Original statistical analysis plan

Version 1.0, published in July 2019.

Conservative versus Liberal fluid therapy in Septic Shock (CLASSIC) trial – statistical analysis plan

The trial protocol and statistical analysis plan were published prior to conducting the interim analyses.[1] All data analyses in the primary publication will be conducted according to this statistical analysis plan except for the changes outlined below.

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Protocol registration numbers

ClinicalTrials.gov identifier: NCT03668236

Ethics committee number: H-18006255

EudraCT number: 2018-000404-42

Danish Medicines Agency number: 2018020596

Trial design

The CLASSIC trial is an investigator-initiated, pragmatic, international, parallel-grouped, centrally randomised, stratified, analyst-blinded trial with adequate allocation sequence generation and allocation concealment.

Trial conduct

The protocol has been prepared according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.[2] The trial will adhere to this protocol, the Helsinki Declaration in its latest version,[3] the international guidelines for good clinical practice (GCP)[4], and the national laws in the participating countries.

Randomisation

Eligible patients fulfilling all inclusion criteria and no exclusion criteria are randomised 1:1 using a centralised web-based system according to a computer-generated allocation sequence list, the stratification variables and varying block sizes. The allocation sequence list and block sizes are only known by the data manager at Copenhagen Trial Unit, and remain concealed from the investigators until the last patient has completed follow-up.

Blinding

The trial intervention is not blinded for investigators, clinical staff and patients, as blinding of IV fluid restriction versus standard care is not feasible. The statistician assessing all outcomes will be masked for the allocation. The data for 90-day and 1-year mortality will be collected from electronic patient records or central national registries in most participating countries. The remaining outcomes will be provided by local investigators, who are not blinded for the intervention, by entering data from patients' files. The management committee will write the preliminary abstract with the group allocation masked; this abstract will be published as a supplement to the primary trial report.[5,6]

Outcome measures

Primary outcome measure

The primary outcome measure is all-cause mortality at day 90 after randomisation.

Secondary outcome measures

We have 7 secondary outcome measures:

- Number of participants with one or more serious adverse events (SAEs) in the ICU defined as ischaemic events (cerebral, cardiac, intestinal or limb ischaemia) or a new episode of severe AKI (modified KDIGO3 [7])

- Number of participants with one or more serious adverse reactions (SARs) to IV crystalloids in the ICU
- Days alive at day 90 without life support (vasopressor / inotropic support, invasive mechanical ventilation or renal replacement therapy (RRT))
- Days alive and out of hospital until day 90
- All-cause mortality at 1 year after randomisation
- Health-related quality of life (HRQoL) 1 year after randomisation measured using the EuroQoL EQ-5D-5L scores [8]
- Cognitive function 1 year after randomisation as assessed by the telephone MINI-Montreal Cognitive Assessment (MINI-MoCA) score [9]

Detailed definitions of the outcome measures are available in the protocol.

Missing data

If less than 5% of data required for any specific analysis on primary or secondary outcomes are missing, a complete case analysis will be performed. If more than 5% are missing, and it is concluded that data are not 'missing completely at random' (MCAR criterion),[10,11] multiple imputation using chained equations will be performed by creating 25 input datasets under the assumption that the data are 'missing at random' (MAR criterion).[12,13]

In any multiple imputation, we will use all relevant outcomes and the stratification variables (site and metastatic or hematologic cancer), SMS-ICU [14] at baseline, site of infection at baseline, comorbidities at baseline (ischemic heart disease or heart failure, chronic hypertension or chronic RRT), use of corticosteroids at baseline, mechanical ventilation at baseline, highest p-creatinine 24 hours prior to randomisation, habitual p-creatinine, p-lactate at baseline, participant weight at baseline, and volume of IV fluids given prior to randomisation. Multiple imputation will be performed separately in the two intervention groups before pooling the full dataset, and the primary result of the trial will be based on these data. The unadjusted, non-imputed analysis will also be presented. If multiple imputation is used, we will also include a best-worst worst-best case scenario to assess the potential impact of any pattern of missingness including that data are 'missing not at random' (MNAR criterion). In the 'best-worst-case' scenario it is assumed that all participants lost to follow-up in the experimental group e.g. have survived; and that all patients with missing outcomes in the control group have not survived. Conversely, in the 'worst-best-case' scenario, it is assumed that all participants who were lost to follow up in the experimental group have had a harmful outcome; and that all those lost to follow-up in the control group have had a beneficial outcome. When continuous outcomes are used, a 'beneficial outcome' will be defined as the group mean plus two

standard deviations (SD) of the group mean or highest possible value whichever is smallest, and a 'harmful outcome' will be defined as the group mean minus two SD of the group mean or lowest possible value whichever is highest.

General analytical principles

The analyses will be done in the intention-to-treat (ITT) population defined as all randomised participants for whom there is consent for the use of data. The conclusion of the trial will be based on the ITT analysis.

The per-protocol population is defined as the ITT population except those having one or more major protocol violations.

Statistical analyses

Primary outcome

Four analyses will be performed for the primary outcome:

Primary analysis:

1. Logistic regression analysis adjusted for the stratification variables[15] (site and hematologic malignancy /metastatic cancer) in the ITT population. P-values will be two-tailed

Sensitivity analyses:

2. A two-tailed logistic regression analysis adjusted for the stratification variables, the SMS-ICU[14] focus of infection (other foci versus urinary tract infection)[14,16] and use of corticosteroids[17]
3. A two-tailed logistic regression analysis in the per-protocol population adjusted for the stratification variables
4. Two-tailed logistic regression analyses in the pre-planned subgroups adjusted for the stratification variables

We will report absolute and relative risk ratios with 95% CIs for the primary analysis of the primary outcome (analysis 1) (P-value <0.05), computed using glm-models with appropriate link functions and binomial error-distribution. Further, we will report the crude event rates in each group and a Kaplan-Meier survival curve for the crude data of the primary outcome.

Secondary outcomes

Dichotomous secondary outcomes will be analysed in the same way as the primary analysis for the primary outcome, i.e.:

- SAEs
  Two-tailed logistic regression adjusted for the stratification variables in the ITT population
- SARs
  Two-tailed logistic regression adjusted for the stratification variables in the ITT population
- 1-year mortality
  Two-tailed logistic regression adjusted for the stratification variables in the ITT population

A Kaplan-Meier survival curve will be reported for the crude data for secondary outcome 1-year mortality.

The remaining secondary outcomes are continuous measures which we expect to be skewed (non-normally distributed), because of inflation of specific values such as zero for 'days alive outside hospital' for all patients who die while in the ICU. The outcome measures will be analysed as follows:

- Days alive at day 90 without life support
  Generalised linear model or nonparametric test stratified for site in the ITT population
- Days alive and out of hospital at day 90
  Generalised linear model or nonparametric test stratified for site in the ITT population
- HRQoL 1-year after randomisation[8]
  Generalised linear model or nonparametric test stratified for site in the ITT population
- Cognitive function 1-year after randomisation[9]
  Generalised linear model or nonparametric test stratified for site in the ITT population

For the generalised linear model we will initially use Poisson distribution, alternatively negative binomial.[18] If the assumptions for Poisson distribution or negative binomial distribution are not met, data will be analysed using the nonparametric Van Elteren test adjusted for site, but no other variables.[19]

The following secondary outcome measures are composite; SAEs, SARs, days alive at day 90 without life support. We will report each component of these outcomes in an appendix to the primary publication without P-values due to the lack of adjustment for multiple comparisons.

We will report absolute and relative risk ratios with 99% CIs for dichotomous secondary outcomes. For continuous secondary outcomes we will report mean differences with 99% CIs if they are normally distributed and medians with 99% percentile-based bootstrapped CIs for non-normally distributed continuous secondary outcomes (P-value 0.01) due to the multiplicity of these. A detailed definition of the level of significance for the secondary outcomes is available in the supplement to the published statistical analysis plan. [1]

Sample size

Primary outcome

We plan to enrol 1554 (2 x 777) patients to be able to show a 15% relative risk-reduction (RRR) (7% absolute) in the restrictive group on the primary outcome from an estimated 45% 90-day mortality in the standard care group at type 1 and 2 error levels of 5% and 20% respectively, corresponding to a number needed to treat (NNT) of 14 or less. The anticipated relative risk reduction of mortality and the estimated mortality in the control group is based on data from previous RCTs and systematic reviews.[20–24]

Trial sequential analysis of existing trials (n=8) have shown that less than 15% of the required information size of 3956 patients to detect or reject a 15% RRR in all-cause mortality with lower versus higher fluid volumes has been reached.[25]

Secondary outcomes

We expect to have the following statistical power for the secondary outcomes based on 2 x 777 participants, a type 1 error level of 1% and a RRR of 15% in the fluid restriction group versus standard care group:

- 50% power for the number of participants with one or more SAEs (control event rate 25% [21,22])

- 10% power for the number of participants with one or more SARs (control event rate 5%[21,22])

- 80% power for the mortality at 1-year (control event rate 55%[21,22])

The estimates of the control event rates originate from data of previous septic shock trials.

We expect the following outcomes to be highly skewed (non-normally distribution): days alive without life support and out of hospital at day 90 and HRQoL and cognitive function at 1 year. As we lack sufficient knowledge on the details of the non-normal distribution no realistic power analysis can be provided. We therefore refrain from this in order to avoid creating a false impression of precision.

Pre-planned subgroup analyses

We plan to assess heterogeneity of intervention effects of the primary outcome in the following 5 subgroup analyses based on patient characteristics at baseline:

1. Respiratory support at randomisation (hypothesised increased effect of fluid restriction in patients receiving respiratory support)
2. Severe AKI defined as modified KDIGO2 or above[7] at randomisation (hypothesised increased effect of fluid restriction in patients with severe AKI) [7]

3. Severe metabolic failure at randomisation defined as plasma lactate level above 4 mmol/l (hypothesised increased effect of fluid restriction in patients with severe metabolic failure)
4. Participant weight at randomisation with higher weight defined as bodyweight (measured or estimated) ≥76 kg[20–22] versus lower weight as <76 kg (hypothesised increased effect of fluid restriction in patients with lower weight)
5. Patients who received ≥30ml/kg body weight IV fluids in the 24 hours prior to randomisation versus patients who received a lower volume (hypothesised increased effect of fluid restriction in patients with less fluids given 24 hours prior to randomisation)

For all subgroups a P-value <0.01 in the test of interaction will be considered statistically significant. Detailed definitions of the subgroup analyses are available in the protocol.

Trial profile

At trial completion, the flow of trial participants will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement.[26]

Data Monitoring and Safety Committee

A Data Monitoring and Safety Committee (DMSC) has been formed, consisting of independent ICU trialists/clinicians and a biostatistician who collectively have experience in the management of ICU patients and in the conduct, monitoring and analysis of RCTs. The charter for the DMSC is available in the protocol.

Interim analyses

We will perform 3 interim analyses:

1. Interim analysis when 10% of patients have completed 30-days follow-up
2. Interim analysis when 30% of patients have completed 30-days follow-up
3. Interim analysis when 50% of patients have completed 90-days follow-up

For the first two interim analyses the DMSC will evaluate data on:

- Fluid volumes and protocol violations

For the third interim analysis the DMSC will evaluate data on:

- Fluid volumes, protocol violations, 90-day mortality and rates of SAEs and SARs in the ICU

The DMSC will be provided with the following masked (as group 0 and 1) data from the coordinating centre:

- Number of patients randomised
- Number of patients randomised per intervention group
- Number of patients stratified per stratification variable per intervention group
- Number of events, according to the outcomes, in the two groups

Based on evaluation of these outcomes, the DMSC will decide if they want further data from the coordinating centre. The DMSC can, at any time during the trial, request the distribution of events, including outcome measures and SARs according to intervention groups. Further, the DMSC can request unblinding of the interventions. Additionally, the DMSC will yearly be informed about SARs in the two groups of the trial.

The interim analyses will be performed by an independent statistician. The DMSC may recommend pausing or stopping the trial if a group-difference in the primary outcome measure, SARs or SUSARs are found in the interim analyses with statistical significance levels adjusted according to the LanDeMets group sequential monitoring boundaries based on O'Brien Fleming alfa-spending function.[27] If the recommendation is to stop the trial, the DSMC will discuss and recommend on whether the final decision to stop the trial will be made after the analysis of all participants included at the time (including participants randomized after participant number 777) and whether a moratorium shall take place (setting the trial at hold) in the further inclusion of participants during these extra analyses. If further analyses of the participants included after 777 participants is recommended, the rules for finally recommending stopping of the trial should obey the LanDeMets stopping boundary.

Furthermore, the DMSC can recommend pausing or stopping the trial if continued conduct of the trial clearly compromises participant safety. The Management Committee will make the final decision regarding the continuing, pausing or stopping of the trial. However, stopping for futility to show an intervention effect of 15% RRR or RRI will not occur, as intervention effects <15% RRR or RRI in all-cause mortality may be clinically relevant.

Data sharing statement

The final de-identified dataset used for analysis will be made publicly available 9 months after the publication of the outcome data according to the recent ICMJE recommendations.[28] All trial-related documents are available from www.cric.nu/CLASSIC

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Appendix to the CLASSIC trial statistical analysis plan, version 1.0, published in July 2019.

1. Statistical analyses: significance level for the secondary outcomes

We applied the methods as suggested by Jakobsen et al. [1] As a full Bonferoni correction for multiple comparisons may be too conservative, a pragmatic approach is used dividing the pre-specified P-value threshold with the value halfway between 1 (no adjustment) and the number of primary outcome comparisons (Bonferroni adjustment).

As we have 7 secondary outcomes, the threshold for the P-value for these outcomes was calculated as follows:

0.05/ ((7+1)/2)= 0.0125

A full Bonferoni correction would equal a P-value as follows:

0.05/7 = 0.0071

We then chose the significance level of P 0.01 which is between the two corrections.

2. Definitions of pre-planned subgroup analyses

Heterogeneity of the intervention effects on the primary outcome will be analysed in the following subgroups based on baseline characteristics

Subgroup	**Definition**	**Hypothesised direction**	**Statistical test**
Participants who receive respiratory support	Respiratory support within the last 24 hours prior to randomisation(yes/no) Definition: Invasive or non-invasive mechanical ventilation including continuous mask CPAP or CPAP via tracheostomy within the last 24 hours prior to randomisation. Intermittent CPAP and high flow nasal cannula oxygen therapy are NOT considered respiratory support	Larger effect of fluid restriction in patients who receive respiratory support	Test of interaction in the adjusted analysis; P-value 0.01
Participants with severe acute kidney injury	Modified KDIGO stage 2 or above [3] (yes/no) Definition: Modified KDIGO because we don't have urine output available at randomisation. Stage 2: p-creatinine 2.0-2.9*baseline Stage 3: p-creatinine 3.0*baseline or increase in to ≥354	Larger effect of fluid restriction in acute kidney injury	Test of interaction in the adjusted analysis; P-value 0.01

	mmol/l or initiation of RRT		
Participants with severe metabolic failure	Plasma lactate level >4 mmol/l (yes/no)	Larger effect of fluid restriction in severe metabolic failure	Test of interaction in the adjusted analysis; P-value 0.01
Participant weight	Bodyweight (measured or estimated) ≥76 kg versus lower weight as <76 kg [10–12]	Larger effect of fluid restriction with lower weight	Test of interaction in the adjusted analysis; P-value 0.01
IV fluid volume given 24 hours prior to randomisation	Patients who received ≥30 ml/kg body weight IV fluids prior to randomisation versus patients who received a lower volume Definition: Defined as all crystalloids (any saline, NaHCO3-, Ringer's and Plasmalyte™ solutions), colloids (albumin 4, 5 or 20%, gelatine, hydroxyethyl starch and dextran solutions) and blood products (units of red cells, plasma or platelets) the participant has received within the last 24-hours independent of location (in- or pre-hospital) including fluids with IV medication and IV	Larger effect of fluid restriction with less fluid given	Test of interaction in the adjusted analysis; P-value 0.01

	nutrition. Intraosseous fluid will be counted as IV.		

3. References

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Summary of changes to statistical analysis plan

Changes during conduct of the final statistical analyses in March 2022:

- The relative risks with 95% CIs of the primary outcome were computed by G-computation based on the logistic regression and not generalized linear models with log and identity links as the latter models did not converge.
- We specified that major protocol violations included both discontinuation or withdrawal from the trial protocol by patient, surrogate, clinician, or investigator AND violation of the IV fluid protocol. Patients having one of these violations were not included in the per-protocol population.
- We specified the planned subgroup of mechanical ventilation to include both invasive and non-invasive mechanical ventilation including continuous CPAP as this was the variable which had been collected in the baseline form throughout the trial period.