NICE-SUGAR Study Statistical Analysis Plan

Authors: Simon Finfer and Stephane Heritier

Completion date: August 8, 2008

Approved by:

NICE Study management committee and

SUGAR Study executive committee

Signatures:

Simon Finfer   **Stephane Heritier**

Tables of contents

1. INTRODUCTION

1.1 Study overview

1.1.1 Title

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

1.1.2 Patient population

In previous studies of glucose control, the benefit of maintaining blood glucose concentration in the range of 4.4-6.1 mmol/l was limited to ventilated patients who stayed longer in the Intensive Care Unit (ICU) and who were admitted to the study soon after the time of 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 attending Intensive Care physician will make this assessment.

We also wish to exclude patients who are expected to stay more than one 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 who are tube fed due to pre-existing bulbar or laryngeal dysfunction) by the end of the day after admission and patients whose severity of illness is not great 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 if they 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 **<u>INCLUSION</u>** in the study if BOTH of 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 after the day of admission.
2. 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.
3. 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 **<u>EXCLUDED</u>** from the study if ONE or MORE of the following criteria are present:

1. Age less than 18 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 should be confirmed by a documented treatment-limitation order that exceeds a "not-for-resuscitation" order.

3. Patient admitted to the ICU for treatment of diabetic ketoacidosis or hyperosmolar state.
4. Patient is expected to be eating before the end of the day following admission
5. Patient who has suffered hypoglycaemia without documented full neurological recovery.
6. Patient thought to be at abnormally high risk of suffering hypoglycaemia (e.g. known insulin secreting tumour or history of unexplained or recurrent hypoglycaemia or fulminant hepatic failure)
7. Patient has previously been enrolled in the NICE-SUGAR Study.
8. Patient can not 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 – absence of informed consent will be an exclusion criterion)
9. Patient has been in the study ICU or another ICU for longer than 24 hours as part of this ICU admission episode.

There is no upper age limit for inclusion in the study.

1.1.5 Objectives
The primary aim of the study is to compare the effects of the two regimens targeting different blood glucose concentrations 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 null hypothesis is that there is no difference in the relative risk of death between patients assigned to a target glucose concentration of 4.5 - 6.0 mmol/L and those assigned to target a glucose concentration of less than 10.0 mmol/L with insulin being infused if blood glucose exceeds 10.0 mmol/L, and adjusted when needed to maintain blood glucose of 8.0 – 10.0 mmol/L.

1.1. *Unblinding*
Access to the interim data/results will be limited to the Data and Safety Monitoring Board (DSMB) members and the statistician(s) in charge of writing the reports. The statistical analysis plan (SAP) will be written by an independent statistician and the principal investigator; both 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 DSMB reports will remain blinded and work on dummy treatment until validation of their code has been performed – 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 post-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 CT evidence of traumatic brain injury and a last pre-sedation and pre-randomization Glasgow Coma Scale score of 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 post-randomization; in addition, in patients with TBI, the extended Glasgow outcome scale (GOSE) measured at 6 months and two years will be assessed.

The extended Glasgow outcome scale has 8 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 purpose of analysis the score will be condensed into 4 categories:
    1 - dead or vegetative state
    2 - severe disability
    3 - moderate disability
    4 - good recovery

Loss to follow-up of patients with traumatic brain injury is expected to be somewhat higher than in the overall population but still less than 10%; missing values will not be imputed.

1.2.2 Definition of secondary outcomes
The secondary outcomes will include:
1. Survival time from randomization to day 90
2. Cause specific mortality within the 90 day follow-up period. Primary cause of death will be categorized into:
    a. cardiovascular-distributive shock,
    b. cardiovascular-other,
    c. respiratory
    d. neurological-traumatic brain injury,
    e. neurological-other,
    f. other
3. Duration of ICU stay - days
4. Duration of hospital stay - days
5. Mechanical ventilation (yes/no) and duration of mechanical ventilation per randomised patient with available data
6. 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

1. 28-day all cause mortality
2. Place of death (ICU, elsewhere in hospital, after discharge from hospital)
3. Incidence of new organ failure.
    a. Respiratory: SOFA* at baseline 0,1 or 2, maximum SOFA >2
    b. Coagulation: SOFA at baseline 0,1 or 2, maximum SOFA >2
    c. Liver: SOFA at baseline 0,1 or 2, maximum SOFA >2
    d. Cardiovascular: SOFA at baseline 0,1 or 2, maximum SOFA >2
    e. Renal: SOFA at baseline 0,1 or 2, maximum SOFA >2
    *SOFA (sequential organ failure assessment score) is a score coded on 0-4 for the 5 domains representing different stages of organ dysfunction (0=normal, 1-2=organ dysfunction 3-4=organ failure). A new organ failure is then identified by a SOFA score of 0-2 at baseline that becomes greater than 2 (maximum >2) further on. A

  binary indicator specific to each organ will then be constructed (1 = new failure, 0 = no new failure)

4. Number of patients with positive blood cultures in the ICU from time of randomization to 90 days. This will be identified by a binary indicator with 1 for yes or 0 for no.

5. Number of patients who receive a transfusion of packed red blood cells in 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. Previous studies suggest that employing strict glycemic control in a population of Intensive Care patients will result in between 5 and 42 episodes of severe hypoglycemia for every 100 patients recruited to the lower range group and less than 5 episodes of severe hypoglycemia for every 100 patients recruited to the higher range group. The incidence of severe hypoglycemia and clinical consequences of severe hypoglycemia will be compared across treatment arms.

1. Number of patients suffering severe hypoglycemia (documented blood glucose concentration of 2.2mmol/L or less [40mg/dL or less] at any time in the ICU within 90-days of randomization) and number of episodes of severe hypoglycaemia occurring in the ICU within 90-days of randomization.

2. Incidence of clinical consequence of severe hypoglycemia
   I. Neurological
   II. Cardiovascular
   III. Other

1.4 Analysis principles

1. All analyses will be conducted on an intention-to-treat basis.
2. All tests are two-sided and the nominal level of α will be 5%.
3. All statistical analyses will be unadjusted except where indicated.
4. Subgroup analyses will be carried out irrespective of whether there is a significant effect of treatment on the primary outcome.
5. 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, e.g. the SOFA scores.
6. P-values will not be adjusted for multiplicity. However the outcomes are clearly categorized by degree of importance (primary to tertiary) and a limited number of subgroup analyses are pre-specified.

2. DESIGN ISSUES

2.1 Data collection Follow-up

The different stages of data collection and follow-up can be summarised in the diagram below:

Form No.	*Period of study*	Data collection
	Randomization	Patient demographics and inclusion/exclusion criteria
1	Baseline	Source and date of admission to ICU, ICU admission diagnosis, sub-group categorize operative or non-operative admission and presence or absence of 'severe sepsis', 'trauma', traumatic brain injury and patients with Type I or Type II diabetes, Acute Physiology and Chronic Health Evaluation (APACHE) II score, SOFA scores (CVS, respiratory, hepatic, renal, haematologic), use of renal replacement therapy, use of mechanical ventilation, blood glucose concentration (last measurement before randomization), height and weight, prior treatment with insulin and corticosteroids.
2	Hourly, Days 1 - 90	Post-randomization blood glucose concentration whilst 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[#] blood glucose concentration measured from randomization to the earlier of ICU discharge or 90 days, the mean and SD early morning (first measurement after 08.00) and time-weighted[#] average blood glucose concentration measured from randomization 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 over time by treatment arm. They will be truncated at a relevant number of days. e.g. 14 days.
3	Daily, Days 1 - 90	Whilst in ICU: Daily SOFA scores (CVS, respiratory, hepatic, renal, haematologic), treatment with renal replacement therapy or mechanical ventilation, type (enteral versus parenteral) and volume of nutrition administered (total non-protein calories, protein, carbohydrate, lipid will be calculated from type and volume of enteral and parenteral nutrition administered), all iv glucose administered, all positive blood culture results that are clinically significant by predefined criteria. Total amount of insulin administered. Total amount of corticosteroids given (calculated as hydrocortisone equivalent). Number of patients transfused RBCs and volume of red blood cells (RBCs) transfused per randomised patient. Number of patients with treatment limitation order timing of and reason for treatment limitation.

4	28 Day Summary	Vital status (alive or dead) at day 28. Place, date and cause of death, date of discharge from ICU, date of discharge from hospital, number of days in ICU, type of consent obtained.
5	90 Day Summary	Vital status at day 90, length of stay in ICU, length of stay in hospital, place, date and cause of death
6	Serious Adverse Event of Hypoglycaemia	Description, date and time, cause and resolution of any serious adverse events whether or not study-related, severe hypoglycaemia (no. of episodes < 2.2 mmol/L or 40mg/dL, signs & symptoms, treatment given)
7	Extended Glasgow Outcome Score	Outcome score at 6 month and 2 year follow up for patients with TBI (history of trauma, cranial CT scan consistent with traumatic brain injury, and last unsedated pre-randomization GCS <14)

A daily time-weighted blood glucose (weighting based on time difference between two consecutive measurements applied to the average of two consecutive measurements) is to be computed for Item 2. Any consecutive BGA measurements within a study day are treated as continuous process. In the case where BGA 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.

Due to local legal considerations, patients or their legal surrogate may have an absolute right to request that their data be removed from the study database; as a result there are potentially two data sets: the randomized patients and the randomized patients where data is available. The latter is obtained after *deleting the data for randomized patients who withheld or withdrew their consent and did not allow their data to be submitted or maintained* in the database – see section II 6 for details. Only the latter dataset can be used in the analysis.

2.2 Study design

The NICE-SUGAR study is a multi-centre, open label, randomized concealed, controlled trial.

2.3 Treatment allocation

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

2.4 Power

We plan to enrol 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 Van den Berghe's first study,[1] this difference is clinically important and if detected would likely lead to widespread change in the practice of glycemic control in ICU's in Australia, New Zealand, North America and beyond.

2.5 Interim analyses

An independent Data and Safety Monitoring Board (DSMB) chaired by Professor Sir Richard Peto in Oxford, England, 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 DSMB which will generate terms of reference. The DSMB will be charged with informing the Study Management and Executive Committees if at any time there emerges: 1) Evidence beyond reasonable doubt of a difference between randomized groups in all-cause mortality, or 2) 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 and a patient or their legal surrogate may be asked for a delayed consent. Two important situations can lead to the cessation of study treatment: 1) a patient or next of kin or legal surrogate may withdraw consent or 2) 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 is 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 only occur in case of 'real' loss to follow-up, i.e. discharged patients with no information beyond some point in time. In that case the date of censoring will be the last day of contact or the date of hospital discharge if no other information is available.
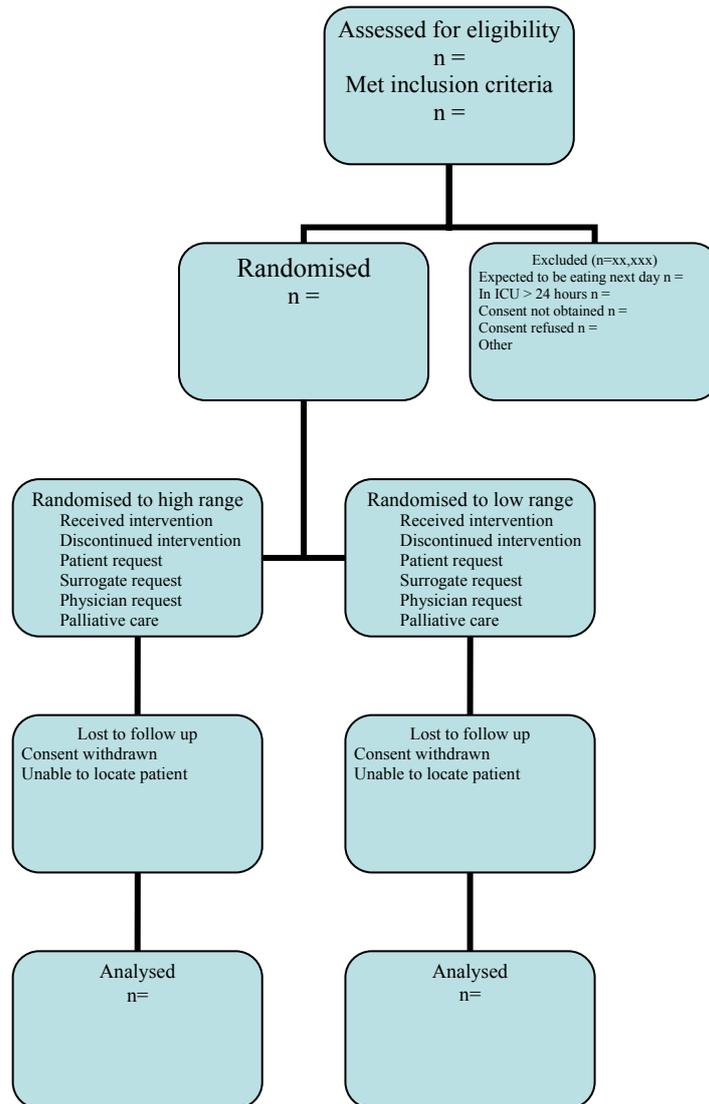
2.7 Permanent discontinuations

The data of patients who withdraw or withhold consent to continued study treatment but consent to the use of their data will remain in the analysed data set and will be analyzed 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 number of screened patients who met study inclusion criteria and number included, reasons for exclusion of non-included patients and information as below:

Assessed for eligibility
n =
Met inclusion criteria
n =

Randomised
n =

Excluded (n=xx,xxx)
Expected to be eating next day n =
In ICU > 24 hours n =
Consent not obtained n =
Consent refused n =
Other

Randomised to high range
Received intervention
Discontinued intervention
Patient request
Surrogate request
Physician request
Palliative care

Randomised to low range
Received intervention
Discontinued intervention
Patient request
Surrogate request
Physician request
Palliative care

Lost to follow up
Consent withdrawn
Unable to locate patient

Lost to follow up
Consent withdrawn
Unable to locate patient

Analysed
n=

Analysed
n=

Loss to follow up = any patient for whom the primary outcome was not available; analysed = all patients for whom the primary outcome was available.

3.2 Characteristics of patients and baseline comparisons

Description of the following baseline characteristics will be presented by treatment group. Discrete variables 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 will be less than the number of patients assigned to the treatment group) will be stated in either the body or a footnote in the corresponding summary table. In some instances frequencies and percentage of patients in the category will be reported as indicated in the list below.

Continuous variables will be summarised by use of standard measures of central tendency and dispersion, either mean and SD for variables identified with #, or median and interquartile range (IQR) for symbol [†]. Medians (IQR) will be added as summary measures.

Baseline measures for all patients
1. Sex
2. Age #
3. Weight #
4. Height #
5. Calculated body mass index #
6. Geographic region (Australia and New Zealand vs. North America)
7. Source of admission to ICU (emergency department, hospital floor, another ICU, another hospital, operating room (OR) following emergency surgery, OR following elective surgery, readmission to the same ICU during same hospitalization)
8. Time from ICU admission to randomization
9. Operative versus non-operative
10. Operative admission diagnosis (number and % in categories a-k)
    a. Cardiovascular
    b. Respiratory
    c. GIT
    d. Neurological
    e. Trauma without traumatic brain injury
    f. Traumatic brain injury +/- multiple trauma
    g. Burns
    h. Renal
    i. Gynecology
    j. Other orthopedic
    k. Other surgical
11. Non-operative admission diagnosis (number and % in categories a-l)
    a. Cardiovascular
    b. Respiratory
    c. GIT
    d. Neurological
    e. Sepsis
    f. Trauma without traumatic brain injury
    g. Traumatic brain injury +/- multiple trauma
    h. Metabolic
    i. Hematological
    j. Burns
    k. Renal
    l. Other medical
12. Severe sepsis at baseline
13. Trauma with or without brain injury at baseline
14. Traumatic brain injury at baseline

15. APACHE II score [#]
16. SOFA score
    a. Cardiovascular component
    b. Respiratory component
    c. Renal component
    d. Hepatic component
    e. Haematologic component
17. Last blood glucose concentration before randomization #
18. Prior history of diabetes mellitus
    a. Type I
    b. Type II
19. Patient normally treated with insulin (n / %)
20. Renal replacement therapy at baseline (n / %)
21. Mechanical ventilation at baseline (n / %)
22. Treatment with corticosteroids at baseline (n / %)

Additional baseline measures for patients with trauma

Injury severity score (1998 version)[†]

Additional baseline measures for patients with traumatic brain injury

1. Glasgow coma score at baseline [†]
    a. Eye component [†]
    b. Verbal component [†]
    c. Motor component [†]
2. Marshall score for CT brain
    (n and % of patients in each of the 5 categories)
3. Incidence of hypotension (SBP<90mmHg or MAP<65mmHg) prior to randomization
4. Intracranial pressure (ICP) monitor at baseline (n / %)
5. ICP 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 1. When indicated, frequencies and percentages of patients per category will also be given. Again the same coding using # for mean (SD) and † for median and IQR will be used to indicate the presentation of measures of central tendency and dispersion. Standard Chi-square tests will be performed to compare frequencies and t-test or Wilcoxon rank sum test used for continuous data. In case of rare events (expected number per cell lower than 1) the Fisher test will be used.

Process Measures

1. Time on study treatment
2. Time from cessation of study treatment to (last) discharge from the ICU
3. Number (%) patients treated with insulin in the ICU within 90 days of randomization
4. Daily insulin dose (IU/days on study treatment) #
5. Mean morning (first measurement after 08.00) blood glucose concentration by group#
    a. Averaged over time from randomization to time of ICU discharge #
    b. Averaged over time from randomization 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) #
6. Mean time-weighted blood glucose concentration by group
    a. Averaged over time from randomization to time of ICU discharge #

     b. Averaged over time from randomization 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) #

Concomitant treatments

7. Non-protein calories administered in the ICU (by day, up to day 14) #
    a. Non-protein calories by all routes (by day, up to day 14) #
    b. Non-protein calories by enteral route (by day, up to day 14) #
    c. Non-protein calories by parenteral route (by day, up to day 14) #
    d. Non-protein calories as intravenous glucose (by day, up to day 14) #

In addition, bar graphs displaying means (SD) of total non-protein calories and non-protein calories by the enteral route per treatment group by the day in ICU will also be produced (detailed in Section 5). In the event that the number of patients remaining in the ICU becomes too small, the means will be truncated prior to 14 days. Conversely the maximum of 14 days will be extended if considered relevant by the study statistician.

8. Patients treated with corticosteroids at any time in the ICU
    Daily dose of corticosteroid as hydrocortisone equivalent (by day, up to day 14) #

Limitation of treatment
9. Patients for whom there was limitation of treatment.
10. Patients for whom treatment limited or withheld
    a. Patients for whom treatment limited as terminal event
    b. Patients for whom maximal treatment was not indicated
11. Time from randomization to first treatment limitation order (overall and for limitations indicated in 10 a. and 10 b.)
    Treatment limitation refers to a) withdrawing a treatment that might otherwise prolong life as it is no longer considered appropriate for that individual, i.e. stopping of a previously provided treatment or b) withholding treatment that might otherwise prolong life as it is not considered appropriate for that individual, i.e. not commencing a treatment. Each of these will have been authorized by a treating clinician independent of the study and documented in the medical record. The specific treatments limited or withdrawn will not be reported.

Consent and Permanent discontinuation of study treatment
12. Consent (n and % in each category a-f)
    a. Prior informed consent from patient
    b. Prior informed consent from a legal surrogate
    c. Delayed informed consent from patient
    d. Delayed informed consent from a legal surrogate
    e. Consent from other legal body before or after patient's death
    f. No consent obtained – data withdrawn

13. Patients for whom study treatment permanently discontinued (n and % in each category a-f)
    a. Patients for whom informed consent withdrawn
    b. Patients for whom delayed informed consent withheld
    c. Study treatment discontinued by treating clinician (not due to SAE or palliative care)
    d. Study treatment discontinued due to SAE
    e. Study treatment discontinued as focus of treatment changed to palliative care
    f. Study treatment discontinued for other reason

3.4 Description of analyses

3.4.1 Primary outcome

A standard Chi-square 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, 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 minimization, i.e. post-operative versus non-operative patients and region and the following predictors: age, ICU admission source, APACHE II score and mechanical ventilation at baseline. In the event the DSMB considers early stopping of the trial, the results of this analysis will be reported to the management committee and DSMB 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 (TBI)

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

    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-randomization Glasgow coma score (GCS), presence of pre-randomization hypotension (defined as a documented systolic arterial blood pressure of less than 90mmHg or documented mean arterial blood pressure of less than 65mmHg) and presence of traumatic subarachnoid hemorrhage (tSAH) on a pre-randomization computerized tomographic (CT) 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 Chi-square test with odds ratio and 95% CI.

3.4.2 Secondary/tertiary outcomes

A standard Chi-square test will be used to assess the effect of treatment on binary or categorical outcomes, i.e. 28-day all cause mortality, cause of death, place of death, incidence of a new organ failure, 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 chi-square test.
In addition the number of new organ failures will be tabulated per treatment arm - frequencies and percentages for all values 0-5 new organ failures.

Survival time from randomization 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 presented. 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 of greater 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 summarized 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 study their data will be censored. The use of packed red blood cell transfusion will be summarized as number and percentage of patients per arm who receive packed red blood cells and mean (SD) volume of packed red blood cells per treatment arm. The effect of treatment allocation will be tested using a two-sample t-test or Wilcoxon rank sum test as appropriate.

Analyses adjusted for the same predictors as the primary outcome will also be done for the secondary outcomes as subsidiary analyses. They will be based on a linear, logistic or Cox regression as appropriate depending on the type of outcome.

3.4.3 Safety outcomes

1. Severe hypoglycemia: Number of patients with blood glucose (BG) ≤2.2mmol/L (≤ 40mg/dL) in the ICU during the 90-day study period.
    a. Number of episodes of BG ≤2.2mmol/L (≤ 40mg/dL) per patient
    b. Number of patients with clinical sequelae of severe hypoglycemia
        1. Neurological sequelae
        2. Cardiovascular sequelae
        3. Other sequelae

Number of episodes of severe hypoglycemia (measured blood glucose concentration ≤2.2mmol/L or ≤ 40mg/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 Chi squared statistic or Fisher's 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-randomization variable, we will not select any subgroups based on post-randomization events. [4, 5]

The primary outcome for planned subgroup analyses will be the same as in the main analysis, i.e. 90 day all-cause mortality. Most subgroup analyses will be exploratory and aim at generating new hypotheses although 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 studies.[1, 2, 6] Unadjusted p-values will be reported but the number of declared subgroups 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, e.g. 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, analyses considering continuous variables will also be performed, in that case only the interaction test will be reported.

The following status *at baseline* specifies the 6 subgroup analyses:
1. operative patients versus non-operative patients
2. patients with diabetes mellitus versus those without
3. patients with severe sepsis versus those without
4. patients diagnosed with trauma versus those without
5. APACHE II score of 25 or more versus APACHE II score of less than 25
6. patients treated with corticosteroids versus those not treated

Rationale

The rationale for considering these subgroup is as follows:

1. Contrasting evidence in 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.

2. 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 normalization of blood glucose.[6]

3. Conflicting signals in patients with sepsis versus those without. In Van den Berghe and colleagues' SICU trial, the excess mortality was attributed to deaths from sepsis.[1] In Van den Berghe and colleagues' 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 a person's ability to deal with infections. Despite the potentially beneficial effects of IIT in patients with severe sepsis, a trial of IIT conducted by the German Sepsis Network was stopped early due to safety concerns in the absence of a beneficial treatment effect.[7]

4. Patients admitted to the ICU because of trauma have a very different demographic profile to other ICU patients. They are younger and have less co-morbidity. The mortality rate of trauma patients without traumatic brain injury is much lower that the general ICU population but a recent publication by Vogelzang et al. reported that the association between hyperglycaemia and adverse outcome was stronger in trauma patients than in other critically ill patients.[8]

5. The NICE-SUGAR patients represent a heterogeneous population treated in ICUs (diagnoses, severity of disease). A criticism of Van den Berghe's studies has been that the patients had a 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]

6. Following the publication of Annane's study in 2002,[11] corticosteroids have been used to treat critically ill patients with increasing frequency and were being received at time of randomization by over 50% of patients in Van den Berghe'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 Forrest plots - with p-values for heterogeneity for each pair of subgroups.

3.5 Control of type I error for multiples looks

The Peto rule with a maximum of 3 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 3 interim analyses are equally spaced. This value will be recalculated if more interim analyses are considered or they are not roughly equally spaced. Although naïve 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 CI's at each interim analysis - if required by the DSMB - 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

Tables include baseline characteristics of the participants, process measures and concomitant treatments – time on treatment algorithm, number of patients treated with insulin and amount of insulin administered, blood glucose concentration, treatment with corticosteroids, non-protein calories administered and route, outcomes including safety outcomes and subgroup analyses. The content and proposed formatting is displayed in the spreadsheet attached to this document.

Planned figures are:

1. A CONSORT diagram illustrating flow of patients through the study

2. Bar graphs for mean (SD) total non-protein kilocalories administered and mean (SD) non-protein kilocalories administered by enteral route per day by treatment arm for the first 14 days (2 plots), and mean (SD) time-weighted blood glucose concentration on study treatment by treatment group for the first 14 days (3rd plot)

3. A Forrest plot of odds ratios for death at 90 days for all patients and for *a priori* subgroups as described in III 3.4.

4. A Kaplan Meier curve for survival to 90 days

3.7 References

1. Van den Berghe G, Wouters P, Weekers F et al. Intensive insulin therapy in critically ill patients. N Engl J Med 2001; 345:1359-1367.

2. Van den Berghe G, Wilmer A, Hermans G et al. Intensive Insulin Therapy in the Medical ICU. N Engl J Med 2006; 354(5):449-461.

3. Maas AI, Steyerberg EW, Murray GD et al. Why have recent trials of neuroprotective agents in head injury failed to show convincing efficacy? A pragmatic analysis and theoretical considerations. Neurosurgery 1999; 44(6):1286-1298.

4. Assmann SF, Pocock SJ, Enos LE, Kasten LE. Subgroup analysis and other (mis)uses of baseline data in clinical trials. Lancet 2000; 355(9209):1064-1069.

5. Pocock SJ, Assmann SE, Enos LE, Kasten LE. Subgroup analysis, covariate adjustment and baseline comparisons in clinical trial reporting: current practice and problems. Stat Med 2002; 21(19):2917-2930.

6. Van den Berghe G, Wilmer A, Milants I et al. Intensive Insulin Therapy in Mixed Medical/Surgical Intensive Care Units: Benefit Versus Harm. Diabetes 2006; 55(11):3151-3159.

7. Brunkhorst FM, Engel C, Bloos F et al. Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis. N Engl J Med 2008; 358(2):125-139.

8. Vogelzang M, Nijboer JM, van der Horst IC, Zijlstra F, ten Duis HJ, Nijsten MW. Hyperglycemia has a stronger relation with outcome in trauma patients than in other critically ill patients. J Trauma 2006; 60(4):873-877.

9. Dhainaut JF, Laterre PF, Janes JM et al. Drotrecogin alfa (activated) in the treatment of severe sepsis patients with multiple-organ dysfunction: data from the PROWESS trial. Intensive Care Med 2003; 29(6):894-903.

10. Ely EW, Laterre PF, Angus DC et al. Drotrecogin alfa (activated) administration across clinically important subgroups of patients with severe sepsis. Crit Care Med 2003; 31(1):12-19.

11. Annane D, Sebille V, Charpentier C et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 2002; 288(7):862-871.