Conservative vs liberal fluid therapy in septic shock (CLASSIC) trial—Protocol and statistical analysis plan

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Published in:
Acta Anaesthesiologica Scandinavica

DOI (link to publication from Publisher):
10.1111/aas.13434

Publication date:
2019

Document Version
Accepted author manuscript, peer reviewed version

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Article type : Clinical investigation

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

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Conflict of interest: The Department of Intensive Care, Rigshospitalet receives support for research from Ferring Pharmaceuticals.

Funding: The CLASSIC trial is funded by The Novo Nordisk Foundation (NNF17OC0028608) and Sofus Friis' foundation. The funding parties have no influence on the trial design or conduction of the trial.

ABSTRACT

Introduction

Intravenous (IV) fluid is a key intervention in the management of septic shock. The benefits and harms of lower versus higher fluid volumes are unknown and clinical equipoise exists. We describe the protocol and detailed statistical analysis plan for the Conservative versus Liberal Approach to fluid therapy of Septic Shock in the Intensive Care (CLASSIC) trial. The aim of the CLASSIC trial is to assess benefits and harms of IV fluid restriction versus standard care in adult intensive care unit (ICU) patients with septic shock.

Methods

CLASSIC trial is an investigator-initiated, international, randomised, stratified, and analyst-blinded trial. We will allocate 1554 adult patients with septic shock, who are planned to be or are admitted to an ICU, to IV fluid restriction versus standard care. The primary outcome is mortality at day 90. Secondary outcomes are serious adverse events, serious adverse reactions, days alive at day 90 without life support, days alive and out of hospital at day 90, and mortality, health-related quality of life, and cognitive function at 1 year. We will conduct the statistical analyses according to a pre-defined statistical analysis plan, including three interim analyses. For the primary analysis we will use logistic regression adjusted for the stratification variables comparing the two interventions in the intention-to-treat population.

Discussion

The CLASSIC trial results will provide important evidence to guide clinicians' choice regarding IV fluid therapy in adults with septic shock.

INTRODUCTION

Intravenous (IV) fluid therapy is a mainstay intervention in the treatment of sepsis. However, international guidelines lack firm evidence for the optimal volume.[1] Patients with septic shock in the intensive care unit (ICU) may receive IV fluids according to several indications: [2,3] to improve hemodynamics, replace fluid loss, correct electrolyte imbalance or dehydration, as maintenance fluid, as a carrier for medication, or as nutrition.[4–6] Administration of IV fluids in the ICU may lead to over-hydration, which has been associated with adverse outcomes,[7–9] and data from randomised clinical trials (RCTs) both in a pre-clinical[10] and a clinical setting[11–15] have raised concerns about harms from higher IV fluid volumes.

In a landmark trial in African children with infection and circulatory impairment, increased mortality was observed in children who received fluid boluses as compared to those who did not.[12] Other African trials in adult patients with infection and hypotension have shown higher mortality in patients who received higher IV fluid volumes; one trial was stopped early after all patients with hypoxemic respiratory failure died,[14] another trial, in which patients with severe respiratory failure were excluded, showed higher mortality in patients who received higher IV fluid volumes as part of a complex protocol.[15] As most patients with septic shock in Europe are cared for in ICUs, extrapolating results from trials conducted in resource-limited settings is challenging.

In the CLASSIC pilot trial,[11] a protocol aiming at restricting IV resuscitation fluid volumes compared with standard care in adult ICU patients with septic shock was feasible and resulted in lower resuscitation fluid volumes given in the first 5 days and during the entire ICU stay. The trial showed no statistically significant difference in mortality, serious adverse reactions, ischemia, total fluid input, or fluid balances. Fewer patients had worsening of acute kidney injury (AKI) among those who received less fluid. However, this was an exploratory outcome measure.[11]

In a systematic review of RCTs aiming at separation in IV fluid volumes in adult patients with sepsis, we have currently identified 8 trials including a total of 524 patients; all trials were judged to have overall high risk of bias. We found very low quantity and certainty of the evidence for lower versus higher fluid volumes across all patient-important outcomes (Meyhoff 2019, in preparation)[16]

Altogether, there is a need for high-quality data from RCTs to inform the decision on fluid volume strategies in septic shock.

The aim of the CLASSIC trial is to assess the effects of IV fluid restriction versus standard care on patient-important outcome measures in adult ICU patients with septic shock. We hypothesise that fluid restriction will improve patient-important outcomes. In this manuscript, we outline the rationale, methods and the detailed statistical analysis plan.

METHODS

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.[17] The trial will adhere to this protocol, the Helsinki Declaration in its latest version,[18] the international guidelines for good clinical practice (GCP)[19], 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.[20,21]

Inclusion criteria

Patients must fulfil all the inclusion criteria;

- Age ≥18 years
- Admitted or planned admitted to the ICU regardless of trial participation
- Septic shock defined according to the Sepsis-3 criteria:[22]
    - Suspected or confirmed site of infection or positive blood culture AND
    - On-going infusion of vasopressor/inotrope agent to maintain a mean arterial blood pressure of 65 mmHg or above AND

    - Lactate of 2 mmol/L or above in any plasma sample performed within the last 3-hours
- At least 1 L of IV fluid administered (all crystalloids, colloids or blood products including that given with medication and nutrition) in the last 24 hours prior to screening

A detailed description of the inclusion criteria is available in Supplementary Appendix 1.

Exclusion criteria

Patients who fulfil all inclusion criteria and one or more of the exclusion criteria below will be excluded;

- Septic shock for more than 12 hours at the time of screening
- Life-threatening bleeding
- Acute burn injury of more than 10% of the body surface area
- Known pregnancy
- Consent not obtainable as per the model approved for the specific site

A detailed description of the exclusion criteria is available in Supplementary Appendix 2.

Trial interventions

The CLASSIC intervention period is the time spent in ICU from randomisation to a maximum of 90 days. If a patient is discharged and readmitted to a CLASSIC ICU within the 90-day period, the allocated fluid intervention continues.

IV fluid restriction group

No IV fluids should be given unless one of the below extenuating circumstances occurs; in these cases, IV fluid may be given in measured amounts:

1. In case of severe hypoperfusion or severe circulatory impairment defined by either:
    - Lactate 4 mmol/L or above
      OR
    - Mean arterial blood pressure below 50 mmHg (with or without vasopressor/inotrope) **OR**
    - Mottling beyond the kneecap (mottling score >2, Supplementary Appendix 3)
      OR
    - Urinary output less 0.1mL/kg bodyweight/h, but only in the first 2 hours after randomisation

A bolus of 250-500 ml of IV crystalloid solution *may* be given followed by re-evaluation. These criteria identify patients at increased risk of death,[23–25] and were found feasible and not associated with harm in the CLASSIC pilot trial.[11]

2. In case of overt fluid losses (e.g. vomiting, large aspirates, diarrhoea, drain losses, bleeding or ascites tap). IV fluid *may* be given to correct for the loss, but not above the volume lost

3. In case the oral/enteral route for water or electrolyte solutions is contraindicated or has failed as judged by the clinical team, IV fluids *may* be given to:
    - Correct dehydration or electrolyte imbalances
    - Ensure a total fluid input of 1L per 24 hours (fluids with medication and nutrition count as input)

IV fluids may be given as carrier for medication, but the volume should be reduced to the lowest possible volume for the given medication. Oral/enteral fluids are not restricted in the IV fluid restriction group.

Standard care group

There will be no upper limit for the use of IV or oral/enteral fluids. In particular:

- IV fluids *should* be given in the case of hypoperfusion or circulatory impairment and *should* be continued as long as hemodynamic variables improve including static or dynamic variable(s) as chosen by the clinicians. These criteria are based on the Surviving Sepsis Campaign guideline[1]
- IV fluids *should* be given as maintenance if the ICU has a protocol recommending maintenance fluid
- IV fluids *should* be given to substitute expected or observed loss, dehydration or electrolyte imbalances

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 [26])
- Number of participants with one or more serious adverse reactions (SARs) to IV crystalloids in the ICU (Supplementary Appendix 5)
- 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 [27]
- Cognitive function 1 year after randomisation as assessed by the telephone MINI-Montreal Cognitive Assessment (MINI-MoCA) score [28]

Detailed definitions of the outcome measures are available in Supplementary Appendix 4.

Registered variables

Baseline variables

1. Sex
2. Age
3. Date of admission to hospital
4. Date and time of the first ICU admission during the current hospitalisation
5. From where the participant was admitted to ICU
6. Focus of infection (pulmonary, gastrointestinal, urinary tract, skin or soft tissue or other infectious focus documented or suspected including meningitis, endocarditis, osteomyelitis, arthritis and bacteraemia)
7. Co-morbidities prior to ICU admission (active hematological malignancy, metastatic cancer, ischemic heart disease or heart failure, chronic hypertension or chronic RRT)
8. Blood values, interventions and vital parameters including participant weight, highest plasma lactate within 3 hours prior to randomisation, highest dose of noradrenaline within 3 hours prior to randomisation, volume of IV fluid 24 hours prior to randomisation, use of systemic corticosteroids 24 hours prior to randomisation, highest plasma creatinine value within 24 hours prior to randomisation, use of acute

RRT 3 days prior to randomisation and habitual plasma creatinine value prior to current hospitalisation

9. Values for the Simplified Mortality Score in ICU (SMS-ICU),[29] which is based on 7 variables obtained within the 24 hours prior to randomisation (age, lowest systolic blood pressure, acute surgical admission, hematologic malignancy or metastatic cancer, and use of vasopressors/inotropes, respiratory support (invasive or non-invasive mechanical ventilation) and RRT)

Daily during ICU admission

1. Fluid input and output cumulated from the 24-hour ICU charts
   - Total volume and specific type of IV isotonic crystalloids
   - Total volume of other IV fluids: e.g. <10% glucose
   - Total volume of albumin
   - Total volume of fluids with medications: both parenteral and enteral
   - Total volume of fluids with enteral and parenteral nutrition
   - Total volume of non-nutritional enteral/oral fluids
   - Total volume of blood products
   - Urinary output on this day
   - Any fluid volume removed during RRT
   - Total volume of other losses on this day including drainage, aspirates, stools and bleeding
2. Major protocol violation on this day:
   - Restrictive group: IV fluids given without one of the extenuating circumstances on this day
   - Standard care group: the violations (no IV fluid given) will be assessed from all day form registrations regarding fluid input at the end of the trial
3. Infusion of vasopressor or inotrope on this day
4. Use of systemic corticosteroids on this day
5. Use of invasive mechanical ventilation on this day
6. Use of RRT on this day
7. Plasma concentration of creatinine on this day
8. Serious adverse events (SAEs) (at least one episode of either the following):
   - Ischemic events defined as either
     - Cerebral ischemia
     - Acute myocardial ischemia
     - Intestinal ischemia
     - Limb ischemia

- A new episode of severe AKI (defined as modified KDIGO3,[26] Supplementary Appendix 4)

9. Serious adverse reactions:
   - General tonic-clonic seizures
   - Anaphylactic reactions
   - Central pontine myelinolysis
   - Severe hypernatremia defined as p-Na >159 mmol/L
   - Severe hyperchloraemic acidosis defined as pH <7.15 AND p-chloride >115 mmol/L
   - Severe metabolic alkalosis defined as pH >7.59 AND SBE >9 mmol/L

Follow-up 90 days after randomisation

1. Death (y/n, if yes date of death)
2. Date of discharge from hospital
3. Additional hospital admissions

Follow-up 1 year after randomisation

1. Death (y/n, if yes date of death)
2. EQ-5D-5L and EQ-VAS score
3. Telephone MoCA score

Detailed definitions of the registered variables are available in Supplementary Appendix 6.

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),[30,31] 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).[32,33]

In any multiple imputation, we will use all relevant outcomes and the stratification variables (site and metastatic or hematologic cancer), SMS-ICU[29] 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[34] (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[29] focus of infection (other foci versus urinary tract infection)[29,35] and use of corticosteroids[36]
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[27]
  Generalised linear model or nonparametric test stratified for site in the ITT population
- Cognitive function 1-year after randomisation[28]
  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.[38] 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.[39]

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. Definition of the level of significance for the secondary outcomes is available in Supplementary Appendix 7.

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.[11,40–43]

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. (Meyhoff 2019, in preparation).[16]

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% [40,41])

- 10% power for the number of participants with one or more SARs (control event rate 5%[40,41])

- 80% power for the mortality at 1-year (control event rate 55%[40,41])

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[26] at randomisation (hypothesised increased effect of fluid restriction in patients with severe AKI)[26]
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[11,40,41] 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)
6.

For all subgroups a P-value <0.01 in the test of interaction will be considered statistically significant. Detailed definitions of the subgroups analysis is provided in Supplementary Appendix 8.

Trial profile

At trial completion, the flow of trial participants will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement.[44]

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 from Supplementary Appendix 9.

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.[45] 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.

DISCUSSION

The optimal strategy for IV fluid therapy in adults with septic shock is largely unknown, and existing data on lower versus higher fluid volumes is of low/very low quality.
Together with existing data, and data from other on-going RCTs,[46,47] the CLASSIC trial will provide important knowledge on the use of lower versus higher IV fluid volumes in adult ICU patients with septic shock.

Strengths

Prior to initiation of the CLASSIC trial, we have assessed current evidence in a systematic review[16] and the feasibility of the fluid protocol in an international pilot RCT.[11]
The CLASSIC trial is a large international trial designed to provide data on the effect of fluid volumes on patient-important outcomes with the lowest possible risk of bias. The trial is monitored according to the standards of GCP.[19] The trial design is pragmatic with all other treatments than fluid therapy following routine practice to increase external validity. Prior to data analysis, we will publish this protocol and statistical analysis plan paper, including detailed power estimations. Finally, we report several secondary outcomes as composite outcomes to increase the power. As we will include 1554 patients with septic shock, we expect that our trial together with other on-going RCTs[46,47] will provide data to increase the acquired information and getting closer to the required information size of 3956 patients estimated so far by trial sequential analysis. (Meyhoff 2019, in preparation)[16]

Limitations

The CLASSIC trial intervention is not masked for investigators, clinicians and patients, as blinding of different fluid strategies is not feasible. This increases the risk of bias,[48,49] in particularly it may affect the clinicians behaviour regarding fluid administration over the course of the trial. Current practice of IV fluid therapy may already be changing without firm evidence. Therefore, we will conduct two early interim analyses assessing IV fluid volumes in the two groups, enabling the Management Committee to act to ensure separation in fluid volumes between the two groups during the trial. Also, our primary outcome is 90-day mortality, which may be less likely to be affected by lack of blinding in RCTs,[50] although conflicting data exist.[51]

Our trial participants may be subjected to protocol violations, expected to occur more frequently in the restrictive group. In general, protocol violations may be more frequent in trials of complex interventions in ICU.[11,40,41,52] In the CLASSIC pilot trial, a difference in resuscitation fluid volumes was observed despite protocol violations.[11] Further, there was no indication of safety concerns in that trial, why we will encourage trial site staff to administer IV fluids in accordance with the protocol.

In conclusion, the CLASSIC trial is a large European trial assessing the effects of IV fluid restriction versus standard care on patient-important outcome measures in adult ICU patients with septic shock. The trial results will provide important evidence to guide intravenous fluid therapy in this critically ill population.

Ethical considerations and consent to participate

The CLASSIC trial is registered at the European Clinical Trials Database (2018-000404-42) and www.clinicaltrials.gov (NCT03668236), is approved by the Danish Medicines Agency (2018020596), the Danish National Committee on Health Research Ethics (H-18006255), and the Danish Data Protection Agency (VD-2018-392).

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.[53] All trial-related documents are available from www.cric.nu/CLASSIC

Dissemination

After completion of the CLASSIC trial, all trial results will be submitted to a peer-reviewed medical journal irrespective of the direction of the results. Further, the trial results will be published at www.cric.nu. We will adhere to the CONSORT statement including the accountability of all patients screened.[44]

Status

The Trial was initiated on November 27th 2018 and is expected to be completed within 2 years.

Acknowledgements

We would like to thank the clinical staff at all intensive care units who participate or will participate in the CLASSIC trial and all patients and relatives who have provided consent for the trial.

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