Statistical Analysis Plan for the Classic Trial

Outcome measures

The outcome measure “Amount of resuscitation fluid given during ICU stay” has been changed from a secondary outcome measure to a co-primary outcome measure, which differs from the Classic Trial protocol. The Classic Trial intervention period is entire ICU stay and we consider it appropriate to have an outcome measure addressing this as co-primary outcome measure. Multiplicity issues will be addressed (see Analyses section).

Co-primary outcome measures:

1.1. Amount of resuscitation fluid given in the first 5 days after randomisation

1.2. Amount of resuscitation fluid given during ICU stay

Secondary outcome measures:

2.1a Fluid balance at day 5 after randomisation

2.1b Fluid balance for entire ICU stay

2.2a Total fluid input at day 5 after randomisation

2.2b Total fluid input during ICU stay

2.3 Number of patients with major protocol violations (violations/length of ICU stay).

Major protocol violation defined as: One or more resuscitation fluid boluses given without fulfilment of one or more of the Classic-criteria in the conservative (Trigger-guided) group.

2.4 Accumulated serious adverse reactions (SARs) in ICU (SARs/length of ICU stay).

Exploratory outcome measures:

a. Death within 90 days following randomisation, Y/N

b.Time to death with censoring on the date at 90 days after the last patient had been randomized.

c. Days alive without use of mechanical ventilation (rate: 1-(days with event/days alive(1-90))

d. Days alive without use of RRT (rate: 1-(days with event/days alive (1-90))

e. Worsening of acute kidney injury according to KDIGO criteria during ICU stay as compared to baseline value, Y/N. During the monitoring of missing values it was noted that 10% of the habitual p-creatinine (pre-admission creatinine) values were missing. In these cases the MDRD equation

was used to calculate these values. During the monitoring of missing values it was noted that in 2% of the cases the p-creatinine value prior to randomisation was missing and additionally 2% did not have any p-creatinine measurements during their ICU stay. Because of the low number of missing data for worsening of KDIGO score (4%) this will be ignored in that a complete case analysis will be done.

f. Delta-creatinine (defined as highest p-creatinine during ICU stay minus most recent p-creatinine prior to randomisation). During the monitoring of missing values it was noted that in 2% of the cases the p-creatinine value prior to randomisation was missing and additionally 2% did not have any p-creatinine measurements during their ICU stay. Because of the low number of missing delta-creatinine values (4%) this will be ignored in that a complete case analysis will be done.

g. One or more ischemic events in ICU Yes/No.

Analyses

All statistical tests will be 2-tailed.

Multiplicity adjustment. Dealing with multiplicity, the parallel gate keeping method with truncation parameter lambda = 0 will be used to adjust the observed (raw) P values for primary and secondary outcomes (Dmitrienko A, Tamhane AC, Bretz F. Multiple testing problems in pharmaceutical statistics. Chapman & Hall/CRC biostatistics series (2010)).

By this approach the null hypotheses are divided into two families: F1 including null hypotheses related to the two co-primary outcomes and F2 including null hypotheses related to the secondary outcomes. The raw P values are then adjusted. If at least one of the adjusted P values in family 1 is less than the chosen level of significance the hypotheses in family 2 are also tested. If not the hypotheses in family 2 are all accepted without test. However, in all events all raw P values as well as the adjusted ones will be presented.

Lambda may be varied between 0 and 1. If the effect sizes of the primary outcomes (corresponding to the null hypotheses of F1) are uniformly high a lambda near 1 will help improve the overall power. On the other hand if the effect sizes are expected to vary across the endpoints, the overall power is likely to be maximized when lambda is small (Dmitrienko A, Tamhane AC, Bretz F. Multiple testing problems in pharmaceutical statistics. Chapman & Hall/CRC biostatistics series (2010)).

We expect a degree of correlation between the two co-primary outcome measures somewhat in between full correlation and no correlation, so a conventional adjustment of the significance level (0.05/2=0.025) may result in a too conservative adjustment. Thus, we have chosen to adjust the level of significance by a factor in between a full Bonferroni adjustment and no adjustment at all, that is 0.05/1.5=0.033. In the above procedure the raw P values and not the significance level are adjusted and usually α (the significance level) is chosen to be 0.05. In family 1 the smaller raw P value is adjusted by multiplying it with 2. Therefore, we implement the above adjustment solving 2*0.0.033 ≤ level of significance => level of significance = 0.066 to secure that a raw P value ≤0.033 for a co-primary outcome will imply that the corresponding null hypothesis will be rejected.

Revised power calculation

The multiplicity adjustments for the co-primary outcome measures infer changes in the power calculations. The revised power calculations are based on 150 included patients with α=0.033 and β=0.80:

Outcome measure 1.1: Power to show a 1.8 L (opposed to 1.7 L with α=0.05) difference in fluid volumes between the groups based on the mean volume of resuscitation fluid given within first 5 days observed in the 6S trial of 5.3 L (SD 3.7 L)
Outcome measure 1.2: Power to show a 4.1 L (opposed to 3.7 L with α=0.05) difference based on mean of 8.0 L (SD 8.1 L) total resuscitation fluid volume during ICU stay days in the 6S trial.
We regard the revised power to be sufficient to address the research question; thus, the sample size will not be changed.

1. Analysis of outcome measures

Two analyses will be done for the co-primary outcome measures:
(1) an analysis adjusted by the stratification variable (site) - primary analysis
(2) an analysis adjusted by the stratification variable and baseline covariates ((a) surgery during current hospitalisation but prior to randomisation Y/N, (b) Age, (c) more than 5 L of fluid (crystalloids, colloids and blood products combined) given in the 24 hours prior to randomisation Y/N, (d) highest dose of noradrenalin in the 24 hours prior to randomization, (e) estimated weight at randomisation
For exploratory outcome (b) we will perform both an unadjusted analysis (for log rank test) and an analysis adjusted by the stratification variable site.
The remaining outcome measures will only be analysed adjusted by the stratification variable (site).

Co-primary outcome, secondary outcomes 2.1, 2.2 and and exploratory outcome (f) will be analyzed using the general linear model.

The exploratory outcomes (a) and (e) will be analyzed using logistic regression.

The exploratory outcome (b) will be analyzed using Kaplan Meier survival plots and the log rank test. Adjusted analysis will be done using Cox regression model stratified by site.

Secondary outcome 2.3 will not be compared between intervention groups , because major protocol violations can only occur in the conservative (Trigger-guided) group.
Secondary outcomes, 2.4 and exploratory outcomes (c), (d) and (g) will be analyzed using the Poisson distribution with link = log and offset or the negative binomial distribution with link=log and offset as appropriate. As a sensitivity analysis the two groups will also be compared using a non-

parametric test (van Elteren test adjusted for site) and major differences in the results obtained by the two approaches will be discussed.

2. Sensitivity analyses

The primary outcomes will be analyzed using each of the two per-protocol populations.

Populations

Intention-to-treat population: All randomised patients except those who withdraw their consent for the use of data.

Per-protocol population:

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

1. One or more resuscitation fluid boluses given without fulfilment of one or more of the Classic-criteria in the Conservative (Trigger-guided) group.
   OR
2. Use of colloids (either Albumin or synthetic colloids) for resuscitation
   OR
3. Monitoring revealed that one or more in- or exclusion criteria were violated
   OR
4. Stopped/withdrawn patients

Subgroups:

1. Patients with more than 5 L of fluid (crystalloids, colloids and blood products combined) given in the 24 hours prior to randomisation

The results of the subgroup analysis will be presented if P of test of interaction between subgroup indicator and intervention group indicator for primary outcome is < 0.05. The P-value of the test of interaction will be presented regardless.

Missing Data

Missing primary outcome data:
We do not expect missing data on the co-primary outcome measures. Only complete case analysis will be made.

Missing secondary outcome data
We do not expect missing data on the secondary outcome measures 2.3 and 2.4. Only complete case analysis will be made.
Missing data on secondary outcomes 2.1 and 2.2: Since the predictors (centre indicator and intervention indicator) will not be missing only the outcome may be missing. In this case a complete case analysis will be unbiased since the cases with outcome missing carry no information. However, auxiliary variables (i.e. variables not included in the analytical model such as e.g. other outcomes) may be correlated with the outcome and their inclusion in the analysis will improve the efficiency. This possibility is best dealt with using a structural equation model for the regression analysis with direct maximum likelihood estimation and inclusion of the auxiliary variables (the SAS proc calis for continuous dependent variable may be used). However, the data may still be missing not at random. Therefore, a sensitivity analysis estimating the range of potential bias that may be caused by data missing not at random is done where the missing values in one group are replaced by the minimum value in the whole material and the missing values in the other group are replaced by the maximum value in the whole material and vice versa. The corresponding P values will be estimated. The standard error of each of the two estimates of the regression coefficient will be replaced by the corresponding standard error from the complete case analysis (or the direct ML analysis if auxiliary variables are used) if it is smaller than the former

Missing baseline data

Fluids given prior to randomization Yes/no
The previous approach for multiple imputation we feel had power problems and was too complicated. The simplest and safe approach is to conduct a monotone logistic multiple imputation of the missing baseline covariate. We have therefore changed the approach accordingly (see below)
Some patients may have missing data on fluids given prior to randomisation.

In this case it is a regression of each of the co-primary outcomes on center, and the above mentioned baseline covariates of which only fluids given prior to randomization Yes/no has missing values. Therefore, a multiple imputation of the missing baseline variable will be done using monotone logistic regression.