

6S-Trial Statistical Analyses

Populations

Intention-to-treat: All randomised patients. This population is not analysed in the 6S-trial.

Modified intention-to-treat:

All randomised patients except patients who

- were not eligible for randomisation according to the inclusion/exclusion criteria

AND

- who never had any of the interventions (masked trial fluid).

Per-protocol #1:

All randomised patients except patients having one or more major protocol violations defined as

- Patients who were not eligible for randomisation according to the inclusion/exclusion criteria.

OR

- Patients who never had the intervention (masked trial fluid).

OR

- Patients who accidentally received wrong intervention (intervention error).

OR

- Patients who received any synthetic colloid after randomisation.

Per-protocol #2:

All randomised patients except patients having one or more major protocol violations defined as

- Patients who were not eligible for randomisation according to the inclusion/exclusion criteria.

OR

- Patients who never had the intervention (masked trial fluid).

OR

- Patients who accidentally received wrong intervention (intervention error).

OR

- Patients in the Ringer's acetate arm, who received any synthetic colloid after randomisation.

Subgroups:

- Patients where renal failure define severe sepsis (renal component of SOFA-score = 2 OR higher)
- Patients with shock at time of randomisation (mean arterial pressure < 70 mmHg after the initial fluid resuscitation OR ongoing treatment with noradrenalin, adrenalin, dopamin, dobutamin, vasopressin, phenylephrine, milrinone or levosimendan OR arterial or venous lactate > 4.0 mmol/L within the last hour)

Analyses

Primary analysis:

Unadjusted Chi-square test.

Secondary analysis (will only be made for the modified intention-to-treat population):

Multiple (logistic) regression with the following covariates:

Binary covariates

- Center is a university hospital Y/N (stratification variable)
- Diagnose of hematological malignancy at time of randomisation Y/N (stratification variable)
- Shock at time of randomisation Y/N (as defined above) (stratification variable)
- Diabetes at time of randomisation Y/N
- Use of nephrotoxic drugs during current admission and prior to randomisation Y/N
- Previous renal dysfunction ('normal' creatinine >100 µmol/l = baseline variable #2) Y/N
- Acute Kidney Failure at randomisation (renal failure defining severe sepsis as defined above)

Continuous covariates

- Age
- SAPS II
- SOFA-score

Outcomes

Primary outcome measure

The composite outcome measure of 90-day mortality or end-stage kidney disease defined as dialysis-dependency 90 days after randomisation (+/- 4 days) as retrieved from the National Patient Hospital Register and the National Dialysis Database.

These two outcome measures will also be analysed separately.

Secondary outcome measures

- Twenty-eight-day, 6-month and 1-year mortality
- Mortality to the length of maximal follow-up. A time to event analysis exploiting the whole observation time for all patients when the last randomised patient has been followed for 90-days, 6 months and 1-year
- SOFA-score without cerebral component (see Appendix 5) on day 5 after randomisation.
- Development of kidney failure defined as

- Renal component of SOFA-score (renal-SOFA) = 3 or higher at any time in the ICU after randomisation, but renal-SOFA < 3 before randomisation (baseline values)
- OR
- Patient requiring dialysis at any time after randomisation
- Development of kidney failure at any time in the ICU after randomisation defined as
 - Doubling of p-creatinine values = 2 x 'normal creatinine' (baseline variable #2)
 - Development of acidosis (pHa < 7,35) in the ICU after randomisation
 - As data from day 1 may reflect baseline characteristics, the analysis will be made with and without day 1.
 - Need of dialysis/haemofiltration at any time after randomisation
 - Need of ventilation at any time after randomisation
 - Days alive without dialysis/haemofiltration in 90 days after randomisation

We define a "period of dialysis" which runs from the day where dialysis is initiated till the day where the last dialysis is performed. The outcome measure is calculated as 90 days minus the "period of dialysis".
 - Days alive without ventilation in 90 days after randomisation

If the patient is on the ventilator at 8 am, the day is a ventilator-day. The outcome measure is calculated as 90 days minus the number of "ventilator days".
 - Hospital length of stay for survivors censored at 90 days after randomisation

Level of statistical significance for all analyses: P = 0.05

Missing Data

Kidney failure at time of randomisation: If the patient doesn't have kidney failure on day 1, this observation will be carried backward.

'Normal' creatinine < 100 mmol/l: If there is a measurement of creatinine < 100 mmol/l noted in the baseline form or day 1-form, the 'normal' creatinine will be considered < 100 mmol/l.

SOFA-score: There will be missing data for patients who

- die before day 5

OR

- are discharged from the ICU before day 5 and are still alive on day 5.

Initially, we will perform a complete case-analysis. Then a supplementary analysis where patients who die before day 5 get the maximum score (20 points), and where patients who are discharged from the ICU and alive on day 5 will get 0 points.

For patients, who are still in the ICU on day 5, last observation will be carried forward.

If the frequency of missing data after the above implemented "imputations" is $> 5\%$, we will perform an additional analysis using the multiple imputation method.