

The NICE-SUGAR (Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation) Study: statistical analysis plan

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1. Introduction

The Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) Study is the largest study to date of glycaemic control in critically ill patients. Here, we describe the study's pre-determined statistical analysis plan, which was finalised while data collection was still ongoing, and to which the investigators adhered in analysing the data from the trial.

ABSTRACT

Background: The Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) Study is the largest study to date of glycaemic control in critically ill patients.

Objective: To describe in detail and make public the study's pre-determined statistical analysis plan, which was finalised while data collection was still ongoing, and to which the investigators will adhere in analysing the data from the trial.

Methods: The data collected by researchers as part of the trial protocol were reviewed and formally assessed. Information relevant to baseline characteristics was selected and, for each item, statistically relevant descriptive elements were described. Information relevant to the process of care and delivery of prescribed trial therapy was similarly classified and, for each item, appropriate descriptive statistical analysis was planned with appropriate comparison between groups. Finally, trial outcomes were classified as primary, secondary or tertiary, and an appropriate statistical comparison between groups was planned and described.

Results: A standard analysis plan was developed for the results of the NICE-SUGAR Study. This plan allows a comprehensive description of baseline characteristics, features of the process of care, and trial treatment delivery, along with pre-determined statistical assessment of relevant outcome measures in a way that is transparent, available to the public, verifiable and pre-determined before completion of data collection.

Conclusion: We have developed a pre-determined statistical analysis plan for the NICE-SUGAR Study. This plan will be followed to avoid analysis bias arising from prior knowledge of the study findings.

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The statistical analysis plan was completed and signed as approved by the Study Management and Executive Com-

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mittees on 8 August 2008. Participant recruitment was completed in August 2008, and final patient follow-up was completed in November 2008; the database was locked on 28 November 2008, and the statistical analysis specified in the statistical analysis plan was performed in December 2008 and January 2009.

1.1 Study overview

1.1.1 Title

The NICE-SUGAR Study is a multicentre, open-label, randomised controlled trial that compares the effects of two regimens, targeting either a higher or lower blood glucose level (BGL), in critically ill patients. The targets are a BGL in the range 4.5–6.0 mmol/L (lower range); and a BGL less than 10.0 mmol/L, with insulin infused if BGL exceeds 10.0 mmol/L, and adjusted when needed to maintain BGL in the range 8.0–10.0 mmol/L (higher range).

1.1.2 Patient population

Previous studies of glucose control suggested that maintaining BGL in the range 4.4–6.1 mmol/L may have benefited ventilated patients who stayed longer in the intensive care unit and who were admitted to the studies soon after ICU admission.^{1,2} For that reason, we will screen all patients admitted to the participating ICUs but exclude those expected to be discharged alive before the end of the day following the day of admission. The intensive care physicians will make this assessment.

There is no upper age limit for inclusion in the study. We will also exclude patients who are expected to stay more than 1 day in the ICU but who have a very low risk of death. For this reason, we will exclude patients who are expected to be eating (or are tube-fed because of pre-existing bulbar or laryngeal dysfunction) by the end of the day after admission, and patients whose illness is not severe enough to require insertion of an arterial catheter as part of their routine intensive care management. At the other end of the spectrum, we will also exclude patients who are moribund and at imminent risk of death (brain death or cardiac standstill) on the basis that allocation to either study treatment is unlikely to alter the patient's outcome.

1.1.3 Inclusion criteria

Patients are eligible for inclusion in the study if all of the following criteria are met:

- At the 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 after the day of admission.

- The patient has an arterial catheter in situ, or placement of an arterial catheter is imminent (within the next hour) as part of routine ICU management.
- Consent has been obtained or, where delayed consent is allowed, the investigator expects that delayed consent will be obtained.

1.1.4 Exclusion criteria

Patients will be excluded from the study if one or more of the following criteria are present:

- Age is less than 18 years.
- Death is imminent (cardiac standstill or brain death expected within 24 hours), and the treating clinicians are not committed to full supportive care. This should be confirmed by a documented treatment-limitation order that exceeds a "not-for-resuscitation" order.
- The patient was admitted to the ICU for treatment of diabetic ketoacidosis or hyperosmolar state.
- The patient is expected to be eating before the end of the day following admission.
- The patient has suffered hypoglycaemia without documented full neurological recovery.
- The patient is considered at abnormally high risk of hypoglycaemia (eg, known insulin-secreting tumour or history of unexplained or recurrent hypoglycaemia or fulminant hepatic failure).
- The patient has previously been enrolled in the NICE-SUGAR Study.
- The patient cannot provide prior informed consent, 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. (In some jurisdictions where delayed consent is not permitted, the absence of informed consent will be an exclusion criterion.)
- The patient has been in the study ICU or another ICU for longer than 24 hours as part of this ICU admission episode.

1.1.5 Objectives

The primary aim of the study is to compare the effects of the two regimens targeting different BGLs on 90-day all-cause mortality in intensive care patients who are predicted on admission to the ICU to be treated in the ICU on three consecutive calendar days. The hypothesis is that there is no difference in the relative risk of death between patients assigned to a target BGL of 4.5–6.0 mmol/L and those assigned to a target BGL of less than 10.0 mmol/L, with insulin infused if the BGL exceeds 10.0 mmol/L and adjusted when needed to maintain a BGL of 8.0–10.0 mmol/L.

1.1.6 Unblinding

Access to the interim data and results will be limited to members of the Data Monitoring Committee (DMC) and the statistician(s) in charge of writing the reports. The statistical analysis plan will be written by an independent statistician and the principal investigator, both of whom will be blinded to treatment allocations and study results until the final study results are released by the study statistician. Treatment allocations will be stored securely in a separate location for that purpose. Statistician(s) not involved in the writing of DMC reports will remain blinded and work on dummy datasets until the statistical computer code has been validated — this will be done in accordance with the Standard Operating Procedures of the George Institute for International Health.

1.2 Definition of the efficacy variables

1.2.1 Definition of primary outcomes

The primary endpoint is all-cause mortality 90 days after randomisation. As loss to follow-up is expected to be minimal, missing values will not be imputed.

In the subset of patients with traumatic brain injury (TBI; defined as computed tomography evidence of TBI and a last pre-sedation and pre-randomisation score on the Glasgow Coma Scale less than 14), mortality is not considered to be the most appropriate outcome. Patients with TBI will be included in the analysis of all-cause mortality 90 days after randomisation; in addition, in patients with TBI, the score on the Extended Glasgow Outcome Scale (GOSE) measured at 6 months and 2 years will be assessed.

The GOSE has eight categories:

- 1 = dead
- 2 = vegetative state
- 3 = lower severe disability
- 4 = upper severe disability
- 5 = lower moderate disability
- 6 = upper moderate disability
- 7 = lower good recovery
- 8 = upper good recovery.

For the analysis, the score will be condensed into four categories:

- 1 = dead or vegetative state
- 2 = severe disability
- 3 = moderate disability
- 4 = good recovery.

Loss to follow-up is expected to be higher in patients with TBI than in the overall study population, but still less than 10%; missing values will not be imputed.

1.2.2 Definition of secondary outcomes

The secondary outcomes will include:

- Survival time from randomisation to Day 90.
- Cause-specific mortality within the 90-day follow-up period.
 - Primary cause of death will be categorised as:
 - Cardiovascular — distributive shock
 - Cardiovascular — other
 - Respiratory
 - Neurological — TBI
 - Neurological — other
 - Other.
- Duration of ICU stay in days.
- Duration of hospital stay in days.
- Mechanical ventilation (yes/no) and duration of mechanical ventilation per randomised patient with available data.
- Treatment with renal replacement therapy (yes/no) and duration of renal replacement therapy received per randomised patient with available data.

1.2.3 Definition of tertiary outcomes

- 28-day all-cause mortality.
- Place of death (ICU, elsewhere in hospital, after discharge from hospital).
- Incidence of new organ failure (SOFA score at baseline 0, 1 or 2, maximum SOFA > 2):*
 - Respiratory
 - Haematological
 - Hepatic
 - Cardiovascular
 - Renal.
- Number of patients with positive blood cultures in the ICU from time of randomisation to 90 days. This will be identified by a binary indicator (1 = yes, 0 = no).
- Number of patients who receive a transfusion of packed red blood cells in the ICU and average volume of packed red blood cells received per randomised patient.

1.3 Definition of the safety variables

Hypoglycaemia is the main adverse event and safety issue in the study. Results of previous studies suggest that using tight glycaemic control in a population of intensive care patients results in five to 42 episodes of severe glycaemia for every 100 patients recruited to the lower-range group,

* SOFA (Sequential Organ Failure Assessment) score is a score coded 0–4, representing different stages of organ dysfunction (0 = normal, 1–2 = organ dysfunction, 3–4 = organ failure), for each of five domains. A new organ failure is identified by a SOFA score of 0–2 at baseline that later increases to more than 2 (“maximum > 2”). A binary indicator specific to each organ will be constructed (1 = new failure, 0 = no new failure).

and fewer than five episodes for every 100 recruited to the higher-range group. The incidence of severe hypoglycaemia and clinical consequences of severe hypoglycaemia will be compared across treatment arms:

- Number of patients suffering severe hypoglycaemia (documented BGL of 2.2 mmol/L or less [40 mg/dL or less] at any time in the ICU within 90 days of randomisation), and number of episodes of severe hypoglycaemia occurring in the ICU within 90 days of randomisation.
- Incidence of clinical sequelae of severe hypoglycaemia:
 - Neurological sequelae
 - Cardiovascular sequelae
 - Other sequelae.

1.4 Analysis principles

- All analyses will be conducted on an intention-to-treat basis.
- All tests will be two-sided, and the nominal level of α will be 5%.
- All statistical analyses will be unadjusted except where indicated.
- Subgroup analyses will be carried out irrespective of whether there is a significant effect of treatment on the primary outcome.
- We will not impute missing values unless specified otherwise. Where the number of missing observations is substantial, we will report the number of observations used in the analysis. Last observations will not be carried forward for continuous outcomes such as SOFA scores.
- *P* values will not be adjusted for multiplicity. However, the outcomes are clearly categorised by degree of importance (primary to tertiary), and a limited number of subgroup analyses are pre-specified.

2. Design issues

2.1 Data collection and follow-up

The different stages of data collection and follow-up are summarised in Box 1.

Because of local legal considerations, patients or their legal surrogates may have an absolute right to request that their data be removed from the study database. As a result, there are potentially two datasets: the randomised patients, and the randomised patients who have data available. The latter dataset is obtained after deleting the data for randomised patients for whom consent has been withheld or withdrawn, and whose data cannot be submitted or maintained in the database (see *Section 2.6*). Only the latter dataset can be used in the analysis.

2.2 Study design

The NICE-SUGAR study is a multicentre, open-label, randomised concealed, controlled trial.

2.3 Treatment allocation

Eligible patients will be randomised to one of the two blood glucose targets using minimisation. Two strata will be considered: the type of critical illness (postoperative versus non-operative) and geographic region (Australia and New Zealand versus North America). Centralised randomisation will be achieved via a password-protected web-based program.

2.4 Sample size and statistical power

The sample size is set at 6100 patients, providing 90% power to detect an absolute decrease in mortality of 3.8% from a baseline of 30% (two-sided $\alpha < 0.05$). The study is powered to detect a relative risk reduction of 12.7%, which is 37% of the treatment effect documented in the first study of Van den Berghe et al.¹ This difference is clinically important and, if detected, would likely lead to widespread change in the practice of glycaemic control in ICUs in Australia, New Zealand, North America and beyond.

2.5 Interim analyses

An independent Data Monitoring Committee (DMC), chaired by Professor Sir Richard Peto, Oxford University, United Kingdom, will review unblinded data on patient characteristics, treatment compliance and study outcomes at two interim analyses (availability of primary outcome for 1500 and 4000 patients), and at the final analysis. Recruitment will be reviewed at regular intervals during the trial, to be determined by the DMC, which will generate terms of reference. The DMC is charged with informing the Study Management and Executive Committees if at any time there emerges either evidence beyond reasonable doubt of a difference between randomised groups in all-cause mortality, or evidence likely to change the practice of many clinicians already familiar with the available evidence about the trial interventions.

2.6 Dates and consent-related issues

Dates will be queried so that no missing values remain. Due to the specific nature of the study, informed prior consent is not always possible; in these circumstances and where approved by the local ethics committee, the patient or their legal surrogate may be asked for delayed consent. Two important situations can lead to cessation of study treatment: a patient, next of kin or legal surrogate may with-

Box 1. Data collected at different stages of the study

Randomisation

Patient demographics and inclusion/exclusion criteria.

Form 1. Baseline

Source and date of admission to ICU; ICU admission diagnosis; subgroup categories operative or non-operative admission and presence or absence of severe sepsis, trauma, traumatic brain injury and type 1 or type 2 diabetes; Acute Physiology and Chronic Health Evaluation (APACHE) II score;

SOFA scores (cardiovascular, respiratory, hepatic, renal and haematological); use of renal replacement therapy; use of mechanical ventilation; blood glucose concentration (last measurement before randomisation); height and weight; and previous treatment with insulin and corticosteroids.

Form 2. Hourly, Days 1–90

Post-randomisation BGL while in ICU for maximum of 90 days. We will report the overall mean and standard deviation (SD) of daily early morning (first measurement after 08:00) blood glucose and daily time-weighted mean BGL* measured from randomisation to the earlier of ICU discharge or 90 days, the mean and SD early morning (first measurement after 08:00) and time-weighted mean BGL* measured from randomisation to the time the patient's blood glucose is no longer managed according to the treatment algorithm (indicating cessation of study treatment).

Results will be displayed as a plot of mean versus time by treatment arm. They will be truncated at a relevant number of days, such as 14 days.

* A daily time-weighted BGL (weighting based on time difference between two consecutive measurements applied to the average of two consecutive measurements) is to be computed for Form 2. Any consecutive blood glucose measurements within a study day are treated as a continuous process. In the case that blood glucose measurements are taken over more than a study day, they are treated as the start of new treatment and discontinuous from the first. Unweighted blood glucose calculations will also be provided for comparison.

Form 3. Daily, Days 1–90

While in ICU: daily SOFA scores (cardiovascular, respiratory, hepatic, renal and haematological); treatment with renal replacement therapy or mechanical ventilation; type (enteral versus parenteral) and volume of nutrition administered (total non-protein calories, protein, carbohydrate, and lipid will be calculated from type and volume of enteral and parenteral nutrition administered); all intravenous glucose administered; all positive blood culture results that are clinically significant by pre-defined criteria.

Total amount of insulin administered.

Total amount of corticosteroids given (calculated as hydrocortisone equivalent).

Number of patients transfused with red blood cells (RBCs) and volume of RBCs transfused per randomised patient.

Number of patients with treatment-limitation order, timing of order and reason for treatment limitation.

Form 4. 28-day summary

Vital status (alive or dead) at Day 28.

Place, date and cause of death. If discharged, date of discharge from ICU and from hospital, and number of days in ICU.

Type of consent obtained.

Form 5. 90-day summary

Vital status at Day 90. Place, date and cause of death, length of stay in ICU, and length of stay in hospital.

Form 6. Serious adverse events and hypoglycaemia

Description, date and time, cause and resolution of any serious adverse events, whether or not study-related, and episodes of severe hypoglycaemia (number of episodes with BGL \leq 2.2 mmol/L [\leq 40 mg/dL], signs and symptoms, treatment given).

Form 7. Score on Extended Glasgow Outcome Score

Outcome score at 6-month and 2-year follow-up for patients with traumatic brain injury (history of trauma, cranial computed tomography scan consistent with traumatic brain injury, and last unsedated pre-randomisation score on Glasgow Coma Scale, < 14).

draw consent; or they may refuse continuation of study treatment when delayed consent is sought (as opposed to withdrawing an existing consent). In both cases, the study treatment will cease, and the patient will receive glycaemic control as prescribed by their treating clinicians. In this situation, specific consent will be sought to continue study follow-up procedures and to use study data. If consent for use of data is withheld, that patient's data will be removed from the analysis, except for data related to consent. Censoring dates will be used only in case of "real" loss to follow-up — discharged patients with no information beyond some point in time. In those cases, the date of censoring will be the last day of contact, or the date of hospital discharge if no other information is available.

2.7 Permanent discontinuations

The data of patients for whom consent to continue study treatment is withdrawn, but for whom consent to the use of

their data is given, will remain in the analysed dataset and will be analysed on an intent-to-treat basis. Vital status at 28 or 90 days will not be imputed if this information is missing.

3. Statistical analysis

3.1 Trial profile

Flow of patients through the study will be displayed in a CONSORT diagram. We will report the number of screened patients who met study inclusion criteria and the number included, reasons for exclusion of non-included patients and information, as shown in Box 2.

3.2 Characteristics of patients and baseline comparisons

Description of the baseline characteristics listed below will be presented by treatment group. Discrete variables

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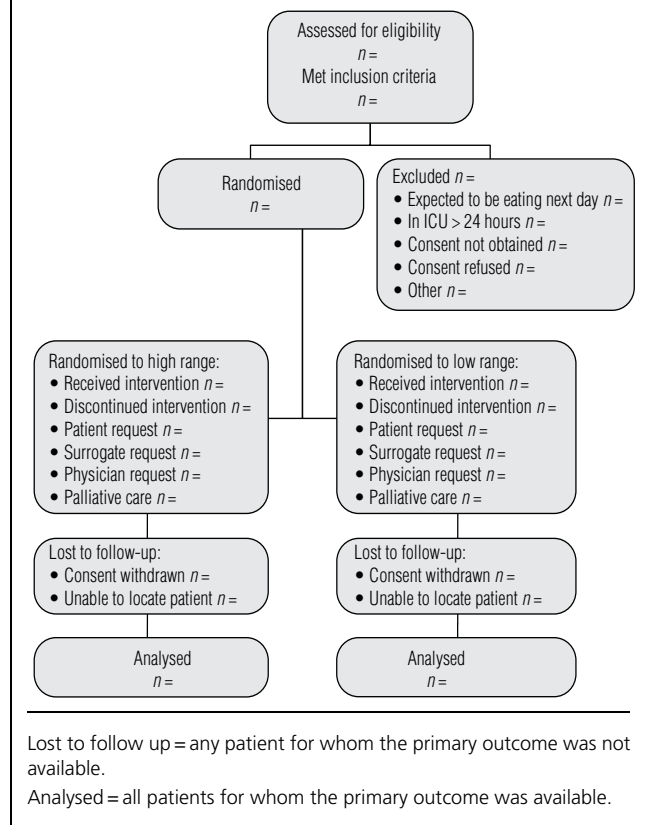
will be summarised by frequencies and percentages. Percentages will be calculated according to the number of patients for whom data are available. Where values are missing, the denominator (which is less than the number of patients assigned to the treatment group) will be stated in either the body or footnote of the corresponding summary table. In some instances, frequency and percentage of patients in the category will be reported as indicated below.

Continuous variables will be summarised using standard measures of central tendency and dispersion, either mean and SD for variables identified with an asterisk (*), or median and interquartile range (IQR) for those identified with a cross (†).

3.2.1 Baseline measures for all patients

- Sex.
- Age.*
- Weight.*
- Height.*
- Calculated body mass index.*
- Geographic region (Australia and New Zealand versus North America).
- Source of admission to ICU (emergency department, hospital floor, another ICU, another hospital, operating room after emergency surgery, operating room after elective surgery, readmission to the same ICU during same hospitalisation).
- Time from ICU admission to randomisation.
- Operative versus non-operative admission diagnosis.
- Operative admission diagnosis (number and % in each category)
 - Cardiovascular
 - Respiratory
 - Gastrointestinal
 - Neurological
 - Trauma without traumatic brain injury
 - Traumatic brain injury ± multiple trauma
 - Burns
 - Renal
 - Gynaecology
 - Other orthopaedic
 - Other surgical.
- Non-operative admission diagnosis (number and % in each category)
 - Cardiovascular
 - Respiratory
 - Gastrointestinal
 - Neurological
 - Sepsis
 - Trauma without traumatic brain injury
 - Traumatic brain injury ± multiple trauma

Box 2. CONSORT diagram for flow of patients through the study



- Metabolic
- Haematological
- Burns
- Renal
- Other medical.
- Severe sepsis at baseline.
- Trauma with or without brain injury at baseline.
- Traumatic brain injury at baseline.
- APACHE II score.*
- SOFA score
 - Cardiovascular component
 - Respiratory component
 - Renal component
 - Hepatic component
 - Haematological component.
- Last BGL before randomisation.*
- Prior history of diabetes mellitus
 - Type 1 diabetes
 - Type 2 diabetes.
- Patient usually treated with insulin (number and %).
- Renal replacement therapy at baseline (number and %).
- Mechanical ventilation at baseline (number and %).
- Treatment with corticosteroids at baseline (number and %).†

3.2.2 Additional baseline measures for patients with trauma

- Injury Severity Score (1998 version).[†]

3.2.3 Additional baseline measures for patients with traumatic brain injury

- Score on Glasgow Coma Scale at baseline[†]
 - Eye component[†]
 - Verbal component[†]
 - Motor component.[†]
- Marshall score for computed tomography of the brain (number and % of patients in each of the five categories).
- Incidence of hypotension (systolic blood pressure <90 mmHg or mean arterial pressure <65 mmHg) before randomisation.
- Intracranial pressure monitor at baseline (number and %).
- Intracranial pressure at baseline (when measured).*

3.3 Process measures and concomitant treatments

Categorical or continuous variables and times-to-event will be summarised as described in Box 1. When indicated, frequencies and percentages of patients per category will also be given. Again the same coding is used to indicate the presentation of measures of central tendency and dispersion (* for mean [SD]; and † for median [IQR]). Standard χ^2 tests will be performed to compare frequencies, and *t* tests or Wilcoxon rank sum tests will be used for continuous data. In case of rare events (expected number per cell less than 1), the Fisher test will be used.

3.3.1 Process measures

- Time on study treatment.
- Time from cessation of study treatment to (last) discharge from the ICU.
- Number (%) patients treated with insulin in the ICU within 90 days of randomisation.
- Daily insulin dose (IU/days on study treatment).*
- Mean morning (first measurement after 08:00) BGL by group*
 - Averaged over time from randomisation to time of ICU discharge*
 - Averaged over time from randomisation to time study treatment stopped (if study treatment is stopped and then restarted, all episodes on study treatment will be used to calculate the average).*
- Mean time-weighted BGL by group
 - Averaged over time from randomisation to time of ICU discharge*
 - Averaged over time from randomisation to time study treatment stopped (if study treatment is stopped and

then restarted, all episodes on study treatment will be used to calculate the average).*

3.3.2 Concomitant treatments

- Non-protein calories administered in the ICU (by day, to Day 14)*
 - Non-protein calories by all routes
 - Non-protein calories by enteral route
 - Non-protein calories by parenteral route
 - Non-protein calories as intravenous glucose.
- In addition, bar graphs will be produced displaying means (SD) of total non-protein calories, and non-protein calories by the enteral route per treatment group by day in ICU. If the number of patients remaining in the ICU becomes too small, the means will be truncated before 14 days. Conversely, the maximum of 14 days will be extended if considered relevant by the study statistician.
- Patients treated with corticosteroids at any time in the ICU (number and % in each treatment group).
- Daily dose of corticosteroid as hydrocortisone equivalent (by day, up to Day 14).*

3.3.3 Limitation of treatment

- Patients for whom there was limitation of treatment.
- Patients for whom treatment was limited or withheld
 - Patients for whom treatment was limited as terminal event
 - Patients for whom maximal treatment was not indicated.
- Time from randomisation to first treatment limitation order (overall and for the limitations indicated in the preceding point).

Treatment limitation refers to withdrawing a treatment that might otherwise prolong life as it is no longer considered appropriate for that individual (ie, stopping of a previously provided treatment); or withholding treatment that might otherwise prolong life as it is not considered appropriate for that individual (ie, not commencing a treatment). Each of these will have been authorised by a treating clinician independent of the study and documented in the medical record. The specific treatments limited or withdrawn will not be reported.

3.3.4 Consent and permanent discontinuation of study treatment

- Consent (number and % in each of the following categories)
 - Prior informed consent from patient
 - Prior informed consent from a legal surrogate
 - Delayed informed consent from patient
 - Delayed informed consent from a legal surrogate

- Consent from other legal body before or after patient's death
- No consent obtained — data withdrawn.
- Patients for whom study treatment was permanently discontinued (number and % in each of the following categories)
 - Patients for whom informed consent was withdrawn
 - Patients for whom delayed informed consent was withheld
 - Study treatment discontinued by treating clinician (not due to serious adverse event or palliative care)
 - Study treatment discontinued because of serious adverse event
 - Study treatment discontinued as focus of treatment changed to palliative care
 - Study treatment discontinued for other reason.

3.4 Description of analyses

3.4.1 Primary outcome

A standard χ^2 test will be used as the primary test of statistical significance of the effect of treatment allocation on 90-day all-cause mortality. Frequencies and percentages per arm, and an odds ratio measuring the treatment effect and its 95% confidence interval (CI) will also be reported. We will also perform an adjusted analysis for sensitivity purposes. It will be based on a multivariate logistic regression analysis adjusted for strata used in minimisation (postoperative versus non-operative patients and region) and the following predictors: age, ICU admission source, APACHE II score and mechanical ventilation at baseline. If the DMC considers early stopping of the trial, the results of this analysis will be reported to the Management Committee and the DMC before a final decision to suspend recruitment is made. A sensitivity analysis will be performed if more than 5% of the 90-day mortality data are missing.

Specific analysis for patients with traumatic brain injury

In addition, a specific analysis will be carried out for patients with TBI. In that case, the primary outcome will be the GOSE score at 2 years. A Wilcoxon rank-sum test, adjusted for ties, will be used to assess the effect of treatment on the GOSE score condensed to four categories:

- 1 = dead or vegetative state
- 2 = severe disability
- 3 = moderate disability
- 4 = good recovery.

Frequencies and percentages will be presented by categories. We will also perform an adjusted analysis for sensitivity purposes. It will be based on an ordinal regression analysis,³

adjusted for the following known predictors: age, last unsedated pre-randomisation GCS score, presence of pre-randomisation hypotension (defined as a documented systolic arterial blood pressure < 90 mmHg or documented mean arterial blood pressure < 65 mmHg) and presence of traumatic subarachnoid haemorrhage on a pre-randomisation computed tomography brain scan. If the proportional odds assumption needed for ordinal regression to be valid is grossly violated, alternative models will be investigated. The list of predictors used for adjustment can be shortened in case of instability — for example, if there are too many zero values, or if missing values on a particular covariate substantially reduce the size of the working sample size. In the extreme case of small numbers, categories in 1–4 will also be collapsed, the decision being made on blinded data by the Study Management Committee.

The vital status at 90 days of TBI patients will also be displayed as number and percentage of deaths per treatment arm. A comparison of these proportions will be based on a χ^2 test with odds ratio and 95% CI.

3.4.2 Secondary and tertiary outcomes

A standard χ^2 test will be used to assess the effect of treatment on binary or categorical outcomes — 28-day all-cause mortality, cause of death, place of death, incidence of a new organ failure, and incidence of positive blood cultures. Frequencies and percentages per arm, an odds ratio measuring the treatment effect and its 95% CI will also be reported along with the *P* value of the χ^2 test. In addition, the number of new organ failures suffered by individual patients will be tabulated per treatment arm, with frequencies and percentages of patients with different numbers of new organ failures (0–5).

Survival time from randomisation to Day 90 will be analysed using a log-rank test. The *P* values and a hazard ratio with its 95% CI obtained from a Cox proportional hazards model will also be calculated. The proportional hazard assumption across treatment arms will be checked graphically using a log-cumulative hazard plot or the addition of a time-dependent covariate to the model. Probability of survival by treatment group will also be presented as Kaplan–Meier curves.

Length of stay in the ICU and the hospital will be censored due to early deaths or a stay in the ICU or hospital longer than 90 days. They will therefore be considered as times to discharge from the respective unit and analysed with a log-rank test. Summary statistics will include the median and the interquartile range computed separately for each treatment arm. These statistics, when available, will account for censoring (see, for instance, SAS procedure LIFETEST or comparable tools in other packages). Mechanical ventilation and renal replacement therapy are resource

consumption measures and treatments that are not performed on all patients. They will be summarised in two ways: number and percentage of patients per arm who received such a therapy; and mean (SD) duration in days per treatment arm. If patients are still being treated with mechanical ventilation or renal replacement therapy at the end of the study, their data will be censored. The use of packed red blood cell (RBC) transfusion will be summarised as number and percentage of patients per arm who receive packed RBCs and mean (SD) volume of packed RBCs per treatment arm. The effect of treatment allocation will be tested using a two-sample *t* test or Wilcoxon rank-sum test, as appropriate.

In addition, analyses adjusted for the same predictors as the primary outcome will be done for the secondary outcomes as subsidiary analyses. They will be based on a linear, logistic or Cox regression, as appropriate for the outcome.

3.4.3 Safety outcomes

The number of episodes of severe hypoglycaemia (measured BGL ≤ 2.2 mmol/L or ≤ 40 mg/dL) at any time in the ICU, and incidence of clinical consequences of severe hypoglycaemia (neurological, cardiovascular and other) will be compared between groups using a χ^2 statistic or the Fisher exact test, with odds ratios and 95% CI when these quantities are computable. Frequencies and percentages per treatment group will be presented. Adjusted analysis will not be performed for safety endpoints.

3.4.4 Subgroup analyses

All subgroups will be defined by the presence or absence of a pre-randomisation variable; we will not select any subgroups based on post-randomisation events.^{4,5}

The primary outcome for planned subgroup analyses will be the same as in the main analysis (90-day all-cause mortality). Most subgroup analyses will be exploratory with the aim of generating new hypotheses. However, for the first two subgroup analyses described below, we are seeking to examine the presence of the interaction inferred from the results of Van den Berghe et al.^{1,2,6} Unadjusted *P* values will be reported, but the number of declared subgroup analyses will be specified in all publications.

Analysis

The main analysis for each subgroup will be an unadjusted test of interaction in a logistic model to determine whether the effect of treatment differs significantly across categories (eg, in patients with sepsis versus those without sepsis). The number of deaths over total number of participants per arm, the treatment effect (odds ratio), and its confidence interval for each category within each subgroup will be presented, along with the *P* value for the interaction test.

Where appropriate, continuous variables will also be analysed; in those cases, only the interaction test will be reported.

The following status at baseline specifies the six subgroup analyses:

- operative patients versus non-operative patients
- patients with diabetes mellitus versus those without
- patients with severe sepsis versus those without
- patients diagnosed with trauma versus those without
- patients with an APACHE II score of 25 or more versus those with an APACHE II score of less than 25
- patients treated with corticosteroids versus those not treated.

Rationale

The rationale for considering these subgroups is as follows:

- Conflicting evidence was obtained from two large trials conducted by Van den Berghe and colleagues, the first in surgical (SICU) patients and the second in medical (MICU) patients.^{1,2} A significant reduction in the relative risk of death was found in the intention-to-treat population of the SICU trial, but not in the MICU study.
- In a publication combining the results of their MICU and SICU studies, Van den Berghe and colleagues identified patients with diabetes as a subgroup who did not benefit from normalisation of blood glucose.⁶
- Conflicting results were seen in patients with sepsis. In the SICU trial, the excess mortality was attributed to deaths from sepsis.¹ In the MICU trial, the authors claimed that deaths from all causes were reduced.² Hyperglycaemia is thought to impair white blood cell function and so may theoretically reduce ability to deal with infections. Despite the potential benefits of intensive insulin therapy in patients with severe sepsis, a trial of this therapy by the German Sepsis Network was stopped early because of safety concerns, in the absence of a beneficial treatment effect.⁷
- Patients admitted to the ICU because of trauma have a very different demographic profile to other ICU patients. They are younger and have less comorbidity. The mortality rate in trauma patients without traumatic brain injury is much lower than that in the general ICU population, but a recent publication by Vogelzang and colleagues reported that the association between hyperglycaemia and adverse outcome was stronger in trauma patients than in other critically ill patients.⁸
- The NICE-SUGAR patients represent a heterogeneous population treated in ICUs in terms of diagnoses and severity of disease. A criticism of the studies of Van den Berghe et al is that the patients had low severity of illness, as assessed by the APACHE II score, and inappropriately high mortality. In addition, some treatments may be

beneficial in ICU patients with higher risk of death as assessed the APACHE II score or similar tools.^{9,10}

- Following publication of the study by Annane et al in 2002,¹¹ corticosteroids have been increasingly used to treat critically ill patients, and were being received at the time of randomisation by over 50% of patients in Van den Berghe et al's MICU study.² Corticosteroid therapy increases glucose intolerance and could theoretically influence the treatment effect of intensive insulin therapy.

Presentation of results

Subgroup results for categorical variables will be presented as forest plots, with *P* values for heterogeneity for each pair of subgroups.

3.5 Control of type I error for multiple looks

The Peto rule with a maximum of three analyses will be used to decide on early stopping. The last critical value is $c_3 = 1.975$ if the trial goes to completion, and the three interim analyses are equally spaced. This value will be recalculated if more interim analyses are considered or they are not roughly equally spaced. Although naive estimates obtained after stopping a trial earlier can theoretically be slightly biased, we will not correct the estimates on termination, as bias is likely to be negligible with this design. However, to be conservative, we will report repeated CIs at each interim analysis, if required by the DMC, or on termination. As a result, the critical value used to compute the last CI should be 1.975, as opposed to the classical 1.96. This will hold for the primary and secondary analyses.

3.6 Tables and figures

Table 1 will report all collected baseline characteristics of the participants by treatment group. Table 2 will report process measures and concomitant treatments: time on treatment algorithm, number of patients treated with insulin, and amount of insulin administered, mean time-weighted and early morning BGL, treatment with corticosteroids, non-protein calories administered and route. Table 3 will report primary, secondary and tertiary outcomes. The content and proposed formatting of the tables is shown in the Appendixes.

In addition, the following figures will be prepared:

- A CONSORT diagram illustrating flow of patients through the study (Box 2).
- Bar graphs showing mean (SD) total non-protein kilocalories administered by the enteral and parenteral routes per day, by treatment arm, for the first 14 days, and mean (SD) time-weighted BGL by treatment group for the first 14 days.

- A forest plot of point estimate and its 95% confidence interval for odds ratios for death at 90 days for all patients and for a-priori subgroups as described in Section 3.4.4.
- A Kaplan–Meier curve for survival to 90 days.

Acknowledgements

The statistical analysis plan was completed on 8 August 2008 and has been approved by the NICE Study Management Committee and the SUGAR Study Executive Committee.

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STATISTICAL ANALYSIS PLANS

Appendix 1. Table 3 — Outcomes with adverse events

Outcome measure	Definition	High range		Low range		Odds ratio	95% CI	P
		No. of observations	Value	No. of observations	Value			
Day 90 status – all patients								
Death – no. (%)		x	x	x	x	x	x	x
Day 28 status – all patients								
Death – no. (%)		x	x	x	x	x	x	x
Cause of death – no. (%)								
Cardiovascular – distributive shock		x	x	x	x			
Cardiovascular – other		x	x	x	x			
Respiratory failure		x	x	x	x			
Neurological – traumatic brain injury		x	x	x	x			
Neurological – other		x	x	x	x			
Other		x	x	x	x			
						Absolute difference		
Days in ICU		x	x	x	x			x
Days in hospital (excluding ICU stay)		x	x	x	x			x
No. (%) patients treated with mechanical ventilation		x	x	x	x			x
Days of mechanical ventilation		x	x	x	x			x
No. (%) patients treated with renal replacement therapy		x	x	x	x			x
Days of renal replacement therapy		x	x	x	x			x
Place of death								
ICU		x	x	x	x			
Elsewhere in hospital		x	x	x	x			
After discharge from hospital		x	x	x	x			
No. of new organ failures – all patients, no. (%)								
No new failure		x	x	x	x			
1 new organ failure		x	x	x	x			
2 new organ failures		x	x	x	x			
3 new organ failures		x	x	x	x			
4 new organ failures		x	x	x	x			
5 new organ failures		x	x	x	x			
No. (%) patients with severe hypoglycaemia		x	x	x	x	x	x	x
No. (%) patients with sequelae of severe hypoglycaemia								
Neurological		x	x	x	x	x	x	x
Cardiovascular		x	x	x	x	x	x	x
Other		x	x	x	x	x	x	x
No. (%) patients with positive blood cultures		x	x	x	x	x	x	x
No. (%) patients transfused packed cells		x	x	x	x	x	x	x
Volume packed cells transfused		x	x	x	x			x

STATISTICAL ANALYSIS PLANS

Appendix 2. Outcomes — traumatic brain injury

Outcome measure	Definition	High range		Low range		Odds ratio	95% CI	P
		No. of observations	Value	No. of observations	Value			
Vital status								
Dead at 90 days		x	x	x	x	x	x	x
GOSE score at 2 years								
Dead or vegetative state		x	x	x	x			x
Severe disability		x	x	x	x			
Moderate disability		x	x	x	x			
Good recovery		x	x	x	x			

GOSE = Extended Glasgow Outcome Scale.

Appendix 3. Subgroup analysis — forest plot

	No. of deaths/total no.		Odds ratio	95% CI	P for heterogeneity
	Higher range	Lower range			
Dead at 90 days — all patients	x	x	x	x	
Operative patients					
Yes	x	x	x	x	
No	x	x	x	x	
Patients with severe sepsis					
Yes	x	x	x	x	
No	x	x	x	x	
Trauma patients					
Yes	x	x	x	x	
No	x	x	x	x	
Patients with APACHE II score >24					
Yes	x	x	x	x	
No	x	x	x	x	
Patients treated with corticosteroid at baseline					
Yes	x	x	x	x	
No	x	x	x	x	
Patients with diabetes mellitus at baseline					
Yes	x	x	x	x	
No	x	x	x	x	