BMJ Open

Protocolised reduction of non-resuscitation fluids versus usual care in patients with septic shock (REDUSE): a protocol for a multicentre feasibility trial

Anja Lindén ,[1] Jane Fisher ,[1] Gisela Lilja,[2] Markus Harboe Olsen,[3,4] Fredrik Sjövall ,[5] Mårten Jungner,[6] Martin Spångfors ,[7] Line Samuelsson,[8] Jonatan Oras,[9] Adam Linder,[2] Johan Unden,[10] T Kander ,[11] Miklós Lipcsey,[12,13] Niklas Nielsen,[1] Janus C Jakobsen,[3,14] Peter Bentzer[1]

To cite: Lindén A, Fisher J, Lilja G, *et al*. Protocolised reduction of non-resuscitation fluids versus usual care in patients with septic shock (REDUSE): a protocol for a multicentre feasibility trial. *BMJ Open* 2023;**13**:e065392. doi:10.1136/bmjopen-2022-065392

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-065392).

Received 06 June 2022
Accepted 12 February 2023

For numbered affiliations see end of article.

Correspondence to
Dr Anja Lindén;
anja.linden@gmail.com

ABSTRACT

Introduction Administration of large volumes of fluids is associated with poor outcome in septic shock. Recent data suggest that non-resuscitation fluids are the major source of fluids in the intensive care unit (ICU) patients suffering from septic shock. The present trial is designed to test the hypothesis that a protocol targeting this source of fluids can reduce fluid administration compared with usual care.

Methods and analysis The design will be a multicentre, randomised, feasibility trial. Adult patients admitted to ICUs with septic shock will be randomised within 12 hours of admission to receive non-resuscitation fluids either according to a restrictive protocol or to receive usual care. The healthcare providers involved in the care of participants will not be blinded. The participants, outcome assessors at the 6-month follow-up and statisticians will be blinded. Primary outcome will be litres of fluids administered within 3 days of randomisation. Secondary outcomes will be proportion of randomised participants with outcome data on all-cause mortality; days alive and free of mechanical ventilation within 90 days of inclusion; any acute kidney injury and ischaemic events in the ICU (cerebral, cardiac, intestinal or limb ischaemia); proportion of surviving randomised patients who were assessed by European Quality of Life 5-Dimensions 5-Level questionnaire and Montreal Cognitive Assessment; proportion of all eligible patients who were randomised and proportion of participants experiencing at least one protocol violation.

Ethics and dissemination Ethics approval has been obtained in Sweden. Results of the primary and secondary outcomes will be submitted for publication in a peer-reviewed journal.

Trial registration number NCT05249088.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The REDUSE feasibility trial is a multicentre randomised trial designed to evaluate the efficacy of a protocolised reduction in administration of non-resuscitation fluids versus usual care.
⇒ The trial is powered to detect a 2 L reduction in volume of fluid administered within the first 3 days of randomisation.
⇒ Because of the complexity of the intervention, healthcare providers will not be blinded but participants, outcome assessors and statisticians will be blinded.
⇒ The strict protocolisation of the intervention will ensure standardised treatment in the intervention group.
⇒ A potential limitation is that usual care may differ from site to site.

INTRODUCTION

Septic shock is a subgroup of sepsis with particularly severe circulatory and metabolic abnormalities and a 90-day mortality of 40%–50%.[1–5] Administration of fluids is an essential component of the care of patients suffering from septic shock. Fluids are administered for different reasons. Resuscitation fluids are administered intravenously to ensure adequate tissue perfusion and oxygenation whereas non-resuscitation fluids are administered intravenously and enterally as vehicles for medications and nutrition, to correct electrolyte disturbances, to replace pathophysiological losses and to ensure adequate hydration (maintenance fluids). A wide variety of different fluids can be given as non-resuscitation fluids, including crystalloids, glucose solutions and enteral water. More than 50% of patients with septic shock receive a total of 4 L or more during the first day in the intensive care unit (ICU)[6] and non-randomised studies have indicated that fluids in large volumes might have detrimental adverse effects.[7–10] These observations have

inspired trials investigating if restrictive fluid administration improves outcomes in patients with septic shock.

Previous trials

In a recent systematic review with meta-analysis, nine trials comparing a restrictive approach of fluid administration with usual care in adult patients with sepsis and/or septic shock were identified.[11] Eight of these trials assessed interventions with the objective to reduce administration of only resuscitation fluids and one trial assessed interventions with the objective to reduce both resuscitation fluids and non-resuscitation fluids.[12] A meta-analysis of the four trials, where a significant separation in fluid volumes was shown, demonstrated no difference in mortality but the point estimate favoured the restrictive approach (Risk ratio: 0.81 (95% CI: 0.60 to 1.10, I^2=0%)). Furthermore, trial sequential analysis showed that there was insufficient information to confirm or reject a relative risk reduction of 15% and all of the identified trials had a high risk of bias and the certainty of the evidence was low.[11]

We have identified three trials that were completed after the meta-analysis by Meyhoff *et al*, comparing a restrictive approach for fluid therapy to usual care in septic shock.[11 13–15] The first trial assessed a protocol using fluid responsiveness to guide administration of resuscitation fluids in 124 patients with septic shock. Separation in fluid volumes was achieved but no effect on mortality was detected.[13] The second is the recently published CLASSIC trial which assessed the effects of restrictive administration of resuscitation fluids in 1554 patients with septic shock. The intervention resulted in a reduction in administration of fluids of about 2 L and no effect on mortality was found.[14] The third is the newly published CLOVERS trial, in which a restrictive fluid strategy was assessed in 1563 patients with sepsis-induced hypotension. The results were similar to CLASSIC with a fluid reduction in the intervention group of 2.1 L and no effect on mortality.[15]

Trial rationale

In septic shock, similar volumes of resuscitation and non-resuscitation fluids are administered the first day in the ICU whereas non-resuscitation fluids dominate thereafter.[1 16] Modelling based on a recent survey of administration of non-resuscitation fluids indicates that the volume of non-resuscitation fluids may be reduced by about 3 L in the first days of admission in patients with septic shock.[16] Such a reduction might have an impact on patient important outcomes.[9] Moreover, the magnitude of this reduction in fluid volume is at least 1 L larger than the most effective protocols targeting restriction of resuscitation fluids to date.[14 15] No trial has evaluated a protocolised restrictive administration of non-resuscitation fluids in patients with septic shock. The balance between benefit and harm when reducing resuscitation fluids may be different than the balance when reducing non-resuscitation fluids. A randomised clinical trial assessing the effects of a protocolised restrictive administration of non-resuscitation fluids in patients with septic shock is therefore important regardless of the results in trials comparing restrictive and less restrictive approaches to administration of either resuscitation fluids alone or both resuscitation fluids and non-resuscitation fluids.

Objective

The objective of this trial is to assess the feasibility and efficacy of a protocol purposed to compare a protocolised reduction in administration of non-resuscitation fluids to usual care in patients with septic shock.

METHODS AND ANALYSIS

Study setting

This will be an investigator-initiated, non-commercial, multicentre, parallel-group, randomised, controlled trial including patients in ICUs both at university hospitals and non-university hospitals in Sweden. Level of care is equal across participating sites. For a complete study protocol and study sites, please see online supplemental files 1 and 2, as well as clinicaltrials.gov.

Eligibility

Patients will be eligible for inclusion if they fulfil all the inclusion criteria and none of the exclusion criteria.

Inclusion criteria

- Adult (≥18 years of age).
- Septic shock according to Sepsis-3 criteria while in the ICU.[17]
- Ongoing vasopressor treatment.
- Inclusion within 12 hours of ICU admission.

Exclusion criteria

- Confirmed or suspected pregnancy.

Participants readmitted to the ICU during the same hospital stay will be allocated to the same intervention arm regardless of diagnosis. Participants readmitted to the ICU after hospital discharge will not be eligible for re-inclusion.

Intervention

Non-resuscitation fluids will be defined as fluids other than colloids, blood products and crystalloids administered to correct haemodynamic impairment as noted in patient charts. Type of maintenance fluids will be given according to local routine at each centre with the objective to use similar types of fluids in both groups. In participants who require surgery, administration of all fluids will be at the discretion of the anaesthetist.

The intervention group

- Maintenance fluids will be discontinued in participants who are positive in cumulative fluid balance and are judged not to be dehydrated by the treating physician.
- Intravenous fluid and enteral water will be given as needed to correct electrolyte disturbances.

- Enteral nutrition will have an energy density of at least 2 kcal/mL and will be administered according to local practice.
- Glucose may be used at a maximum dose of 1 g/kg/day, using a concentration of 20% or greater starting at 72 hours after inclusion as nutrition if enteral feeding is not tolerated. Glucose at this (or lower) dose may be started earlier in participants with insulin-dependent diabetes if enteral feeding is not tolerated and if local protocol mandates this.
- Parenteral nutrition will be administered according to local protocol.
- Intravenous medications will be concentrated according to a trial-specific protocol (online supplemental appendix B).
- Participants who are neutral or negative in cumulative fluid balance will receive fluids in a dose that ensures that the total dose of fluids covers the daily need of water (1 mL/kg/hour) and ongoing losses.

The usual care group

- Participants will receive non-resuscitation fluids according to local routines.
- Maintenance fluids (crystalloids and/or glucose solutions and/or enteral water) will be given at a dose of 1 mL/kg/hour unless local protocol states otherwise.
- Glucose will be used at a maximal concentration of 10% for maintenance/nutrition unless local protocol states otherwise.
- Medications will be concentrated according to local protocol.
- Enteral nutrition will be administered according to local routines.

Site investigators will establish what constitutes usual care in their unit prior to start of the trial.

In both groups, resuscitation fluids will be administered according to the surviving sepsis campaign guidelines during the salvage and optimisation phases of resuscitation and according to local protocol during the stabilisation and de-escalation phases.[18 19] Type of resuscitation fluids will be given according to local routine at each centre with the objective to use similar types of fluids in both groups. Sepsis-specific treatment other than fluids, such as antibiotics and vasopressors, will be administered according to the surviving sepsis campaign guidelines in both groups. All other care of participants will be according to local routines.

Outcomes

Feasibility outcomes

Primary feasibility outcome

- Litres of fluids administered within 3 days (day 0–3) of randomisation.

Secondary feasibility outcomes

- Proportion of participants with clinical outcome data for all-cause mortality, days alive and free of mechanical ventilation, acute kidney injury and ischaemic events in the ICU (cerebral, cardiac, intestinal or limb ischaemia) within 90 days of inclusion.
- Proportion of surviving participants assessed by the European Quality of Life 5-Dimensions 5-Levels questionnaire (EQ-5D-5L) and the Montreal Cognitive Assessment (MoCA) at 6 months after inclusion.
- Proportion of eligible patients who were randomised and consented.
- Proportion of participants experiencing at least one protocol violation.

Exploratory clinical outcomes

We will explore the clinical outcomes which we plan to assess in a future larger randomised trial.

Primary exploratory clinical outcomes

- All-cause mortality at 90 days after inclusion.
- One or more complications in the ICU (cerebral, cardiac, intestinal or limb ischaemia or any acute kidney injury) within 90 days of inclusion.
- Days alive and free of mechanical ventilation within 90 days of inclusion.
- Cognitive function measured using the MoCA at 6 months after inclusion.[20 21]
- Health-Related Quality of Life using the EQ-5D-5L at 6 months after inclusion.[22]

Secondary exploratory clinical outcomes

- Total volume of non-resuscitation fluids at day 3 and 5 after inclusion.
- Any acute kidney injury according to Kidney Disease Improving Global Outcomes criteria in the ICU and days alive and free of renal replacement therapy within 90 days of inclusion.[23]
- Gastrointestinal function (days alive with full enteral nutrition within 90 days of inclusion).
- Total volume of resuscitation fluid at day 3 and 5 after inclusion (crystalloids given to correct haemodynamic impairment, colloids and blood products).
- Cumulative fluid balance at day 3 and 5 after inclusion (excluding evaporation).
- Daily dose and type of diuretics during the first 5 days of inclusion.
- Haemodynamic stability during the first 5 days of inclusion (daily highest dose of norepinephrine, daily lactate and cardiovascular sequential organ failure assessment score).
- Functional outcome by the Glasgow Outcome Scale Extended (GOSE) at 6 months after inclusion.[24 25]

Harms

Patients with septic shock in the ICU experience a host of complications, of which only a small number are likely related to the intervention. In addition to the patient-centred complications, we will assess primary exploratory clinical outcomes, the following complications will be reported:

- Hypoglycaemia (≤3.9 mmol/L).

- Electrolyte and metabolic disturbances (hypernatremia >159 mmol/L, hyperchloremic acidosis (pH <7.15 and plasma Cl^- >115), metabolic alkalosis (pH >7.59 and standard base-excess >9)).
- Suspected unexpected serious adverse complications (SUSAC, an adverse event not reasonably explained by other factors than the intervention which may cause death or be life threatening, prolong hospitalisation or may result in significant disability/incapacity).

All complications observed by the investigator or other healthcare providers will be recorded in the electronic case report form (eCRF). The circumstances of a SUSAC will be described and the causality between the intervention and the complication will be assessed by the site investigator. The site investigator is required to follow each participant with a SUSAC until resolution of symptoms. SUSACs will be reported by site investigators to the principal investigator without undue delay. Reports of a SUSAC will be assessed for safety by a qualified physician in the trial management group (medical monitor).

Participant timeline

Clinical investigators at each participating ICU will be responsible for screening of all admitted patients with a diagnosis of septic shock within a screening window of 12 hours from ICU admission. Participants will receive non-resuscitation fluids according to their allocated intervention within 2 hours of randomisation. The intervention will be continued for the duration of the ICU admission up to a maximum of 90 days. At 6 months, a blinded outcome assessor will invite the surviving participant to a face-to-face follow-up visit, if possible with a relative or close friend (figure 1).

Procedures for screening and recruitment

We will involve key medical personnel at the different departments and hold information sessions to ensure they are informed of the trial. Potential participants will be identified by the clinician caring for the patient and will be approached according to the inclusion and exclusion criteria.

Assignment of interventions

Patients will be randomised 1:1 to protocolised restrictive administration of non-resuscitation fluids or usual care using an internet-based eligibility module for screening and randomisation, which will be integrated in the eCRF (Spiral Software, Wellington, New Zealand). This will allow for adequate generation and concealment of allocation sequence until the intervention is assigned. Randomisation will be stratified for trial site with permuted blocks of varying block size unknown to the trial investigators.

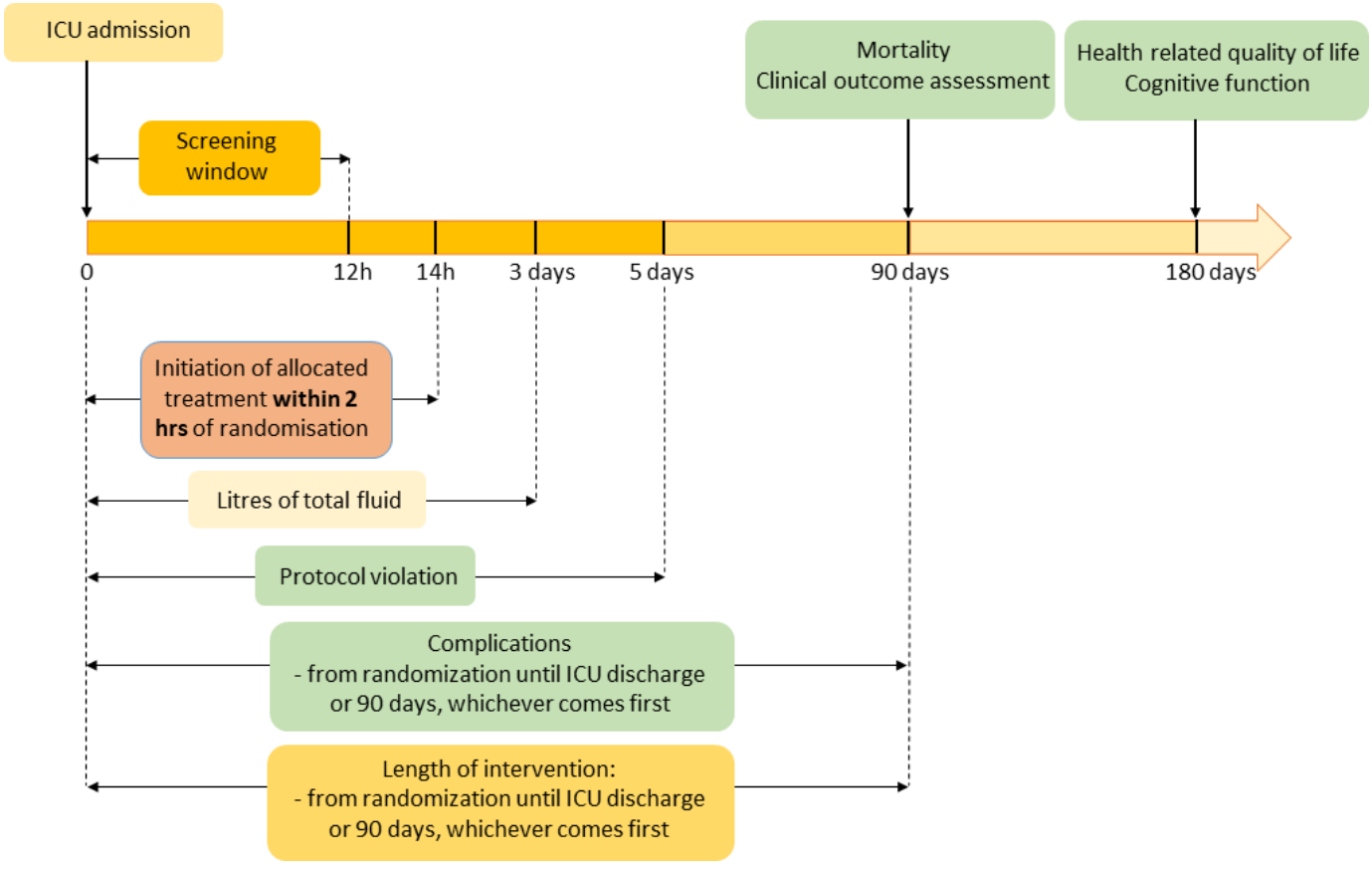


Figure 1 Trial timeline. Vertical arrows indicate specific time points for events or assessments, whereas horizontal arrows describe a certain time period. Complications: cerebral, cardiac, intestinal or limb ischaemia or any acute kidney injury. ICU, intensive care unit.

Blinding

The clinical team caring for participants will not be blinded due to the nature of the intervention. Study participants, their relatives, outcome assessors at the 6-month follow-up visit and trial statisticians will be blinded to the treatment allocation. The outcome assessors will not be involved in patient care. In the event of a SUSAC, it is permissible for the trial managing group to reveal a participant's allocated treatment.

Data collection

Clinical, laboratory and background data will be collected at enrolment, during the first 5 days of the ICU stay, at ICU-discharge and at the 6-month follow-up. Data will be obtained from hospital records, the participants, relatives and/or close friends, and will be entered into a web-based eCRF by site personnel who will be trained in data entry at study initiation. The site investigator must sign all eCRFs before trial completion to verify that recorded data are correct and complete. Data not obtainable will be registered as missing and measures to obtain data will not delay intervention or concomitant treatment. Data from the web-based forms will be migrated to a trial database. For detailed description of data to be collected, see online supplemental appendix A.

A specially trained outcome assessor will perform structured interviews and administer EQ-5D-5L, MoCA and GOSE evaluations. In cases where the participants' neurological outcome is too poor to complete the tests, a relative or close friend will be asked to proxy-rate the participant's health-related quality of life by the EQ-5D-5L and provide information for the GOSE score. To promote participant retention, we will use alternative methods including visiting the participants' homes or performing the follow-up by telephone or by an audio-visual web-based meeting. If needed, we will use an authorised interpreter. Follow-up rates will be monitored continuously and, if necessary, strategies to improve follow-up rates will be employed.

Data management

Variables will be collected directly into the eCRF. Site responsible investigators will train research staff on how to enter variables correctly. To promote data quality, eCRFs will have several built-in mechanisms to prevent data entry errors such as range checks for data values. Adherence to intervention protocols will be monitored by calculations in the eCRF to check fluid balance and recorded fluid.

Sample size and feasibility thresholds

Data from our previous study suggest that total volume of fluids may be reduced by a median of 3.12 (IQR: 1.50–4.95) L in the first 3 days after ICU admission by restrictive administration of non-resuscitation fluids in Swedish ICUs (see online supplemental appendix D for further details on the modelling).[16] We believe that a median reduction in total volume of fluids in the first 3 days of ICU admission above 2 L may have an impact on outcome. To detect a difference of 2 L with an SD of 2.8 L, with an alpha of 0.05, and a power of 90% we need 42 participants in each arm. To account for data not being normally distributed, we aim to include 15% more participants than the calculated sample size using a conventional rule-of-thumb.[26] Thus, we aim to include 49 participants in each arm resulting in a total sample size of 98 participants. We will encourage all participating centres to randomise at least 10 participants.

Feasibility thresholds for the secondary feasibility outcomes will be as follows:

- The proportion of participants with outcome data on all-cause mortality, days alive without mechanical ventilation, acute kidney injury and ischaemic events in the ICU within 90 days of inclusion, should be more than 95% corresponding to a CI of 89%–98% (1-sample proportions test).
- The proportion of surviving participants who were assessed by EQ-5D-5L and MoCA should be more than 85% of survivors based on a predicted all-cause mortality of 45%[1–5] corresponding to a CI of 73%–92%.
- The proportion of eligible patients who were randomised and consented should be more than 75% corresponding to a CI of 67%–81%.
- The proportion of participants experiencing at least one protocol violation should be less than 10% corresponding to a CI of 6%–18%.

Each feasibility outcome will be investigated for possible optimisation for a future pragmatic trial, especially if the feasibility threshold is not reached in this trial.

This trial will have a power of 11%–29% to detect relevant treatment effects on the primary exploratory clinical outcomes. Analysis results including effect estimates will be interpreted with caution and as hypothesis generating only.

Statistical methods

Analyses will be performed according to an intention to treat principle. All analyses will be adjusted for participating site. The primary feasibility outcome will be analysed using the van Elteren test. Median difference and corresponding CIs will be estimated using Hodges-Lehman method. The secondary feasibility outcomes are all proportions and will be presented as percentages with CIs calculated using 1-sample proportions test without continuity correction.

The exploratory primary and secondary clinical outcomes will be analysed depending on the type of data. For the exploratory clinical outcomes, we will analyse count outcomes using the van Elteren test with adjustment for site; continuous outcomes using mixed effects linear regression with site as a random intercept and dichotomous outcomes using mixed effects logistic regression with site as a random intercept. Risk ratios will be estimated using the 'nlcom' Stata command and/or by G-computation in R. Underlying assumptions will be

assessed according to the recommendation by Nørskov *et al*.[27] Because of the exploratory nature of the trial, we will not adjust p values for multiple comparisons. Before any analysis is carried out, we will publish a detailed statistical analysis plan in a public domain (eg, Zenodo.org).

Missing data

All randomised participants will be included in the primary analysis of all outcomes. In secondary analyses, a value of −1 will be imputed for all participants who died when analysing health-related quality of life (EQ-5D-5L) and neurocognitive function (MoCA). We will handle other missing data according to the recommendation by Jakobsen *et al*.[28]

Informed consent procedures

Because cognitive symptoms are hallmark symptoms of septic shock, it will in most cases be impossible to obtain informed consent at the time of presentation.[17] The trial will therefore use a deferred consent process. A member of the local research team will approach the legal representative or a personal consultee (relative or close friend) as soon as practically possible to inform about the trial and seek their opinion about the participation of the patient in the trial. Surviving participants will be provided with written and oral information for an informed decision about participation in the trial and asked for written consent as soon as they can make an informed decision. The consent form must be signed by the participant according to Swedish legislation.

A participant is free to withdraw his/her consent from the trial at any time. The participant making the withdrawal will be asked for permission to use data obtained prior to withdrawal and to obtain data for the primary outcome. If permission is obtained, the participant will be included in the final analyses. If the patient declines, all data from that patient will be destroyed.

Patient and public involvement

A patient organisation for patients with sepsis (Sepsisföreningen) in Sweden was formed in March 2021. The 'Sepsisföreningen' has reviewed the protocol and endorse the trial objectives. A representative from 'Sepsisföreningen' will be consulted if/when aspects of the conduct of the trial which are deemed to be of importance from a patient perspective are discussed. Such aspects include any change in the protocol with ethical implications.

DISCUSSION

The strengths of this trial include the generalisability embedded in the multicentre design, where both university and non-university hospitals will recruit patients. Also, the use of few exclusion criteria will broaden the number of patients eligible for inclusion and increase the external validity. Another strength is that the intervention is based on the most restrictive practice for administration of non-resuscitation fluids in use at any of the units included in our previous observational study, and the most concentrated dilutions of commonly used medications described in the literature.[16] We believe that this supports both safety and the clinical relevance of the intervention. Last, our methodology is defined in detail before randomisation begins which limits the risk of data-driven bias.

The trial also has limitations. Non-resuscitation fluids are a major source of glucose and electrolytes administered in the critically ill and we do not believe that it is feasible to protocolise amounts of these solutes.[29 30] Consequently, differences in administration of these solutes between the treatment groups may act as confounders and limit which conclusions can be drawn with regard to the causality between fluid volumes and outcomes. In an attempt to address this possible limitation, we will carefully collect data on solute administration as well as the occurrence of complications related to differences in solute administration.

The fact that there is variation in practice between intensive care units regarding administration of non-resuscitation fluids means that the potential to reduce fluid administration is likely to vary between sites.[9 16] Moreover, some units do not have written guidelines for administration of maintenance fluids and glucose.[16] Given the increased awareness of the risks of fluid overload, there is a risk for a drift in practice in the control group towards a more restrictive prescription of non-resuscitation fluids in such units. To mitigate this risk, site investigators will be encouraged to establish written guidelines for usual care based on local practice.

It could be argued that the expected reduction in administration of non-resuscitation fluids could lead to haemodynamic instability which could result in increased administration of resuscitation fluids, which in turn could offset the expected reduction in the total administered intravenous fluids. We believe that this is unlikely because glucose solutions are poor plasma volume expanders and because intravascular retention of crystalloids over time is most likely low, reported to be <10% in inflammatory conditions.[31–33] Should we be wrong in our assumption that our intervention will not influence haemodynamic stability, we believe that that non-protocolised administration of resuscitation fluid is an important safety mechanism by which clinically apparent hypovolemia caused by our intervention will trigger administration of resuscitation fluids.

ETHICS AND DISSEMINATION

Research ethics approval

The first version of the protocol was approved by Swedish ethics review authority on 8 February 2021 (#2020-06594). Amendments of the protocol were approved on 14 October 2021 (#2021-05363-02) and on 6 February 2022 (#2022-00253-02).

Trial conduct

This trial will be conducted according to good clinical research practice and the latest version of the Declaration of Helsinki.[34]

Data monitoring

Because this is a feasibility trial, we will not perform an interim analysis and hence no data safety and monitoring committee will be used.

Monitoring

The trial will be monitored by national monitoring offices coordinated by Clinical Studies Sweden, Forum South. All sites will participate in an online meeting by an external monitor before the start of inclusion to ensure that the study can be performed according to protocol and that the essential study documents are at the site. Monitors will also conduct a close-out visit at all sites which will include control of routines for data collection, data entry and source data verification for a selected subset of the data.

Data access and dissemination

Beginning 9 months after publication of the main study report, individual de-identified data will be available for sharing with researchers who provide a methodologically sound proposal as judged by the steering committee. To gain access, data requestors will need to sign a data access agreement. The main trial report will be submitted to a peer-reviewed international journal. The main publication will report the primary and secondary feasibility outcomes and the clinical exploratory outcomes.

Individual participant data will be handled as ordinary chart records and kept according to the Swedish legislation. The electronic data capture module of the eCRF fulfils the criteria for handling of patient data according to the Swedish legislation on management of personal data and will be compliant with the General Data Protection Regulation of the EU (European Parliament and Council of the European Union. Directive 2001/20/EC). All original records will be retained at trial sites or at the trial administration for 15 years to allow inspection by relevant authorities. The trial database will be maintained for 15 years and anonymised if requested for revision.

Study dates

Recruitment started in March 2022.

Protocol and amendments

The protocol version outlined herein is V.1.1. Protocol modifications will be communicated to all site investigators and updated on clinicaltrials.gov promptly, and major modifications will be subjected to ethical review as required.

Author affiliations
[1]Anesthesiology and Intensive Care, Department of Clinical Sciences Lund, Helsingborg Hospital, Lund University, Helsingborg, Sweden
[2]Department of Clinical Sciences Lund, Neurology, Skåne University Hospital, Lund University, Lund, Sweden
[3]Copenhagen Trial Unit, Centre for Clinical Intervention Research, The Capital Region, Copenhagen University Hospital, Copenhagen, Denmark
[4]Department of Neuroanaesthesiology, The Neuroscience Centre, Copenhagen University Hospital, Kobenhavn, Denmark
[5]Intensive and Perioperative Care, Department of Clinical Sciences Lund, Skane University Hospital, Lund University, Malmö, Sweden
[6]Intensive and Perioperative Care, Department of Clinical Sciences Malmö, Skane University Hospital, Lund University, Malmö, Sweden
[7]Department of Anesthesiology and Intensive Care, Kristianstad Hospital, Central Hospital in Kristianstad, Kristianstad, Sweden
[8]Department of Anesthesiology and Intensive Care, Östersund Hospital, Ostersund, Sweden
[9]Department of Anesthesiology and Intensive Care Medicine, University of Gothenburg, Goteborg, Sweden
[10]Department of Operation and Intensive Care, Halland Hospital Halmstad, Halmstad, Sweden
[11]Intensive and Perioperative Care, Department of Clinical Sciences Lund, Skane University Hospital, Lund University, Lund, Sweden
[12]Anesthesiology and Intensive Care Medicine, Department of Surgical Sciences, Uppsala University, Uppsala, Sweden
[13]Hedenstierna Laboratory, Department of Clinical Sciences, Uppsala University, Uppsala, Sweden
[14]Department of Regional Health Research, The Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark

Acknowledgements We acknowledge pharmacists Karin Storm and Linda Andersson for their expert help in preparing the trial-specific protocol for the concentration of intravenous medications in the intervention group.

Contributors PB contributed to study conception. ALinden, PB, JCJ, GL and NN developed the first version of protocol. MJ, MS, LS, JO, ALinder, JU, TK, ML, ALinden, JF, FS contributed to development of protocol. JCJ and MHO developed the statistical analysis plan and performed power calculations. ALinden, JF and PB drafted the manuscript. All authors critically revised the manuscript and approved the final manuscript.

Funding This work was supported by the Anna och Edwin Bergers stiftelse, the Gorthon foundation and a Swedish government grant (ALF grant number 86626). Funding sources had no role in the design of this study and will not have any role in or authority over the study design, collection, management, analysis, interpretation of data, writing of the report and decision to submit the report for publication.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Anja Lindén http://orcid.org/0000-0003-4839-921X
Jane Fisher http://orcid.org/0000-0002-3780-901X
Fredrik Sjövall http://orcid.org/0000-0001-5612-0325
Martin Spångfors http://orcid.org/0000-0001-8754-899X
T Kander http://orcid.org/0000-0002-5404-2981

REFERENCES

1 Hjortrup PB, Haase N, Bundgaard H, *et al*. Restricting volumes of resuscitation fluid in adults with septic shock after initial management: the classic randomised, parallel-group, multicentre feasibility trial. *Intensive Care Med* 2016;42:1695–705.
2 Perner A, Haase N, Guttormsen AB, *et al*. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med* 2012;367:124–34.
3 Shankar-Hari M, Phillips GS, Levy ML, *et al*. Developing a new definition and assessing new clinical criteria for septic shock: for the third International consensus definitions for sepsis and septic shock (sepsis-3). *JAMA* 2016;315:775–87.
4 Hernández G, Ospina-Tascón GA, Damiani LP, *et al*. Effect of a resuscitation strategy targeting peripheral perfusion status vs serum lactate levels on 28-day mortality among patients with septic shock: the ANDROMEDA-SHOCK randomized clinical trial. *JAMA* 2019;321:654–64.
5 Holst LB, Haase N, Wetterslev J, *et al*. Lower versus higher hemoglobin threshold for transfusion in septic shock. *N Engl J Med* 2014;371:1381–91.
6 Marik PE, Linde-Zwirble WT, Bittner EA, *et al*. Fluid administration in severe sepsis and septic shock, patterns and outcomes: an analysis of a large national database. *Intensive Care Med* 2017;43:625–32.
7 Boyd JH, Forbes J, Nakada T, *et al*. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. *Crit Care Med* 2011;39:259–65.
8 Sakr Y, Rubatto Birri PN, Kotfis K, *et al*. Higher fluid balance increases the risk of death from sepsis: results from a large international audit. *Crit Care Med* 2017;45:386–94.
9 Silversides JA, Fitzgerald E, Manickavasagam US, *et al*. Deresuscitation of patients with iatrogenic fluid overload is associated with reduced mortality in critical illness. *Crit Care Med* 2018;46:1600–7.
10 Payen D, de Pont AC, Sakr Y, *et al*. A positive fluid balance is associated with a worse outcome in patients with acute renal failure. *Crit Care* 2008;12:R74.
11 Meyhoff TS, Møller MH, Hjortrup PB, *et al*. Lower vs higher fluid volumes during initial management of sepsis: a systematic review with meta-analysis and trial sequential analysis. *Chest* 2020;157:1478–96.
12 Chen C, Kollef MH. Targeted fluid minimization following initial resuscitation in septic shock: a pilot study. *Chest* 2015;148:1462–9.
13 Douglas IS, Alapat PM, Corl KA, *et al*. Fluid response evaluation in sepsis hypotension and shock. *Chest* 2020;158:1431–45.
14 Meyhoff TS, Hjortrup PB, Wetterslev J, *et al*. Restriction of intravenous fluid in ICU patients with septic shock. *N Engl J Med* 2022;386:2459–70.
15 Shapiro NI, Douglas IS, Brower RG, *et al*. Early restrictive or liberal fluid management for sepsis-induced hypotension. *N Engl J Med* 2023;388:499–510.
16 Lindén-Søndersø A, Jungner M, Spångfors M, *et al*. Survey of non-resuscitation fluids administered during septic shock: a multicenter prospective observational study. *Ann Intensive Care* 2019;9:132.
17 Singer M, Deutschman CS, Seymour CW, *et al*. The third International consensus definitions for sepsis and septic shock (sepsis-3). *JAMA* 2016;315:801–10.
18 Evans L, Rhodes A, Alhazzani W, *et al*. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Intensive Care Med* 2021;47:1181–247.
19 De Backer D, Cecconi M, Chew MS, *et al*. A plea for personalization of the hemodynamic management of septic shock. *Crit Care* 2022;26:372.
20 Brown SM, Collingridge DS, Wilson EL, *et al*. Preliminary validation of the Montreal cognitive assessment tool among sepsis survivors: a prospective pilot study. *Ann Am Thorac Soc* 2018;15:1108–10.
21 Nasreddine ZS, Phillips NA, Bédirian V, *et al*. The Montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005;53:695–9.
22 Herdman M, Gudex C, Lloyd A, *et al*. Development and preliminary testing of the new five-level version of eq-5d (eq-5d-5l). *Qual Life Res* 2011;20:1727–36.
23 Kellum JA, Lameire N, KDIGO AKI, *et al*. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). *Crit Care* 2013;17:204.
24 Wilson JT, Pettigrew LE, Teasdale GM. Structured interviews for the Glasgow outcome scale and the extended Glasgow outcome scale: guidelines for their use. *J Neurotrauma* 1998;15:573–85.
25 Wilson L, Boase K, Nelson LD, *et al*. A manual for the Glasgow outcome scale-extended interview. *J Neurotrauma* 2021;38:2435–46.
26 Lehmann EL. *Nonparametrics: statistical methods based on ranks, revised*. Prentice Hall, 1998: 76–81.
27 Nørskov AK, Lange T, Nielsen EE, *et al*. Assessment of assumptions of statistical analysis methods in randomised clinical trials: the what and how. *BMJ Evid Based Med* 2021;26:121–6.
28 Jakobsen JC, Gluud C, Wetterslev J, *et al*. When and how should multiple imputation be used for handling missing data in randomised clinical trials - a practical guide with flowcharts. *BMC Med Res Methodol* 2017;17:162.
29 Van Regenmortel N, Verbrugghe W, Roelant E, *et al*. Maintenance fluid therapy and fluid creep impose more significant fluid, sodium, and chloride burdens than resuscitation fluids in critically ill patients: a retrospective study in a tertiary mixed ICU population. *Intensive Care Med* 2018;44:409–17.
30 Nihlén S, Kawati R, Rasmusson J, *et al*. Hidden sources of fluids, sodium and potassium in stabilised Swedish ICU patients: a multicentre retrospective observational study. *Eur J Anaesthesiol* 2021;38:625–33.
31 Hahn RG, Lyons G. The half-life of infusion fluids: an educational review. *Eur J Anaesthesiol* 2016;33:475–82.
32 Ernest D, Belzberg AS, Dodek PM. Distribution of normal saline and 5 % albumin infusions in cardiac surgical patients. *Crit Care Med* 2001;29:2299–302.
33 Statkevicius S, Frigyesi A, Bentzer P. Effect of ringers acetate in different doses on plasma volume in rat models of hypovolemia. *Intensive Care Med Exp* 2017;5:50.
34 World Medical Association (WMA). Declaration of helsinki [online]. fortaleza, brazil: world medical association. 2013. Available: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

Feasibility 2023-02-07

Clinical Trial Protocol

Protocolised REDUction of non-resuscitation fluids versus usual care in SEptic shock patients (REDUSE). A protocol for a multicentre feasibility trial

Version 1.1

Sponsor: Region Skåne - Skånevård SUND - Helsingborgs Hospital, Charlotte Yhléns gata 10,25223 Helsingborg, Sweden Principal Investigator: Peter Bentzer, Prof., MD, PhD, DESA, EDIC Department of Anaesthesiology and Intensive Care Helsingborg Hospital Lund University, Faculty of Medicine

Contents

REDUSE Feasibility 2023-02-07

1. Trial overview

The REDUSE trial is a multicentre, investigator initiated, randomised clinical superiority trial comparing protocolised restrictive strategy for administration of non-resuscitation fluids with usual care in participants with septic shock. Adult patients with septic shock will be eligible for inclusion. Participants will be randomised within 12 hours of admission to the intensive care unit. In the intervention arm participants will not receive maintenance fluids unless total volume of fluid is insufficient to provide hydration. All intravenous drugs and nutrition will be concentrated and administered with the objective to reduce volume of fluid. Resuscitation fluids will be administered according to local routines. The intervention will last for the duration of the intensive care unit stay. Participants in the control arm will receive usual care. The primary outcome will be litres of fluid administered within three days. Secondary outcomes will be proportion of participants with clinical outcome data for all-cause mortality, days alive and free of mechanical ventilation and complications during ICU stay at 90 days from randomisation, neuro-cognitive function and health related quality of life at 6 months from randomisation. Also, proportion of participants who experienced at least one protocol violation as well as proportion of eligible patients who were randomised and consented will be assessed. Healthcare staff involved in the care of the participant will not be blinded to the intervention but participants, outcome assessors, statisticians, data managers, and manuscript authors will be blinded to treatment allocation.

2. Background and study rationale

2.1 Background

Sepsis is defined as life-threatening organ dysfunction caused by a host response to infection[1]. Recent estimates suggest that 48 million cases of sepsis occur globally every year and that 11 million sepsis related deaths occur annually with most cases occurring in developing countries[2]. Septic shock is a subgroup of sepsis with particularly severe circulatory and metabolic abnormalities and with a 90-day mortality of 40-50 %[3,4,5,6,7].

Administration of fluids is an essential component of the care of patients suffering from septic shock. Fluids are administered for different reasons. Resuscitation fluids are administered intravenously to ensure adequate tissue perfusion and oxygenation whereas non-resuscitation fluids are administered intravenously and enterally as vehicles for medications and nutrition, to correct electrolyte disturbances, and to ensure adequate hydration (maintenance fluids)[8]. The latter purpose is considered to require a total of about 1-2 litres of fluids per day (1 ml/kg/h) in the healthy humans and may increase in pathophysiological conditions due to higher-than-normal losses[9]. More than 50% of patients with septic shock receive 4 L or more of fluids in the first day in the ICU[10]. This may be adequate in patients with pre-existing deficits, but data suggest that large volumes of fluids are not without risks. Non-randomised studies have indicated that excessive fluid administration might have detrimental adverse effects such as tissue oedema, with impaired oxygen delivery and organ function, and compartment syndromes [11,12,13,14]. These observations have inspired trials investigating if restrictive fluid administration improve outcomes in septic shock participants.

2.2 Previous evidence

In a recent systematic review with meta-analysis, nine trials comparing a restrictive approach of fluid administration with usual care in adult patients with sepsis and/or septic shock were identified[15]. Eight of these trials assessed interventions with the objective to reduce administration of only resuscitation fluids and one trial assessed interventions with the objective to reduce both resuscitation fluids and non-resuscitation fluids[16]. Meta-analysis of the four trials where a significant separation in fluid volumes was shown, showed no difference in mortality but the point estimate favoured the restrictive approach (RR: 0.81 [95% CI; 0.60-1.10, I^2 = 0%]. Furthermore, Trial Sequential Analysis showed that there was insufficient information to confirm or reject a relative risk reduction of 15%. Moreover, all identified trials were at high risk of bias and the certainty of evidence was low[15].
We have identified three trials that were completed after the meta-analysis by Meyhoff et al., comparing a restrictive approach of fluid therapy to usual care in septic shock[15,17,18,19]. The first trial assessed a protocol using fluid responsiveness to guide administration of resuscitation fluids in 124 patients with septic shock. Separation in fluid volumes was achieved but no effect on mortality was detected[17]. The second is the recently published CLASSIC trial, which assessed the effects of restrictive administration of resuscitation fluids in 1554 patients with septic shock. The intervention resulted in a reduction in administration of fluids of about 2 L and no effect on mortality was detected[18]. The third is the newly published CLOVERS trial, in which a restrictive fluid strategy was assessed in 1563 patients with sepsis-induced hypotension. The results were similar to CLASSIC with a fluid reduction in the intervention group of 2.1 L and no effect on mortality[19].

2.3 Rationale for a new trial

Patients with septic shock receive large volumes of intravenous fluids and an intervention with the objective to reduce fluid administration may have a large effect in this population. In septic shock, similar volumes of resuscitation- and non-resuscitation fluids are administered the first day in the ICU, non-resuscitation fluid dominates thereafter [18,20,21]. Modelling based on a recent survey of administration of non-resuscitation fluids in six Swedish ICUs, indicates that most fluids are delivered as non-resuscitation fluid and that the volume of non-resuscitation fluids may be reduced by about 3 L in the first days after ICU admission[20]. Such a reduction might have a positive impact on patient important outcomes such as mortality, health related quality of life and cognitive function[12]. Moreover, the magnitude of this reduction is at least one litre larger than the most effective protocols targeting restriction of resuscitation fluids[18,19]. To date no trial has evaluated a protocolized restrictive administration of non-resuscitation fluids in patients with septic shock and it is unclear if the modelled reductions in fluid administration can be achieved in a clinical setting. A randomised clinical feasibility trial assessing the effects of protocolized restrictive administration of non-resuscitation fluids in patients with septic shock is therefore important before undertaking a large-scale trial powered to detect patient important outcomes.

3. Trial objectives and outcomes

The objective of this feasibility trial is to assess the efficacy and feasibility of a protocol purposed to compare a protocolised reduction in administration of non-resuscitation fluids to usual care in patients with septic shock.

3.1 Primary feasibility outcome

Litres of fluids administered within three days (D0-3) of randomisation.

3.2 Secondary feasibility outcomes

- Proportion of participants with sufficient clinical outcome data. These include all-cause mortality, days alive and free of mechanical ventilation, acute kidney injury, and ischemic events in the ICU (cerebral, cardiac, intestinal or limb ischemia) within 90 days of inclusion
- Proportion of surviving participants assessed by European Quality of Life-5 Dimensions 5- Level questionnaire (EQ-5D-5L) and The Montreal Cognitive Assessment (MoCA) at 6 months
- Proportion of all eligible patients who were randomised and consented
- Proportion of participants experiencing at least one protocol violation

3.3 Primary exploratory clinical outcomes

We will assess clinical outcomes which are planned to be assessed in a future larger randomised trial. These outcomes will only be investigated in an exploratory manner in this feasibility trial.

- All-cause mortality at 90 days after inclusion
- One or more complication in the ICU (cerebral, cardiac, intestinal or limb ischemia or any acute kidney injury) within 90 days of inclusion
- Days alive and free of mechanical ventilation within 90 days of inclusion
- Cognitive function measured using MoCA at 6 months after inclusion[22,23]
- Health-Related Quality of Life using the EQ-5D-5L at 6 months after inclusion [24]

3.4 Secondary exploratory clinical outcomes

- Total volume of non-resuscitation fluids administered at day 3 and 5 after inclusion
- Renal function (acute kidney injury stages according to Kidney Disease Improving Global Outcomes [KDIGO] criteria and days alive and free of renal replacement therapy [RRT] within 90-days of inclusion)[25]
- Gastrointestinal function (days alive with full enteral nutrition within 90 days of inclusion)
- Total volume of resuscitation fluid administered up to day 3 and 5 after inclusion
- Cumulative fluid balance at day 3 and 5 after inclusion (excluding evaporation)
- Daily dose and type of diuretics administered during the first 5 days after inclusion
- Hemodynamic stability during the first 5 days after inclusion (daily highest dose of noradrenaline, daily lactate, and cardiovascular sequential organ failure assessment [SOFA] score)
- Functional outcome by the Glasgow Outcome Scale Extended (GOSE) at 6 months after inclusion[26,27]

Description of all outcomes are provided in **Appendix A**.

4. Eligibility

Patients will be eligible for inclusion if they fulfil all the inclusion criteria and none of the exclusion criteria.

4.1 Inclusion criteria

- Adult (≥ 18 years of age)
- Septic shock according to Sepsis-3 criteria while in the ICU[1]
- Ongoing vasopressor treatment
- Inclusion within 12 hours of ICU admission

4.2 Exclusion Criteria

- Confirmed or suspected pregnancy

Participants readmitted to the ICU during the same hospital stay will be allocated to the same intervention arm regardless of diagnosis. Participants readmitted to the ICU after hospital discharge will not be eligible for re-inclusion.

4.3 Exit from the trial

4.3.1 Exit by participant

A participant is free to withdraw his/her informed consent from the trial at any time. A participant will exit the trial if this participant withdraws consent. The participant will be asked to specify which aspects of the trial he/she is withdrawing consent and participation from: attending the follow-up visits, diagnostic testing, inclusion of their data (including survival data) in a database, or publication. The participant making the withdrawal will be asked for permission to use data obtained prior to withdrawal and to obtain data for the primary outcome measure unless national regulations specify that data collected prior to withdrawal may be used without consent. If permission is obtained, the participant will be included in the final analyses. If the participant declines, all data from that participant will be destroyed.

4.3.2 Exit by treating physician

A treating physician may withdraw the participant from the trial should the physician be convinced that further participation in the trial may harm the participant. If the trial intervention is discontinued by the treating physician because of adverse events, or any other reason, this does not constitute subject withdrawal from the trial and the patient will not exit the trial.

5. Trial design

The trial is a multicentre, randomised trial with a 1:1 concealed allocation conducted in both large university hospitals and smaller local hospitals in Sweden. One university hospital can offer extracorporal membrane oxygenation (ECMO) treatment in addition to the treatments that the other hospitals offer. Participants will receive either a protocolized reduction in

administration of non-resuscitation fluids or usual care. The trial will be investigator-initiated and non-commercial. Please see **Figure 1** for the study timeline.

5.1 Screening and randomisation

Clinical investigators at each participating ICU will be responsible for screening of all admitted patients with a diagnosis of septic shock within a screening window of 12 hours from ICU admission. A screening log will be compiled and include all patients with an admission diagnosis of septic shock whether they are eligible for inclusion, or not. Informed consent will be obtained as described below. Trial sites will have access to an internet-based randomisation application, which will be integrated in the eCRF (Spiral Software, Wellington, NZ), to allow for immediate allocation and adequate concealment of the allocation sequence. Each participant will be assigned a unique trial and randomisation number. Randomisation will be performed with permuted blocks of varying block size unknown to the trial investigators and stratified for trial site.

5.2 Intervention

- Participants will receive non-resuscitation fluids according to the protocol described below within two hours of randomization. Non-resuscitation fluids will be defined as fluids other than crystalloids administered to correct hemodynamic impairment, colloids, and blood products. The type of maintenance fluids will be given according to usual care at each respective centre with the objective to use similar types of fluids in both groups. If surgery is needed for participants, administration of non-resuscitation fluids will be at the discretion of the anaesthetist. The intervention will be continued for the duration of the ICU stay up to a maximum of 90 days.

5.2.1 The intervention group

- Maintenance fluids will be discontinued in participants who are positive in cumulative fluid balance and are judged not to be dehydrated by the treating physician.
- Intravenous fluid and enteral water will be given as needed to correct electrolyte disturbances.
- Enteral nutrition will have an energy density of at least 2 kcal/ml and administered according to local practice.
- Glucose may be used at a maximal dose of 1g/kg/day using 20% glucose or greater starting at 72 hours after inclusion as nutrition if enteral feeding is not tolerated. Glucose at this (or lower) dose may be started earlier in participants with insulin dependent diabetes if enteral feeding is not tolerated and if local protocol mandates this.
- Parenteral nutrition will be administered according to local protocol.
- The intervention group will receive intravenous medications concentrated according to protocol (**Appendix B**).
- Participants who are neutral or negative in cumulative fluid balance will receive maintenance fluids and other fluids in a dose that ensures that the total dose of fluids covers the daily need of water and ongoing losses (about 1ml/kg/h).

5.2.2 Usual Care group

- The usual care arm will receive non-resuscitation fluids according to local routines.
- Maintenance fluids (crystalloids and/or glucose and/or enteral water) will be given at a dose of 1 ml/kg/h unless local protocol states otherwise.
- Glucose will be used at maximum concentration of 10% for maintenance/nutrition unless local protocol states otherwise.
- Enteral nutrition will be administered according to local practice.
- Medications will be concentrated according to local protocol.

Site investigators will establish what constitutes usual care is in "their" ICU prior to initiation of the trial. Site investigators will be responsible for preventing drift in the usual care group.

In both groups, resuscitation fluids (crystalloids administered to correct hemodynamic impairment, colloids and blood products) will be administered according to the surviving sepsis campaign guidelines during the salvage- and optimization phases of resuscitation and according to local protocol during the stabilisation and de-escalation phases[8,28]. Type of resuscitation fluids will be given according to local routine at each centre with the objective to use similar fluids in both groups All other care of participants will be according to local routines and will not be protocolized. For a flow chart of treatment in the intervention group please see **Appendix C.**

5.3 Follow up

At 6 months, all surviving participants will be invited to a face to face visit, if possible with a relative or close friend. At these visits specially trained, blinded assessors will perform structured interviews, administer performance-based tests and collect patient reported outcome measures in a standard order for the secondary and exploratory outcomes. In cases where the participants outcome is too poor to complete the tests, a relative or close friend will be asked to proxy-rate the participant´s health related quality of life by the EQ-5D-5L test. The outcome-assessor may be an occupational therapist, physician, research nurse, psychologist or similar. Outcome-assessors will be provided with a written trial manual with detailed guidelines for performing the questionnaires and assessments. Training sessions will be provided by the trial coordinating team to increase inter-rater reliability and data quality. Prevention of avoidable missing data is important and includes for example alternative strategies for participants who will be unable or not willing to visit a clinic. These include visiting the participants' home or performing the follow up by telephone or by an audio-visual web-based meeting. If needed an authorized interpreter will be used. In cases where the participant´s outcome is too poor outcome to complete the tests, proxy rating by a relative or close friend will be allowed. Follow-up rates will be monitored continuously and, if necessary, strategies to improve follow-up rates will be employed. The participants will be informed about abnormal test results and will receive information concerning where to get help. If needed outcome assessors may also help with referrals to appropriate healthcare professionals.

5.4 Blinding

The clinical team caring for participants will not be blinded due to nature of the intervention. Participants, their relatives, outcome assessors at the 6-month follow-up visit, and trial

statisticians will be blinded to the treatment allocation. The outcome assessors will not be involved in patient care. In the event of a suspected unexpected serious adverse complication (SUSAC) it is permissible for the trial managing group to reveal a participant's allocated treatment.

5.5 Definitions

5.5.1. Days

Day 0 is from time of randomisation to the start of a new 24-hour period as per local protocol. Day 1 is the next 24-hour period. Last day of ICU stay is from start of new 24-hour period as per local protocol until discharge.

5.5.2. Fluids

Fluid balance will be calculated as sum of all input of enteral and parenteral fluids minus all measured losses. Estimated loss through evaporation will not be included in fluid balance. Stool will not be included in balance unless the paticipant has a faecal management system or similar device in place.

Crystalloids will be classified as resuscitation fluids if administered to correct hemodynamic impairment as noted in the patient chart or given at a rate > 5 ml/kg/h[29].

5.6 Protocol deviations

Protocol deviations include randomization of a non-eligible patient and non-compliance with treatment algorithm in the intervention arm as described above.

6. Data collection

Clinical, laboratory and background data will be collected at the time of enrolment, during the first five days of the ICU stay, at ICU-discharge and at the 6-month follow-up. Data will be obtained from hospital records, participants, relatives, and close friends, and will be entered into a web-based electronic case record form (eCRF) by site personnel. The site investigator must sign all eCRFs before trial completion to verify that the recorded data is correct and complete. Data from the web-based forms will be migrated to a trial database, which will be handled by the coordinating team. The sponsor supplies a standard description of all units of measurement in the eCRF. If a trial site uses different units of measurement and this might be a potential source of error, the site investigator should contact the coordinating team to have the data capture module modified. Data not obtainable will be registered as missing and measures to obtain data should not delay intervention or concomitant treatment. A detailed description of data is provided in **Appendix A**.

6.1 Background data

Background data include date of admission to hospital, date and time of admission to ICU, ward prior to ICU admission, age, sex, height, weight, frailty score, baseline creatinine, Charlson comorbidity index, origin of sepsis, pathogen and initial antimicrobial treatment.

6.2 Baseline data

Baseline data include Simplified Acute Physiology Score (SAPS) III, admission Sequential Organ Failure Assessment (SOFA) score, highest vasopressor dose in the 6 hours preceding inclusion, highest lactate while in the ICU and receiving vasopressors, lowest systolic blood pressure in the 6 hrs preceding inclusion, volume of resuscitation and non-resuscitation fluids administered by health care providers in the preceding 24 hours, type of respiratory support and baseline laboratory measurements.

6.3 Daily data during first five days of ICU stay

Daily data include volume and type of enteral nutrition and other enteral fluids, volume of parenteral nutrition, volume and type of vehicles for medications, volume and type of resuscitation fluids, volume and type of blood products, concentration of noradrenaline, fluid losses (drains, urine, bowel movements, bleeding, renal replacement therapy [RRT]), fluid balance, fluid balance goal, respiratory support, RRT, acute kidney injury stage, use of diuretics (dose and type), complications, protocol violations, weight, SOFA score, and highest lactate, creatinine, urea and haemoglobin.

6.4 At discharge

Discharge data include date and time of discharge (ICU and hospital), readmission data,, status at discharge (alive/deceased),specification of where participant is discharged to, withdrawal of life sustaining therapies, complications.

6.5 At 90-days

Survival and days alive and free of organ support (invasive mechanical ventilation, renal replacement therapy), complications in the ICU at 90-days, date of discharge from hospital. If deceased, date of death will be recorded.

6.6 At 6 months

Patient reported Health-Related Quality of Life by EQ-5D-5L, cognitive function by the performance based cognitive screening MoCA, and clinician reported functional outcome by the GOSE, Renal replacement therapy (Y/N).

7. Ethics and Informed consent

Septic shock is a critical illness with an acute onset and most patients suffer from altered mentation[1]. This means that patients fulfilling inclusion criteria will only rarely be able to give informed consent prior to inclusion in the early phase of septic shock. Moreover, relatives are often in a state of psychological shock or may be difficult to locate. It could be argued that information about a trial and the requirement for an immediate decision concerning participation in the trial will be stressful and inappropriate. Given that the largest volumes of non-resuscitation fluids are administered in the acute phase of the illness, the intervention will presumably have the largest potential to reduce the volume of fluids if started within the first hours of diagnosis of septic shock. Accordingly, a deferred start of treatment would hamper the scientific validity of the trial.

The above creates an ethical dilemma as the intervention, to have best chance to be useful, must be started before informed consent from the participant or his/her relative can be obtained. Because the intervention should be started early to have the greatest effect on fluid balance and ultimately on outcome, we believe that it is ethically acceptable to include patients using a deferred consent procedure. Relatives will be informed about the trial as soon as possible. The ethical review board in Sweden has approved this procedure for the REDUSE trial (protocol: # 2020-06594, 2021-02-08, amendments: # 2021-05363-02, 2021-10-14 and #2022-00253-02, 2022-02-06).

Surviving partcipants will be asked for consent as soon as they are mentally capable (**Appendix E**). If consent has not been obtained during hospitalisation, a letter with information about the trial and a consent form will be sent by mail to the participant. If needed, two phone calls will be made to acquire the consent. If we, in spite of these attempts, cannot reach the participant, already collected data will be included in the analysis. We consider this strategy to be compatible with the Declaration of Helsinki, paragraph 30 on research on incapacitated patients. The delayed consent procedure also aligns with consent procedures used in several previous studies assessing interventions in septic shock[7,30,31]. The recently formed patient organization that represents sepsis patients in Sweden (Sepsisföreningen) has reviewed the protocol and approved the delayed consent procedure. Moreover, we recently surveyed the opinion of a representative sample (n ≈ 1,000) of the Swedish population and nearly 80 % were positive to deferred consent procedure in a similar scenario[32].

8. Data management

8.1 Data handling and record keeping

Individual participant data will be handled as ordinary chart records and will be kept according to the legislation (e.g. data protection agencies) of each participating country. Data will be entered into the eCRF. The electronic data capture module fulfils criteria for handling of patient data according to the Swedish legislation on management of personal data will be compliant with the General Data Protection Regulation of the EU (European Parliament and Council of the European Union. Directive 2001/20/EC) and with the Federal Drug Administration's guidelines for electronic signatures (FDA 21 CFR Part 11 Guidelines for Electronic Signatures). All original records on paper will be retained at trial sites or at the trial for 15 years to allow inspection by relevant authorities. The trial database will be maintained for 15 years and anonymised if requested for revision.

8.2 Quality control and quality assurance

The trial will be externally monitored by national monitoring offices coordinated by the clinical trial manager and Clinical Studies Sweden, Forum South. All variables will be collected in a participant-specific ledger or directly in the eCRF. Site principal investigators will be responsible for training of clinical staff on how to enter variables correctly. Special emphasis will be given to how to record fluid administration and fluid balance in a standardized manner. Instructions will be available in the trial ledger, on the trial homepage

and in the eCRF. All sites will have a digital site initiation meeting with monitors before start of inclusion and at end of study. Moreover, all sites will receive a close out visit by monitors. The visits will include control of routines for data collection and data entry as well as quality control of data by comparing selected source data with data entered in eCRF. The site investigator will be responsible for ensuring that all relevant data are entered into the eCRF. To promote data quality, the eCRF will have several inbuilt mechanisms to prevent data entry errors such as range checks for data values.

9. Safety

Detection, documentation, and reporting of the following complications will be the responsibility of the site investigator.

9.1 Definitions

Patients with septic shock in the ICU experience a host of complications. Only a small number of those could be related to the intervention, and only those will be reported. In addition to the patient-centred complications that we will assess as primary exploratory clinical outcomes, the following complications will be reported:

- Hypoglycaemia (≤ 3.9 mmol/l)
- Electrolyte and metabolic disturbances (hypernatremia > 159 mmol/L, hyperchloremic acidosis [pH < 7.15 and plasma Cl^- > 115], metabolic alkalosis [pH > 7.59 and standard base-excess (S-BE) > 9])
- Suspected unexpected serious adverse complication (SUSAC) - an adverse event not reasonably explained by other factors than the intervention which may cause death, or be life threatening, prolong hospitalisation, or may result in significant disability/incapacity

9.2 Reporting of complications

All complications observed by the investigator or other healthcare providers must be recorded in the eCRF. Suspected unexpected serious complication should be reported by site investigators to the sponsor without undue delay. The circumstances of a suspected unexpected serious adverse complication should be described. The causality between the trial intervention and the unexpected complication should be assessed by the site investigator. The site investigator is required to follow each participant with a suspected unexpected serious adverse complication until resolution of symptoms. Reports of a suspected unexpected serious adverse complication will be assessed for safety by a qualified physician in the trial management group (medical monitor).

10. Statistical analysis plan

Data will be analysed by two independent statisticians blinded to the treatment on an intention to treat basis. Patients will be included in the trial when randomized.
Before any analysis is carried out, we will publish a detailed statistical analysis plan in a public domain (e.g. Zenodo.org).

10.1 Sample size

10.1.1 Primary outcome

Data from our previous study suggest that total volume of fluids may be reduced by a median of 3.12 (IQR: 1.50-4.95) L in the first 3 days after ICU admission (D0-3) by restrictive administration of non-resuscitation fluids in Swedish ICUs[20] (see **Appendix D** for further details on the modelling). We believe that a median reduction in total volume of fluids in the first 3 days of ICU admission above 2 L is likely to have an impact on outcome. To detect such a difference, with an alpha of 0.05, a power of 90%, and a standard deviation of 2.8 L, we need 42 participants in each arm. To account for data not being normally distributed we aim to include 15% more participants than the calculated sample size using a conventional rule-of-thumb[33]. Thus, we aim to include 49 participants in each arm resulting in a total sample size of 98 participants.

We will encourage all participating centres to randomise at least 10 participants.

10.1.2 Feasibility threshold for secondary feasibility outcomes

The feasibility thresholds are defined below:

- The proportion of participants with outcome data on all-cause mortality, days alive and free of mechanical ventilation within 90 days of inclusion, acute kidney injury, and ischemic events in the ICU (cerebral, cardiac, intestinal or limb ischemia) should be more than 95% (n = 93) corresponding to a confidence interval of 89-98% (1-sample proportions test);
- The proportion of surviving participants who were assessed by EQ-5D-5L and MoCA should be more than 85 % (n=45) of survivors (n=53; based on a predicted all-cause mortality of 45 % corresponding to a confidence interval of 73-92%[3,4,5,6,7]
- The proportion of all eligible patients who were randomised should be more than 75% (i.e. 98 randomised of 131 eligible) corresponding to a confidence interval of 67-81%;
- The proportion of participants experiencing at least on protocol violation should be less than 10% (n=10) corresponding to a confidence interval of 6-18%

Each feasibility outcome will be investigated for any possibility for optimization for a future pragmatic trial, especially if the feasibility threshold is not reached in this trial.

10.1.3 Power estimations of primary exploratory clinical outcomes

For the primary exploratory clinical outcomes the power estimation is based on inclusion of 98 (49 in each group) participants without any missing data, and an alpha of 0.05.

- Based on an expected all-cause mortality at 90 days of 45% in the control group this trial will have a power of 11% to detect an absolute risk reduction of 7.5% which corresponds to a relative risk reduction of 16.7%[3,4,5,6,7].
- Based on an expected mortality of 45% (n=53) and SD of 5 point for MoCA this trial will have a power of 29% to detect a minimal important difference of 2 points[22]

- Based on an expected mortality of 45% (n=53) and SD of 20 point for EQ-5D-5L this trial will have a power of 14% to detect a minimal important difference of 5 points[34, 35,36]
- Based on an expected SD of 12 point for days alive and free of mechanical ventilation and a 15% reduction in sample size because of the non-normal distribution of these data this trial will have a power of 11% to detect a minimal important difference of 2 points[5,33]
- Based on an expected rate of complications in the ICU of 50% in the control group [4,7,37] this trial will have a power of 15% to detect an absolute risk reduction of 10% corresponding to a relative risk reduction of 20%.

Since the power of the primary exploratory clinical outcomes is low, point estimates including any statistically significant differences will be interpreted with caution and as hypothesis generating only.

10.2 Analysis methods

Analyses will be performed according to an intention to treat principle. All analyses will be adjusted for site of admission. The primary feasibility outcome will be analysed using van Elteren test. Median difference and corresponding CIs will be estimated using Hodges-Lehman method. The secondary feasibility outcomes are all fractions and will be presented as percentages with confidence intervals calculated using 1-sample proportions test without continuity correction.

The explorative primary and secondary clinical outcomes will be analysed depending on the type of data. For the exploratory clinical outcomes, we will analyse count data using van Elteren test with adjustment for site; continuous variables using mixed effects linear regression with site as a random intercept (all other variables will be fixed effects); and dichotomous variables using mixed effects logistic regression with site as a random intercept (all other variables will be fixed effects). RRs will be estimated using the 'nlcom' STATA command. Underlying assumptions will be assessed according to the recommendation by Nørskov et al[38].

All conclusions will be based on our primary outcome and, a priori, secondary outcome results will be considered as hypothesis generating. Based on this we will not adjust P-values for multiple comparisons.

10.3 Missing data

All randomised participants will be included in the primary analysis of all outcomes. In the analysis of health-related quality of life and neuro-cognitive function a value of - 1 will be imputed for all participants who died. However, we will handle missing data according to the recommendation by Jakobsen et al[39].

10.4.2 Exploratory clinical outcomes

Due to the low power of this trial any positive finding for the clinical outcomes may be due to error and will be regarded as exploratory.

10.5 Statisticians
Analyses of results will be performed by two independent statisticians.

10.6 Interim analysis
Because this is a feasibility trial we will not perform an interim analysis and hence no data safety and monitoring committee will be used.

11. Publication of Data
The final main publication will be submitted to a peer-reviewed international journal. Authorship will be granted using the Vancouver definitions and depending on personal involvement and fulfilment of the author's respective roles. The author list will include the management group, site investigators and statisticians. After the author list, there will be added: "and the REDUSE-trial group" and a reference to an appendix with all sites, site investigators and number of participants enrolled. The main publication will report the primary, secondary and exploratory outcomes.

11.1 Data sharing
Beginning 9 months after publication of the main report of this trial, individual de-identified data will be available for sharing with researchers who provide a methodologically sound proposal as judged by the steering committee. To gain access, data requestors will need to sign a data access agreement.

12. Insurance
When pre-existing insurance is not available, indemnity to meet the potential legal liability of investigators/collaborating hospitals for harm to participants arising from the conduct of the research will be provided by the REDUSE trial through the sponsor: Region Skåne - Skånevård SUND.

13. Funding
The trial will be funded by non-commercial foundations for medical research. Patient recruitment will not commence until there is sufficient funding to allow for inclusion and follow-up of the proposed sample size.

14. Timeline
2020: application for ethical permission submitted (approved 8/2-2021 # 2020-06594)

2021: trial design, ethics application, site recruitment, application for funding, site recruitment, design of eCRF, online randomization platform.

2022: first patient recruitment, run in period during which more than 8 sites should have received training in MoCA, EQ-5D-5L and GOSE evaluations and received a site initiation visit from monitors and started to include patients.

2023: follow up of last patient, data analysis, and publication of main trial results

15. Investigators

15.1 Management group

Peter Bentzer, MD, PhD principal investigator, peter.bentzer@med.lu.se
Niklas Nielsen, MD, PhD senior investigator, niklas nielsen@med.lu.se
Janus Christian Jakobsen, MD, PhD, chief trialist, janus.jakobsen@ctu.dk
Gisela Lilja, OT, PhD, coordinator of patient reported outcomes, gisela.lilja@med.lu.se
Jane Fischer, PhD, trial manager, jane.fisher@med.lu.se
Anja Lindén, MD, site investigator, anja.linden@med.lu.se
Fredrik Sjövall, PhD, trialist, fredrik.sjovall@med.lu.se
Markus Harboe Olsen, MD, trialist, markus.harboe.olsen@regionh.dk

15.2 Steering group

Site investigators and the management group will be part of the steering group. A representative from the newly formed patient organisation "Sepsisföreningen" will be invited to the steering group meetings if/when aspects of the conduct of the trial which are deemed to be of importance from a patient perspective are discussed. Such aspects include any change in the protocol with ethical implications.

References

1. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315(8):801–810.
2. Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet 2020;395(10219):200-211.
3. Hjortrup PB, Haase N, Bundgaard H, et al. Restricting volumes of resuscitation fluid in adults with septic shock after initial management: the CLASSIC randomised, parallel-group, multicentre feasibility trial. Intensive Care Med 2016;42:1695-1705.
4. Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl starch 130/0.42 versus ringer's acetate in severe sepsis. N Engl J Med 2012;367:124-134.
5. Hernández G, Ospina-Tascón GA, Damiani LP, et al. Effect of a Resuscitation Strategy Targeting Peripheral Perfusion Status vs Serum Lactate Levels on 28-Day Mortality Among Patients With Septic Shock: The ANDROMEDA-SHOCK Randomized Clinical Trial. JAMA 2019;321(7):654-664.
6. Shankar-Hari M, Phillips GS, Levy ML, et al. Developing a new definition and assessing new clinical criteria for septic shock: for the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:775–787.
7. Holst LB, Haase N, Wetterslev J, et al. Lower versus higher hemoglobin threshold for transfusion in septic shock. N Engl J Med 2014;371:1381-1391.
8. Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med 2021;47:1181-1247.
9. Martin J, Fuller, J., Granton, J., & McConachie, I. Handbook of ICU Therapy (3rd ed.). Cambridge: Cambridge University Press 2014:209-220.

10. Marik PE, Linde-Zwirble WT, Bittner EA, Sahatjian J, Hansell D. Fluid administration in severe sepsis and septic shock, patterns and outcomes: an analysis of a large national database. Intensive Care Med 2017;43:625-632.
11. Boyd JH, Forbes J, Nakada TA, Walley KR, Russell JA: Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. Crit Care Med 2011;39:259-265.
12. Silversides JA, Fitzgerald E, Manickavasagam US, et al. Deresuscitation of patients with iatrogenic fluid overload is associated with reduced mortality in critical illness. Crit Care Med 2018;46:1600-1607.
13. Sakr Y, Rubatto Birri PN, Kotfis K, et al. Higher fluid balance increases the risk of death from sepsis: results from a large international audit. Crit Care Med 2017;45:386–94.
14. Payen D, de Pont AC, Sakr Y, et al. A positive fluid balance is associated with a worse outcome in patients with acute renal failure. Crit Care 2008;12:R74.
15. Meyhoff TS, Møller MH, Hjortrup PB, Cronhjort M, Perner A, Wetterslev J. Lower vs Higher Fluid Volumes During Initial Management of Sepsis: A Systematic Review With Meta-Analysis and Trial Sequential Analysis. Chest 2020;157(6):1478-1496.
16. Chen C, Kollef MH. Targeted Fluid Minimization Following Initial Resuscitation in Septic Shock: A Pilot Study. Chest 2015;148:1462-1469.
17. Douglas IS, Alapat PM, Corl KA et al. Fluid Response Evaluation in Sepsis Hypotension and Shock: A Randomized Clinical Trial. Chest 2020:S0012-3692:30768-6.
18. Meyhoff TS, Hjortrup PB, Wetterslev J, Sivapalan P, Laake JH, Cronhjort M, et al. Restriction of Intravenous Fluid in ICU Patients with Septic Shock. NEJM 2022;386(26):2459-70
19. National Heart, Lung, and Blood Institute Prevention and Early Treatment of Acute Lung Injury Clinical Trials Network, Shapiro NI, Douglas IS, et al. Early Restrictive or Liberal Fluid Management for Sepsis-Induced Hypotension [published online ahead of print, 2023 Jan 21]. *N Engl J Med*. 2023;10.1056/NEJMoa2212663.
20. Lindén-Søndersø, A, Jungner, M, Spångfors, M, et al. Survey of non-resuscitation fluids administered during septic shock: a multicenter prospective observational study. Ann. Intensive Care 2019;9:132.
21. Semler MW, Janz DR, Casey JD, Self WH, Rice TW. Conservative Fluid Management After Sepsis Resuscitation: A Pilot Randomized Trial. J Intensive Care Med 2020;35:1374-1382.
22. Brown SM, Collingridge DS, Wilson EL, et al. Preliminary Validation of the Montreal Cognitive Assessment Tool among Sepsis Survivors: A Prospective Pilot Study. Ann Am Thorac Soc 2018 ;15(9):1108-1110.
23. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53(4):695-9.
24. Herdman M, Claire Gudex, A Lloyd, et al. Development and preliminary testing of the new five-level version of eq-5d (eq-5d-5l). Qual life res 2011;20(10):1727–1736.
25. Kellum JA, Lameire N, KDIGO AKI Guideline Work Group. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). Crit Care 2013;17:204.

26. Wilson JT, Pettigrew LE, Teasdale GM. Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use. J Neurotrauma 1998;15(8):573-85.
27. Wilson L, Boase K, Nelson LD, et al. A Manual for the Glasgow Outcome Scale-Extended Interview. J Neurotrauma 2021;38(17):2435-46.
28. De Backer D, Cecconi M, Chew MS, et al. A plea for personalization of the hemodynamic management of septic shock. Crit Care 2022;26(1):372.
29. Finfer S, Liu B, Taylor C, et al. Resuscitation fluid use in critically ill adults: an international cross-sectional study in 391 intensive care units. Crit Care 2010; 14:R185.
30. Lamontagne F, Richards-Belle A, Thomas K, et al. Effect of Reduced Exposure to Vasopressors on 90-Day Mortality in Older Critically Ill Patients With Vasodilatory Hypotension: A Randomized Clinical Trial. JAMA 2020;323(10):938-949
31. Mouncey PR, Osborn TM, Power S, et al. ProMISe Trial Investigators. Trial of early, goal-directed resuscitation for septic shock. N Engl J Med 2015;372:1301-11.
32. Sjövall F. Novus. Forskande intensivvård [online]. 2020. https://www.lu.se/sites/www.lu.se/files/2020-12/17012_novusrapport_forskande_intensivvard_lang_version_formular.pdf (Accessed 03 June 2022)
33. Lehmann EL. Nonparametrics : Statistical Methods Based on Ranks, Revised. Prentice Hall 1998:76–81.
34. Granja C, Dias C, Costa-Pereira A, Sarmento A. Quality of life of survivors from severe sepsis and septic shock may be similar to that of others who survive critical illness. Crit Care 2004;8(2):R91-8.
35. Hammond NE, Finfer SR, Li Q, et al. Health-related quality of life in survivors of septic shock: 6-month follow-up from the ADRENAL trial. Intensive Care Med 2020;46(9):1696-1706.
36. McClure NS, Sayah FA, Ohinmaa A, Johnson JA. Minimally Important Difference of the EQ-5D-5L Index Score in Adults with Type 2 Diabetes. Value Health 2018;21(9):1090-1097.
37. Poukkanen M, Vaara ST, Pettilä V, et al. Acute kidney injury in patients with severe sepsis in Finnish Intensive Care Units. Acta Anaesthesiol Scand 2013;57(7):863-72.
38. Nørskov AK, Lange T, Nielsen EE, et al. Assessment of assumptions of statistical analysis methods in randomised clinical trials: the what and how. BMJ Evid Based Med 2021;26:121-126.
39. Jakobsen JC, Gluud C, Wetterslev J, Winkel P: When and how should multiple imputation be used for handling missing data in randomised clinical trials - a practical guide with flowcharts. BMC Med Res Methodol 2017;17:162.

Figure 1. Trial timeline.

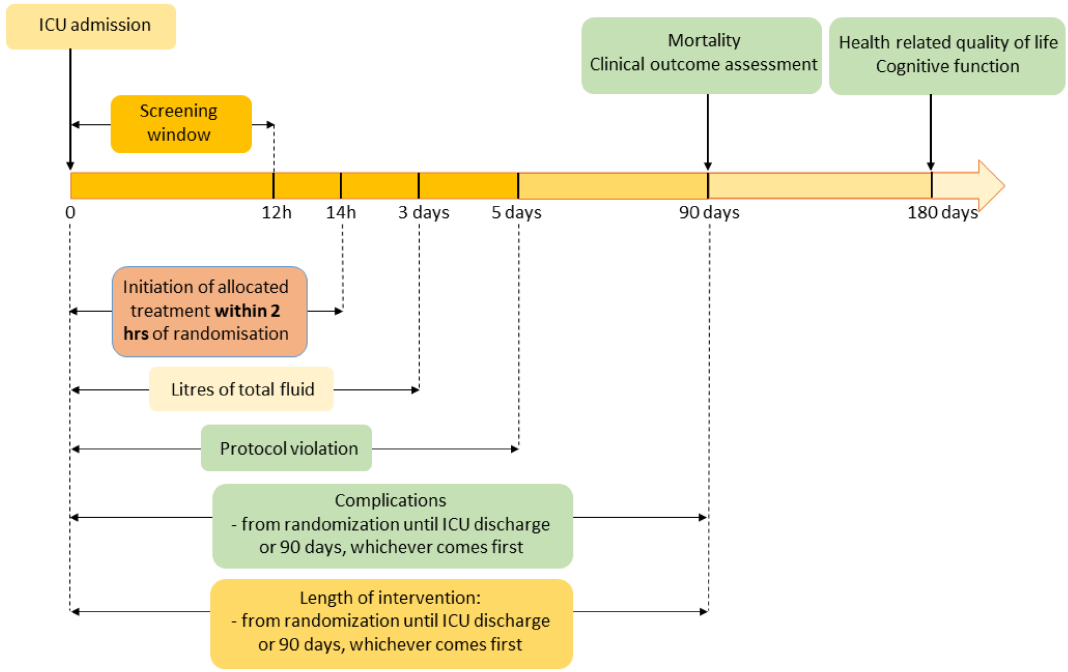


Fig 1. Trial timeline. Vertical arrows indicate specific time points for events or assessments, whereas horizontal arrows describe a certain time period.
Complications: cerebral, cardiac, intestinal or limb ischemia or any acute kidney injury.
DAF: Days alive and free.

Appendix A. Description of collected data and outcomes

Primary feasibility outcome	Litres of fluids administered within three days of randomisation.
Secondary feasibility outcomes	Fraction of randomised patients with sufficient clinical outcome data. These include all-cause mortality, days alive and free of mechanical ventilation, acute kidney injury, and ischemic events in the ICU (cerebral, cardiac, intestinal or limb ischemia) within 90 days of inclusion.
	Fraction of surviving randomized patients who were assessed by European Quality of Life-5 Dimensions 5- Level questionnaire (EQ5D-5L) and The Montreal Cognitive Assessment (MoCA).
	Fraction of all eligible patients who were randomised and consented
	Fraction of patients experiencing at least one protocol violation
Primary explorative clinical outcomes	All-cause mortality at 90 days after inclusion
	One or more complications in the ICU (dichotomous outcome) (Y/N), if yes, specify: - Cerebral ischemia (on MRI or CT scan) (Y/N) - Cardiac ischemia [myocardial infarction/unstable angina AND treatment as a consequence; PCI/thrombolysis or initiation/increased antithrombotic treatment] (Y/N) - Intestinal ischemia [diagnosed during surgery or by angiography] (Y/N) - Limb ischemia [in combination with treatment; open/percutaneous vascular intervention, amputation, initiation of/increased antithrombotic treatment] (Y/N) Any acute kidney injury [KDIGO-classification] (Y/N)
	Days alive and free of mechanical ventilation within 90 days of inclusion
	MoCA at 6 months after inclusion
	HRQoL at 6 months after inclusion (Visual analogue scale and EQ5D-5L)
Secondary exploratory clinical outcomes	Total volume of non-resuscitation fluids administered up to day 3 and 5 after inclusion (crystalloids > 5 ml/kg/h, colloids and blood products) (ml)
	Renal function (KDIGO-classification, days alive and free of renal replacement therapy (RRT) within 90 days after inclusion (days)
	Gastrointestinal function (days alive with full enteral nutrition within 90 days of inclusion)(days)
	Total volume of resuscitation fluid administered up to day 3 and day 5 after inclusion (ml)
	Cumulative fluid balance at day 3 and 5 after inclusion (evaporation excluded)(ml)
	Dose of loop diuretics first 5 days after inclusion (mg)

	Hemodynamic stability first 5 days after inclusion (highest dose of noradrenaline (ug/kg/h), highest daily lactate (mmol(l), Cardiovascular Sequential Organ Failure Assessment (SOFA)-score
	Glasgow Outcome Scale Extended (GOSE) at 6 after inclusion
Demographic/background variables	Age (years)
	Sex (F/M)
	Gender (F/M/other)
	Height (cm)
	Weight at baseline (kg, standardized according to local practice)
	Clinical Frailty Score
	Baseline creatinine [lowest in the 12 months preceding randomization] (µmol/L)
	Charlson Comorbidity Index
	Type of initial antibiotic treatment
	Suspected pathogen
	Suspected pathogen sensitive to initial antibiotic treatment (Y/N)
	Hospital admission (dd-mmm-yyyy, hh:mm)
	ICU admission (dd-mmm-yyyy, hh:mm)
	Hospital location prior to randomization - Emergency department - Operating room - Other ICU - Other unit
	Surgery prior to randomization (Y/N), if yes, specify: - Head and neck - Thorax - Abdominal/pelvic - Extremities - Trauma - Other
	Origin of sepsis (according to criteria developed by Linder/Mellhammar. Mellhammar et al. Crit Care Exp 2022;4:e0697).
	Previous cardiac disease (Y/N), if yes, specify; previous PCI, CABG, ICD, atrial fibrillation/flutter, or cardiomyopathy)
	Hypertension with pharmacological treatment (Y/N)
Baseline variables at study inclusion (all values are recorded values closest in time to inclusion, within ± 6 h unless other time frame is specified).	Body temperature (degrees Celsius)
	Simplified Acute Physiology Score (SAPS) 3

	Sequential Organ Failure Assessment (SOFA) score
	Glasgow Coma Scale (GCS)
	Creatinine (µmol/L)
	Renal replacement therapy (Y/N)
	Urine output [hourly data extracted to 24 hrs], (ml/day)
	Bilirubin (µmol/L)
	Platelet count (x10^9/ml)
	Mean arterial pressure (mmHg)
	Systolic pressure (mmHg)
	Type of vasoactive drugs (noradrenaline, adrenaline, vasopressin, dobutamine, dopamine, levosimendan, milrinone, angiotensin II, or other)
	Noradrenaline dose (highest dose in the 6 hours prior to enrollment; µg/kg/min)
	Atrial fibrillation/flutter (Y/N)
	Ischemic events (Y/N), if yes, specify: - Limb - Cerebral - Heart - Intestine (Criteria described above)
	Heart rate (bpm)
	Ventilatory support (nasal catheter, nasal high flow oxygen, Hudson mask or similar, reservoir mask, non-invasive mechanical ventilation, invasive mechanical ventilation, or none)
	CRP (g/L)
	Albumin (g/L)
	Leucocytes (x109 cells/L)
	Haemoglobin (g/L)
	Potassium (mmol/L)
	Sodium (mmol/L)
	Chloride (mmol/L)
	Blood glucose (mmol/L)
	Plasma lactate [Highest value at any time while the patient is in the ICU and receiving vasopressors] (mmol/L)
	FiO2 (%)
	PaO2 (kPa)
	PaCO2 (kPa
	pH
	Base excess (BE, mEq/L)
Fluid administration variables prior to inclusion	Resuscitation fluids in the 24 hrs prior to inclusion - Colloids (specify) • Albumin 4-5% (ml) • Albumin 20% (ml) • Other (ml)

	- Crystalloids administered to correct hemodynamic impairment as noted in the patient chart or given at a rate > 5 ml/kg/h (specify)
	  • Ringers acetate/lactate (ml)
	  • 0.9% NaCl (ml)
	  • Other (ml)
	- Blood products (specify)
	  • Erythrocyte (ml)
	  • Plasma (ml)
	  • Platelets (ml).
	
	Maintenance and nutrition fluids in the 24 h prior to inclusion
	- Crystalloids administered for reasons other than correcting hemodynamic impairment. If indication in the medical charts is unclear, crystalloids at a rate below 5 ml/kg/h will be classified as maintenance fluids
	  • Ringer's acetate/lactate (ml)
	  • 0.9% NaCl (ml)
	  • Other (ml)
	- Glucose solution (specify concentration)
	  • Glucose solution 2.5% (ml)
	  • Glucose solution 5% (ml)
	  • Glucose solution 10% (ml)
	  • Glucose solution 20% (ml)
	  • Other glucose strength
	- Parenteral nutrition (ml)
	- Enteral nutrition (ml)
	- Enteral water (ml)

Daily variables for the first 5 days after inclusion (only collected if patient is in the ICU)	Resuscitation fluids
	- Crystalloids administered to correct hemodynamic impairment as noted in the patient chart or given at a rate > 5 ml/kg/h (specify)
	  • Ringer's acetate/lactate (ml)
	  • 0.9% NaCl (ml)
	  • Other (ml)
	- Colloids (specify)
	  • Albumin 4-5% (ml)
	  • Albumin 20% (ml)
	  • Other (ml)
	- Blood products (specify)
	  • Erythrocytes (ml)
	  • Plasma (ml)
	  • Platelets (ml)

	Volumes of intravenous vehicles and drugs Vehicles for drugs

	- Ringer's Acetate/Ringer's Lactate (ml) - 0.9% NaCl (ml) - Other crystalloids (mL) - Glucose 5% (ml) - Sterile water (ml) - Premixed drugs (ml) - Other fluid as vehicle (mL) Drugs regardless of vehicle - Antibiotics (mL) - Inotropes (includes dobutamine, levosimedan, or dopamine <5mcg/kg/min) (mL) - Vasopressors (mL) - Analgesics (mL) - Sedatives (mL) - Insulin (mL) - Potassium (mL) - Other electrolytes (mL) - Other drugs (mL)
	Maintenance/replacement and nutrition fluids - Crystalloids administered for reasons other than correcting hemodynamic impairment. If indication in the medical charts is unclear, crystalloids at a rate below 5 ml/kg/h will be classified as maintenance fluids • Ringer's acetate/lactate (ml) • 0.9% NaCl (ml) • Other (ml) - Glucose solution (specify concentration) • Glucose solution 2.5% (ml) • Glucose solution 5% (ml) • Glucose solution 10% (ml) • Glucose solution 20% (ml) • Other glucose strength - Parenteral nutrition [premixed bags with fats, proteins and glucose] (ml) - Enteral nutrition (ml) - Enteral water (ml) Full enteral nutrition [as per calculated daily need of calories] (Y/N) Total caloric intake [including Propofol and glucose solutions] (kcal) Any extra sodium added to any of the intravenous fluids (mmol)
	Fluids for electrolyte disturbances - Intravenous fluids given to correct electrolyte disturbances (mL)

	- Enteral water given to correct electrolyte disturbances (mL)
	Diuretics (Y/N), if yes, specify: - Loop diuretics (mg/24h) - Carbanhydrase inhibitors (Y/N) - Other
	Fluid output - Urinary output (ml) - Drains (ml) - Hemorrhage (ml) - Faeces [if liquid] (ml) - Fluid removal in RRT (ml) - Other losses [evaporation excluded] (ml)
	Weight (kg)
	Fluid balance goal for next 24h (Y/N, and volume in mL)
	Body temperature [highest] (degrees Celsius)
	Glasgow Coma Scale [highest] (GCS)
	Creatinine [highest](µmol/L)
	Renal replacement therapy (Y/N)
	Earliest urea (mmol/L)
	Plasma bilirubin [highest] (µmol/L)
	Platelet count [lowest] ($x10^9$/L)
	Mean arterial pressure [lowest value] (mmol/L)
	Type of vasoactive drugs (dobutamine, dopamine, vasopressin, levosimendan, angiotensin II, noradrenaline, adrenaline, angiotensin II, or other)
	Noradrenaline dose [highest dose that day] (µg/kg/min)
	Cardiac arrhythmia - Atrial fibrillation/flutter (Y/N) - Ventricular tachycardia (Y/N - Ventricular fibrillation(Y/N)
	Ischemic events (Y/N), if yes; specify: - Limb - Cerebral - Heart - Intestine (Definitions described above)
	Mechanical ventilation (Y/N)
	Lowest PaO2 (kPa)
	FiO2 (at time of lowest PaO2; %)
	Haemoglobin [earliest] (g/L)
	Potassium [earliest] (mmol/L)
	Sodium [earliest] (mmol/L)
	Chloride [earliest] (mmol/L)
	Lactate [highest] (mmol/L)
	Blood glucose [earliest] (mmol/L)

	Insulin dose (E/day)
	Complications - Hypoglycemia [≤ 3.9 mmol/L] (Y/N) - Hypernatriemia [>159 mmol/L] (Y/N) - Hyperchloremic acidosis [pH<7.15 and plasma-chloride >115 mmol/L] (Y/N) - Metabolic alkalosis [pH>7.59 and base excess >9] (Y/N) - Suspected unexpected complications (SUSAC) - none
Variables at discharge	ICU discharge - Date and time of ICU discharge (dd-mmm-yyyy, hh:mm) - Status at ICU discharge (alive/deceased)
	ICU readmission - Readmission (Y/N) - Readmission date and time (dd-mmm-yyyy, hh:mm) - ICU discharge date and time (dd-mmm-yyyy, hh:mm) - Status at ICU discharge (alive/deceased)
	Hospital discharge - Date and time of hospital discharge (dd-mmm-yyyy, hh:mm) - Status at hospital discharge (alive/deceased) - Patient discharged to • Home • Rehabilitation facility • Nursing home • Other hospital (ward) • Other ICU • Other
	Withdrawal of life sustaining therapies (WLST) (Y/N), if yes, specify reason: - Irreversible organ failure (Y/N) • Cardiac • Lung • Liver • Kidney • Coagulation • Brain • Other - Medical comorbidity (Y/N) - Other (Y/N); specify - Date and time when WLST decision was made (dd-mmm-yyyy, hh:mm)
	Date and time of death (dd-mmm-yyyy, hh:mm)
	Complications - Ischemic events (Definitions described above) (Y/N), if yes; specify:

	- Limb - Cerebral - Heart - Intestine - Hypoglycemia [≤ 3.9 mmol/L] (Y/N) - Hypernatriemia [>159 mmol/L] (Y/N) - Hyperchloremic acidosis [pH<7.15 and plasma-chloride >115 mmol/L] (Y/N) - Metabolic alkalosis [pH>7.59 and base excess >9] (Y/N) - Suspected unexpected complications (SUSAC)
Consent	Patient responsible informed (Y/N) and patient informed (Y/N) - Date informed (if Y) - Reasons (if N) - Objected to participation/consented (Y/N) Consent withdrawn (Y/N by patient or by person responsible) - Date of withdrawal Can the data be used (Y/N)
90-day follow-up	Date of follow-up Status (alive/deceased) Days alive and free of renal replacement therapy (RRT) Days alive and without invasive (intubated or tracheostomy) mechanical ventilation Days alive without vasopressors Days alive with full enteral nutrition
6 month follow-up	Date of follow-up Status (alive/deceased) Place of follow up (Institution/ home of patient/ telephone/ digital)
	Health-Related Quality of Life using the European Quality of Life-5 Dimensions 5-Level questionnaire
	Life satisfaction (scale of 1-10)
	Background information - Does the patient have a native language other than the test language (Y/N) - capabilities that may interfere with the patient's ability to perform the tests - No problems - Hearing - Vision - Speech problems - Dyslexia - Paresis - Memory problems or other cognitive problems prior to the episode of sepsis - Other - Known neurological disease

	- Highest education level
	  - No formal education
	  - Incomplete primary/lower secondary school
	  - Complete primary/lower secondary school
	  - Incomplete upper secondary school
	  - Complete upper secondary school
	  - Some university-level education, without degree
	  - University-level education, with degree
	- Marital status (married/living together as married or living alone)
	- Current place of residence
	  - Home
	  - Hospital
	  - Rehabilitation centre
	  - Nursing home
	  - Other
	- Occupational status before the episode of sepsis
	  - Working full-time
	  - Working part-time
	  - Unemployed
	  - Retired due to age
	  - Retired due to disability / health problems
	  - On sick leave
	  - Other (e.g. student, housewife)
	- Occupational status at the time of the follow-up
	  - Working full-time
	  - Working part-time
	  - Unemployed
	  - Retired due to age
	  - Retired due to disability / health problems
	  - On sick leave
	  - Other (e.g. student, housewife)
	- Date of return-to-work (if applicable)
	- Rehabilitation after the episode of sepsis
	  - None
	  - Inpatient rehabilitation
	  - Outpatient rehabilitation
	  - Home-based rehabilitation (community)
	  - Physiotherapist only
	  - Occupational therapist only
	  - Counselling (by e.g. social worker or psychologist)
	  - Cognitive Behavioural Therapy
	Other

	Glasgow Outcome Scale Extended (GOSE) modified for use after Sepsis
	Montreal Cognitive Assessment (MoCA) (face-to-face /digital /telephone)

Appendix B. Dilutions of medications in the intervention group.

MEDICATIONS in the intervention group. The concentrated solutions should only be used once the patient has a central line. To avoid waste of drug, apply protocol when it´s time to change syringe. Glucose may also be supplied as a vehicle for medication rather than a separate infusion of 20% glucose in patients receiving glucose for the indications described in the treatment algorithm (Appendix D). More concentrated solutions than those described below are allowed if already in use at trial site. Drugs not included in the table below should be used in the most concentrated dilution already in use at trial site.

Drug	Conc. in stem solution	Suggested dilution in intervention group	Reference	Comments
Suggested dilutions may only be used if patient has a central line **Vasoactive drugs**				
Adrenaline	1 mg/ml	Start at 80 µg/ml and change to 160 µg/ml if infusion rate >10 ml/h	SPC, IM, Micromedex, Halmstad, UKCPA	**IM;** IV inf 40 - 320 µg/ml, diluted in G. **Halmstad**; 80 µg/ml i NaCl. **UKCPA**; Up to 500ug/ml has been used
Amiodarone (Cordarone, Amiodaron Hameln)	50 mg/ml	Dilute to 15mg/ml (20 ml G per 300mg amiodarone) Note! Dilute according to local guidelines in cardiac arrest,	SPC, ePED, UKCPA	**SPC**; Dilute in 5% G. **ePed;** 15mg/ml as infusion. **UKCPA**; Many centres infuse daily dose (up to 900mg) in a total volume of 48-50ml
Dobutamine Hameln	12,5 mg/ml	10 mg/ml	SPC, IM, UKCPA	**IM**; Fluid restr. Adult 2 amps (2x20 ml) + 10 ml NaCl/G give 10 mg/ml.
Isoprenaline	0,2 mg/ml	use according to local protocol	Micromedex, Gahart´s, UKCPA	**Halmstad**; 10 ml 0,2 mg/ml in 40 ml G, gives 40 µg/ml. **Micromedex och Gahart´s**; recommend 20 ug/ml for iv bolus and 2 to 4 ug/ml for infusion.
Milrinone	1mg/ml	use according to local protocol	SPC	**SPC** dilute to 200 ug/ml using G/NaCl.
Nitroglycerin (Abcur och BioPhausia)	1 mg/ml	use according to local protocol	SPC, IM	**SPC**; May be given udiluted using a pump. Can be diluted in G/NaCl. **IM**; 1 mg/ml may be given undiluted

Drug	Conc. in stem solution	Suggested dilution in intervention group	Reference	Comments
Noradrenaline (Abcur, Pfizer)	1 mg/ml	Start at 80 µg/ml and change to 160 µg/ml if infusion rate >10 ml/h	SPC, IM, Micromedex, Stabilis	**SPC**; Noradrenaline 1 mg/ml should be diluted with G/NaCl before use. **IM**; 160 µg/ml. **Micromedex**; G may protect against oxidation. **Stabilis**; 0.5 mg/ml Norepinephrine bitartrate is stabile in G for 48 h at 20-25 °C.
Levosimendan	2.5 mg/ml	0.05 mg/ml (10 ml levosimendan 2,5 mg/ml in 500 ml G	SPC, IM	
Phenylefrine (Abcur och Unimedic)	0.1 mg/ml	use according to local protocol	Micromedex, IM	**Micromedex**; for iv bolus use 100 µg/ml and 20 µg/ml for inf.
Vasopressin/ Argipressin (Empressin)	20 IE/ml	0.4 E/ml	IM, UKCPA	**IM;** 1 amp. (1 ml, 20 units in 50 ml med G, will give conc 0.4 units/ml. **Gahart´s;** 1 E/ml
Antibiotiotics				
Acyklovir	25mg/ml	5mg/ml Dilute 10 ml 25 mg/ml with 40 ml of NaCl/G	SPS, UKCPA	**UKCPA;** 25mg/ml over 1 hour by controlled rate infusion. If diluted 5mg/ml infused over at least 1 hour**.**
Ampicillin		1 g in 10 ml of sterile water 2 g in 20 ml of sterile water	SPC, Micromedex	**SPC;** For iv inj. 10 and 20 ml for 1 and 2 g, respectively. **Micromedex;** 1 and 2 g may be diluted in 7.4 and 14.8 ml sterile water, respectively and given in 10-15 min tom minimize risk of seiziures. **SPC Meda/Mylan**. Give slowly (minimum 3-4 minutes).
Anidulafungin		100 mg in 30 ml of sterile water and add to 100 ml G/NaCl.	SPC, Stabilis, Micromedex, Gahart´s	Infusion rate 1,4 ml/min resulting a total infusion time of 90 min.
Bensylpenicillin		1 g in 10 ml of sterile water 3 g in 20 ml of sterile water	SPC, IM	**SPC;** dissolve 1 g in 10 ml of sterile water and 3 g in 20-40 ml of sterile water. **IM;** 600 mg in 4-

REDUSE Feasibility 2023-02-07

Drug	Conc. in stem solution	Suggested dilution in intervention group	Reference	Comments
				10 ml. Inject slowly (> 3-5 minutes)
Caspofungin	50 mg 70mg	Carefully dissolve 50 mg in 10,5 ml of sterile water. Add to 100 ml NaCl. Carefully dissolve 70 mg l in 10,5 ml of sterile water. Add to 140 ml NaCl	Micromedex, SPC, IM	Give drug during at least 60 min!
Cefotaxim		1 g in 4 ml sterile water 2 g in 10 ml sterile water	SPC	**SPC**; Note that rapid injection of cefotaxim in central line has been reported to cause life threatening arythmia in rare cases.
Ceftazidim		1 g in 10 ml of sterile water 2 g in 10 ml of sterile water	SPC, IM, Micromedex	
Ceftriaxon		1 g in 10 ml of sterile water 2 g in 20 ml of sterile water	SPC , Stabilis, IM. Micromedex	**SPC**, Use NaCl or G for 2 g. **Stabilis;** 100 mg/ml in water is ok. **Micromedex;** 2 g in 10 ml. **IM;** Infusion if dose ≥ 2 g.
Cefuroxim		750 mg in 6 ml of sterile water 1,5 g in 15 ml of sterile water	SPC, IM	
Clindamycin	150 mg/ml	600 mg in 50 ml G/NaCl (gives 11 mg/ml)	SPC, IM	**IM;** Final concentration max 18 mg/ml. **SPC, IM;** shortest infusion time is 600 mg in 20 min.
Cloxacillin		1 g in 20 ml of sterile water 2 g in 40 ml of sterile vatten	SPC, Stabilis	**Stabilis** conc up to 250 mg/ml are ok.
Doxycyklin	20 mg/ml	100 mg in 100 ml G/NaCl 200 mg in 200 ml G/NaCl	SPC	

REDUSE Feasibility 2023-02-07

Drug	Conc. in stem solution	Suggested dilution in intervention group	Reference	Comments
Erytromycin		1 g in 20 ml sterile water and add 80 NaCl.	IM, ePed, SPC,	**IM**; Final concentration should not be greater than 10 mg/ml. **ePed;** Give dose in > 1h to mimimize risk of arythmias.
Gentamycin	40 mg/ml	May be given undiluted as bolus. Repeated doses either diluted or as boluses over 3-5 minutes depending on dosing regimen.	SPC, UKCPA	**SPC**; If administered twice daily gentamycin may be given undiluted in 3-5 minutes. **UKCPA**; For large doses most centers dilute with 50 ml G/NaCl.
Imipenem/Cilastatin		500/500 mg in 10 ml NaCl and add to 90 ml NaCl/G. Maximum concentration of imipenem 5 mg/ml	IM, SPC, UKCPA	**SPC;** doses ≤ 500 mg/500 mg should be given over 20 to 30 minutes and doses >500 mg/500 mg should be given over 40 to 60 minutes.
Meropenem		For bolus dilute in sterile water to a final concentration of 100mg/ml For infusion dilute to 20mg/ml with NaCl	IM, SPC, UKCPA	**IM;** 0.5 - 1 g doses in 5 min. 2 g doses in 15-30 min. **SPC**. Meropenem diluted to 20mg/ml in NaCl stable for 3 h in room temperature.
Metronidazol	5 mg/ml	Undiluted		
Piperacillin/Tazobactam		2/0,25 g in 10 ml of sterile water/NaCl 4/0,5 g in 20 ml of sterile water/NaCl For infusions dilute further with G/NaCl to 50ml	SPC, IM,	
Tobramycine	40 mg/ml	Use undiluted	IM, SPC	

Drug	Conc. in stem solution	Suggested dilution in intervention group	Reference	Comments
Tobramycine	80 mg/ml	80 mg/ml dilute with 50 ml G/NaCl	SPC	**SPC;** shorter infusion time than 20 minutes will increase risk for toxic side-effects and is not recommended.
Trimetoprim/Sulfametoxazol	16+80 mg/ml (5 ml/amps)	2 amps. in 150 ml G. Observe carefully for precipitates. 4 amps. in 300 ml G	SPC, IM	**SPC;** Stable for 2 h! **IM;** possible to give undiluted stock solution in 60-90 min (off label).
Vancomycin		500 mg in 10 ml sterile water. Add to 40 ml NaCl/G to give a conc. of 10 mg/ml 1 g in 20 ml of sterile water. Add to 80 ml NaCl/G to give a conc. of 10 mg/ml	IM, UKCPA	**IM;** In exceptional circumstances 20 mg/ml may be given via a central line. **UKCPA;** 10mg/ml is a commonly used dilution. 20mg/ml has been used in some centers. **IM;** give in 1 h. **Regional dilution routine;** Give a dose of 500 mg in 60 min and 1g in a 100 min.
Vorikonazole	200 mg	200 mg in 19 ml of sterile water to a conc. of 10 mg/ml. For doses 50-500 mg: add to 100 ml G/NaCl. For doses > 500 mg: add to 250 ml G/NaCl.	IM, SPC	Final concentration should be 0,5-5,0 mg/ml. Max infusion rate is 3 mg/kg/h.
Fluconazol	2 mg/ml	Use undiluted	SPC	Infusion rate 10 ml/min or lower.
Other drugs				
Clonidine	150 µg/ml (1 ml ampull)	30 µg/ml	SPC, IM, UKCPA	**UKCPA;** 6-50 micrograms/ml infusion. Diluent: Sodium chloride 0.9% or glucose 5%.
Dexdmedetomidine	100ug/ml	8ug/ml	SPC	
Sodium glycerophosphate (Glycophos)	1 mmol/ml	0.5 mmol/ml 20 ml sodium glycerophosphate	ePED	**ePED**; Administer in no less than 8 h.

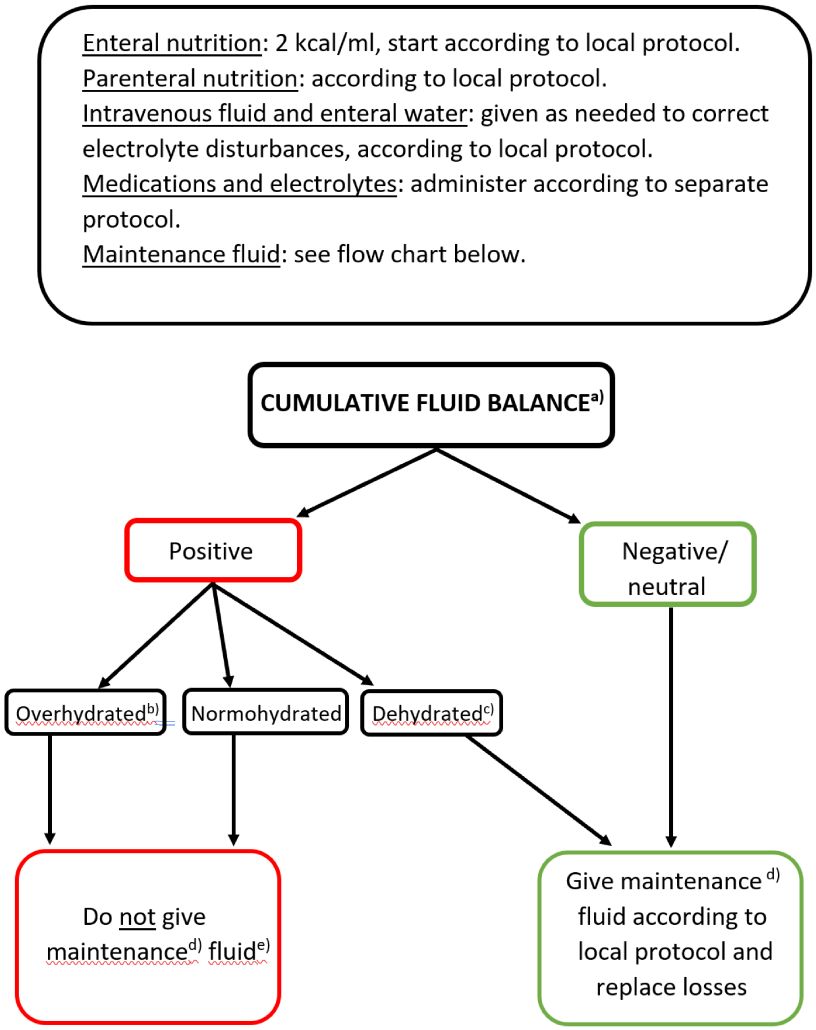
REDUSE Feasibility 2023-02-07

Drug	Conc. in stem solution	Suggested dilution in intervention group	Reference	Comments
		1mmol/ml in 20 ml NaCl.		
Insulin (Humulin Regular, Actrapid)	Insulin, humant (Humulin Regular)	1 E /ml	Stabilis	**Stabilis;** Dilute in NaCl
Levetiracetam	100 mg/ml (5 ml flaska)	250 - 1500 mg in 100 ml NaCl/G, ges på 15 min.	SPC, IM, Micromedex, Gahart´s	**Micromedex;** Do not exceed a final max cons of 15 mg/ml. Can be given as iv bolus, 3-5 min and cont infusion 200-400 mg/h.
Magnesium sulphate (Addex-Mg)	1 mmol/ml	0.5 mmol/ml, (20 ml in 20 ml NaCl, giving a conc. 0,5 mmol/ml). Give in no less than 10 min.	IM, Gahart´s, VGR guideline, UKAP	**Gahart´s;** D5W and NS are the most common diluents. **UKCPA**; suggested dilutions 1-2mmol/ml
Potassiumhydroxide/ Potassium phosphate (Addex-Kalium)	2 mmol/ml	1-2 mmol/ml dilute in NaCl if needed	SPC	**SPC;** Give at most 20 mmol potassium/h.
Potassium Chloride	2 mmol/ml	1-2 mmol/ml, in NaCl dilute if needed	SPC	**SPC;** Give at most 20 mmol potassium/h.
Propofol (Propofol-Lipuro)	10 or 20 mg/ml	20 mg/ml for infusion. According to local routine for intubation	SPC	

NaCl = Sodiumchloride 9 mg/ml = NS, **G=**Glukose 50 mg/ml=Dextrose 5%=D5W

Gahart´s = Gahart´s 2021 intravenous medication via https://www.clinicalkey.com. **Halmstad** = vårdriktlinje "Inotropa läkemedel och vasopressorer HSH" published in 200913, **IM** = UCL Hospitals Injectable Medicines Administration Guide: Pharmacy Department, 3rd Edition, University College London Hospitals, ISBN: 978-1-405-19192-0, **Micromedex** = https://www.micromedexsolutions.com, **Regional dilution routine Region Skåne, Sweden** = www.lakemedelshantering.se, **Stabilis** = https://www.stabilis.org, **UKCPA.** United Kingdom Clinical Pharmacy association: Minimum infusion volumes for fluid restricted critically ill patients. 4th edition Dec 2012

Appendix C. Treatment algorithm for non-resuscitation fluids in the intervention arm.



a) Measured ins and outs:
Ins: nutrition, maintenance fluids, medications and electrolytes, crystalloids given to correct hemodynamic impairment, blood transfusions and colloids.
Outs: diuresis, fluid removal from renal replacement therapy, tube drainage, vomiting/gastric tube drainage, bleeding and contents from faecal management system.
Cumulative fluid balance is calculated from hospital admission.

b) Overhydrated (increased total body water relative to baseline) as suggested by weight above baseline/preadmission body weight, and/or peripheral/radiological oedema.

c) Dehydrated (decreased total body water relative to baseline) as suggested by body weight below baseline/preadmission body weight, decreased skin turgor, dry mucus membranes. Adjust baseline bodyweight according estimated weight loss during ICU stay.

[d] Maintenance fluid is defined as intravenous fluid (crystalloids not given to correct hemodynamic impairment and/or glucose solutions) or enteral water prescribed to ensure that total volume of fluid covers basic need of water (approximately 1 ml/kg/h). Starting on day 4 after randomization, glucose solutions at a maximal dose of 1g/kg/day may be given if enteral nutrition is not tolerated. Glucose at this- or a lower dose may be started earlier in patients with insulin dependent diabetes if enteral feeding is not tolerated and if local protocol mandates this. Glucose solution should be at a concentration of 20% or above unless the patient is dehydrated

[e] Diuretics may be given to achieve desired fluid balance.

Appendix D. Estimation of potential for a reduction of fluid input by application a restrictive protocol for administration of non-resuscitation fluids.

The potential to reduce administration of non-resuscitation fluids was modelled as described previously in our study characterizing fluid administration in septic shock patients in 8 ICUs in Sweden and Canada (Lindén-Søndersø et al 2019). Briefly, we devised a pragmatic "restrictive" protocol for administration of non-resuscitation fluids based on the most restrictive practice already in place for non-resuscitation fluids at any of the participating ICUs. In this protocol, we assumed the following: no maintenance fluid was given to patients with a positive cumulative fluid balance, no intravenous glucose was given for nutritional purposes, and enteral nutrition was changed to a concentration of 2 kcal/ml in centres using less concentrated formulas. For Swedish sites this modelling suggested that administration of non-resuscitation fluids could be reduced by a median of 3.1 (IQR1.5-4.9) L in the first three days in the ICU (day 0 to 3). For the purpose of the power calculation we used the estimated standard deviation of 2.8 L.

REDUSE Feasibility 2023-02-07

Appendix E. Informed consent form

Information till dig som vårdats på intensivvårdsavdelning för septisk chock angående studien:

Kan protokollstyrd administration av vätska som ges i andra syften än att stabilisera cirkulationen förbättra utfallet vid septisk chock?

Forskningshuvudman: Region Skåne
Huvudansvarig forskare: Professor, överläkare Peter Bentzer, Charlotte Yhléns gata 252 23 Helsingborg, 042 - 4061000.

Du har varit inlagd på intensivvårdsavdelning och vårdats för tillståndet septisk chock, ett tillstånd som orsakas av en infektion i kroppen. Vid septisk chock är det vanligt att man får stora mängder vätska. En del av vätskan ges för att upprätthålla en tillräcklig blodvolym, en annan del ges tex tillsammans med läkemedel eller som näring. Vätskebehandling kan vara livräddande men det finns forskning som tyder på att för mycket vätska är skadligt. Vi genomför därför en undersökning för att se om vi, genom att minska vätsketillförsel, kan förbättra vårdförloppet och prognosen för dig som patient.
Vi har låtit slumpen bestämma om du fått ”vanlig” mängd vätska eller minskad mängd vätska. Eftersom du var medtagen av din sjukdom har vi inte kunnat fråga om du vill vara med i undersökningen förrän nu, men vi har samrått med dina anhöriga och informerat om din medverkan i undersökningen.
Vi har samlat in information om vården på intensivvårdsavdelningen.
För att kunna studera om skillnaderna i behandling mellan de två grupperna har betydelse för återhämtningen över tid så kommer du bli kallad till ett uppföljningsbesök ca 6 månader efter det att du skrevs in på intensivvårdsavdelningen. Vid detta besök kommer vi att fråga dig om hur du upplever din hälsa och hur du klarar att utföra dina dagliga aktiviteter. Vid besöket kommer du också få göra ett test av ditt minne. Besöket tar ca en timme. Detta räknar inte in tiden det tar att transportera sig till och från sjukhuset. Till besöket är du välkommen att ta med dig en nära vän/närstående om du så önskar. Reseersättning ges i så fall till er båda.
För studien är det av stor betydelse att så många som möjligt deltager i uppföljningen, oavsett om du upplever dig må bra eller dåligt. De tester vi använder för att samla in information om din återhämtning har använts i många andra studier, och kan upptäcka även små besvär med exempelvis minne som kan påverka din återhämtning och vardagen. Skulle vi upptäcka att du har kvarstående besvär kommer vi fråga dig om du upplever att du fått den hjälp du behöver, och om inte hänvisa dig till en lämplig specialist inom området, såsom en arbetsterapeut, fysioterapeut, psykolog, neurolog, rehabiliteringsläkare eller allmänläkare för vidare undersökning, råd och stöd.
All data som samlas in är sekretesskyddad. Den kommer kodas och lagras i en elektronisk databas som uppfyller alla krav på sekretess för att skydda din integritet. Informationen

sparas i 15 år och ingen obehörig kommer ha tillgång till den. Anonymiserade data kan komma delas med utländska forskare.
Deltagande i studien är frivilligt och du kan när som helst avböja deltagande i studien och vidare insamling av data kommer då avbrytas. Du kan begära att användningen av data begränsas. Du har också rätt att få se vilken information som samlats in och vid eventuella felaktigheter rätt att begära att de korrigeras eller helt tas bort. Du är välkommen att när som helst kontakta nedanstående ansvariga forskare om du har några frågor kring undersökningen. Om du är missnöjd med hur dina personuppgifter behandlas har du rätt att ge in klagomål till Integritetsskyddsmyndigheten, som är tillsynsmyndighet.

Region Skåne är ansvarig för era personuppgifter enligt Dataskyddsförordningen (GDPR). Vid frågor kring hanteringen via Dataskyddsförordningen kan ni vända er till:
Personuppgiftsombudet i Region Skåne, 291 89 Kristianstad.
Patientskadeförsäkringen gäller för denna undersökning.

Helsingborg, 2022-03-01

Anja Lindén, specialistläkare
Kliniken för anestesi och intensivvård
Helsingborgs lasarett
Charlotte Yhléns gata 10
25223 Helsingborg

Telefon: 042- 406 37 24
e-mail: anja.linden@med.lu.se

REDUSE Feasibility 2023-02-07

SAMTYCKESFORMULÄR

Kan protokollstyrd administration av vätska som ges i andra syften än att stabilisera cirkulationen förbättra utfallet vid septisk chock?

Jag har informerats om studien muntligt och i skriftlig patientinformation.

Jag anser att jag har fått tillfälle att ställa frågor och att jag har fått dessa besvarade.

Jag samtycker till att delta i ovanstående studie samt samtycker till att mina personuppgifter lagras.

Jag samtycker också till att mina uppgifter som noterats i min patientjournal granskas för att se att de överensstämmer med de uppgifter som har lagrats i studiedatabasen. Denna granskning kommer att genomföras av en extern studiemonitor (granskare) för att säkerställa studiens kvalitet.

Patient

Ort: …… Datum: ……

Namnteckning: ……

Namnförtydligande: ……

	Protocolized Reduction of Non-resuscitation Fluids vs Usual Care in Septic Shock
Tracking Information	Clinicaltrials.gov, No. NCT05249088.
First Submitted Date ICMJE	February 8, 2022
First Posted Date ICMJE	February 21, 2022
Last Update Posted Date	April 5, 2022
Actual Study Start Date ICMJE	March 1, 2022
Estimated Primary Completion Date	August 31, 2022 (Final data collection date for primary outcome measure)
Current Primary Outcome Measures ICMJE **(submitted: February 18, 2022)**	Difference in fluid administration [Time Frame: Within the first three days after inclusion (days 0-3)] Total difference in litres of administered fluids between groups
Original Primary Outcome Measures ICMJE	*Same as current*

Change History	Complete list of historical versions of study NCT05249088 on ClinicalTrials.gov Archive Site
Current Secondary Outcome Measures ICMJE **(submitted: February 18, 2022)**	• Proportion of participants with sufficient clinical outcome data [Time Frame: Within 90 days after inclusion] Fraction of randomised patients with sufficient data for the following clinical outcomes: all-cause mortality, days alive and free of mechanical ventilation, acute kidney injury, and ischemic events in the ICU (cerebral, cardiac, intestinal or limb ischemia) • Proportion of participants assessed by EQ5D-5L and MoCA [Time Frame: 6 months after inclusion] Fraction of surviving randomized patients who were assessed by European Quality of Life-5 Dimensions 5- Level questionnaire (EQ5D-5L) and The Montreal Cognitive Assessment (MoCA) • Inclusion of eligible patients [Time Frame: During inclusion] Fraction of all eligible patients who were randomised and consented • Protocol violations [Time Frame: Within 90 days after inclusion] Fraction of patients experiencing at least one protocol violation
Original Secondary Outcome Measures ICMJE	*Same as current*
Current Other Pre-specified Outcome Measures (submitted: February 18, 2022)	• Mortality [Time Frame: 90 days after inclusion] All-cause mortality • Complications in the ICU [Time Frame: from randomization until final discharge from ICU or death, whichever comes first, assessed up to 90 days]

	Number of patients with one or more of the following complications in the ICU: cerebral, cardiac, intestinal or limb ischemia, or any acute kidney injury • Days alive and free of mechanical ventilation [Time Frame: Within 90 days after inclusion] Days alive and free of mechanical ventilation • Cognitive function [Time Frame: 6 months after inclusion] Cognitive function measured using MoCA • Health-Related Quality of Life [Time Frame: 6 months after inclusion] Health-Related Quality of Life measured using the EQ5D-5L questionnaire • Total volume of non-resuscitation fluids administered [Time Frame: Within the first three days (days 0-3) and within the first five days (days 0-5) after inclusion] Total volume of non-resuscitation fluids administered • Renal function [Time Frame: Within 90 days after inclusion] Acute kidney injury stages according to Kidney Disease Improving Global Outcomes [KDIGO] criteria, urea, and days alive and free of renal replacement therapy [RRT] • Gastrointestinal function [Time Frame: Within 90 days after inclusion] Days alive with full enteral nutrition • Total volume of resuscitation fluids administered [Time Frame: Within the first three days (days 0-3) and within the first five days (days 0-5) after inclusion] Total volume of resuscitation fluids administered • Cumulative fluid balance [Time Frame: On day 3 and day 5 after inclusion] Cumulative fluid balance (excluding evaporation) • Diuretics administered [Time Frame: Within the first five days (days 0-5) after inclusion]

	Daily dose and type of diuretics administered • Hemodynamic stability [Time Frame: Within the first five days (days 0-5) after inclusion] Daily highest dose of noradrenaline, daily lactate, and cardiovascular sequential organ failure assessment [SOFA] score • Ischemic events [Time Frame: from randomization until final discharge from ICU or death, whichever comes first, assessed up to 90 days] Number of patients with one or more ischemic events while in the ICU (cerebral, cardiac, intestinal or limb ischemia) • GOSE score [Time Frame: 6 months after inclusion] Glasgow Outcome Scale Extended (GOSE) score
Original Other Pre-specified Outcome Measures	*Same as current*
Descriptive Information	
Brief Title ICMJE	Protocolized Reduction of Non-resuscitation Fluids vs Usual Care in Septic Shock
Official Title ICMJE	Protocolized Reduction of Non-resuscitation Fluids Versus Usual Care in Septic Shock Patients: A Multicentre Feasibility Trial
Brief Summary	The objectives of this feasibility trial are to assess the efficacy and feasibility of methods and procedures of a protocol purposed to compare a reduction of administration of non-resuscitation fluids to usual care in patients with septic shock.
Detailed Description	*Not Provided*
Study Type ICMJE	Interventional

Study Phase ICMJE	Not Applicable
Study Design ICMJE	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Investigator, Outcomes Assessor) Masking Description: The clinical team caring for participants will not be blinded due to nature of the intervention. The participants, their family and health personnel responsible for outcome assessment at follow-up will be blinded to the allocation of the intervention. The steering group, author group, trial statistician, outcome assessors, prognosticators, statisticians, and the trial coordinating team will be blinded to group allocation. Primary Purpose: Other
Condition ICMJE	Shock, Septic

Intervention ICMJE	• Other: Protocolised reduction of non-resuscitation fluids
	  ○ Maintenance fluids are discontinued in participants with positive cumulative fluid balance who are not dehydrated
	  ○ Intravenous fluid and enteral water are given as needed to correct electrolyte disturbances
	  ○ Enteral nutrition with energy density of at least 2 kcal/ml is administered according to local practice
	  ○ Starting 72 hours after inclusion, glucose at a concentration of at least 20% and a maximal dose of 1g/kg/day may be used as nutrition if enteral feeding is not tolerated. Glucose at this dose or lower may be started earlier in patients with insulin dependent diabetes if enteral feeding is not tolerated and local protocol mandates this
	  ○ Parenteral nutrition is administered according to local protocol
	  ○ Intravenous medications are concentrated according to a predefined protocol

	○ Patients with neutral or negative cumulative fluid balance receive maintenance and other fluids such that total dose of fluids covers the daily need of water (about 1ml/kg/h) • Other: Usual care Participants receive non-resuscitation fluids according to local routines, with the following stipulations: ○ Maintenance fluids (crystalloids and/or glucose and/or enteral water) are given at a dose of 1 ml/kg/h unless local protocol states otherwise ○ Glucose is used at maximal concentration of 10% unless local protocol states otherwise. ○ Medications are concentrated according to local protocol
Study Arms ICMJE	• Experimental: Protocolised reduction of non-resuscitation fluids Participants receive non-resuscitation fluids according to a pre-defined protocol starting within two hours of randomization. The intervention is continued for the duration of the ICU admission up to a maximum of 90 days. Intervention: Other: Protocolised reduction of non-resuscitation fluids • Usual Care Participants receive non-resuscitation fluids according to local routines. Intervention: Other: Usual care
Publications *	*Not Provided*

*** Includes publications given by the data provider as well as publications identified by ClinicalTrials.gov Identifier (NCT Number) in Medline.**

Recruitment Information	
Recruitment Status ICMJE	Recruiting
Estimated Enrollment ICMJE **(submitted: February 18, 2022)**	98
Original Estimated Enrollment ICMJE	*Same as current*
Estimated Study Completion Date ICMJE	May 31, 2023
Estimated Primary Completion Date	August 31, 2022 (Final data collection date for primary outcome measure)
Eligibility Criteria ICMJE	Inclusion Criteria: • Adult (≥ 18 years of age) • Septic shock according to the Sepsis 3 criteria: suspected or confirmed infection AND infusion of vasopressor/inotrope to maintain mean arterial pressure of 65 mmHg or above despite adequate fluid resuscitation AND lactate of 2 mmol/L or above at any time following ICU admission when there was a simultaneous need for vasopressor/inotrope. • Inclusion within 12 hours after ICU admission. Exclusion Criteria: • Confirmed or suspected pregnancy
Sex/Gender ICMJE	Sexes Eligible for Study: All

Ages ICMJE	18 Years and older (Adult, Older Adult)
Accepts Healthy Volunteers ICMJE	No
Contacts ICMJE	Contact: Peter Bentzer, MD, PhD +46 42-4061111 Peter.Bentzer@med.lu.se Contact: Jane Fisher, PhD jane.fisher@med.lu.se
Listed Location Countries ICMJE	Sweden
Removed Location Countries	

Administrative Information

NCT Number ICMJE	NCT05249088
Other Study ID Numbers ICMJE	REDUSE feasibility trial
Has Data Monitoring Committee	No
U.S. FDA-regulated Product	Studies a U.S. FDA-regulated Drug Product: No Studies a U.S. FDA-regulated Device Product: No
IPD Sharing Statement ICMJE	Plan to Share IPD: Yes Plan Description: Beginning 9 months after publication of the main report of this trial individual de-identified data will be available for sharing with researchers who provide a methodologically sound proposal as judged by the steering

	committee. To gain access, data requestors will need to sign a data access agreement.
Current Responsible Party	Region Skane
Original Responsible Party	*Same as current*
Current Study Sponsor ICMJE	Region Skane
Original Study Sponsor ICMJE	*Same as current*
Collaborators ICMJE	*Not Provided*
Investigators ICMJE	Principal Investigator: Peter Bentzer, MD, PhD Region Skåne
PRS Account	Region Skane
Verification Date	April 2022