BMJ Open

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

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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

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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.

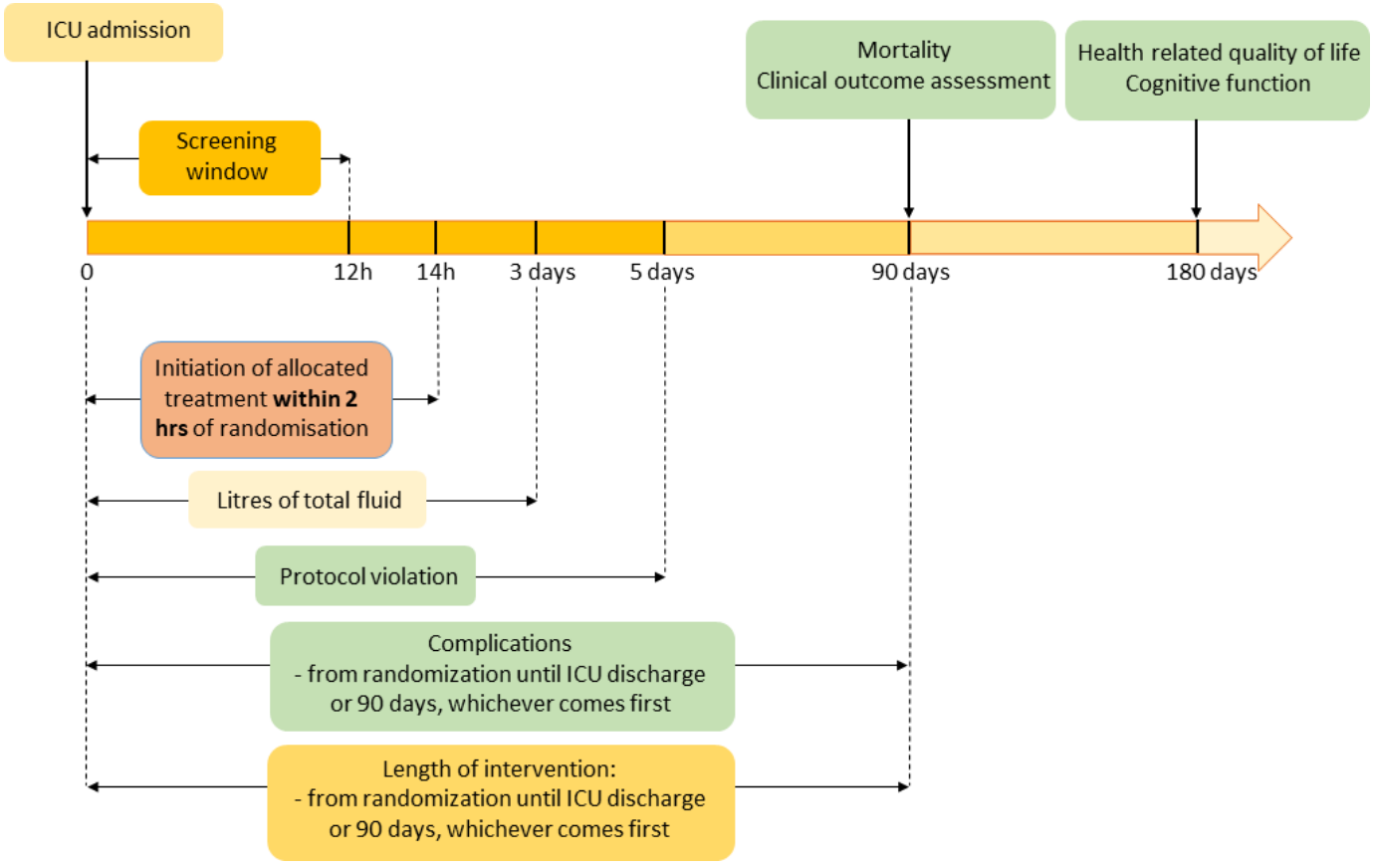

Figure 1 Trial timeline. Vertical arrows indicate specific time points for events or assessments, whereas horizontal arrows describe a certain time period. Complications: cerebral, cardiac, intestinal or limb ischaemia or any acute kidney injury. ICU, intensive care unit.

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.

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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.

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