



Feasibility 2023-02-07

1

## 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

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Feasibility 2023-02-07

2

## Contents

<b>1. Trial overview</b>	<b>4</b>
<b>2. Background and study rationale</b>	<b>4</b>
2.1 Background	4
2.2 Previous evidence	5
2.3 Rationale for a new trial	5
<b>3. Trial objectives and outcomes</b>	<b>5</b>
3.1 Primary feasibility outcome	6
3.2 Secondary feasibility outcomes	6
3.3 Primary exploratory clinical outcomes	6
3.4 Secondary exploratory clinical outcomes	6
<b>4. Eligibility</b>	<b>7</b>
4.1 Inclusion criteria	7
4.2 Exclusion Criteria	7
4.3 Exit from the trial	7
4.3.1 Exit by participant	7
4.3.2 Exit by treating physician	7
<b>5. Trial design</b>	<b>7</b>
5.1 Screening and randomisation	8
5.2 Intervention	8
5.2.1 The intervention group	8
5.2.2 Usual Care group	9
5.4 Blinding	9
5.5 Definitions	10
5.5.1. Days	10
5.5.2. Fluids	10
5.6 Protocol deviations	10
<b>6. Data collection</b>	<b>10</b>
6.1 Background data	10
6.2 Baseline data	11
6.3 Daily data during first five days of ICU stay	11
6.4 At discharge	11
6.5 At 90-days	11
6.6 At 6 months	11
<b>7. Ethics and Informed consent</b>	<b>11</b>
<b>8. Data management</b>	<b>12</b>
8.1 Data handling and record keeping	12
8.2 Quality control and quality assurance	12
<b>9. Safety</b>	<b>13</b>
9.1 Definitions	13
9.2 Reporting of complications	13
<b>10. Statistical analysis plan</b>	<b>13</b>
10.1 Sample size	14
10.1.1 Primary outcome	14
10.1.2 Feasibility threshold for secondary feasibility outcomes	14



## Feasibility 2023-02-07

3

10.1.3 Power estimations of primary exploratory clinical outcomes.....	14
10.2 Analysis methods.....	15
10.3 Missing data .....	15
10.4.2 Exploratory clinical outcomes .....	15
10.5 Statisticians.....	16
10.6 Interim analysis .....	16
<b>11. Publication of Data.....</b>	<b>16</b>
11.1 Data sharing.....	16
<b>12. Insurance .....</b>	<b>16</b>
<b>13. Funding.....</b>	<b>16</b>
<b>14. Timeline .....</b>	<b>16</b>
<b>15. Investigators .....</b>	<b>17</b>
15.1 Management group.....	17
15.2 Steering group.....	17
<b>References.....</b>	<b>17</b>
<b>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. ....</b>	<b>20</b>
<b>Appendix A. Description of collected data and outcomes .....</b>	<b>21</b>
<b>Appendix B. Dilutions of medications in the intervention group. ....</b>	<b>30</b>
<b>Appendix C. Treatment algorithm for non-resuscitation fluids in the intervention arm. ....</b>	<b>36</b>
<b>Appendix D. Estimation of potential for a reduction of fluid input by application a restrictive protocol for administration of non-resuscitation fluids.....</b>	<b>37</b>
<b>Appendix E. Informed consent form.....</b>	<b>38</b>



## 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<sup>1</sup>. 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<sup>2</sup>. Septic shock is a subgroup of sepsis with particularly severe circulatory and metabolic abnormalities and with a 90-day mortality of 40-50 %<sup>3,4,5,6,7</sup>.

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)<sup>8</sup>. 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<sup>9</sup>. More than 50% of patients with septic shock receive 4 L or more of fluids in the first day in the ICU<sup>10</sup>. 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<sup>11,12,13,14</sup>. 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<sup>15</sup>. 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<sup>16</sup>. 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<sup>15</sup>.

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<sup>15,17,18,19</sup>.

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<sup>17</sup>. 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<sup>18</sup>. 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<sup>19</sup>.

## 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<sup>18,20,21</sup>. 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<sup>20</sup>. Such a reduction might have a positive impact on patient important outcomes such as mortality, health related quality of life and cognitive function<sup>12</sup>. Moreover, the magnitude of this reduction is at least one litre larger than the most effective protocols targeting restriction of resuscitation fluids<sup>18,19</sup>. 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<sup>22,23</sup>
- Health-Related Quality of Life using the EQ-5D-5L at 6 months after inclusion<sup>24</sup>

### 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)<sup>25</sup>
- 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<sup>26,27</sup>



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 ( $\geq 18$  years of age)
- Septic shock according to Sepsis-3 criteria while in the ICU<sup>1</sup>
- 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 extracorporeal 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<sup>8,28</sup>. 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 participant 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  $> 5 \text{ ml/kg/h}^{29}$ .

## 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<sup>1</sup>. 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 participants 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<sup>7,30,31</sup>. 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 ( $n \approx 1,000$ ) of the Swedish population and nearly 80 % were positive to deferred consent procedure in a similar scenario<sup>32</sup>.

## 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 ( $\leq 3.9$  mmol/l)
- Electrolyte and metabolic disturbances (hyponatremia  $> 159$  mmol/L, hyperchloremic acidosis [pH  $< 7.15$  and plasma  $\text{Cl}^- > 115$ ], 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<sup>20</sup> (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<sup>33</sup>. 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%<sup>3,4,5,6,7</sup>
- 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 one 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%<sup>3,4,5,6,7</sup>.
- 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<sup>22</sup>



- 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<sup>34, 35,36</sup>
- 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<sup>5,33</sup>
- Based on an expected rate of complications in the ICU of 50% in the control group<sup>4,7,37</sup> 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<sup>38</sup>.

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<sup>39</sup>.

#### 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

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### 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.

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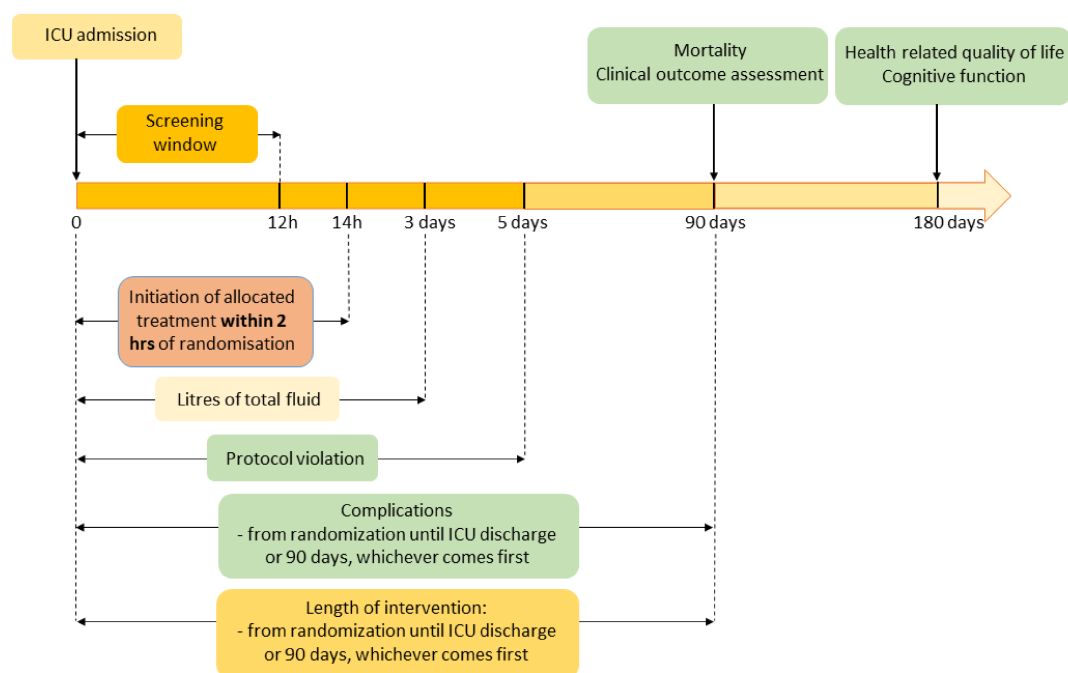


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Feasibility 2023-02-07

20

**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

<b>Primary feasibility outcome</b>	Litres of fluids administered within three days of randomisation.
<b>Secondary feasibility outcomes</b>	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
<b>Primary explorative clinical outcomes</b>	All-cause mortality at 90 days after inclusion
	One or more complications in the ICU (dichotomous outcome) (Y/N), if yes, specify: <ul style="list-style-type: none"> <li>- Cerebral ischemia (on MRI or CT scan) (Y/N)</li> <li>- Cardiac ischemia [myocardial infarction/unstable angina AND treatment as a consequence; PCI/thrombolysis or initiation/increased antithrombotic treatment] (Y/N)</li> <li>- Intestinal ischemia [diagnosed during surgery or by angiography] (Y/N)</li> <li>- Limb ischemia [in combination with treatment; open/percutaneous vascular intervention, amputation, initiation of/increased antithrombotic treatment] (Y/N)</li> </ul>
	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)
<b>Secondary exploratory clinical outcomes</b>	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
<b>Demographic/background variables</b>	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 <ul style="list-style-type: none"> <li>- Emergency department</li> <li>- Operating room</li> <li>- Other ICU</li> <li>- Other unit</li> </ul>
	Surgery prior to randomization (Y/N), if yes, specify: <ul style="list-style-type: none"> <li>- Head and neck</li> <li>- Thorax</li> <li>- Abdominal/pelvic</li> <li>- Extremities</li> <li>- Trauma</li> <li>- Other</li> </ul>
	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)	
<b>Baseline variables at study inclusion</b> (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



Feasibility 2023-02-07

23

	Sequential Organ Failure Assessment (SOFA) score
	Glasgow Coma Scale (GCS)
	Creatinine ( $\mu\text{mol/L}$ )
	Renal replacement therapy (Y/N)
	Urine output [hourly data extracted to 24 hrs], (ml/day)
	Bilirubin ( $\mu\text{mol/L}$ )
	Platelet count ( $\times 10^9/\text{ml}$ )
	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; $\mu\text{g/kg/min}$ )
	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 ( $\times 10^9$ 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)
	FiO <sub>2</sub> (%)
	PaO <sub>2</sub> (kPa)
	PaCO <sub>2</sub> (kPa)
	pH
	Base excess (BE, mEq/L)
<b>Fluid administration variables prior to inclusion</b>	Resuscitation fluids in the 24 hrs prior to inclusion - Colloids (specify) • Albumin 4-5% (ml) • Albumin 20% (ml) • Other (ml)



	<ul style="list-style-type: none"> <li>- Crystalloids administered to correct hemodynamic impairment as noted in the patient chart or given at a rate &gt; 5 ml/kg/h (specify) <ul style="list-style-type: none"> <li>• Ringers acetate/lactate (ml)</li> <li>• 0.9% NaCl (ml)</li> <li>• Other (ml)</li> </ul> </li> <li>- Blood products (specify) <ul style="list-style-type: none"> <li>• Erythrocyte (ml)</li> <li>• Plasma (ml)</li> <li>• Platelets (ml).</li> </ul> </li> </ul> <p>Maintenance and nutrition fluids in the 24 h prior to inclusion</p> <ul style="list-style-type: none"> <li>- 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 <ul style="list-style-type: none"> <li>• Ringer's acetate/lactate (ml)</li> <li>• 0.9% NaCl (ml)</li> <li>• Other (ml)</li> </ul> </li> <li>- Glucose solution (specify concentration) <ul style="list-style-type: none"> <li>• Glucose solution 2.5% (ml)</li> <li>• Glucose solution 5% (ml)</li> <li>• Glucose solution 10% (ml)</li> <li>• Glucose solution 20% (ml)</li> <li>• Other glucose strength</li> </ul> </li> <li>- Parenteral nutrition (ml)</li> <li>- Enteral nutrition (ml)</li> <li>- Enteral water (ml)</li> </ul>
<p><b>Daily variables for the first 5 days after inclusion (only collected if patient is in the ICU)</b></p>	<p>Resuscitation fluids</p> <ul style="list-style-type: none"> <li>- Crystalloids administered to correct hemodynamic impairment as noted in the patient chart or given at a rate &gt; 5 ml/kg/h (specify) <ul style="list-style-type: none"> <li>• Ringer's acetate/lactate (ml)</li> <li>• 0.9% NaCl (ml)</li> <li>• Other (ml)</li> </ul> </li> <li>- Colloids (specify) <ul style="list-style-type: none"> <li>• Albumin 4-5% (ml)</li> <li>• Albumin 20% (ml)</li> <li>• Other (ml)</li> </ul> </li> <li>- Blood products (specify) <ul style="list-style-type: none"> <li>• Erythrocytes (ml)</li> <li>• Plasma (ml)</li> <li>• Platelets (ml)</li> </ul> </li> </ul> <p>Volumes of intravenous vehicles and drugs</p> <p>Vehicles for drugs</p>





- 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, levosimendan, 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)



Feasibility 2023-02-07

26

- Enteral water given to correct electrolyte disturbances (mL)
Diuretics (Y/N), if yes, specify: <ul style="list-style-type: none"> <li>- Loop diuretics (mg/24h)</li> <li>- Carbanhydrase inhibitors (Y/N)</li> <li>- Other</li> </ul>
Fluid output <ul style="list-style-type: none"> <li>- Urinary output (ml)</li> <li>- Drains (ml)</li> <li>- Hemorrhage (ml)</li> <li>- Faeces [if liquid] (ml)</li> <li>- Fluid removal in RRT (ml)</li> <li>- Other losses [evaporation excluded] (ml)</li> </ul>
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]( $\mu\text{mol/L}$ )
Renal replacement therapy (Y/N)
Earliest urea (mmol/L)
Plasma bilirubin [highest] ( $\mu\text{mol/L}$ )
Platelet count [lowest] ( $\times 10^9/\text{L}$ )
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] ( $\mu\text{g/kg/min}$ )
Cardiac arrhythmia <ul style="list-style-type: none"> <li>- Atrial fibrillation/flutter (Y/N)</li> <li>- Ventricular tachycardia (Y/N)</li> <li>- Ventricular fibrillation(Y/N)</li> </ul>
Ischemic events (Y/N), if yes; specify: <ul style="list-style-type: none"> <li>- Limb</li> <li>- Cerebral</li> <li>- Heart</li> <li>- Intestine</li> </ul> (Definitions described above)
Mechanical ventilation (Y/N)
Lowest PaO <sub>2</sub> (kPa)
FiO <sub>2</sub> (at time of lowest PaO <sub>2</sub> ; %)
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)



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



	<ul style="list-style-type: none"> <li>- Limb</li> <li>- Cerebral</li> <li>- Heart</li> <li>- Intestine</li> <li>- Hypoglycemia [<math>\leq 3.9</math> mmol/L] (Y/N)</li> <li>- Hypernatremia [<math>&gt;159</math> mmol/L] (Y/N)</li> <li>- Hyperchloremic acidosis [pH<math>&lt;7.15</math> and plasma-chloride <math>&gt;115</math> mmol/L] (Y/N)</li> <li>- Metabolic alkalosis [pH<math>&gt;7.59</math> and base excess <math>&gt;9</math>] (Y/N)</li> <li>- Suspected unexpected complications (SUSAC)</li> </ul>
<b>Consent</b>	<p>Patient responsible informed (Y/N) and patient informed (Y/N)</p> <ul style="list-style-type: none"> <li>- Date informed (if Y)</li> <li>- Reasons (if N)</li> <li>- Objected to participation/consented (Y/N)</li> </ul> <p>Consent withdrawn (Y/N by patient or by person responsible)</p> <ul style="list-style-type: none"> <li>- Date of withdrawal</li> </ul> <p>Can the data be used (Y/N)</p>
<b>90-day follow-up</b>	<p>Date of follow-up</p> <p>Status (alive/deceased)</p> <p>Days alive and free of renal replacement therapy (RRT)</p> <p>Days alive and without invasive (intubated or tracheostomy) mechanical ventilation</p> <p>Days alive without vasopressors</p> <p>Days alive with full enteral nutrition</p>
<b>6 month follow-up</b>	<p>Date of follow-up</p> <p>Status (alive/deceased)</p> <p>Place of follow up (Institution/ home of patient/ telephone/ digital)</p> <p>Health-Related Quality of Life using the European Quality of Life-5 Dimensions 5-Level questionnaire</p> <p>Life satisfaction (scale of 1-10)</p> <p>Background information</p> <ul style="list-style-type: none"> <li>- Does the patient have a native language other than the test language (Y/N)</li> <li>- capabilities that may interfere with the patient's ability to perform the tests <ul style="list-style-type: none"> <li>- No problems</li> <li>- Hearing</li> <li>- Vision</li> <li>- Speech problems</li> <li>- Dyslexia</li> <li>- Paresis</li> <li>- Memory problems or other cognitive problems prior to the episode of sepsis</li> <li>- Other</li> </ul> </li> <li>- Known neurological disease</li> </ul>



	<ul style="list-style-type: none"> <li>- Highest education level             <ul style="list-style-type: none"> <li>- No formal education</li> <li>- Incomplete primary/lower secondary school</li> <li>- Complete primary/lower secondary school</li> <li>- Incomplete upper secondary school</li> <li>- Complete upper secondary school</li> <li>- Some university-level education, without degree</li> <li>- University-level education, with degree</li> </ul> </li> <li>- Marital status (married/living together as married or living alone)</li> <li>- Current place of residence             <ul style="list-style-type: none"> <li>- Home</li> <li>- Hospital</li> <li>- Rehabilitation centre</li> <li>- Nursing home</li> <li>- Other</li> </ul> </li> <li>- Occupational status before the episode of sepsis             <ul style="list-style-type: none"> <li>- Working full-time</li> <li>- Working part-time</li> <li>- Unemployed</li> <li>- Retired due to age</li> <li>- Retired due to disability / health problems</li> <li>- On sick leave</li> <li>- Other (e.g. student, housewife)</li> </ul> </li> <li>- Occupational status at the time of the follow-up             <ul style="list-style-type: none"> <li>- Working full-time</li> <li>- Working part-time</li> <li>- Unemployed</li> <li>- Retired due to age</li> <li>- Retired due to disability / health problems</li> <li>- On sick leave</li> <li>- Other (e.g. student, housewife)</li> </ul> </li> <li>- Date of return-to-work (if applicable)</li> <li>- Rehabilitation after the episode of sepsis             <ul style="list-style-type: none"> <li>- None</li> <li>- Inpatient rehabilitation</li> <li>- Outpatient rehabilitation</li> <li>- Home-based rehabilitation (community)</li> <li>- Physiotherapist only</li> <li>- Occupational therapist only</li> <li>- Counselling (by e.g. social worker or psychologist)</li> <li>- Cognitive Behavioural Therapy</li> </ul> </li> </ul>
	<p>Other</p> <p>Glasgow Outcome Scale Extended (GOSE) modified for use after Sepsis</p>
	<p>Montreal Cognitive Assessment (MoCA) (face-to-face /digital /telephone)</p>



## 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
<b>Suggested dilutions may only be used if patient has a central line</b>				
<b>Vasoactive drugs</b>				
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	<b>IM</b> ; IV inf 40 - 320 µg/ml, diluted in G. <b>Halmstad</b> ; 80 µg/ml i NaCl. <b>UKCPA</b> ; 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	<b>SPC</b> ; Dilute in 5% G. <b>ePed</b> ; 15mg/ml as infusion. <b>UKCPA</b> ; 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	<b>IM</b> ; 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	<b>Halmstad</b> ; 10 ml 0,2 mg/ml in 40 ml G, gives 40 µg/ml. <b>Micromedex och Gahart's</b> ; recommend 20 ug/ml for iv bolus and 2 to 4 ug/ml for infusion.
Milrinone	1mg/ml	use according to local protocol	SPC	<b>SPC</b> dilute to 200 ug/ml using G/NaCl.
Nitroglycerin (Abcur och BioPhausia)	1 mg/ml	use according to local protocol	SPC, IM	<b>SPC</b> ; May be given undiluted using a pump. Can be diluted in G/NaCl. <b>IM</b> ; 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	<b>SPC</b> ; Noradrenaline 1 mg/ml should be diluted with G/NaCl before use. <b>IM</b> ; 160 µg/ml. <b>Micromedex</b> ; G may protect against oxidation. <b>Stabilis</b> ; 0.5 mg/ml Norepinephrine bitartrate is stable 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 Unimedica)	0.1 mg/ml	use according to local protocol	Micromedex, IM	<b>Micromedex</b> ; 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	<b>IM</b> ; 1 amp. (1 ml, 20 units in 50 ml med G, will give conc 0.4 units/ml. <b>Gahart's</b> ; 1 E/ml
<b>Antibiotics</b>				
Acyklovir	25mg/ml	5mg/ml Dilute 10 ml 25 mg/ml with 40 ml of NaCl/G	SPS, UKCPA	<b>UKCPA</b> ; 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	<b>SPC</b> ; For iv inj. 10 and 20 ml for 1 and 2 g, respectively. <b>Micromedex</b> ; 1 and 2 g may be diluted in 7.4 and 14.8 ml sterile water, respectively and given in 10-15 min to minimize risk of seizures. <b>SPC Meda/Mylan</b> . 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	<b>SPC</b> ; dissolve 1 g in 10 ml of sterile water and 3 g in 20-40 ml of sterile water. <b>IM</b> ; 600 mg in 4-







Feasibility 2023-02-07

33

Drug	Conc. in stem solution	Suggested dilution in intervention group	Reference	Comments
Erythromycin		1 g in 20 ml sterile water and add 80 NaCl.	IM, ePed, SPC,	<b>IM</b> ; Final concentration should not be greater than 10 mg/ml. <b>ePed</b> ; Give dose in > 1h to minimize risk of arrhythmias.
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	<b>SPC</b> ; If administered twice daily gentamycin may be given undiluted in 3-5 minutes. <b>UKCPA</b> ; 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	<b>SPC</b> ; 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	<b>IM</b> ; 0.5 - 1 g doses in 5 min. 2 g doses in 15-30 min. <b>SPC</b> . 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	<b>SPC</b> ; shorter infusion time than 20 minutes will increase risk for toxic side-effects and is not recommended.
Trimetoprim/Sulfamethoxazol	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	<b>SPC</b> ; Stable for 2 h! <b>IM</b> ; 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	<b>IM</b> ; In exceptional circumstances 20 mg/ml may be given via a central line. <b>UKCPA</b> ; 10mg/ml is a commonly used dilution. 20mg/ml has been used in some centers. <b>IM</b> ; give in 1 h. <b>Regional dilution routine</b> ; Give a dose of 500 mg in 60 min and 1g in a 100 min.
Voriconazole	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.
<b>Other drugs</b>				
Clonidine	150 µg/ml (1 ml ampull)	30 µg/ml	SPC, IM, UKCPA	<b>UKCPA</b> ; 6-50 micrograms/ml infusion. Diluent: Sodium chloride 0.9% or glucose 5%.
Dexmedetomidine	100ug/ml	8ug/ml	SPC	
Sodium glycerophosphate (Glycophos)	1 mmol/ml	0.5 mmol/ml 20 ml sodium glycerophosphate	ePED	<b>ePED</b> ; Administer in no less than 8 h.



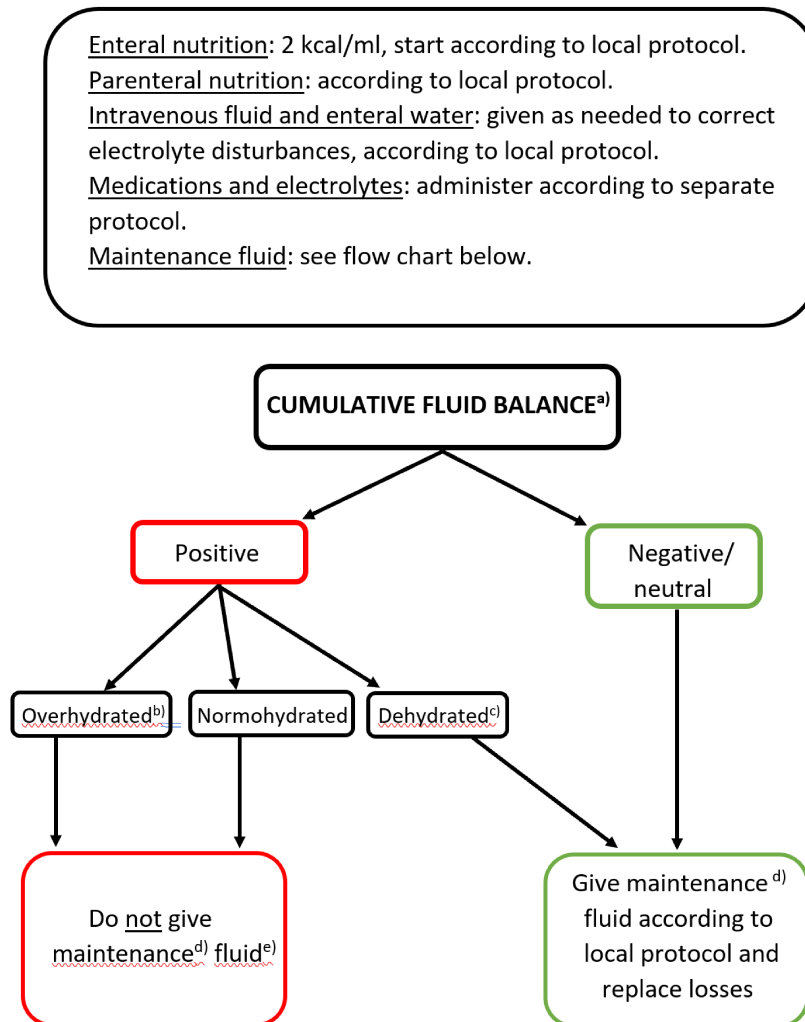
Drug	Conc. in stem solution	Suggested dilution in intervention group	Reference	Comments
<b>Insulin (Humulin Regular, Actrapid)</b>	Insulin, humant (Humulin Regular)	1mmol/ml in 20 ml NaCl. <b>1 E /ml</b>	Stabilis	<b>Stabilis</b> ; Dilute in NaCl
<b>Levetiracetam</b>	100 mg/ml (5 ml flask)	<b>250 - 1500 mg in 100 ml NaCl/G, ges på 15 min.</b>	SPC, IM, Micromedex, Gahart's	<b>Micromedex</b> ; 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.
<b>Magnesium sulphate (Addex-Mg)</b>	1 mmol/ml	<b>0.5 mmol/ml, (20 ml in 20 ml NaCl, giving a conc. 0,5 mmol/ml). Give in no less than 10 min.</b>	IM, Gahart's, VGR guideline, UKAP	<b>Gahart's</b> ; D5W and NS are the most common diluents. <b>UKCPA</b> ; suggested dilutions 1-2mmol/ml
<b>Potassiumhydroxide/ Potassium phosphate (Addex-Kalium)</b>	2 mmol/ml	<b>1-2 mmol/ml dilute in NaCl if needed</b>	SPC	<b>SPC</b> ; Give at most 20 mmol potassium/h.
<b>Potassium Chloride</b>	2 mmol/ml	<b>1-2 mmol/ml, in NaCl dilute if needed</b>	SPC	<b>SPC</b> ; Give at most 20 mmol potassium/h.
<b>Propofol (Propofol-Lipuro)</b>	10 or 20 mg/ml	<b>20 mg/ml for infusion. According to local routine for intubation</b>	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 "Inotropia 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](http://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.



<sup>a)</sup> 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.

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

<sup>c)</sup> 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.



## 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 deltar 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 koda 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

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e-mail: anja.linden@med.lu.se



Feasibility 2023-02-07

40

**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: .....

Namnsteckning: .....

Namnförtydligande: .....