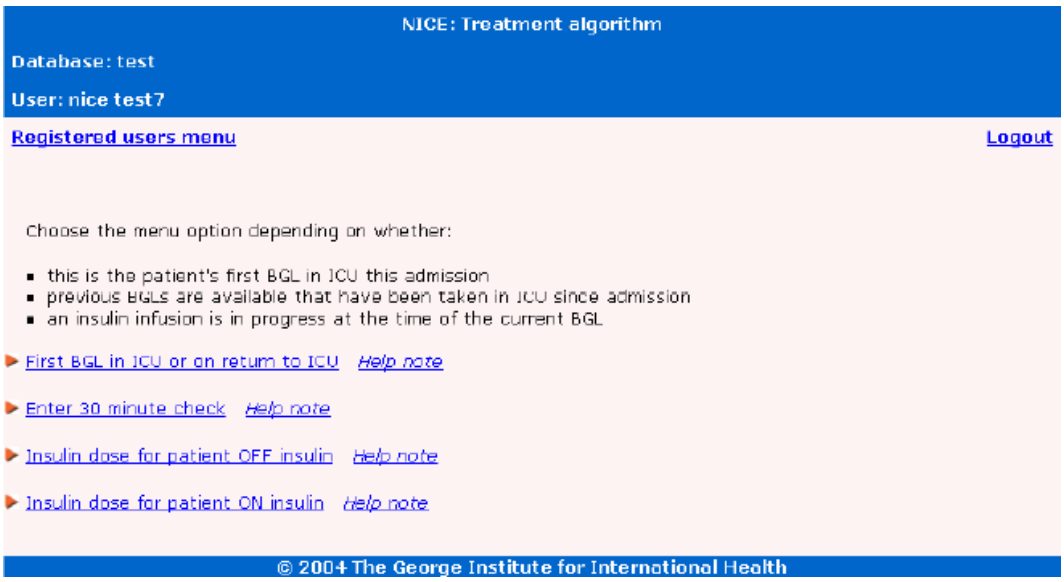


Figure 6. NICE – SUGAR website. Treatment algorithm data entry screen (BGL = blood glucose level. To convert to mg/dL multiply by 18.02. [5.4mmol/L = 97.3mg/dL, 3.6mmol/L = 64.9mg/dL])

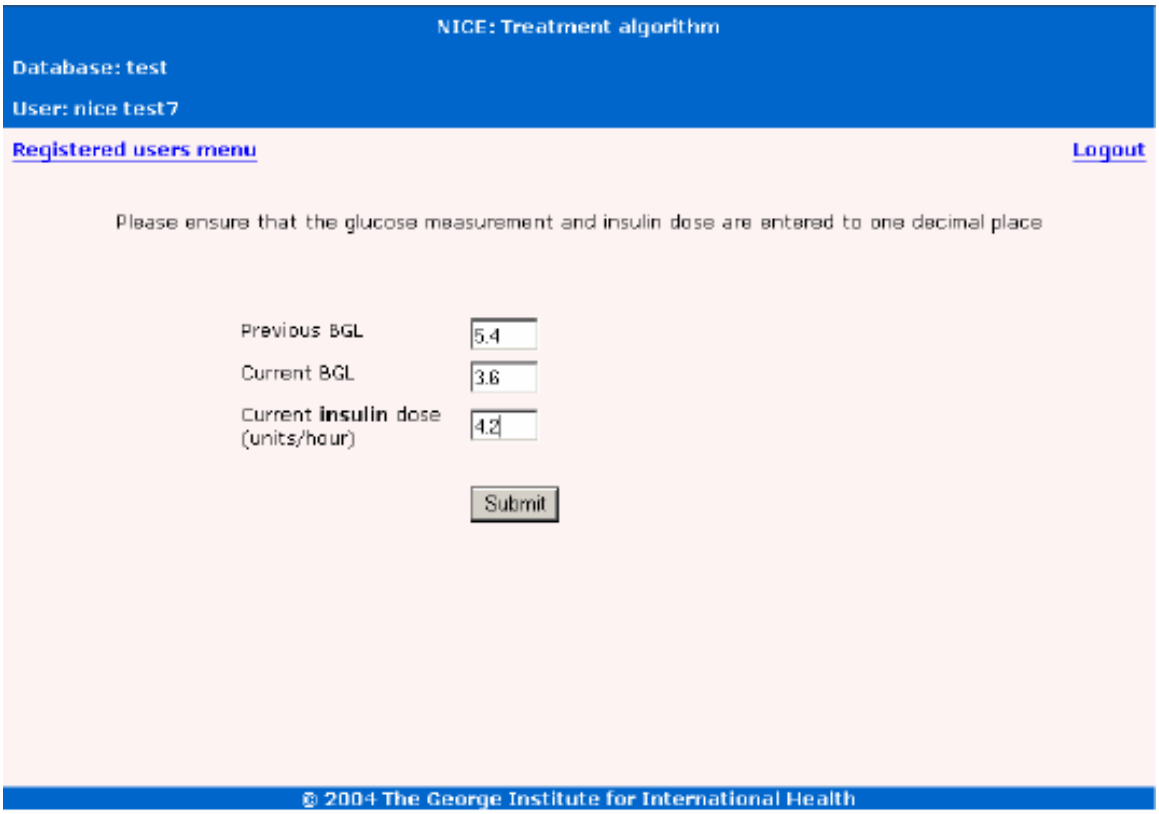
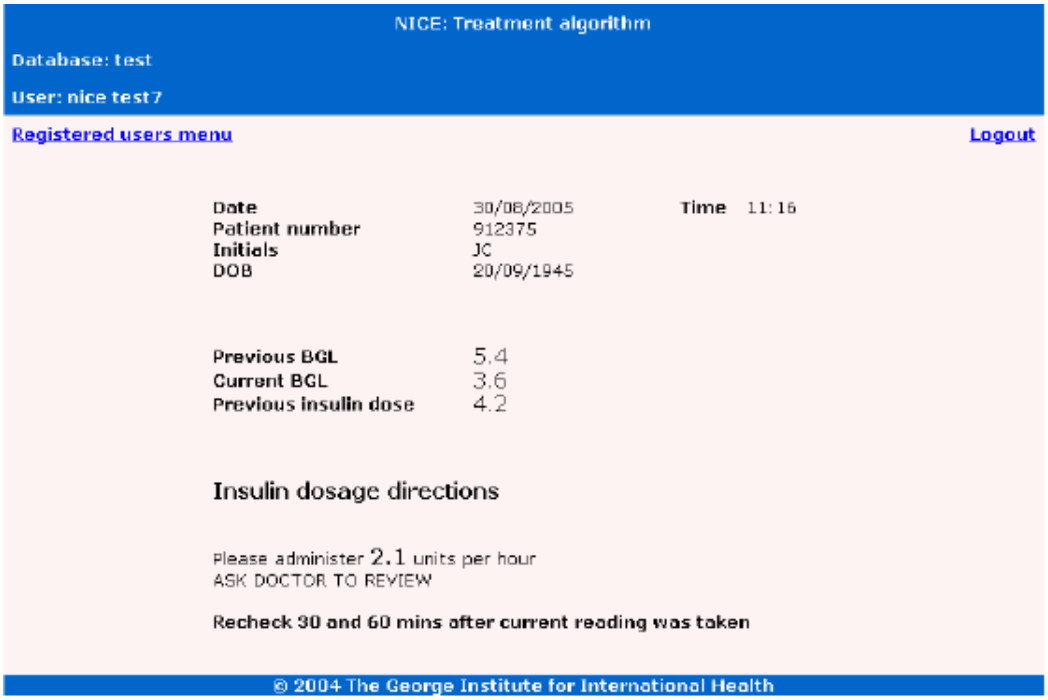


Figure 7. NICE – SUGAR website. Treatment algorithm instruction screen with instructions for insulin dosage and timing of next blood glucose concentration measurements. In this example as the blood glucose is below range and decreasing and this may indicate impending hypoglycaemia, the algorithm recommends reducing the insulin infusion rate by 50%, checking the blood glucose concentration in 30 minutes and also requests a doctor review the patient. (BGL = blood glucose level. To convert to mg/dL multiply by 18.02. [5.4mmol/L = 97.3mg/dL, 3.6mmol/L = 64.9mg/dL])



On discharge from the ICU, patients receive conventional blood glucose management under the control of the treating clinicians on the ward.

Risk of hypoglycemia

The major perceived risk to participants is the potential for severe hypoglycemia. Education of ICU staff about both insulin regimens and the need to reduce insulin dosage independent of the algorithm whenever

nutritional support is reduced is continued throughout the study. All episodes of hypoglycemia (blood glucose concentration of 40 mg/dL [2.2mmol/L] or less) regardless of evident consequences are considered serious adverse events and are reported to the coordinating center within 24 hours.

Discontinuation of trial intervention

The trial intervention continues until the patient is not requiring supplementary enteral or parenteral nutrition and is eating, or until the earlier of ICU discharge or death or 90 days after randomization. We chose to discontinue the trial intervention once eating was a patient's sole source of nutrition as this was a criterion used in Van den Berghe original study and it is a clear and identifiable marker of improvement a patient's clinical condition. If during the 90-day follow up period the trial intervention is discontinued and the patient subsequently satisfies the trial entry criteria again, the intervention is recommenced.

The attending ICU physician may withdraw the trial intervention for an individual patient if it is deemed to be in that patient's best interest (for example if a patient suffers significant or repeated episodes of hypoglycemia). Patients withdrawn from the randomized treatment will be followed up and analyzed according to the intention-to-treat principle. The only exception will be if the patient or their legal surrogate specifically requests that such follow up be ceased.

Study outcomes

Given that this is a large effectiveness trial, 90 day all cause mortality is the primary outcome. The 90 day observation window was chosen because a high proportion of patients remain in the ICU at 28 days and a longer window of observation is more relevant to critically ill patients.[19] To ascertain survival status, the research coordinators verify the source documentation at each monitoring visit. We are also recording several secondary outcomes:

- Death in the ICU and mortality at 28 days
- Length of ICU stay
- Length of hospital stay
- Need for organ support (inotropic agents, renal replacement therapy and invasive or noninvasive positive pressure ventilation)
- Incidence, severity and duration of organ dysfunction
- Incidence of blood stream infection
- Incidence and severity of hypoglycemia
- In the subgroup of patients diagnosed with traumatic brain injury, the Extended Glasgow Outcome Scores (GOSE) at day 90 and at 6 months

Research ethics committee approval and consent

The human research ethics committees at each hospital and at the University of Sydney have approved the trial. In Australia and New Zealand, the provision for delayed consent has been allowed for those situations in which direct consent cannot be obtained in a timely fashion from a critically ill patient. As soon as practicable, the patient, or his or her legal surrogate, is approached and consent is obtained. In instances where consent is obtained

from a patient's legal surrogate, consent will also be sought from the patient if that patient regains the ability to give informed consent. The patient or legal surrogate is free to withdraw consent at any time.

In Canada, written consent to participate will be obtained from the patient or their legal surrogate as usual. The patient or legal surrogate is free to withdraw consent at any time.

Sample size and power

As the 90 day mortality rate for the study population is not known precisely, we used four sources of data to arrive at an estimate of this rate:

1) The overall hospital mortality rate from a Canadian observational study was 32%.[10]

2) The control group hospital mortality rate in a Canadian pilot RCT was 20%.[12]

3) From 2000-2004, the Vancouver General Hospital adult patient database reported that approximately 4000 patients were admitted to ICU for at least 48 hours; their hospital mortality rate was 27%. (D. Chittock – unpublished data)

4) From 2000-2002, the ANZICS adult patient database reported that 43,760 patients were admitted to ICU for at least 48 hours; their hospital mortality rate was 22% (ANZICS Adult patient Database – unpublished data).

As we anticipate that more patients will be recruited from Australia and New Zealand than from Canada, we have given greatest weighting to the ANZICS Adult Patient Database figure and have estimated that hospital mortality for trial patients will be 22%. Assuming baseline mortality in our trial cohort to be 5% higher at 90 days than at hospital discharge,[20] we estimate a 90-day mortality rate of 27% in the control group. We plan to enroll 4500 patients thus providing 90% power to detect an absolute difference in mortality of 4.3% from a baseline of 27% (two-sided alpha less than 0.05). Our study is powered to detect a

relative risk reduction of 16%, which is 49% of the treatment effect documented in Van den Berghe's original study. Our Trials Groups consider this difference to be clinically important and if detected it would likely lead to widespread change in the practice of glycemic control in ICUs in Australia, Canada, New Zealand and beyond.

Statistical Analysis

The George Institute for International Health will conduct the statistical analyses. All analyses will be conducted on an intention-to-treat basis. We will describe the baseline characteristics of both treatment groups using standard measures of central tendency and dispersion. The primary outcome, 90 day all cause mortality will be analyzed using a Chi-square test statistic. We will construct Kaplan-Meier survival curves to test for differences in mortality from randomization to 90 days with censoring for death. A log-rank statistic will be used to compare the two survival distributions. Cox proportional hazards modeling will be used to assess the effects of multiple risk factors on survival times. For all estimates, 95% confidence intervals will be reported. A priori subgroup analyses will not be conducted until trial completion. An independent statistician will conduct two blinded interim analyses when we have primary outcome data for one third and two-thirds of planned recruitment and these will be submitted to the independent Data and Safety Monitoring Committee.

Using the approach outlined for primary and secondary analyses, we will perform similar steps for specific subgroups of patients comparing treatment effects in the following:

- post-operative patients versus non-operative patients
- patients with diabetes mellitus versus patients without diabetes mellitus
- patients with severe sepsis versus patients without severe sepsis

These subgroup analyses will be primarily hypothesis generating in nature.

Data and safety monitoring (DSMC)

An independent DSMC, comprising experts in clinical trials, biostatistics, and intensive care has been established. The DSMC will review unblinded data on patient characteristics, treatment compliance and study outcomes at two interim analyses, at any other time the committee may deem necessary to protect study participants, and at the final analysis.

The NICE - SUGAR study will be stopped if evidence beyond reasonable doubt emerges of a difference between the two treatment groups in all cause mortality or if the evidence suggests a likely change in clinical practice prior to the completion of recruitment.

The DSMC will also be provided with data on serious adverse events and would not be precluded from making recommendations based on other outcomes such as cause-specific death or serious adverse events.

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Current status

Patient recruitment commenced in four Australian hospitals in April 2005. By the end of August 2005, 20 hospitals in Australia and New Zealand were recruiting and over 450 patients had been recruited to the study. On current projections, patient recruitment (n=4500) will be completed by the end of 2006.

Summary

While there is published, peer-reviewed evidence that intensive insulin therapy may reduce mortality and morbidity in ventilated surgical ICU patients, large multi-center randomized control trials are warranted to ensure that these findings can be extrapolated to heterogeneous ICU populations cared for in many centers in other geographic locations. The NICE - SUGAR study fulfils these requirements and will randomly assigned 4500 patients to one of two blood glucose targets. An innovative web-based treatment algorithm is being used to achieve the blood glucose targets in a prompt and safe manner. The findings of the study should assist ICU clinicians who are currently uncertain of the role of intensive insulin therapy in the treatment of their patients. The findings have the potential to influence the management of blood glucose control in ICUs worldwide.

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Canadian Site investigators:

Up to 16 centers – details to be confirmed

Conflict of Interest Statement

None of the authors have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

References

1. Umpierrez, G. E., Isaacs S. D., Bazargan, N. You, X. Thaler L. M., and Kitabchi A. E.. Hyperglycemia: An Independent Marker of In-Hospital Mortality in Patients with Undiagnosed Diabetes. *J Clin Endocrinol Metab* 2002;87:978-982.

2. Van den Berghe, G., P. Wouters, F. Weekers, C. Verwaest, F. Bruyninckx, M. Schetz, D. Vlasselaers, P. Ferdinande, P. Lauwers, and R. Bouillon. Intensive insulin therapy in critically ill patients. *N.Engl.J.Med.* 2001;345:1359-1367.

3. Brown, G. and P. Dodek. Intravenous insulin nomogram improves blood glucose control in the critically ill. *Crit Care Med* 2001;29:1714-1719.

4. Krinsley, J. S. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. *Mayo Clin Proc* 2003; 78:1471-1478.

5. Knaus, W. A., E. A. Draper, D. P. Wagner, and J. E. Zimmerman. APACHE II: a severity of disease classification system. *Crit Care Med.* 1985;13:818-829.

6. Dhingra, V., Chittock, D., Henderson, W., Fenwick, J. C., and Ronco, J. J. Nutrition in the ICU: How sweet is it? [Abstract] *Crit Care Med* 2003; 31, A84.

7. Mackenzie, I., Ingle S., Zaidi S., and Buczaski S.. Tight glycaemic control: a survey of intensive care practice in large English hospitals. *Intensive Care Med* 2005;31:1136.

8. Mitchell, I. A., Finfer S. R., Bellomo, R. and Higlett T. Management of Blood Glucose in the Critically Ill in Australia and New Zealand. [Abstract] *Intensive Care Med* 2004;30:S216.

9. McMullin, J., Brozek J., Jaeschke R., Hamielec C., Dhingra V., Rocker G., Freitag A., Gibson J., and Cook D.. Glycemic control in the ICU: a multicenter survey. *Intensive Care Med* 2004; 30:798-803.

10. Chittock, D., Dhingra V., Henderson W., Schulzer M., and Ronco J. Hyperglycemia: Not a risk factor for death in the ICU? [Abstract] *Am.J Respir.Crit Care Med* 2005;171:A204.

11. McMullin, J., McDonald, E., Clarke, F., Jaeschke, R., Gibson, J., and Cook, D. J. Lowering Of Glucose In Critical Care (LOGIC): Pilot Trial in Medical-Surgical ICU Patients. [Abstract] *Critical Care* 2004; *Critical Care* 2004, **8**(Suppl 1):P251

12. Henderson, W., Dhingra, V., Chittock, D., and Ronco, J. Survival Using Glucose Algorithm Regulation (SUGAR) Trial - Pilot Data. [Abstract] *Am.J Respir.Crit Care Med* 2003;167: A253.

13. Mitchell, I. A., Whiting, J., Gissane, J., Kolli, R., Tamhane, R., and Leditschke, A. Intensive Insulin Therapy in General Intensive Care patients. [Abstract] *Intensive Care Med* 2004;30: S58.

14. The SAFE Study Investigators. A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit. *N Engl J Med* 2004;350:2247-2256.

15. Hebert, P. C., Wells, G. Blajchman, M. AMarshall, .J. Martin, C. Pagliarello, G. Tweeddale, M. Schweitzer, I. and Yetisir, E. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *N Engl J Med* 1999;340:409-417.

16. Richard, C., Warszawski, J. Anguel, N. Deye, N. Combes, A. Barnoud, D. Boulain, T. Lefort, Y. Fartoukh, M. Baud, F. Boyer, A. Brochard, L. and Teboul, J. L. Early use of the pulmonary artery catheter and outcomes in patients with shock and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2003;290:2713-2720.

17. Harvey, S., Harrison, D. A., Singer, M. Ashcroft, J. Jones, C. M. Elbourne, D. Brampton, W. Williams, D. Young, D. and Rowan, K. Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomised controlled trial. *Lancet* 2005;366:472-477.

18. Hebert, P. C., Cook, D. J. Wells, G. and Marshall, J. The Design of Randomized Clinical Trials in Critically Ill Patients*. *Chest* 2002;121:1290-1300.

19. Cohen, J., Guyatt, G. Bernard, G. R. Calandra, T. Cook, D. Elbourne, D. Marshall, J. Nunn, A. Opal, S. and UK Medical Research Council International Working Party. New strategies for clinical trials in patients with sepsis and septic shock. *Crit Care Med.* 2001;29:880-886.

20. Graf, J., Wagner, J. Graf, C., Koch, K. C. and Janssens, U. Five-year survival, quality of life, and individual costs of 303 consecutive medical intensive care patients-a cost-utility analysis. *Crit Care Med* 2005;33:547-555.