Individual Patient Meta-analysis of Intensive Insulin Therapy Trials in Critically Ill Patients

Statistical Analysis Plan

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Contents

1 Introduction

1.1 Study synopsis

Critical illness is frequently accompanied by an increased blood glucose concentration irrespective of the underlying pathology. Hyperglycaemia is caused by a combination of insulin resistance and increased glucose production and is part of the pronounced endocrine and metabolic abnormality that accompanies critical illness. It has been known for a long time that hyperglycaemia is associated with increased risk of death. However, the concept of intensive glucose control through intensive insulin therapy (IIT) in critically ill patients only appeared in 2001.

To date there have been over 30 randomised controlled trials of IIT in intensive care, using different tools and target levels for blood glucose control, with the majority of trials reporting non-significant differences in mortality. However, many of the trials were small and had insufficient statistical power to examine the effects of IIT on mortality. Larger trials, although differing in several design aspects, have reported discordant results, notably the Surgical and Medical ICU trials in Leuven reported IIT to reduce morbidity and/or mortality, whilst the NICE SUGAR study reported it to increase mortality.

1.1.1 Explanations for discrepancies in the evidence

There are a number of potential reasons why studies may have reported discrepant results. These include differences in the populations studied, the duration of hyperglycaemia prior to the start of the intervention, the blood glucose concentrations targeted in the IIT and control (intermediate or high control group) groups, the insulin protocols or guidelines used to control blood glucose, the separation in blood glucose concentrations achieved between groups, differences in other treatments administered in the intensive care unit (e.g. use of glucose infusion and parenteral feeding), differences in the techniques used to measure blood glucose concentration and differences in the duration of follow-up.

1.1.2 Rationale for an individual patient data meta-analysis

The advantages of having individual patient data for a meta-analysis have been described previously and include: the provision of more information than is available in study-specific meta-analysis and hence increased precision of estimates; the ability to perform more complex analyses such as survival analyses and risk adjusted multivariate analyses; facilitate more flexibility in the categorization of subgroups; a reduction in biases included in meta-analyses of published data achieved through checking the consistency of individual patient data according to standard protocols.

Hence an individual patient data meta-analysis (IPD-MA) will allow a collaboration of researchers who have conducted trials of IIT in intensive care patients to address this controversy using a uniquely powerful database.

This individual patient data meta-analysis **will aim to explore the reasons for the contrasting effects of intensive insulin therapy in critically ill patients**.

As the IPD-MA will be **exploratory**, its results will only **generate hypotheses** that may be a guide to future trials addressing specific issues in intensive insulin therapy. These may help to develop guidelines for intensive care physicians on the optimum management of blood glucose in critically ill patients.

1.1.3 Objective

The objective of the meta-analysis is to **identify the factors**, at patient, hospital or trial level, that **influence** whether targeting a blood glucose concentration of ≤6.6 mmol/L (≤120 mg/dL) **generated outcome benefit or harm**, as compared to a higher blood glucose target (either intermediate or high glucose target in control group). Mortality will be the primary endpoint and morbidity aspects will be secondary endpoints. As the individual trials have used different time points to assess mortality, the primary analysis of mortality will examine **in-hospital mortality**.

This meta-analysis will be based on individual patient data, whenever these are available and hospital/trial level data when individual patient data are unavailable.

1.2 Study population

1.2.1 Trial identification

We performed computerised searches in MEDLINE, EMBASE, CCTR, clinical trials.gov, the Australian New Zealand Clinical Trials Registry and Japan's University Hospital Medical Information Network Clinical Trial Registry with the following search terms critical care, intensive care, insulin, blood glucose, intensive insulin therapy with results limited to humans and randomised controlled trials.

We manually searched abstracts from conference proceedings (2000-2012) of the Society of Critical Care Medicine, the European Society of Intensive Care Medicine, the International Symposium on Intensive Care and Emergency Medicine, the American Thoracic Society, the American Endocrine Society and the American Diabetes Association.

1.2.2 Trial eligibility

Inclusion criteria:

Randomized controlled trials in which patients are **randomly assigned** to one of two or more groups as defined below, which report an intention-to-treat analysis that meet the following criteria will be included:

1. Study population is critically ill adults (defined as being treated in an ICU that can provide invasive mechanical ventilation and advanced organ support).
2. Intervention is a blood glucose target in IIT group of ≤120 mg/dL (≤6.6 mmol/L) using intravenous insulin administration in the intervention arm of the study.
3. The comparison group receiving usual care, which allows a higher blood glucose concentration than in the intervention arm

4. Reporting randomised treatment allocation, date of randomisation, date of death or, for patients with no death recorded, the date when the patient was last known to be alive

Exclusion criteria:

The following studies will be excluded:

1. Studies using glucose-insulin-potassium infusions
2. Studies with upper limit of blood glucose target in IIT group of > 6.6 mmol/L (>120 mg/dL)
3. If IIT was exclusively performed in the intra-operative period
4. If more than 10% of patients have either a missing date of death or a missing date when they were last known to be alive

1.1.1 Data collection (definitions and data dictionary to be agreed)

Data can be accepted in any commercial database or statistical package

Period of study	Data collection
Baseline	patient identifier, sex, date of birth, date of randomisation, treatment allocation, history of diabetes, ICU admission diagnosis: operative vs. non-operative using APACHE II system on-admission BG, baseline serum creatinine / SOFA RRT prior to trial entry, Ventilator support, Renal replacement therapy (RRT), Acute brain injury, Severe sepsis, Prior corticosteroid treatment, APACHE-II score, SOFA (total and individual domains), HbA1c Additional study level and hospital level data, collected retrospectively if necessary: 1. Type of glucose monitoring device: 2. Site of blood sampling 3. Type of insulin-infusing system 4. Control group target: classified as insulin treatment initiated at an intermediate (any below 180 mg/dl or 10 mmol/l) or high (any above 180 mg/dl or 10 mmol/l) blood glucose level. 5. Unit experience with IIT, 6. Early parenteral feeding/glucose administration policy (defined as follows: Early parenteral feeding policy (unit strategy to deliver >400 iv glucose kcal/day by parenteral route in the first 72h).
Follow-up	All BG measurements available and timing, occurrence of severe hypoglycaemia (≤ 40 mg/dL, 2.2 mmol/L), occurrence of moderate hypoglycaemia (≤ 70 mg/dL, 3.9 mmol/L), serum creatinine concentration, serum potassium concentration, serum bilirubin concentration, treated with RRT, ventilator support, treatment with inotropic agents or vasopressors, treatment with corticosteroids, RBC transfusion (volume), caloric intake (total), caloric intake (enteral), iv glucose administered, iv insulin administered and SOFA (total and individual domains).
Outcomes	Date of last follow-up, alive or dead at last follow-up date, date and place of death if died during follow up, date of index ICU discharge and date of index hospital discharge.

Information that will also be requested at the level of the ICU will include:

1. Method of blood glucose analysis: estimated percentage of blood glucose measures using (1)handheld blood glucose meter, (2) blood gas analyser a (3) central laboratory measurement or (4) a mixed methodology
2. Site of blood sampling: estimated percentage of blood glucose measures taken from arterial, capillary or central venous blood

3. Infusion system used: syringe or volumetric
4. Intermediate or high blood glucose target in the control group, defined as follows: intermediate (commence treatment if blood glucose exceeds 180 mg/dl or 10 mmol/l or lower); high (commence treatment at a blood glucose concentration higher than 180 mg/dl or 10 mmol/l).
5. Nutritional strategy in the ICU: Early parenteral feeding policy (unit strategy to deliver >400 iv glucose kcal/day by parenteral route in the first 72h) versus a strategy for late use of parenteral nutrition or concentrated IV glucose (≤400 iv glucose kcal/day in the first 72h).

1.3 Definition of efficacy variables

1.3.1 Primary outcome

The primary outcome will be **Proportion dead at index hospital discharge** analysed **both without and with baseline covariate adjustment**.

Covariates that cannot be obtained for at least 75% of patients will be excluded but included in a sensitivity analysis in which a missing category will be used.

When patients are transferred from the study hospital to another hospital, mortality will be determined at final hospital discharge for the index admission. For studies that collected landmark mortality (e.g. NICE SUGAR Study), the final hospital discharge mortality for the index admission will be determined. For example if a patient who was recruited to the study and recovered to be discharged to home or an equivalent setting [e.g. nursing home or aged care facility] but then subsequently readmitted to hospital during follow up and died, this patient will be counted as having survived to hospital discharge.

1.3.2 Secondary outcomes

The secondary outcomes will be:

1. Proportion dead at **index ICU discharge**. For studies that collected landmark mortality (e.g. NICE SUGAR Study), the ICU discharge mortality for the index ICU admission will be determined. For example if a patient who was recruited to the study and recovered to be discharged from the ICU but not from the hospital and then was subsequently readmitted to ICU during follow up and died, this patient will be counted as having survived to ICU discharge but not to hospital discharge.
2. Proportion dead 90 days after randomization.
3. Survival analysis to 90 days after randomization
4. Proportion of patients treated with mechanical ventilation during index hospital admission.
5. Time to alive cessation of mechanical ventilation
6. Proportion of patients treated with inotropic agents or vasopressors during index hospital admission.

7. Time to alive cessation of inotropic agents or vasopressors.
8. Proportion of patients newly treated with renal replacement therapy during index hospital admission.
9. Time to alive cessation of new treatment with renal replacement therapy.

1.4 Subgroup and covariate analyses

We will examine the effect of treatment allocation on index hospital mortality in patient and hospital / study level subgroups and test for heterogeneity in effects between subgroups. The same variables will also be used as covariates in multivariate models in order to identify factors that may be related to mortality.

1.4.1 Patient level subgroups (patient level analyses)

Patient level **subgroup analyses** will be conducted on clearly defined and *a priori* agreed baseline characteristics, known in individual patients. The following 7 baseline characteristics will define Patient level subgroups/covariates:

1. **Operative versus non-operative patients**: On theoretical grounds one could speculate that in surgical ICU patients the hyperglycaemia is of recent onset while in medical critical illness the duration of the hyperglycaemia may be much longer leading to organ damage beyond full recovery. We hypothesize that a beneficial effect of IIT will be more apparent in surgical patients. Surgical patients will be defined as admission to the ICU direct from the operating room or recovery room after an operation. Admission after endoscopic or radiological procedures will be classified as medical admissions.
2. **Diabetes (Yes/No):** Preliminary post-hoc analyses from the Leuven studies indicated that IIT may lead to increased mortality risk in patients with known diabetes compared to reduced risk in patients without known diabetes. We hypothesize that the beneficial effect of IIT will be more apparent in patients without known diabetes compare to those with known diabetes. Where possible, known diabetes will be defined as a patient taking oral anti-diabetic medication, insulin or a diagnosis of type II diabetes treated with diet.
3. **Severe sepsis or septic shock (Yes/No)**: The VISEP study did not show a benefit from IIT in this specific population of critically ill patient population. We hypothesize that a beneficial effect of IIT will be less apparent in patients with sepsis/severe sepsis/septic shock at baseline. Sepsis/severe sepsis/septic shock will be defined according to the criteria of the ACCP/SCCM Consensus Conference Committee in 1992. Diagnosis of severe sepsis will require the presence of an infection and organ dysfunction at baseline.
4. **Trauma (Yes/No)**: Patients admitted to ICU with trauma have different demographic profile and different survival pattern. We hypothesize that a beneficial effect of IIT will be more apparent in patients admitted following trauma. Patients with isolated traumatic brain injury will be excluded.

5. **Acute brain injury (Yes/No)**: The brain is probably the most vulnerable organ to either hyper or hypoglycaemia. We hypothesize that a beneficial effect of IIT will be more apparent in patients admitted with an acute brain injury. Patients with acute brain injury will be those whose admission to the ICU that resulted in their inclusion in an IIT trial was for treatment of trauma with brain injury, intracranial haemorrhage (including subarachnoid haemorrhage), ischaemic stroke, meningitis or encephalitis.
6. **Systemic corticosteroid treatment at baseline (Yes/No)**: Is the treatment effect of IIT different in patients treated with systemic corticosteroids at baseline versus those not treated? We hypothesize that a beneficial effect of IIT will be more apparent in patients treated with systemic corticosteroids at baseline. Corticosteroid therapy increases glucose intolerance and could theoretically influence the treatment effect of intensive insulin therapy.
7. **Severity of critical illness (Yes/No)**: Differences in survival benefit of IIT have frequently been attributed to the severity of critical illness. We hypothesize that a beneficial effect of IIT will be more apparent in patients who are less severely ill. On-admission APACHE-II or equivalent scores will be examined as continuous data in relationship to mortality in order to maximise the analytical power. For subgroup analysis, severity score will be dichotomized as below the median severity score of the entire population Y/N.

1.4.2 Hospital or study level subgroups (hospital or study level analyses)

Analysis of pre-defined pre-randomisation factors that are known only on a centre or study basis. We will analyse the following six Hospital level subgroups/covariates:

1. **Early parenteral feeding policy** (unit strategy to deliver >400 iv glucose kcal/day in the first 72h) versus a strategy for late use of parenteral nutrition or concentrated IV glucose (≤400 iv glucose kcal/day in the first 72h). We hypothesize that a beneficial effect of IIT will be more apparent in patients cared for in hospitals with an early parenteral feeding policy.
2. **Type of glucose monitoring device**: Classified as (1) predominantly bedside point-of-care (≥80% of samples), (2) predominantly laboratory (≥80% of samples), (3) predominantly blood gas analyser (≥80% of samples) or (4) mixed point-of-care, laboratory or blood gas analyser (all others). We hypothesize that a beneficial effect of IIT will be more apparent in patients whose blood glucose measurements were predominantly laboratory or blood gas analyser measurements.
3. **Site of blood sampling**: Classified as predominantly (1) arterial or central venous (≥80% of samples), (2) predominantly capillary (≥80% of samples) or (3) mixed (all others). We hypothesize that a beneficial effect of IIT will be more apparent in patients whose site of blood sampling was predominantly arterial or central venous.
4. **Unit experience with IIT**: Stratify units into tertiles by number of patients treated with IIT. We hypothesize that a beneficial effect of IIT will be more apparent in patients cared for in units with more experience with IIT.

5. **Type of insulin-infusing system**: Classified as syringe pump or volumetric infusion system or mixed. We hypothesize that the beneficial effect of IIT will be more apparent in patients cared for in units where insulin is delivered by syringe pump.
6. **Control group target**: classified as intermediate (treatment commenced at BG of 10.0 mmol/L or lower value) or high (treatment commenced at BG of >10.1 mmol/L or higher value). We hypothesize that a beneficial effect of IIT will be more apparent when compared with higher control group target.

In addition to the 13 subgroups listed above, the following five baseline variables will be used as covariates for adjusted analyses: sex, age (continuous), baseline blood glucose concentration, baseline treatment with renal replacement therapy and baseline treatment with mechanical ventilation.

2 Statistical analysis

2.1 Analysis principles

- All analyses will be conducted on an intention-to-treat basis.
- Missing values will not be imputed – where variables were not recorded we will ask each trialist to obtain the data. Where data cannot be obtained for ≥75% of total participants included in the meta-analysis, the analyses for which those data are needed will not be performed.
- All tests will be two-sided and the nominal level of alpha will be 5%.
- We will conduct unadjusted and fully adjusted analyses for all analyses except the survival analyses.
- Subgroups/covariates are defined as either Patient level or Hospital level and among individual patients, are only defined at baseline.
- Subgroup/covariates analyses will be carried out irrespective of whether there is a significant effect of treatment allocation on the outcome of interest.
- We will not impute missing values unless specified otherwise. We will report the number of observations used in the analysis.
- P-values will not be adjusted for multiplicity. However the outcomes are clearly categorized by degree of importance (primary to secondary) and the number of subgroup analyses are pre-specified.
- All the analyses will be conducted in SAS, Stata or R

2.2 Meta-analysis steps

The meta-analysis will follow multiple steps. First, each trial will be analysed separately to check the feasibility of the analytic plan and ensure data were not corrupted during transmission to the coordinating centre. Then we will combine the individual patient data from the individual trials to conduct the main analyses.

2.2.1 Analysis of bias and heterogeneity

For each primary and secondary outcome, the assumption of homogeneity between the treatment effects in different trials will be tested with Cochran's Q test. The assumption of homogeneity will be rejected at $p<0.10$. I^2 statistics will be used to estimate the proportion of total variation in study estimates that is due to heterogeneity. Funnel plots will be used to assess the likelihood of publication bias.

2.2.2 Analysis of each trial separately

We will start by analysing primary and secondary outcomes for each trial separately, both as a way to assess the feasibility of the analyses at the trial level and to ensure consistency with the original, previously published, trial-specific analyses. These analyses will be returned to the individual trialists but will not be published or shared with any other trialist without the approval of the trialist to whom the data belong.

No subgroup analysis or covariate adjustment will be done at the trial level.

2.2.3 Pooled data analysis

For the main analyses, the individual patient data from each eligible trial will be concatenated into one master dataset. All the patients will be analysed together with appropriate heterogeneity adjustments at the trial level.

Subgroup analyses and covariate adjustments will only be done using this pooled dataset.

2.3 Baseline characteristics

Description of baseline characteristics (see variables listed in Section 1.1.1) will be presented for each trial, by randomised treatment group (CIT versus IIT) and overall.

Discrete variables will be summarised using frequencies and percentages. Percentages will be calculated according to the number of patients for whom data is available.

Continuous variables including durations will be summarised by use of standard measures of central tendency and dispersion; mean and standard deviation (SD), or median and interquartile range (IQR).

2.4 Follow-up data

2.5 Primary outcome analyses – mortality at hospital discharge

The primary analysis will use the dataset combining the individual patient data from each trial as described in Section 2.2.3. Missing data will not be imputed but the number available and missing will be reported.

2.5.1 Primary analysis

The primary analyses will be all cause mortality at index hospital discharge. It will be analysed using log-binomial regression which will allow direct estimation of risks and risk

ratios (i.e. relative risks). The primary analysis will be conducted both without covariate adjustment (unadjusted analysis) and with covariate adjustment (adjusted analysis).

After having concatenated the individual patient data from every trial, we will compute the difference in proportion of patients who have died at hospital discharge after randomisation between the two groups (conventional versus intensive glucose control) using all available data. We will test the treatment effect by using a log-binomial regression with a random study effect and random study-by-treatment interaction; Chi-square test and 95% confidence intervals (CI) will be computed.

In case of convergence issues with the log-binomial regression, in particular with the adjusted analyses, we will use robust Poisson regression as a back-up (Zou, 2004).

Adjusted analyses:

The relationship between each of the 18 a priori defined co-variables and the primary outcome will be tested using a univariable log-binomial regression (or robust Poisson) and subsequently used for the multivariable adjusted analysis. Covariates with more than 25% of missing values will not be included in the meta-analysis. Every covariate with a univariate p-value smaller than 20% will be retained for a multivariate analysis. In case of strong co-linearity between two covariates i.e. a Pearson correlation coefficient > 0.80, the variable with the smallest univariate p-value will be kept for the multivariate model. We will also test first-order interactions and include those with a p-value smaller than 20% in the multivariate model. We will exclude from the multivariate analysis any covariate where the value is missing for more than 25% of the patients. However, as a sensitivity analysis we will create a "missing" category for variables with more than 25% of values missing and include the "missing" category in the analysis. A similar strategy will be applied for covariates that are completely missing for any single study to allow such studies to contribute to the sensitivity analysis.

When including study/hospital level covariates, the study (or hospital) will be included as a random effect to avoid biases due to ecological fallacy (Blakely, 2000).

2.5.2 Sensitivity analyses

As validation for the primary analysis of mortality at hospital discharge, we will pool the risk ratio estimates obtained from each of the trials using a random effect meta-analysis with inverse variance weighting.

The assumption of homogeneity between the treatment effects in different trials will be tested with Cochran's Q test. The assumption of homogeneity will be rejected at $p<0.10$. I^2 statistics will be used to estimate the proportion of total variation in study estimates that is due to heterogeneity.

2.5.3 Subgroup analyses

We will repeat the unadjusted analysis of the primary outcome outlined in Section **Error! Reference source not found.** for each of the Patient level and Study/ICU/Hospital level subgroups (see Sections 1.4.1 and 1.4.2). For each subgroup variable, we will use a separate

model where we will add two fixed effects: a) the subgroup variable alone and b) the interaction between the subgroup variable and the randomised treatment. Relative risks, 95% confidence intervals and p-values for tests of heterogeneity between the randomised treatment and the subgroup variable will be reported on a forest plot.

2.6 Secondary outcomes

1. Proportion dead at index ICU discharge.
2. Proportion dead 90 days after randomization.
3. Survival analysis to 90 days after randomization
4. Proportion of patients treated with mechanical ventilation
5. Time to alive cessation of mechanical ventilation
6. Proportion of patients treated with inotropic agents or vasopressors
7. Time to alive cessation of treatment with inotropic agents or vasopressors
8. Proportion of patients newly treated with renal replacement therapy
9. Time to alive cessation of new treatment with renal replacement therapy

2.6.1 Secondary dichotomous outcomes

Secondary dichotomous outcomes will include the following:

1. Proportion dead at index ICU discharge.
2. Proportion dead 90 days after randomization.
3. Proportion of patients treated with mechanical ventilation
4. Proportion of patients treated with inotropic agents or vasopressors
5. Proportion of patients newly treated with renal replacement therapy

For those five outcomes, we will replicate the unadjusted and adjusted analyses described in Section **Error! Reference source not found.** for hospital mortality. We will also run the sensitivity analyses described in Section 2.5.2; however, no subgroup analysis will be done.

2.6.2 Secondary survival outcomes

Survival secondary outcomes will include the following:

1. Time from randomisation to death within 90 days of randomization
2. Time to alive cessation of mechanical ventilation
3. Time to alive cessation of inotropic agents or vasopressors.
4. Time to alive cessation of new treatment with renal replacement therapy.

Because those four survival outcomes are subject to informative censoring we will use both a standard survival analysis and a competing risk analysis. For all survival analyses, data will be censored at the latest 90 days after randomisation. No subgroup or adjusted analysis will be done for the survival analyses.

2.6.2.1 Standard survival analysis

For each trial, we will calculate the hazard ratio using a Cox proportional hazard model (Therneau and Grambsch, 2000). Individual hazard ratios will then be combined using a random-effect meta-analysis.

For time to death, survival times will be censored on the date when the subject was last known to be alive or on Day 90, whichever occurred later.

Patients who died before alive cessation of MV/Vasopressors/RRT, will be censored at a time point beyond the longest survivor. Patients still alive and on treatment at end of follow-up will be censored at the end of follow-up.

The proportion surviving over time will be represented using Kaplan-Meier plots.

2.6.2.2 Competing risk analyses

In most studies, mortality was only measured while patients were in hospital; therefore, in many instances, hospital discharge prevented us from observing death. For time to death, hospital discharge will be considered as a competing risk.

For the three endpoints recording time to cessation, death will be considered as the competing risk event.

The sub-distribution hazard (Fine and Gray, 1999) will be calculated for every study separately and estimates will be combined using inverse-variance weighting.

The proportion surviving over time will be represented using Cumulative Incidence Functions (CIF) (Fine and Gray, 1999).

2.7 References

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Therneau, Grambsch. Modelling Survival Data: Extending the Cox Model *Springer*; 2000.

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Blakely TA, Woodward AJ. Ecological effects in multi-level studies. *J Epidemiol Community Health*. 2000;54:367-74.

Fine P, Gray R. A proportional hazards model for the subdistribution of a competing risk. *Journal of the Am Statistical Association* 1999; 94:496–506.

3 Table and figure shells

Table 1. Summary of data obtained by trial

Table 2. Baseline characteristics by trial

Table 2. Analysis of all-cause mortality at hospital and ICU discharge for each trial separately

Will show frequencies, denominators and percentages, risk ratios and 95% CI and p-value from log-binomial regression for each trial separately.

Table 3. Diagnostics

Will show diagnostics/tests of between-trial heterogeneity for each primary and secondary outcome.

Table 3. Analysis of all cause of mortality at hospital discharge, ICU discharge and at 90 days, for each trial separately

Will show frequencies, denominators and percentages, risk ratios and 95% CI and p-value from log-binomial regression for each trial separately.

Table 4. Aggregate analysis of all outcomes

Table will include:

1. *Primary endpoint (unadjusted and adjusted analysis) (see above)*
2. *Secondary dichotomous endpoints (unadjusted and adjusted analysis) (see section 1.3.2 above)*
   Analysis with log-binomial regression with random study effect.

Will show frequencies and percentages, risk ratios and 95% CI and p-value from log-binomial regression.
Note: If log-binomial regression does not work, we will show the results from the Robust Poisson regression.

***Table 4*. Survival analysis of secondary outcomes**

- *Time to alive cessation of mechanical ventilation*
- *Time to alive cessation of treatment with inotropic agents or vasopressors*
- *Time to alive cessation of new treatment with renal replacement therapy*

Table will include:

1. *Standard hazard ratio from each trial and combined using random-effect meta-analysis*
2. *Subdistribution hazard ratios from the competing risk analyses for each trial and combined using random effect meta-analysis*

Will show (sub)hazard ratios with 95% CI and p-value from Cox model or Gray test.

Figure 1. Consort-style diagram showing studies considered for unclusion, those included, those excluded and reason for exclusion, and data flow from each study

Figure 2. Forest plot showing risk ratio of mortality at Hospital discharge between two treatment groups, for each individual trial and overall

Figure 3. Forest plot showing risk ratio of mortality at ICU discharge between two treatment groups, for each individual trial and overall

Figure 4. Forest plot showing risk ratio of mortality at 90 days between two treatment groups, for each individual trial and overall

Figure 5. Forest plot showing risk ratio of proportion treated with mechanical ventilation between two treatment groups, for each individual trial and overall

Figure 6. Forest plot showing risk ratio of proportion treated with inotropic agents or vasopressors between two treatment groups, for each individual trial and overall

Figure 7. Forest plot showing risk ratio of proportion newly treated with renal replacement therapy between two treatment groups, for each individual trial and overall

Figure 8. Forest plot showing hazard ratio and sub-hazard ratio for time to alive cessation of mechanical ventilation between two treatment groups, for each individual trial and overall

Figure 9. Forest plot showing hazard ratio and sub-hazard ratio for time to alive cessation of treatment with inotropic agents or vasopressors between two treatment groups, for each individual trial and overall

Figure 10. Forest plot showing hazard ratio and sub-hazard ratio for time to alive cessation of new treatment with renal replacement therapy between two treatment groups, for each individual trial and overall

Figure 11. Forest plot showing hazard ratio and sub-hazard ratio for time to all-cause mortality between two treatment groups, for each individual trial and overall

Figure 12. Forest plot showing results of 13 subgroup analyses for mortality at Hospital discharge

Plot will show results of the Log-binomial model (risk ratio, CI and heterogeneity p-value) for each subgroup (patient level and hospital level) covariate.
Note: If log-binomial regression does not work, we will show the results from the Robust Poisson regression.

Figure 13. Kaplan-Meier plot of time to death

By randomised treatment group, censored at Day 90.

Figure 14. Kaplan-Meier plot of time to alive cessation of mechanical ventilation

By randomised treatment group, non-survivors censored at a time point beyond the longest ventilated survivor

Figure 15. Kaplan-Meier plot of time to alive cessation of treatment with inotropic agents or vasopressors

By randomised treatment group, non-survivors censored at a time point beyond the longest inotropic/vasopressor-treated survivor

Figure 16. Kaplan-Meier plot of time to alive cessation of new treatment with renal replacement therapy

By randomised treatment group, non-survivors censored at a time point beyond the longest RRT-treated survivor

Figure 17. Cumulative incidence function of time to death

By randomised treatment group, censored at Day 90, with hospital discharge as a competing risk.

Figure 18. Cumulative incidence function of time to cessation of mechanical ventilation

By randomised treatment group, censored at Day 90, with death as a competing risk.

Figure 19. Cumulative incidence function of time to cessation of treatment with inotropic agents or vasopressors

By randomised treatment group, censored at Day 90, with death as a competing risk.

Figure 20. Cumulative incidence function of time to cessation of new treatment with renal replacement therapy

By randomised treatment group, censored at Day 90, with death as a competing risk.