



Effects of restricting intravenous fluids vs. standard care fluid therapy in patients with septic shock

The Conservative vs. Liberal Approach to fluid therapy of Septic Shock in Intensive Care (CLASSIC) Trial

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Abstract

- **Background.** Septic shock is common, often lethal, costly, and associated with prolonged suffering among survivors and relatives. Traditionally, intravenous (IV) fluids are used to optimise the circulation, and the use of higher volumes is recommended by international guidelines. There is, however, no high-quality evidence to support this. In contrast, data from cohort studies, small trials and systematic reviews in sepsis and large trials in other settings and patient groups suggest potential benefits from restriction of IV fluids in patients with septic shock.
- **Objectives.** We aim to assess the benefits and harms of IV fluid restriction vs. standard care on patient-important outcome measures in adult intensive care unit (ICU) patients with septic shock.
- **Design.** CLASSIC is an international, multicentre, parallel-grouped, open-labelled, centrally randomised, stratified, outcome assessor- and analyst-blinded trial.
- **Inclusion and exclusion criteria.** We will screen all adult ICU patients who have septic shock defined according to the Sepsis-3 criteria and have received at least 1 L of IV fluid (crystalloids, colloids or blood products) in the 24-hours before screening. We will exclude patients who have had septic shock for more than 12 hours at the time of screening, who have life-threatening bleeding, or acute burn injury >10% of the body surface area, who are pregnant and those in whom consent cannot be obtained as per the model approved for the specific site.
- **Experimental intervention.** In the IV fluid restriction group no IV fluids should be given in the ICU unless extenuating circumstances occur, including signs of severe hypoperfusion, overt fluid loss or a failing GI tract with a total fluid input of less than 1 L per day. In these circumstances, IV fluid may be given in measured amounts.
- **Control intervention.** In the standard care group there will be no upper limit for the use of IV fluids.
- **Outcomes.** The primary outcome is 90-day mortality; secondary outcomes are serious adverse events in the ICU (ischemic events or severe acute kidney injury); days alive without life support at day 90; days alive and out of hospital at day 90 and mortality, health-related quality of life and cognitive function at 1-year.
- **Trial size.** We will randomise 1554 participants to allow the detection of a 15% relative risk reduction (7% absolute) in the restrictive vs. standard care group in 90-day mortality with a power of 80%.
- **Timeline.**
 - Primo 2018 Authority approvals in DK
 - Medio 2018 1st participant randomised in DK and authority approvals elsewhere
 - Primo 2019 1st interim analysis
 - Medio 2019 2nd interim analysis
 - Ultimo 2019 3rd interim analysis
 - Medio 2020 Last participant randomised
 - Ultimo 2020 Primary report on 90-day outcomes submitted.
 - Medio 2021 Last participant followed for 1 year
 - Ultimo 2021 Long-term outcome report submitted

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List of abbreviations

6S, Scandinavian Starch for Severe Sepsis/Septic Shock
ACE, Angiotensin-Converting-Enzyme
ANG-II, Angiotensin-II
ALL, Acute Lymphoblastic Leukaemia
AML, Acute Myelogenous Leukaemia
ARDS, Acute Respiratory Distress Syndrome
B-PLL, B-cell prolymphocytic leukaemia
CI, Confidence Interval
CLASSIC, The Conservative vs. Liberal Approach to fluid therapy of Septic Shock in Intensive Care Trial
CLL, Chronic Lymphocytic Leukaemia
CML, Chronic Myelogenous Leukaemia
CPAP, Continuous Positive Airway Pressure
CRIC, Centre for Research in Intensive Care
CT, Computed Tomography
CTU, Copenhagen Trial Unit
DMSC, Data Monitoring and Safety Committee
ECG, Electrocardiography
eCRF, electronic Case Report Form
EHOSS-1, The “Early haemodynamic optimization using reload dependence during septic shock” trial
EQ-5D, Euro Qual-5D
EudraCT, European Union Drug Regulating Authorities Clinical Trial
FEAST, Fluid Expansion as Supportive Therapy trial
GI, Gastrointestinal
GRADE, Grading of Recommendations Assessment, Development and Evaluation
hCG, human Chorionic Gonadotropin
HCL, Hairy Cell Leukaemia
HRQoL, health-related quality of life
ICH-GCP, International Conference on Harmonisation on Good-Clinical -Practice
ICMJE, International Committee of Medical Journal Editors
ICU, Intensive Care Unit
IQR, Interquartile Range
ITT, intention-to-treat
IV, Intravenous
KDIGO, Kidney Disease Improving Global Outcomes
LVEF, Left Ventricle Ejection Fraction
MC, Management Committee
MCAR, Missing Completely At Random
MDRD, Modification of Diet in Renal Disease formula
MNAR, Missing Not At Random
MoCa, Montreal Cognitive assessment

MoCa MINI, Montreal Cognitive assessment '5-minute protocol'
MRI, Magnetic Resonance Imaging
NaCl, Sodium Chloride
NYHA, New York Heart Association
PTLD, post-transplant lymphoproliferative disorder
RRI, Relative Risk Increase
RRR, Relative Risk Reduction
SAE, Serious Adverse Event
SAR, Serious Adverse Reaction
SBE, Standard Base Excess
SD, Standard Deviation
SLL, Small Lymphocytic Lymphoma
SMS-ICU score, Simplified Mortality Score for the Intensive Care Unit
SSC, Surviving Sepsis Campaign
SSSP-1 and SSSP-2, Simple Septic Shock Protocol
TARTARE 2S, Targeted Tissue Perfusion versus Macrocirculation-guided Standard Care in Patients with Septic Shock trial
TFM, Targeted Fluid Minimisation trial
T-PLL, T-cell prolymphocytic leukaemia
TRISS, Transfusion Requirements in Septic Shock trial
GLM, Generalised Linear Model
WHO, World Health Organisation

1 Introduction and background

1.1 *The participant population - patients with septic shock*

Septic shock is common and often lethal [1]. The WHO estimates that 6.000.000 patients die of sepsis every year and have declared sepsis a global health priority [1]. Patients with septic shock have 90-day mortality rates around 40% to 50% even in the developed part of the world [2, 3, 4, 5]. Many survivors get readmitted to hospital and have impaired health-related quality of life (HRQoL) [6] and struggle with long-term reduced cognitive function [7]. Sepsis care is, therefore, associated with high use of resources in the developed part of the world [8].

Septic shock is defined as the need for vasopressor therapy and elevated lactate levels related to an infection and most often other organ systems are also impaired, including the brain, lungs and kidneys [9]. The most frequent sources of infection in patients with septic shock are pneumonia and abdominal, urinary tract, and soft tissue infections [10, 2, 3, 4].

Taken together, any improvement in sepsis care will result in reduced suffering among patients and relatives and improved global health [1].

1.2 *Current practice in septic shock*

The mainstay therapy for initial management of patients with septic shock includes intravenous (IV) antibiotics and fluids, source control, and supportive care [11]. In the developed parts of the world, most patients with septic shock are cared for in intensive care units (ICUs) because of the need for continuous monitoring and the use of life-support including vasopressor therapy in most patients, mechanical ventilation in many, and renal replacement therapy in some patients [11]. Patient location before ICU admission for septic shock appear to differ between continents [10], but in Scandinavia approximately half of the patients are admitted from hospital wards and one quarter each from emergency departments and operating rooms [2, 3, 5].

The international Surviving Sepsis Campaign (SSC) guideline [11], which is supported by 25 medical societies, recommends that a fixed IV crystalloid fluid volume of 30 ml/kg is given in the first 3 hours, but this is based on low-quality evidence. The guidance for continued fluid therapy is to give IV fluid as long as circulatory parameters improve, but this also is not supported by firm evidence [11]. Thus, the guideline promotes higher IV fluid volumes merely on physiological grounds.

While the volumes of IV fluid given to patients with septic shock in emergency departments before ICU admission may be less variable [12], the fluid volumes given in ICU vary between ICUs beyond what may be explained by differences in patient mix (Fig 1).

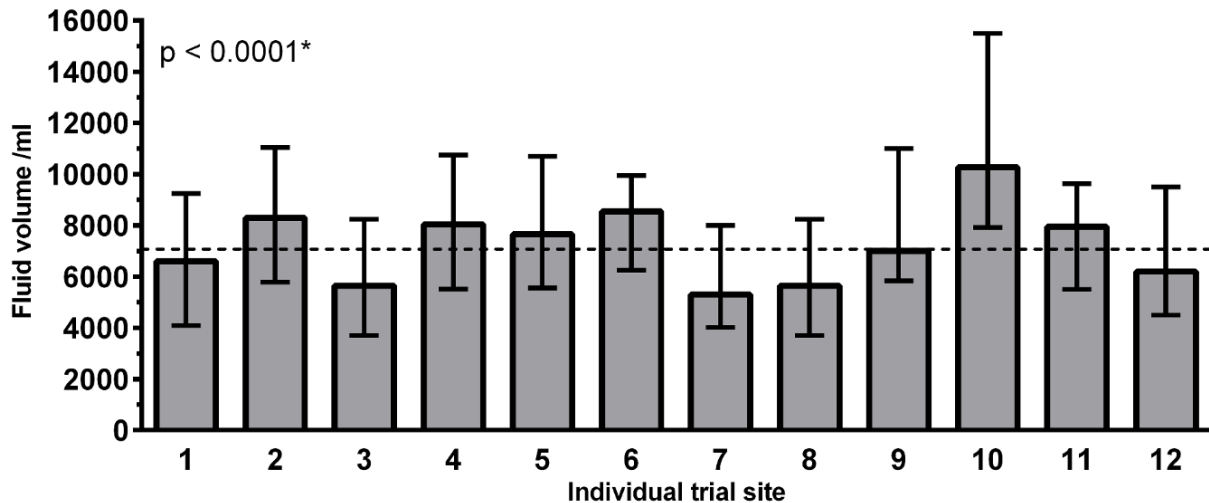


Fig 1. Median (IQR) IV fluid volumes given for resuscitation of patients with septic shock in Scandinavian ICUs participating in a fluid trial [5]. Unadjusted data are shown (the dashed horizontal line denotes the median of all patients), but variation remained after adjustment for important patient characteristics as indicated by the p-value*. The figure is copied from [5].

On the other hand, the types of IV fluids used vary less; crystalloid solutions are used for resuscitation in the majority of ICU patients including those with sepsis [13]. This is in line with the strong recommendation in the SSC guideline to use crystalloid solutions, either saline or buffered solutions, for the resuscitation in patients with septic shock [11]. The guideline recommends against the use of the synthetic colloid solutions (starches and gelatines) and suggests that albumin be considered only if high fluid volumes are given [11]. A restrictive transfusion strategy of blood products is recommended by the SSC guideline and noradrenalin is recommended as first line vasopressor [11].

1.3 Trial interventions – restrictive vs. standard IV fluid therapy

In the present CLASSIC trial, the protocol restricting IV fluids is the experimental intervention and the protocol aiming at standard care is the control intervention.

Observational data

A systematic review of mainly observational studies associated more positive fluid balances with increased mortality [14]. Also earlier administration of the initial 30 ml/kg of IV fluid was not associated with reduced mortality in a large cohort of sepsis patients in the US [15]; in contrast earlier administration of antibiotics was associated with reduced mortality [15]. As noted by the authors of the latter report, confounding by indication is, however, very difficult to control for in observational studies of IV fluids in patients with septic shock.

Randomised trials in septic shock

We are presently conducting a comprehensive systematic review of lower vs. higher IV fluid volumes for resuscitation of adult patients with septic shock using Cochrane methodology, GRADE, and Trial

Sequential Analysis in order to inform methodology of the trial including the sample size estimation [16]. In our search, we have only found 5 randomised trials, in which a difference in fluid volumes was the main aim between intervention groups (Table 1).

One was our own multicentre, pilot CLASSIC trial [5], in which the protocol restricting IV fluid volumes resulted in lower fluid volumes given as compared to a protocol aiming at standard care. Thus, the trial showed that resuscitation fluids could be restricted in patients with septic shock in 9 general ICUs in Scandinavia. Moreover, the exploratory outcome measures suggested benefit from fluid restriction including less kidney impairment [5].

The second trial was a single-centre pilot trial from an ICU in the US, in which IV fluid therapy was guided by daily assessments of fluid responsiveness vs standard care [17]. Less IV fluid may have been given in the intervention group at day 5, but this was not statistically significant; neither were any of the clinical outcomes.

The third trial was a single-centre pilot trial from an ICU in France, in which IV fluid therapy was guided by fluid responsiveness (intervention) vs central venous pressure (control) aiming at reducing fluid volumes [18]. Less IV fluid was given per day in the intervention group, but total intravascular volume expansion may not have differed between groups (Table 1) and none of the clinical outcomes differed.

The fourth and fifth trials were single-centre trials done in patients with sepsis in an emergency department in Zambia [19, 20]. The first of these trials was stopped early because all 8 patients with severe hypoxic respiratory failure allocated to the more liberal fluid protocol died [19]. In the second of the trials, patients with severe hypoxic respiratory failure were excluded [20]. Patients with septic shock were randomised to a simple resuscitation protocol including fixed volume IV fluid with the addition of vasopressor in case of persistent hypotension and blood transfusion in case of severe anaemia vs. treatment according to usual care in that setting. The main difference in the management between the two groups was that higher volumes of IV fluid were given at 6-hours in the protocolised care vs. usual care group. Mortality at hospital discharge and 28-days was higher in the protocolised vs. usual care group. More patients in the protocolised vs. usual care group experienced worsening of respiratory failure (36% vs. 22%), but mechanical ventilation was not available for the trial patients, which reduces the generalisability of the results in a developed world setting.

Table 1. Randomised trials of fluid resuscitation of adult patients with septic shock, in which a strategy was used to obtain differences in fluid volumes between intervention groups

Trial	Setting	Patients	Median IV fluid volumes*	Mortality**
The CLASSIC pilot trial [5]	9 Scandinavian ICUs	153 patients with septic shock who had received 30 ml/kg of IV fluid	Lower fluid group 0.5 L Higher fluid group 2.0 L	Lower fluid group 33% Higher fluid group 41%
Targeted fluid minimisation (TFM) trial [21]	Single US ICU	82 patients with septic shock using vasopressor >12 h after initial resuscitation	Lower fluid group 6.2 L Higher fluid group 8.7 L	Lower fluid group 56% Higher fluid group 49%
Early haemodynamic optimization using reload dependence during septic shock (EHOSS-1) trial [22]	Single French ICU	61 patients with septic shock who had received 25 ml/kg of IV fluid	Lower fluid group 3.0 L Higher fluid group 3.3 L	Lower fluid group 23% Higher fluid group 47%
Simple septic shock protocol (SSSP)-1 [19]	An emergency department in Zambia	120 patients with suspected infection, 2 positive SIRS criteria and organ dysfunction	Lower fluid group 1.6 L Higher fluid group 2.9 L	Lower fluid group 61% Higher fluid group 64%
SSSP-2 [20]	An emergency department in Zambia	212 patients with suspected or proven infection and hypotension	Lower fluid group 2.0 L Higher fluid group 3.5 L	Lower fluid group 33% Higher fluid group 48%

* At 6-h in SSSP-1 and -2, at day 5 in CLASSIC and TFM and at end of study in EHOSS-1; in TFM all fluids were recorded, in the other trials only resuscitation fluids were recorded

**In-hospital in SSSP-1 and -2 and TFM, day 28 in EHOSS-1 and day 90 in CLASSIC

Regarding the period after resuscitation of patients with sepsis, a systematic review of randomised trials indicated a 14% relative (7% absolute) risk reduction in mortality with more restrictive vs. more liberal fluid strategies, but less than 400 patients were included in the sepsis subgroup and the result was not statistically significant [23]. In the analysis of all patients with sepsis or acute respiratory distress syndrome (ARDS), a reduction in the time on mechanical ventilation was observed in the fluid restrictive vs. more liberal fluid strategy groups [23].

Randomised trials in other patient groups

The results of two large randomised trials in other patient groups have favoured restriction of IV fluids as compared to more liberal approaches. A trial done in ICU patients with acute lung injury in the US indicated reduced time on mechanical ventilation and in ICU with restriction of IV fluid vs. standard care [24]. Furthermore, the FEAST trial in African children with infection and circulatory impairment showed increased mortality in the children receiving IV fluid boluses as compared to those who did not receive fluid boluses [25].

Physiological data

Restricting fluid therapy may be beneficial in reducing venous back-pressure and organ oedema, thereby improving organ function including that of the lungs, gut and kidneys [26, 27]. On the other hand, fluid restriction may also compromise peripheral and/or organ perfusion through reduced cardiac output and thereby reduced microcirculation from the arterial side [28]. Thus, the physiological data support the clinical equipoise and the need for large trials on IV fluid volumes in patients with septic shock.

Following these notions, a recent consensus statement from key opinion leaders within the field of intensive care medicine gave the highest priority to trials on restrictive vs. liberal fluid therapy when prioritizing the topics that need testing in patients with septic shock [29].

1.4 Risks and benefits

The CLASSIC trial will be conducted in an ICU-setting where patients around the clock are monitored and cared for by ICU nurses and doctors who are trained to manage patients with circulatory failure including the titration of the different interventions used for these patients (i.e. IV fluids, vasopressors and inotropes). We therefore believe that it is safe for individual patients to be enrolled into the CLASSIC trial.

As described above, clinical practice data, randomised trial data and those from observational and physiological studies do not provide firm evidence that one of the interventions in the CLASSIC trial is superior to the other, i.e. clinical practice variation and equipoise exists. We therefore believe that the CLASSIC trial is safe for the patients also at the group level. As the current guidelines promote higher fluid volumes and our hypothesis is that fluid restriction is beneficial, the CLASSIC trial patients may benefit from participation.

1.5 Ethical justification and trial rationale

Septic shock carries a high risk of death and disability. Currently all patients with septic shock receive IV fluids, but the guidelines are based on low-quality evidence as no large trial has assessed the benefit vs. harm of lower vs. higher fluid volumes in these patients. The CLASSIC trial will be conducted to the highest of methodological standards assessing the benefit and harm of fluid restriction on patient-important outcome measures. Therefore, future patients will benefit from the CLASSIC trial results, regardless of the direction of the effect, as the results will enable better fluid therapy for septic shock. As outlined above, we believe that this can be done without additional risk for the patients enrolled into the trial.

The patients to be enrolled in the CLASSIC trial cannot consent due to the combination of severe infection and circulatory shock. This will be applicable to the entire population of septic shock in the ICU. No other patient groups may be investigated to improve IV fluid therapy in septic shock as no other groups have the combination of infection and shock.

In addition, septic shock is a medical emergency that requires immediate interventions including fluid therapy [11]. Therefore, we cannot delay enrolment and need to use the consent procedures for emergency research.

Consent will be obtained according to national law. In Denmark, we will use the consent procedures for temporarily incompetent patients for all patients (<https://www.retsinformation.dk/Forms/R0710.aspx?id=192671>). The CLASSIC trial patients will be enrolled after informed consent from a doctor, who is independent of the trial, who has knowledge of the clinical condition and who is familiar with the trial protocol to such extent that he or she can judge for each patient if it will be reasonable to enrol the patient in the trial (the first trial guardian). In the CLASSIC trial, the first trial guardian will be named by the investigator at each Danish site before initiation of the trial. As soon as possible after enrolment, consent will be obtained from the patient's next of kin and a second doctor (the second trial guardian). The second trial guardian must be different from the first trial guardian, but also independent of the trial. Patients, who regain competence, will be asked for informed consent as soon as possible (Appendix 5). The process leading to informed consent will be in compliance with all applicable regulations. The consenting subjects will be provided with written and oral information about the trial allowing them to make an informed decision about participation in the trial. Written information and the consent form will be subject to review and approval by the ethical committee system according to national law in all participating countries. The consenting party can at any time, without further explanation, withdraw consent. The process leading to informed consent may differ in the participating countries, but will be described and be in compliance with all applicable regulations in the country.

1.6 Trial conduct

The CLASSIC trial will be conducted in compliance with the published trial protocol, the Helsinki Declaration in its latest version [30], the good clinical practice (GCP) guidelines [31], and national laws in the participating countries. We have written the protocol in accordance with the SPIRIT 2013 Statement [32] and will register the trial in the www.clinicaltrials.gov and European Union Drug Regulating Authorities Clinical Trials (EudraCT) registries before the enrolment of the first participant. No substantial deviation from the protocol will be implemented without prior review and approval of the regulatory authorities except where it may be necessary to eliminate an immediate hazard to the trial participants. In such case, the deviation will be reported to the authorities as soon as possible.

Enrolment will start after approval by the ethics committees, medicines agencies, data protection agencies and health authorities in the participating countries. We will publish the approved protocol at www.cric.nu and submit a manuscript with main points of the protocol including description of design, rationale and statistical analysis plan to a peer-reviewed medical journal.

2 Trial objectives

The objective of the CLASSIC trial is to assess benefits and harms of IV fluid restriction vs. standard of care on patient-important outcome measures in adult ICU patients with septic shock.

We hypothesise that fluid restriction vs. standard care will improve patient-important outcome measures in septic shock.

3 Trial design

3.1 Trial design

The CLASSIC trial is an investigator-initiated, international multi-centre, parallel-grouped, open-labelled, centrally randomised, stratified, outcome assessor- and analyst-blinded trial with adequate generation of allocation sequence, and allocation concealment.

3.2 Randomisation

Patients with septic shock fulfilling the inclusion criteria will be randomised if they do not fulfil an exclusion criterion. The 1:1 randomisation will be centralised and web-based according to the computer-generated allocation sequence list, stratification variables (haematological or metastatic cancer (Y/N) and trial site), and varying block size at Copenhagen Trial Unit (CTU). The allocation sequence list will exclusively be known to the data manager at CTU and will be unknown to the investigators to allow immediate and concealed allocation to one of the two intervention groups. Each participant will be allocated a unique patient-screening number.

3.3 Blinding

Fluid restriction vs standard care fluid therapy cannot be blinded for investigators, clinical staff or participants. We will mask the allocation for the research staff who assess the long-term outcomes and for the trial statistician. Also, the management committee will write two abstracts based on the statistical report with the group allocation masked, one assuming the experimental intervention group is X and the control intervention group is Y, and one assuming the opposite. After this the allocation code will be unmasked [33, 34].

3.4 Participant timeline

We will strive to enrol patients as soon as they fulfil the inclusion criteria. The participants will continue the allocated intervention until they are discharged from the ICU with a maximum of 90 days after randomisation. If the participant is readmitted to the ICU within 90 days after randomisation, she/he will continue the allocated fluid therapy.

We will follow the participants for 1-year after randomisation and identify 1-year survivors in hospital, regional or national registries. We will contact all 1-year survivors approximately 2 weeks after to assess health related quality of life and cognitive function by interview.

4 Selection of participants

All patients admitted or planned to be admitted to an active trial site will be considered for participation. Patients will be eligible, if they comply with the inclusion and exclusion criteria below.

We aim to include the patients as early as possible and exclude patients who may have specific fluid needs.

4.1 Inclusion criteria

All the following criteria must be fulfilled:

- Aged 18 years or above
- Admitted to the ICU or plan to be admitted to the ICU regardless of trial participation
- Septic shock defined according to the Sepsis-3 criteria [9]:
 - o Suspected or confirmed site of infection or positive blood culture AND
 - o Ongoing infusion of vasopressor/inotrope agent to maintain a mean arterial blood pressure of 65 mmHg or above AND
 - o Lactate of 2 mmol/L or above in any plasma sample performed within the last 3-hours
- Have received at least 1 L of IV fluid (crystalloids, colloids or blood products) in the last 24-hours prior to screening.

4.2 Exclusion criteria

We will exclude patients who fulfil any of the following criteria:

- Septic shock for more than 12 hours at the time of screening because we want to include patients early in their course
- Life-threatening bleeding as these patients need specific fluid/blood product strategies
- Acute burn injury of more than 10% of the body surface area as these patients need a specific fluid strategy
- Known pregnancy (details presented in Appendix 2)
- Consent not obtainable as per the model approved for the specific site.

We will not exclude patients enrolled in other interventional trials unless the protocols of the two trials collide; we present the rationale for this in Appendix 7. Co-enrolment agreements will be established with the sponsor/investigator to maintain an updated list of trials approved for co-enrolment (Appendix 7).

4.3 Participant discontinuation and withdrawal

The procedure of handling withdrawal of consent from a participant will follow national regulations and will be described for each participating country.

4.3.1 Discontinuation and withdrawal at the choice of the participant or the proxy

The Danish procedure:

A participant, who no longer wishes to participate in the trial, can withdraw his/her consent at any time without need of further explanation, and without consequences for further treatment. For incompetent participants, consent can be withdrawn at any time by the person(s), who has given proxy-consent. To limit the amount of missing data, we will collect as much data as possible from

each participant. Therefore, if possible, the investigator will ask the participant or the proxy to which extent the withdrawal includes:

- receiving the trial intervention only (allowing for all data registration and follow-up)
OR
- receiving the trial intervention AND further registration of daily data and/or follow-up

Only the participant can demand deletion of already registered data and only if the participant did not consent previously. If so, the data will be deleted, and a new participant will be enrolled to obtain the full sample size.

4.3.2 Discontinuation and withdrawal at the choice of the investigator

A participant may have the intervention stopped by the clinician or investigator at any time, if:

- The participant experiences intolerable adverse reactions or events (including SAR or SUSAR) suspected to be related to the trial intervention.
- The clinicians in conjunction with the coordinating investigator decide it to be in the interest of the participant
- The participant after inclusion is subject to involuntary hospitalization, the intervention will stop.

In these cases, the collection of data and the follow-up will continue, and the participant will remain in the intention-to-treat population.

4.3.3 Discharge to another ICU

Participants who are discharged to another ICU will be regarded as discharged from the ICU unless the receiving ICU is an active CLASSIC trial site. If so, the participant will continue the allocated intervention at the new trial site until discharge from ICU. Participants referred to intermediate or step-up/step-down beds cared for by ICU staff trained in the CLASSIC trial protocol will continue the allocated intervention.

5 Selection of trial sites and personnel

5.1 *Trial sites and setting*

Trial sites will be ICUs in Europe and potentially in Canada and Australasia where we explore the possibilities for collaboration. Trial sites are listed in the section Administrative information (p. 3). This section will be updated during the trial.

5.2 *Trial personnel*

All doctors caring for patients in participating ICUs will be eligible to enrol patients in the trial and all clinicians caring for patients will be eligible to care for and perform the interventions in the trial participants. All participating ICUs will receive written and oral instructions about the trial procedures. A 24-hour hotline will be available for trial-related questions.

6 Trial interventions

The intervention period is the entire ICU admission to a maximum of 90 days.

6.1 *Experimental intervention*

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

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

A bolus of 250-500 ml of IV crystalloid solution may be given followed by re-evaluation. These criteria identify patients at increased risk of death [35, 36, 37], and were found feasible and not associated with harm in the CLASSIC pilot trial [5].

- In case of overt fluid losses (e.g. vomiting, large aspirates, diarrhoea, drain losses, bleeding or ascites tap) IV fluid may be given to correct for the loss, but not above the volume lost.
- In case the oral/enteral route for water or electrolyte solutions is contraindicated or has failed as judged by the clinical team, IV fluids may be given to:
 - Correct dehydration or electrolyte deficiencies.
 - Ensure a total fluid input of 1 L per 24 h (fluids with medications and nutrition counts as input).

IV fluids may be given as carrier for medication, but the volume should be reduced to the lowest possible volume for the given medication.

6.2 *Control intervention*

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

- IV fluids should be given in the case of hypoperfusion or circulatory impairment and should be continued as long as hemodynamic variables improve including static or dynamic variable(s) as chosen by the clinicians. These criteria are based on the SSC guideline [11]
- IV fluids should be given as maintenance if the ICU has a protocol recommending maintenance fluid
- IV fluids should be given to substitute expected or observed loss, dehydration or electrolyte derangements

6.3 *Co-interventions*

Types of fluid to be used in both intervention groups:

- IV fluids given for circulatory impairment: Only isotonic crystalloids are to be used as per the Scandinavian guideline for fluid resuscitation [38]
- Fluids given to substitute overt loss: Isotonic crystalloids are to be used. If large amounts of ascites are tapped, then human albumin may be used [39]
- Fluids used for dehydration: Water or isotonic glucose should be used

- Fluids used for electrolyte disturbances: Fluids should be chosen to substitute the specific deficiency, including water in the case of severe hyponatremia
- Blood products are only to be used on specific indications including severe bleeding, severe anaemia and prophylactic in case of severe coagulopathy.

6.4 Concomitant interventions

The use of concomitant interventions for septic shock should be based on the updated international sepsis guidelines [11]. In particular, we suggest the following to trial sites:

- Relevant antibiotics and source control for the infection
- Noradrenalin as vasopressor
- Renal replacement therapy based on conservative criteria [40] (i.e. severe hyperkalaemia (p-K > 6.0 mmol/L), severe metabolic acidosis (s-bicarbonate < 10 mmol/L and pH < 7.20), persistent kidney injury >72 h (oliguria/anuria or s-creatinine has not declined to 50% of the peak), or severe fluid overload combined with hypoxic respiratory failure (P/F-ratio < (26 kPa (200 mmHg)).

6.5 Criteria for modification of interventions for a given trial participant

The clinical team may at any time violate the protocol if they find it to be in the best interest of the participant. We will have a CLASSIC trial hotline to enable discussion around the clock between the clinicians caring for trial participants and the CLASSIC trial team regarding protocol related issues.

6.6 Assessment of participant compliance

We will monitor protocol compliance at the trial site through the electronic case report form (eCRF) and alert trial sites in the case of clear violation (central monitoring). In addition, the trial will be externally monitored according to the GCP directive and the monitoring plan (section 11).

7 Outcome measures

7.1 Primary outcome

All-cause mortality at day 90 after randomisation

7.2 Secondary outcomes

- Number of participants with one or more serious adverse events (SAEs) in the ICU defined as ischaemic events (cerebral, cardiac, intestinal or limb ischaemia) or as a new episode of severe acute kidney injury (modified KDIGO3 [41])
- Number of participants with one or more serious adverse reactions (SARs) to IV crystalloids in the ICU as defined in section 8.2
- Days alive at day 90 without life support (vasopressor / inotropic support, invasive mechanical ventilation or renal replacement therapy)
- Days alive and out of hospital at day 90
- All-cause mortality at 1-year after randomisation
- HRQoL 1-year after randomisation measured using the EuroQoL (EQ)-5D-5L and EQ-VAS scores. Participants who have died will be assigned the lowest possible scores

- Cognitive function 1-year after randomisation as assessed by the Montreal Cognitive Assessment (MoCa) score

Several of the secondary outcomes above are composite outcomes. The single components of these will also be analysed and presented in a supplement to the primary publication.

8 Safety

8.1 Definitions

In the CLASSIC trial, we will use the definitions below [42].

Adverse Event (AE): any undesirable medical event occurring to a participant during a clinical trial, which does not necessarily have a causal relationship with the intervention.

Adverse Reaction (AR): any undesirable and unintended medical response related to the intervention occurring to a participant during a clinical trial.

Serious Adverse Event (SAE): any adverse event that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

Serious Adverse Reaction (SAR): any adverse reaction that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

Suspected Unexpected Serious Adverse Reaction (SUSAR): any suspected adverse reaction which is both serious and unexpected (the nature or severity of which is not consistent with the information available to date).

8.2 Risk and safety issues in the CLASSIC trial

The trial participants will all be ICU patients for whom all adverse events and reactions are documented routinely in the patient health record (i.e. ICU notes, charges and laboratory reports). We will record in the eCRF the occurrence of SAEs and SARs on all trial days in ICU for all included patients and report SAEs and SARs as outcomes measures.

Both interventions groups will receive IV crystalloids as part of the protocol. We have identified the SARs to these fluids in the Danish Summary of Product Characteristics (SPCs) as listed below. The adverse reactions to the crystalloid solution not registered in the CLASSIC trial are listed in Appendix 3 including the reasoning.

SARs to crystalloid solutions (isotonic saline and buffered solutions (Ringer's lactate, Ringer's acetate and PlasmaLyte™)) assessed in the CLASSIC trial

- Generalised tonic-clonic seizures
- Anaphylactic reactions
- Central pontine myelinolysis
- Severe hyponatremia (defined as p-Na > 159 mmol/L)
- Severe hyperchloraemic acidosis (defined as pH < 7.15 AND p-chloride > 115 mmol/L)
- Severe metabolic alkalosis (defined as pH > 7.59 AND SBE > 9 mmol/L)

8.3 Assessment of adverse events

8.3.1 Timing

In all participants, we will assess the occurrence of SAEs and SARs on all trial days the participants spend in ICU to a maximum of 90 days.

8.3.2 Classification of an event

We will make no inferences about a causal relationship between the intervention and the event/reaction of the SAEs (7.2) and SARs (8.2), but register the occurrence in the two groups and report them in the final report according to the definition given above. As for any other SAE not covered in section 7.2 and 8.2, the investigators will report them if they are unexpected to Sponsor or his delegate without within 24 hours. If such a SAE is deemed related to the intervention by Sponsor and the investigator, it will be considered a SUSAR and reported as such (section 8.4).

8.4 Reporting

Trial investigators will report SAEs, SARs and SUSARs without undue delay to the Sponsor or his delegate. The Sponsor will report it to the Danish Medicine Agency within 7 days after the report of a life-threatening or fatal SUSAR. No later than 8 days after the reporting, the Sponsor will inform the Danish Medicines Agency of relevant information on the Sponsor's and the investigator's follow-up action to the life-threatening or fatal SUSAR. Any other SUSARs will be reported to the Danish Medicines Agency no later than 15 days from the time when the Sponsor is informed.

Once a year, the Sponsor will submit a list of all SARs that have occurred at all sites during the trial period and a report on safety of the trial subjects to the Danish Medicines Agency.

The Sponsor will notify the Danish Medicines Agency when the trial has been completed (no later than 90 days thereafter) and if earlier than planned, the reasons for stopping the trial.

In addition, we will report all SAEs and SARs as outcome measures and all SUSARs in the final trial report and the results of the trial will be reported on EudraCT.

9 Procedures, assessments and data collection

9.1.1 Screening

All patients admitted to, or planned for clinical reasons to be admitted to a participating ICU with septic shock will be eligible for screening.

9.1.2 Procedures for informed consent

Participants will be enrolled after consent by proxy is obtained according to national regulations. The procedure for each participating country will be described; that for Danish participants is described in Appendix 5. The Swedish procedure for consent and specific Swedish regulations are described in Appendix 5.1.

9.2 Data collection

9.2.1 Methods

Data will be obtained from the participant's hospital files and national/regional/hospital registers (source data as defined per site, region and country) and by participant survey/interview and entered in the web-based eCRF by trial investigators or their delegates. For participants transferred from a trial ICU to a non-trial ICU, data related to the outcomes will be collected according to national practice e.g. investigator contact to the non-trial ICU or health care registers.

9.2.2 Timing

All variables are defined in Appendix 2.

Baseline variables:

- Sex
- Date of birth
- Date of admission to hospital
- Date and time of admission to ICU
- From where was the participant admitted to ICU
 - o Emergency department or directly from the pre-hospital setting
 - o Hospital ward
 - o Operating or recovery room
 - o Another ICU
- Focus of infection:
 - o Pneumonia
 - o Gastrointestinal infection
 - o Urinary tract infection
 - o Skin or soft tissue infection
 - o Other
- Co-morbidities:
 - o Active hematologic cancer
 - o History of metastatic carcinoma

- History of ischemic heart disease or heart failure
- History of chronic hypertension
- Chronic dialysis
- Blood values, interventions and vital parameters:
 - Participant weight
 - Highest plasma lactate value within the last 3 hours of randomisation
 - Highest dose of noradrenaline within the last 3 hours of randomisation
 - Volumes of IV fluid within the last 24 hours of randomisation
 - Use of systemic corticosteroids in the last 24 hours of randomisation
 - Highest plasma creatinine value within the last 24 hours of randomisation
 - Use of acute renal replacement therapy in the last 3 days prior to randomisation
 - Habitual plasma creatinine value prior to current hospitalisation (mark estimated or measured)
- Values for the Simplified Mortality Score (SMS score)[43] at ICU admission not covered by the above:
 - Lowest measured systolic blood pressure in the last 24 hours prior to randomisation
 - Respiratory support within the last 24 hours of randomisation (support during surgery excluded)

Daily during ICU admission (day form):

- Fluid input and output
 - Total volume and specific type of IV isotonic crystalloids (isotonic saline and buffered solutions: Ringer's lactate, Ringer's acetate and PlasmaLyte™)
 - Total volume of other IV fluids
 - Total volume of albumin
 - Total volume of fluids with medications
 - Total volume of fluids with nutrition
 - Total volume of blood products
 - Urinary output on this day (ml)
 - Total volume of other losses on this day including drainage, aspirates, stools and bleeding
- Did a major protocol violation occur on this day?
- Use of infusion of vasopressor or inotrope on this day
- Use of systemic corticosteroids on this day
- Use of mechanical ventilation on this day
- Use of renal replacement therapy on this day
- Plasma concentration of creatinine
- SAEs on this day (y/n for everyone)
 - Cardiac ischemic event
 - Cerebral ischemic event
 - Intestinal ischemic event
 - Limb ischemia
- SARs on this day (y/n for everyone)

- General tonic-clonic seizures
- Anaphylactic reactions
- Central pontine myelinolysis.
- Severe hyponatremia
- Severe hyperchloreaemic acidosis
- Severe metabolic alkalosis

ICU discharge form:

- Died in ICU
- Discharged to the ward at the same or another hospital
- Discharged to another ICU participating in CLASSIC
- Discharged to another ICU not participating in CLASSIC
 - Number of days of infusion of vasopressor or inotrope in this ICU
 - Number of days of mechanical ventilation in this ICU
 - Number of days of renal replacement therapy in this ICU

Follow-up 90 days after randomisation:

- Death (y/n, if yes date of death)
- Date of the last session of any renal replacement therapy
- Date of discharge from hospital
- Additional hospital admissions

Follow-up 1 year after randomisation

- Death (y/n, if yes date of death)
- EQ-5D-5L and EQ-VAS scores
- MoCa scores

9.3 Data management

The data manager at CTU or his/her delegate will construct and oversee the eCRF. He/she will, as the only person, have access to the randomisation list during trial. The eCRF and the trial database will be hosted at the server of CTU with appropriate back-up and security as per the GCP regulative.

9.4 Confidentiality

Each participant will receive a unique trial identification number. Trial investigators will receive a personal username and passwords to access the randomisation system and the eCRF. Each site will only have access to site specific participant data. Data will be handled according to the National Data Protection Agency and protected by the Danish national laws 'Loven om behandling af personoplysninger' and 'Sundhedsloven'.

9.5 Collection, handling, storage and transportation of human biological material

No additional sampling of human material will be done in the main trial as data entry will rely on routine testing done in the clinical setting. In sub-studies, blood tests will likely be taken in addition to the routine clinical tests. If so, specific protocols will be submitted for approval, as described in section 12.4.

9.6 Access to data

All original records (incl. consent forms, eCRFs, and relevant correspondences) will be archived for 15 years. De-identified data will be made publicly available 9 months after the publication of the outcome data according to the recent ICMJE recommendations [69]. As it is for all CRIC trials, all trial-related documents will be public available at www.CRIC.nu including those of the site master file, the eCRF template, instructions, educational material etc.

10 Statistical plan and data analysis

The analyses will be done according to the principles stipulated in ICH-GCP guidelines [42] and the detailed statistical analysis plan, which will be published before the randomisation of the last participant.

10.1 Sample size and power

10.1.1 Sample size estimation

By enrolling 1554 (2 x 777) participants, we can show a 15% relative risk reduction (7% absolute) in the restrictive group from an estimated 45% 90-day mortality in the standard care group (data from our previous CLASSIC pilot, TRISS and 6S trials [2, 3, 5], systematic reviews [23, 44] and a recent large cohort study [4]) at type 1 and 2 error levels of 5% and 20% (power=80%), respectively.

10.1.2 Power estimations

We expect to have the following statistical power for the secondary outcomes based on 2 x 777 participants, a type 1 error level of 1% and a relative risk reduction of 15% in the experimental vs control group:

- 50% power for the number of participants with one or more SAEs (control event rate 25%)
- 10% power for the number of participants with one or more SARs (control event rate 5%)
- 80% power for the mortality at 1-year (control event rate 55%).

The estimates of control event rates originate in data of previous septic shock trials [2, 3]. We expect the following outcomes to be highly skewed (non-normally distribution): Days alive without life support and out of hospital at day 90 and HRQoL and cognitive function at 1-year. The power estimations for these are, therefore, somewhat uncertain why we refrain from making these estimates.

10.2 Statistical methods

The analyses will be done in the intention-to-treat (ITT) population defined as all randomised participants for whom there is consent for the use of data. We will perform the primary analyses adjusted for the stratification variables [45] and challenge the primary result in analyses adjusted for important baseline risk factors (co-morbidities, higher SMS score, and focus of infection (other foci vs. urinary tract infection)[43, 46] and use of corticosteroids, which may reduce the time in ICU and thus the time exposed to the protocol [47]) and analyses of subgroups (Table 2) and the per-protocol population being the ITT population except those having one or more major protocol violations as defined below (Table 3). If there is more than 5% missing data for outcomes and/or covariates, we will impute the missing data using multiple imputations as described below (10.2.4).

All analyses will be 2-tailed and we will use Fisher's exact test for unadjusted comparisons of dichotomized outcomes (mortality at 90-days and 1-year, SAEs and SARs) and logistic regressions for adjusted analyses of these outcomes. The remaining secondary outcomes are continuous measures; we expect that these are highly skewed (non-normally distribution), because of inflation of specific values such as zero for days alive outside hospital for all patients who die while at the ICU. We will use statistical methods that can accommodate this type of data; the precise models will be specified in the detailed statistical plan.

Several of the secondary outcome measures are composite; we will also analyse each component of these outcomes as recommended [42]; the precise models will be specified in the detailed statistical plan.

Table 2. Heterogeneity of the intervention effects on the primary outcome will be analysed in the following subgroups based on baseline characteristics

Subgroup	Definition	Expected direction of the interaction	Statistical test
Participants who are mechanically ventilated	Invasive mechanically ventilated (yes/no)	Larger effect of fluid restriction in mechanically ventilated participants	Test of interaction in the adjusted analysis described above; P-value 0.01
Participants with severe acute kidney injury	KDIGO (creatinine) criteria of 2 or above [41] (yes/no)	Larger effect of fluid restriction in acute kidney injury	Test of interaction in the adjusted analysis described above; P-value 0.01
Participants with severe metabolic failure	Plasma lactate level above 4 mmol/l (yes/no)	Larger effect of fluid restriction in severe metabolic failure	Test of interaction in the adjusted analysis described above; P-value 0.01
Participant weight	Weight tertiles as observed in the 6S and TRISS trial cohorts combined [2, 3]	Larger effect of fluid restriction with lower weight	Test of interaction in the adjusted analysis described above; P-value 0.01
IV fluid volume given prior to randomisation	30 ml/kg or more given (yes/no)	Larger effect of fluid restriction with less fluid given	Test of interaction in the adjusted analysis described above; P-value 0.01

Table 3. The definitions of major protocol violations, the exclusion of which will form the per-protocol population

Intervention group	Major protocol violation definition
IV fluid restriction	IV fluids given without one of the extenuating circumstances occurring
Standard of care	No IV fluids given

10.2.1 Significance

We will present the results as adjusted absolute and relative risk differences, computed using glm-models with appropriate link functions and binomial error-distribution, with confidence intervals (CI) using 95% CIs for the analyses of primary outcome (P-value 0.05) and 99% CIs for those of the secondary outcomes (P-value 0.01) due the multiplicity of these.

10.2.2 Interim analysis

We will conduct three interim-analyses; one when 10% of participants have been followed for 30-days, one when 30% of participants have been followed for 30-days and one when 50% of participants have been followed for 90-days. The Data Monitoring and Safety Committee (DMSC) will analyse only the fluid volumes and protocol violations in the two intervention groups in the two interim analyses to ensure that separation is occurring. At the third interim analysis they will assess fluid volumes, protocol violations, the 90-day mortality and the rates of SAEs and SARs in the ICU in the two intervention groups as described in the charter (Appendix 4). The DMSC will submit their recommendations to the Management Committee, which make the final decision regarding the continuing, pausing or stopping of the trial as described in the DMSC charter.

10.2.3 Early stopping criteria

The trial will not be stopped unless the cumulative Z-value for effect size supersedes the Lan DeMets group sequential monitoring boundary corresponding to a P-value for effect of less than 0.005 (approximately). The trial will not be stopped for futility as an intervention effect less than a 15% relative risk reduction may be clinically relevant. However, the DMSC can recommend pausing or stopping the trial if continued conduct of the trial clearly compromises participant safety.

10.2.4 Accountability procedure for missing data/population for analysis

If less than 5% of data are missing for any primary or secondary outcome, a complete case analysis without imputation of missing values will be performed. If missing data are more than 5%, a statistician masked for the intervention will assess whether data are ‘missing completely at random’ (MCAR criterion) based on a rational assessment of the pattern of missing data [48]. Little’s test will be used if doubt remains [49]. If it is concluded that data are not MCAR, multiple imputation using chained equations will be performed by creating 10 input datasets under the assumption that the data are ‘missing at random’ (MAR criterion) [50, 51]. We will use outcomes and the most important baseline characteristics in the multiple imputations as will be outlined in the detailed statistical analysis plan.

If multiple imputations are used, then the primary result of the trial will be based on these data. The unadjusted, non-imputed analysis will also be presented. If multiple imputation is used because of missing outcome data, we will use a best-worst worst-best case scenario as a sensitivity analysis to assess the potential impact of any pattern of missingness including that the data are 'missing not at random' (MNAR criterion). In the 'best-worst-case' scenario it is assumed that all participants lost to follow-up in the experimental group have had a beneficial outcome (e.g. have survived, had no SAE etc.); and all those with missing outcomes in the control group have had a harmful outcome (e.g. have not survived; have had a SAE etc.). Conversely, in the 'worst-best-case' scenario, it is assumed that all participants who were lost to follow up in the experimental group have had a harmful outcome; and that all those lost to follow-up in the control group have had a beneficial outcome. When continuous outcomes are used, a 'beneficial outcome' will be defined as the group mean plus two SD of the group mean or highest possible value whichever is smallest, and a 'harmful outcome' will be defined as the group mean minus two SD of the group mean or lowest possible value whichever is highest.

11 Quality control and quality assurance

The Sponsor and the coordinating investigator will be responsible for organizing the trial sites including education of local investigators, research nurses, and other trial site personnel before the initiation of the trial. This education will be continuously documented in the site master file. An annual investigator meeting will be planned.

After initiation, trial site investigators will be responsible for all trial-related procedures at their site, including education of staff in trial-related procedures, recruitment and follow-up of participants and entry of data. Clinical staff at the trial sites will be responsible for the treatment of trial participants.

11.1 Monitoring

The trial will be externally monitored according to the GCP directive and the monitoring and data verification plan including the documentation of informed consent of trial participants. The monitoring and data verification plan will be developed together with the GCP unit of Copenhagen University Hospital and adhered to by the staff monitoring trial sites in all countries. In addition, we will use central monitoring of site through the eCRF including adherence to the protocol.

11.2 Drug traceability measures

The volumes of IV fluid administered will be registered in the eCRF for every day the participant is in the ICU to a maximum of 90 days. The registration of the batch numbers and the expiry dates of the IV fluids and the identity of the clinician administering the fluid will be registered as per standard practice at the sites. These data will not be registered in the trial documents, but can be obtained by the Sponsor or the authorities if needed. We believe that this is a safe procedure because the IV fluids used in the CLASSIC trial has been in clinical use for many years and the safety of single doses cannot be questioned. The same procedure was approved by the Danish Medicines Agency in the CLASSIC pilot trial (EudraCT no. 2014-000902-37).

12 Legal and organisational aspects

12.1 Finance

12.1.1 Trial funding

The trial is funded by an unrestricted grant from the Novo Nordisk Foundation and Sofus Friis' foundation. None of the funding organisations have been or will be involved in the design, conduct, analyses, or reporting of the trial nor will they have ownership of the data.

12.1.2 Compensation

All trial sites will be paid DKK 3000 (400 EUR) for each participant with completed 1-year follow-up status to partly compensate for the increased workload regarding screening, consent, inclusion, data-entry and follow-up.

12.2 Insurance

In Denmark, the Patient Insurance Association insures all trial participants. Patient insurance will be ensured before initiating the trial in each participating country. We will use external funding for the costs of insurance.

12.3 Plan for publication, authorship and dissemination

All trial results whether positive, negative or neutral will be published preferably in a peer-reviewed medical journal. Furthermore, the results will be published at the CRIC home page (www.cric.nu). We will adhere to the CONSORT statement including the accountability of all patients screened (Appendix 10).

Authorship will be granted according to the guidelines from the International Committee for Medical Journal Editors (ICMJE; <http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html>).

The listing of authors will be as follows on the primary publication: TS Meyhoff will be first author, PB Hjortrup the second, J Wetterslev the third, the next authors will be the national investigators according to the number of included participants per country, then the other members of the Management Committee, the trial statistician and trial site investigators dependent on the number of included participants per site. A. Perner will be the last and corresponding author.

The Management Committee will grant authorship depending on personal input as per the Vancouver definitions. If a trial site investigator is to gain authorship on the primary publication, the site has to include 25 participants or more. If a site includes 50 participants, 2 authorships may be granted, at 75 participants 3 authorships and so on. Investigators on sites including less than 25 participants may be granted authorship on the long-term outcome publication if they contribute significantly as per the Vancouver definitions.

The DMSC and investigators not qualifying for authorship will be acknowledged with their names under 'the CLASSIC Trial investigators' in an *appendix* to the final manuscript.

The funding sources will be acknowledged, but they will have no influence on the data handling or analyses, the writing of the manuscript or the decision to publish.

12.4 Sub-studies

Sub-studies are planned at selected sites and more will be encouraged as long as they do not hamper the completion of the main protocol and can be conducted after approval of the specific protocol by the Management Committee and the authorities. Thus, specific protocols for any sub-studies will be submitted to and approved by the relevant authorities and ethic committees before the commencement of such studies. In Appendix 8, the presently proposed sub-studies are listed.

12.5 Intellectual property rights

The CLASSIC trial group owns the trial data. The Contract between the Sponsor and an investigator will be reviewed and approved by the Unit for Research and Innovation (Law and Contracts) of the Capital Region (<https://www.regionh.dk/english/research-and-innovation/Pages/default.aspx>) and by the Medical Director of Rigshospitalet, dr. Per Jørgensen.

12.6 Organisational framework

The CLASSIC trial will be managed by the Management Committee and overseen by the CRIC Steering Committee (Appendix 1). The day-to-day running of the trial will be done by the Sponsor, the Coordinating Investigator and the CRIC office.

12.7 Trial timeline

November 2017 – January 2018: Finalisation of the protocol among Management Committee and national investigators

January - March 2018: Approval of the protocol by the Danish Medicines Agency and the Ethics Committee of the Capital Region

March - September 2018: Approvals in the other countries, building of the eCRF and recruitment and education of trial sites

September 2018: First Danish participant enrolled

October 2018: Commencement of inclusion in other countries

January 2019: 1st interim analysis

May 2019: 2nd interim analysis

December 2019: 2nd interim analysis

September 2020: Last participant enrolled

January 2021: 90 day follow-up completed, database cleaned

February 2021: Data analysis and submission of the primary report for publication

September 2021: One year follow-up completed

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14 Appendix

Appendix 1: Research programme organisation

Appendix 2: Trial definitions

Appendix 3: Adverse reactions not registered

Appendix 4: Charter for the independent Data Monitoring and Safety Committee

Appendix 5: Informed consent procedure in Denmark

Appendix 5.1: Informed consent procedure in Sweden

Appendix 6: Simplified Mortality Score

Appendix 7: Co-enrolment agreement form

Appendix 8: List of proposed sub-studies

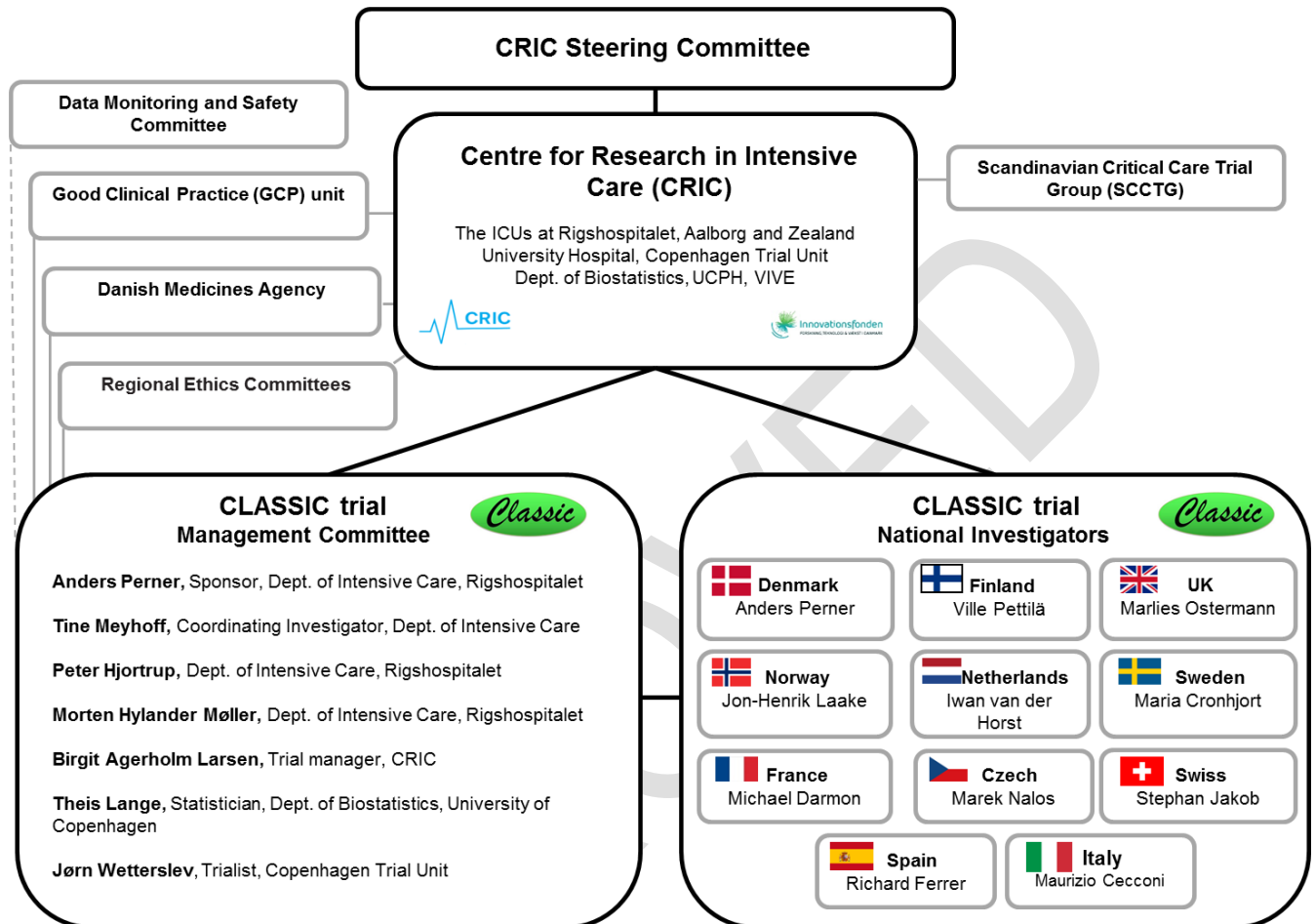
Appendix 9: Preliminary results of our systematic review on restrictive vs. standard of care/more liberal fluid resuscitation in patients with septic shock.

Appendix 10: Trial participant flow chart

Appendix 11: International Committee of Medical Journal Editors (ICMJE) form for potential conflict of interest

APPROVED

14.1 Appendix 1: Research programme organisation



14.2 Appendix 2: Trial definitions

Definition of stratification variables

Site: all participating intensive care units (ICUs) will be assigned a number identifying the unit.

Metastatic cancer or hematologic malignancy:

- Metastatic cancer: proven metastasis by surgery, CT scan or any other method
- Haematological malignancy includes any of the following:
 - o Leukaemia: Acute lymphoblastic leukaemia (ALL), acute myelogenous leukaemia (AML), chronic myelogenous leukaemia (CML), chronic lymphocytic leukaemia (CLL).
 - o Lymphoma: Hodgkin's disease, and Non-Hodgkin lymphoma (e.g. small lymphocytic lymphoma (SLL), diffuse large B-cell lymphoma, follicular lymphoma and mantle cell lymphoma)
 - o Hairy cell leukaemia (HCL), marginal zone lymphoma, Burkitt's lymphoma, post-transplant lymphoproliferative disorder (PTLD), T-cell prolymphocytic leukaemia (T-PLL), B-cell prolymphocytic leukaemia (B-PLL), Waldenström's macroglobulinemia and other NK- or T-cell lymphomas
 - o Multiple myeloma/plasma cell myeloma

Definition of the inclusion criteria

Age: the age of the participant in whole years at the time of randomisation. The age will be calculated from date of birth.

Admitted to the ICU or plan to be admitted to the ICU: We will only recruit sites that have the status as an ICU. These may oversee beds defined as high-dependency, step-up or step-down beds. We will consider these as being part of the trial site ICU if staff trained in the protocol looks after the patients in these beds. The medical doctors at the site ICUs may enrol patients from other locations in the hospital (e.g. emergency departments, general wards or the recovery room) if the patient for clinical reasons is planned to be admitted to the ICU.

Septic shock: We will define septic shock at the time of screening according to the Sepsis-3 criteria [9] i.e.:

- Suspected or confirmed site of infection or positive blood culture AND
- Ongoing infusion of vasopressor/inotrope agent (norepinephrine, epinephrine, phenylephrine, vasopressin analogues, angiotensin, dopamine, dobutamin, milrinone or levosimendan) to maintain a mean arterial blood pressure of 65 mmHg or above AND
- Lactate of 2 mmol/L or above in any plasma sample performed within the last 3-hours prior to screening

Have received at least 1 L of IV fluid in the last 24-hours prior to screening: We will count all crystalloids (isotonic saline, Ringer's and Plasmalyte™ solutions) colloids (albumin 4, 5 or 20%, gelatine, hydroxyethyl starch and dextran solutions) and blood products (units or red cells, plasma or

platelets) the participant has received according to the source data within the last 24-hours independent of location (in- or pre-hospital). Intraosseous fluid will be counted as IV.

Definition of the exclusion criteria

-Septic shock for more than 12 hours at the time of screening: Septic shock according to the Sepsis-3 criteria [9] (definition given above) for more than 12 hours at the time of screening

-Life-threatening bleeding: clinical bleeding needing transfusion of blood products as defined by the clinicians

-Acute burn injury of more than 10% of the body surface area: burn injury leading to the present ICU admission. Patients with burn injury who are readmitted to the ICU or were initially care for in a general ward and admitted to the ICU for infection may be screened to enrolment. The latest documented estimate of the burn area will be used as these may be down-graded after the initial assessments.

-Known pregnancy: women with known pregnancy based on clinical examination, the history or human chorionic gonadotropin (hCG). We will not demand negative hCG-status in all eligible fertile women, because (i) screening for enrolment has to be done within the time window (waiting for the hCG result will delay screening and result in fewer fertile women included), (ii) the pregnancy rate is very low in ICU patients with septic shock and (iii) trial participation will not endanger the woman or the foetus. The same procedure was approved by the Danish Medicines Agency in the TARTARE 2S trial (EudraCT no. 2015-005112-15), which has many similarities to the CLASSIC trial (ICU patients with septic shock randomized to protocolised titration of an approved medicine (noradrenalin).

-Consent not obtainable according to national regulations: patients where the clinician or investigator is unable to obtain the necessary consent before inclusion of the patient according to the national regulations.

Definition of baseline variables

-Sex: the genotypic sex of the participant

-Age: defined in inclusion criteria

-Date of admission to hospital: the date of admission to the first hospital the participant was admitted to during the current hospital admission

-Date and time of admission to the ICU (or high-dependency or step-up/step-down beds; see inclusion criteria): the date of admission to the first ICU the participant was admitted to during the current hospital admission

-From where was the participant admitted to ICU

- Emergency department or directly from the pre-hospital setting:
Accident/Emergency/Casualty/Acute department in the same or another hospital or direct admission to the ICU by an ambulance service or similar
- Hospital ward: Any location in the same or another hospital not covered in the other 3 categories

- Operating or recovery room: including surgical theatre, endoscopy and angiography suite and any recovery facilities observing patients following invasive procedures.
- Another ICU: either within the same or another hospital

Focus of infection (documented or suspected):

- Pulmonary: e.g. pneumonia, or empyema
- Gastrointestinal infection: e.g. primary, secondary or tertiary peritonitis, abscess, cholangitis, cholecystitis, or invasive diarrhoeal disease
- Urinary tract infection: e.g. urinary tract infection, or pyelonephritis
- Skin or soft tissue infection: e.g. cellulitis, phlegmon, erysipelas, or fasciitis
- Other: other infectious focus documented or suspected including meningitis, endocarditis, osteomyelitis, arthritis and bacteraemia

-Co-morbidities, must have been present in the past medical history prior to ICU admission and are defined as follows:

- Active hematologic cancer: defined in the stratification variables
- History of metastatic carcinoma: defined in the stratification variables
- History of ischemic heart disease or heart failure: previous myocardial infarction, invasive intervention for coronary artery disease, stable or unstable angina, NYHA class 3 or 4 or measured LVEF < 40%.
- History of chronic hypertension: treatment at time of hospital admission with any antihypertensive agent e.g. diuretics, adrenergic receptor antagonists (alpha/beta/alpha+beta blockers), alpha-2 receptor agonists, calcium channel blockers, ACE-inhibitors, ANG-II receptor antagonists, aldosterone antagonists.
- Chronic dialysis: use of renal replacement therapy at least once a week e.g. chronic haemodialysis or haemofiltration, peritoneal dialysis

- Blood values, interventions and vital parameters:

- Participant weight: measured or estimated in kg
- Highest plasma lactate value within the last 3 hours of randomisation: in mmol/L
- Highest dose of noradrenaline within the last 3 hours of randomisation: highest infusion rate in $\mu\text{g}/\text{kg}/\text{min}$
- Volumes of IV fluid within the last 24 hours of randomisation: cumulative volume in mL of crystalloid and colloid solutions and blood products given independent of location
- Use of systemic (IV, IM or oral/per GI tube) corticosteroids in the last 24 hours of randomisation including any dose of hydrocortisone, methylprednisolone, dexamethasone or prednisolone
- Highest plasma creatinine value within the last 24 hours of randomisation: in $\mu\text{mol}/\text{L}$
- Use of acute renal replacement therapy in the last 3 days prior to randomisation: any form of renal replacement therapy (e.g. dialysis, hemofiltration or hemo-diafiltration) at any rate in the last 72 hours, which has been initiated during the current hospitalisation (including any stay in another hospital immediately prior that in the site)

- Habitual plasma creatinine value prior to current hospitalisation: estimated or measured in $\mu\text{mol/L}$. If no there are no values recorded in source data, we will estimate habitual plasma creatinine using the MDRD formula.

-The simplified mortality score (Appendix 6) is based on 7 variables obtained in the 24 h prior to randomisation of a patient into the trial [43]. The variables include:

- Age: defined in inclusion criteria
- Lowest systolic blood pressure: either invasive or non-invasive in mmHg. In case of cardiac arrest within the 24-h period '0' will be registered.
- Acute surgical admission: Surgery during current hospital admission that was added to the operating room schedule.
- Hematologic malignancy or metastatic cancer: Defined in the stratification variables.
- Vasopressors/inotropes: Use of continuous infusion of vasopressor or inotrope (defined in the inclusion criteria).
- Respiratory support: Use of invasive or non-invasive mechanical ventilation including continuous mask CPAP or CPAP via tracheostomy. Intermittent CPAP is NOT considered as respiratory support.
- Renal replacement therapy: Use of acute or chronic intermittent or continuous renal replacement therapy.

Definition of daily collected variables:

-Fluid input and output in mL cumulated from the 24-h ICU charts

- Total volume and specific type of IV isotonic crystalloids: isotonic saline and buffered solutions: Ringer's lactate, Ringer's acetate and PlasmaLyte™
- Total volume of other IV fluids: e.g. <10% glucose, glucose-potassium, sodium-potassium-chloride, half-saline
- Total volume of albumin (4, 5 or 20% solutions combined)
- Total volume of fluids with medications: both parenteral and enteral
- Total volume of fluids with enteral and parenteral nutrition: e.g. enteral nutrition solutions and >10% glucose, protein or lipid solutions given parenterally or enterally
- Total volume of non-nutritional enteral/oral fluids: e.g. water or soft drinks
- Total volume of blood products: defined in inclusion criteria
- Urinary output on this day
- Any fluid volume removed during renal replacement therapy
- Total volume of other losses on this day including drainage, aspirates, stools and bleeding

-Major protocol violation on this day:

- Restrictive group: IV fluids given without one of the extenuating circumstances occurring on this day (y/n)
- Standard care group: the violations (no IV fluid given) will be assessed from all the day form registrations regarding fluid input at the end of trial for each participant

-Use of infusion of vasopressor or inotrope on this day: defined in the inclusion criteria

- Use of systemic corticosteroids on this day: defined in the baseline data

-Use of mechanical ventilation on this day: invasive mechanical ventilation as the use of positive pressure ventilation using a ventilator via a cuffed tube (oral, nasal or tracheostomy). CPAP is NOT mechanical ventilation.

-Use of renal replacement therapy on this day: any form of renal replacement therapy (e.g. dialysis, hemofiltration or hemo-diafiltration) at any rate on this day.

-Plasma concentration of creatinine in $\mu\text{mol/L}$ on this day

Definition of outcome measures

Primary outcome:

90 day mortality: death from any cause within 90 days post-randomisation.

Secondary outcomes:

-Serious adverse events as at least one episode of either the following observed in the ICU:

- Ischemic events defined as either
 - o Cerebral ischemia defined as any form of cerebral ischemia on a CT- OR MRI scan
 - o Acute myocardial ischemia defined as participant with acute myocardial infarction (ST-elevation myocardial infarction or non-ST elevation myocardial infarction) or unstable angina pectoris according to the criteria in the clinical setting in question (e.g. elevated biomarkers, ischemic signs on ECG and clinical presentation) **AND** the participant received treatment as a consequence of this (reperfusion strategies (PCI/thrombolysis) OR initiation/increased antithrombotic treatment).
 - o Intestinal ischemia defined as ischemia verified by endoscopy OR open surgery.
 - o Limb ischemia defined as clinical signs **AND** need of open/percutaneous vascular intervention, amputation OR initiation/increased antithrombotic treatment.
- A new episode of severe acute kidney injury defined as modified KDIGO3 [41]: a p-creatinine above $354 \mu\text{mol/L}$ in participants who had a value below this at baseline, or use of renal replacement therapy (any form) in participants who did not receive this before randomisation.

-Serious adverse reactions: total number of SARs and number of SARs per participant in the ICU. Serious adverse reactions are defined below.

-Number of days alive without life support at day 90: will be assessed from the use of life support including vasopressor/inotrope, mechanical ventilation and renal replacement therapy as defined in the inclusion criteria, baseline and daily variables. Total number of days alive without all of the 3 life supporting interventions within 90 days after randomisation.

-Days alive and out of hospital at day 90: will be assessed from the discharge date from the index hospitalisation, the number of days readmitted to hospital (if any) and date of death, if relevant, within the 90-day period

-1-year mortality: landmark mortality 1-year post-randomisation. If the participant has deceased, date of death will be registered.

-HRQoL at 1-year (+/- 2 weeks): EQ-5D-5L and EQ-VAS scores (<https://euroqol.org/>) obtained by survey by mail or phone as chosen by the participant. Non-survivors will be given the worst possible score.

-Cognitive function at 1-year (+/- 2 weeks): the Montreal Cognitive assessment (MoCa) MINI score (or '5-minute protocol') using the translations of the MoCa full v. 7.1 (<http://www.mocatest.org/>). The score will be obtained in all survivors by interview as this was recommended to be the test of cognition in a core outcome set for patients with acute respiratory failure following a modified Delphi process involving patients, researchers and clinicians from multiple continents (<http://www.improvelto.com/>). Non-survivors will be given the worst possible score. If the MoCa MINI, which is validated for phone interview [52], has not been released at the time of the first assessment (1-year after randomisation of the first patient), we will use the MoCa full v. 7.1 at the sites that have the resources to do face-to-face interview needed to obtain the MoCa full score.

SARs will be defined as follows:

-General tonic-clonic seizures: stiffening and/or jerking movements of all 4 extremities in a patient who becomes or is unconscious in the ICU after randomisation

-Anaphylactic reactions defined as urticarial skin reaction **AND** at least one of the following observed in the ICU after randomisation

- Worsened circulation (>20% decrease in blood pressure or >20% increase in vasopressor dose)
- Increased airway resistance (>20% increase in the peak pressure on the ventilation)
- Clinical stridor or bronchospasm
- Subsequent treatment with bronchodilators

-Central pontine myelinolysis seen on CT or MRI scan within the 90-day period after randomisation

-Hyponatremia defined as p-Na > 159 mmol/L on any plasma sample, including point-of-care testing, done in the ICU after randomisation

-Severe hyperchloraemic acidosis defined as pH < 7.15 AND p-chloride > 115 mmol/L on any plasma sample, including point-of-care testing, done in the ICU after randomisation

-Severe metabolic alkalosis defined as pH > 7.59 AND SBE > 9 mmol/L on any plasma sample, including point-of-care testing, done in the ICU after randomisation

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14.3 Appendix 3. Adverse reactions not registered in CLASSIC

The following possible adverse reactions presented in the Danish Summary Product Characteristics for the crystalloid solutions will not be registered in the CLASSIC trial as we do consider these to be serious conditions:

Normal saline (0.9% NaCl):

- Hypervolemia in itself is not regarded as a SAR, but the potentially serious consequence is reflected in the outcome measure days alive without life-support.

Ringer-lactate:

- Sodium retention is not registered as it is not regarded as a SAR.
- Hyperchloraemia is not registered, but is reflected in the SAR hyperchloraemic acidosis.

Ringer-acetate:

- Heart failure is not directly registered, but is reflected in the outcome measure days alive without life-support.
- Conjunctivitis is not registered as it is not regarded as a SAR.
- Pulmonary oedema is not directly registered, but is reflected in the outcome measure days alive without life-support.
- Rhinitis is not registered as it is not regarded as a SAR.
- Overhydration is not directly registered, but is reflected in the outcome measure days alive without life-support. In addition, total fluid balances will be calculated from the daily in- and output

PlasmaLyte™:

- Peripheral oedema is not registered as it is not regarded as a SAR
- Pyrexia not registered as it is not regarded as a SAR
- Hypervolemia in itself is not regarded as a SAR, but the potentially serious consequence is reflected in the outcome measure days alive without life-support.
- Thrombophlebitis and other reactions at the infusion site are not registered as it is not regarded as SARs

14.4 Appendix 4. Charter for the independent data monitoring and safety committee

Introduction

The DMSC will constitute its own plan of monitoring and meetings. However, this charter will define the minimum of obligations and primary responsibilities of the DMSC as perceived of the Management Committee (MC), its relationship with other trial components, its membership, and the purpose and timing of its meetings. The charter will also outline the procedures for ensuring confidentiality and proper communication, the statistical monitoring guidelines to be implemented by the DMSC, and an outline of the content of the open and closed reports which will be provided to the DMSC.

Primary responsibilities of the DMSC

The DMSC will be responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. The DMSC will provide recommendations about stopping or continuing the trial to the MC of the CLASSIC trial. To contribute to enhancing the integrity of the trial, the DMSC may also formulate recommendations relating to the selection/recruitment/retention of participants, their management, improving adherence to protocol-specified regimens and retention of participants, and the procedures for data management and quality control.

The DMSC will be advisory to the MC. The MC will be responsible for promptly reviewing the DMSC recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in trial conduct are required.

The DMSC may meet physically or by phone at their own discretion in order to evaluate the planned interim analyses of the CLASSIC trial. The interim analyses will be performed by an independent statistician selected by the members of the DMSC, NAME (**pending**) from the Dept. of Biostatistics, University of Copenhagen. The DMSC may additionally meet whenever they decide or contact each other by telephone or e-mail to discuss the safety for trial participants. The sponsor has the responsibility to report the overall number of SARs yearly to the DMSC. The DMSC can, at any time during the trial, request the distribution of events, including outcome measures and SARs according to intervention groups. Further, the DMSC can request unmasking of the interventions if suggested by the data, see section on 'closed sessions'. The recommendations of the DMSC regarding stopping, continuing or changing the design of the trial should be communicated without delay to the MC of the CLASSIC trial. As fast as possible, and no later than 48 hours, the MC has the responsibility to inform all investigators of the trial and all the sites including patients in the trial, about the recommendation of the DMSC and the MC decision hereof.

Members of the DMSC

The DMSC is an independent multidisciplinary group consisting of clinicians and a biostatistician that, collectively, has experience in the management of ICU patients and in the conduct, monitoring and analysis of randomized clinical trials.

DMSC Clinician

Pending

DMSC Trialist

Pending

DMSC Biostatistician

Pending. Dept. of Biostatistics, University of Copenhagen

Conflicts of interest

DMSC members will fill in and sign a declaration of conflicts of interests (Appendix 10). DMSC membership has been restricted to individuals free of conflicts of interest. The source of these conflicts may be financial, scientific, or regulatory in nature. Thus, neither trial investigators nor individuals employed by the sponsor, nor individuals who might have regulatory responsibilities for the trial products, are members of the DMSC. The DMSC members do not own stock in the companies having products being evaluated by the CLASSIC trial.

The DMSC members will disclose to fellow members any consulting agreements or financial interests they have with the sponsor of the trial, with the contract research organisation (CRO) for the trial (if any), or with other sponsors having products that are being evaluated or having products that are competitive with those being evaluated in the trial.

The DMSC will be responsible for deciding whether these consulting agreements or financial interests materially impact their objectivity.

The DMSC members will be responsible for advising fellow members of any changes in these consulting agreements and financial interests that occur during the course of the trial. Any DMSC members who develop significant conflicts of interest during the course of the trial should resign from the DMSC.

DMSC membership is to be for the duration of the clinical trial. If any members leave the DMSC during the course of the trial, the MC will appoint the replacement(s).

Formal interim analysis meetings

Three formal interim analysis meetings will be held to review data relating to protocol adherence, treatment efficacy, participant safety, and quality of trial conduct. The three members of the DMSC will meet when day 30 data of 155 participants (10% of sample size) have been obtained, when day 30 data of 466 participants (30% of sample size) have been obtained and again when 90-day follow-up data of 777 (50% of sample size) participants have been obtained.

Proper communication

To enhance the integrity and credibility of the trial, procedures will be implemented to ensure the DMSC has sole access to evolving information from the clinical trial regarding comparative results of

efficacy and safety data, aggregated by treatment group. An exception will be made to permit access to an independent statistician who will be responsible for serving as a liaison between the database and the DMSC.

At the same time, procedures will be implemented to ensure that proper communication is achieved between the DMSC and the trial investigators. To provide a forum for exchange of information among various parties who share responsibility for the successful conduct of the trial, a format for open sessions and closed sessions will be implemented. The intent of this format is to enable the DMSC to preserve confidentiality of the comparative efficacy results while at the same time providing opportunities for interaction between the DMSC and others who have valuable insights into trial-related issues.

Closed sessions

Sessions involving only DMSC membership who generates the closed reports (called closed sessions) will be held to allow discussion of confidential data from the clinical trial, including information about the protocol adherence and the relative efficacy and safety of interventions. To ensure that the DMSC will be fully informed in its primary mission of safeguarding the interest of participating participants, the DMSC will be blinded in its assessment of safety and efficacy data. However, the DMSC can request unblinding from the MC.

Closed reports will include analysis of the volumes of IV fluids (1st and analyses) and the primary outcome measure and rates of SAEs and SARs (3rd analysis). These closed reports will be prepared by independent biostatistician being a member of the DSMC, with assistance from the trial data manager, in a manner that allow them to remain blinded.

The closed reports should provide information that is accurate, with follow-up on mortality that is complete to within two months of the date of the DMSC meeting.

Open reports

For each DMSC meeting, open reports will be provided available to all who attend the DMSC meeting. The reports will include data on recruitment and baseline characteristics, and pooled data on eligibility violations, completeness of follow-up, and compliance. The independent statistician being a member of the DMSC will prepare these open reports in co-operation with the trial data manager.

The reports should be provided to DMSC members approximately three days prior to the date of the meeting.

Minutes of the DMSC Meetings

The DMSC will prepare minutes of their meetings. The closed minutes will describe the proceedings from all sessions of the DMSC meeting, including the listing of recommendations by the committee. Because it is possible that these minutes may contain unblinded information, it is important that they are not made available to anyone outside the DMSC.

Recommendations to the Management Committee

The planned interim analyses will be conducted after participant no. 155 and no. 466 has been followed for 30 days and again when no. 777 has been followed for 90 days.

After the interim analysis meetings, the DMSC will make a recommendation to the MC to make extraordinary efforts to enforce protocol adherence (1st and 2nd interim analyses) and continue, hold or terminate the trial (3rd interim analysis).

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

Furthermore, the DMSC can recommend pausing or stopping the trial if continued conduct of the trial clearly compromises participant safety. However, stopping for futility to show an intervention effect of 15% RRR (or RRI) for mortality will not be an option as intervention effects less than these may be clinically relevant as well.

This recommendation will be based primarily on safety and efficacy considerations and will be guided by statistical monitoring guidelines defined in this charter and the trial protocol.

The MC is jointly responsible with the DMSC for safeguarding the interests of participants and for the conduct of the trial. Recommendations to amend the protocol or conduct of the trial made by the DMSC will be considered and accepted or rejected by the MC. The MC will be responsible for deciding whether to continue, hold or stop the trial based on the DMSC recommendations.

The DMSC will be notified of all changes to the trial protocol or conduct. The DMSC concurrence will be sought on all substantive recommendations or changes to the protocol or trial conduct prior to their implementation.

Statistical monitoring guidelines

The outcome parameters are defined in the statistical analyses plan in the CLASSIC trial protocol. For the two intervention groups, the DMSC will evaluate data on:

First and second interim analyses

Cumulative volumes of IV fluids given in the ICU and rates of protocol violations in the two groups.

Third interim analysis

Cumulative volumes of IV fluids given in the ICU and rates of protocol violations in the two groups.

The primary outcome measure

Mortality in the 90 days after randomisation.

The secondary outcome measures

- The occurrence of SAEs in the ICU
- The occurrence of SARs in the ICU

The DMSC will be provided with these data from the coordinating centre as:

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

Based on evaluations of these outcomes, the DMSC will decide if they want further data from the coordinating centre and when to perform the next analysis of the data.

For analyses, the data will be provided in one file as described below.

DMSC should yearly be informed about SARs occurring in the two groups of the trial.

The DMSC may also be asked to ensure that procedures are properly implemented to adjust trial sample size or duration of follow-up to restore power, if protocol specified event rates are inaccurate. If so, the algorithm for doing this should be clearly specified.

Conditions for transfer of data from the Coordinating Centre to the DMSC

The DMSC will be provided with a SAS file containing the data defined as follows:

Row 1 contains the names of the variables (to be defined below).

Row 2 to N (where N-1 is the number of participants having entered the trial) each contains the data of one participant.

Column 1 to p (where p is the number of variables to be defined below) each contains in row 1 the name of a variable and in the next N rows the values of this variable.

The values of the following variables should be included in the database for the **first and second interim analyses**:

1. screening_id: a number that uniquely identifies the participant
2. rand_code: The randomisation code (group 0 or 1). The DMSC is not to be informed on what intervention the groups received
3. Cum_fluid_indic: Cumulative volumes of IV fluids given in the ICU
4. Protocol_viol_indic: No. of protocol violations in the two groups

The values of the following variables should be included in the database for the **third interim analysis**:

1. screening_id: a number that uniquely identifies the participant
2. rand_code: The randomisation code (group 0 or 1). The DMSC is not to be informed on what intervention the groups received
3. Cum_fluid_indic: Cumulative volumes of IV fluids given in the ICU
4. Protocol_viol_indic: No. of protocol violations in the two groups
5. day_90_indic: 90 day-mortality indicator (2 = censored, 1=dead, 0=alive at day 90)
6. SAE_indic: SAE indicator (1 = one or more SAEs, 0 = no SAE)
7. SAR_indic: SAR indicator (1 = one or more SARs, 0 = no SAR)

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14.5 Appendix 5. Informed consent, Denmark

In Denmark temporarily incompetent patients will be enrolled after informed consent from one medical doctor, who is independent of the trial (first trial guardian). As soon as possible after enrolment, consent will be obtained from the patient's next of kin and a second medical doctor (second trial guardian). The second trial guardian must be different from the first trial guardian and also independent of the trial. Participants, who regain consciousness, will be asked for informed consent as soon as possible. The process leading to the achievement of informed consent will be in compliance with all applicable regulations. The consenting party will be provided with written and oral information about the trial so he/she is able to make an informed decision about participation in the trial. The information will be given in a separate room, and the consenting party has the right to bring a companion.

Written information and the consent form will be subjected to review and approval by the relevant ethic committees.

Lack of informed consent from the participant's next of kin

If information about the participant's next of kin is not available after inclusion, the investigator will seek information from e.g. the participant's general practitioner, the police, nursing homes etc. In these situations it may take 1-2 weeks to conclude that no next of kin can be identified. If no one is identified and the participant remains incompetent the trial intervention will be discontinued. All initiatives to identify the participant's next of kin will be documented in patient files, logs or similar.

Lack of informed consent from the participant's next of kin and the participant deceases

If the participant deceases before informed consent has been obtained (due to rapid progression of critical illness or because the participant's next of kin is not yet identified) and the participant has been correctly included in the trial, the collected data will be kept for analysis.

Deviation from the standard informed consent

According to the standard informed consent form from the National Ethics Committee regarding competent participants, the participant can choose not to receive information about the data collected during the trial. However, the purpose of this trial is not to generate new knowledge about the specific participant, so we find that this question is redundant, and have omitted the question from the consent form to spare the participant from making unnecessary decisions.

Trial personnel

Screening will be performed by medical doctors or medical students working under the responsibility of a trained medical doctor.

Collection of informed consent will be performed by all trial personnel (study nurses, medical students, doctors). If questions arise during informed consent, responsible study personnel can be reached through a 24-h hotline. All personnel with functions in the CLASSIC trial will be trained and approved according to GCP-guidelines before engaging in the trial.

14.5 Appendix 5.1. Informed consent, Sweden

Informed consent

The patients in septic shock will receive written and oral information of the study and they will be asked to give oral consent before enrolment. As/if they recover they will receive written and oral information about the study and they will give written informed consent to continue in the study.

Reporting of Serious Adverse Events

Serious adverse events are any adverse events that results in death, are life-threatening, require hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect. We will specifically be registering ischemic events (cerebral, cardiac, intestinal or limb ischemia and new episodes of severe acute kidney injury. SAEs will be reported to the sponsor within 24 hours, according to LVFS 2011:19. Any SAE that is not listed in the RSI will be considered as unexpected, including all fatal events, and be reported as Suspected Unexpected Serious Adverse Reactions (SUSARs). They will be reported by the sponsor to the Medical Product Agency within 7 days after the report reached the sponsor.

Monitoring

The monitoring and data verification plan is developed by Copenhagen University Hospital GCP Unit, Denmark. National investigators will ensure local monitoring in adherence to the monitoring plan and national regulations. The local investigators will ensure that the monitors and the regulatory personnel will have access to patient records/ source data for monitoring and inspections.

14.6 Appendix 6. Simplified Mortality Score for the Intensive Care Unit (SMS-ICU)

In trial settings, the variables are measured in the 24-h period before randomisation; further details are presented in Appendix 2 and in [43].

SMS-ICU		Total score and predicted 90-day mortality risk	
Age		0	3.3 %
≤ 39 years → 0		3	4.8 %
40-59 years → 5		4	5.5 %
60-79 years → 10		5	6.2 %
≥ 80 years → 13		6	7.1 %
Lowest systolic blood pressure		7	8.0 %
≤ 49 mmHg → 6		8	9.1 %
50-69 mmHg → 5		9	10.3 %
70-89 mmHg → 3		10	11.6 %
≥ 90 mmHg → 0		11	13.1 %
Acute surgical admission		12	14.7 %
No → 3	Yes → 0	13	16.5 %
Hematologic malignancy or metastatic cancer		14	18.4 %
No → 0	Yes → 7	15	20.5 %
Vasopressors/inotropes		16	22.8 %
No → 0	Yes → 4	17	25.3 %
Respiratory support		18	28.0 %
No → 0	Yes → 5	19	30.8 %
Renal replacement therapy		20	33.8 %
No → 0	Yes → 4	21	36.9 %
Total score: 0-42 points		22	40.1 %
		23	43.4 %
		24	46.7 %
		25	50.1 %
		26	53.5 %
		27	56.9 %
		28	60.2 %
		29	63.4 %
		30	66.4 %
		31	69.4 %
		32	72.2 %
		33	74.8 %
		34	77.3 %
		35	79.6 %
		36	81.7 %
		37	83.7 %
		38	85.4 %
		39	87.0 %
		40	88.8 %
		41	89.8 %
		42	91.0 %
Use the worst values recorded during the first 24 hours in the ICU.			

14.7 Appendix 7. Co-enrolment

Based upon an updated critical appraisal of the literature, the CLASSIC Management Committee endorses and encourages co-enrolment in the CLASSIC trial. The following issues have been considered.

Ethical considerations

Preventing eligible patients from co-enrolment in trials, which they would authentically value participating in, and whose material risks and benefits they understand, violates their autonomy - and thus contravenes a fundamental principle of research ethics [53].

Permitting co-enrolment is in accordance with existing recommendations for the conduct of trustworthy clinical practice guidelines, taking into account benefits and harms, quality of evidence, values and preferences (of patients or their proxies) and cost considerations, as outlined by the Institute of Medicine, the Guideline International Network, and according to the GRADE methodology [54, 55, 56].

Patient relatives have limited concerns about co-enrolment [57].

General considerations

Critically ill patients receive many different interventions in addition to the trial intervention because of acute and chronic illness. Consequently, the potential for interactions is a prerequisite in clinical trials in critically ill patients, and co-enrolment is thus little different from what occurs in single-enrolment trials [53].

In large pragmatic trials, like the CLASSIC trial, other interventions will be given at random and are therefore difficult to control for. If interaction in fact is an issue, it may be better controlled for if patients are co-enrolled and randomised to more than one intervention.

Factorial design trials allow detailed assessment of interactions between interventions, and are considered cost-efficient, as two or more treatments are assessed for the price of one [58]. Co-enrolment trials and factorial design trials share many similarities [53].

A pre-planned sub-study will assess the impact of co-enrolment in the CLASSIC trial, and thus generate valuable knowledge on the topic of co-enrolment.

Clinical research with a potential to inform and improve clinical practice is valuable and should be supported. More high-quality clinical research can be conducted in a timely fashion and more information can be generated to guide clinical practice, if co-enrolment is permitted [59].

Scientific and statistical considerations

Pragmatic clinical trials allowing inclusion of a broad range of trial participants and options for drug treatments and other therapies (co-enrolment) have higher external validity/generalizability than non-pragmatic trials with restrictions regarding trial participants and co-enrolment [60].

Non-pragmatic trials with restrictions regarding study participants and co-enrolment are exposed to drugs and other treatments in a less clinically relevant setting where interactions are largely uncontrolled and poorly evaluated. Co-enrolment in pragmatic trials facilitates evaluation of clinically relevant and patient-important interactions [53].

Co-enrolment into two or more trials does not invalidate the original randomization of the individual trials. Separate analysis of each individual trial, ignoring the issue of co-enrolment into the other trial, will retain the balance of patient characteristics expected by standard random assignment within each trial [53].

The National Institute of Health supports co-enrolment [60]; so does the Canadian Critical Care Trials group (<http://www.ccctg.ca/Home.aspx>) and the Australian New Zealand Intensive Care Society's Clinical Trial Group (<http://www.anzics.com.au/Pages/CTG/CTG-home.aspx>). We have co-enrolment agreements with the two latter research groups.

Co-enrolment into two or more trials does not seem to affect the natural course of the disease of the other condition being studied [53].

Co-enrolment does not appear to influence patient safety or trial results [61, 62].

Empirically, co-enrolment has a small effect on study power [53].

In conclusion, we highly support and encourage co-enrolment because of overall benefit, including ethical, practical and scientific benefit, and no evidence of harm.

14.7.1 Co-enrolment agreement form

In general we will encourage engagement in research projects other than the CLASSIC trial. Please, fill in the information of the trial to be evaluated as counterpart for co-enrolment with CLASSIC, and send it by e-mail to contact@cric.nu.

Once we have received the information below, we will contact the principal/coordinating investigator of the trial and facilitate exchange of protocols and other relevant documents between the Management Committees. You will find a list of titles already considered for co-enrolment by clicking <http://www.cric.nu/co-enrolment-list/>

We have prepared the form for only one trial, but please feel free to copy as many forms as you need.

a. Official full/short title of the project:

b. Contact information of principal/coordinating investigator of the trial:

Name:

E-mail:

14.8 Appendix 8. List of proposed sub-studies

- The effect of co-enrolment on the intervention effect in the CLASSIC trial

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14.9 Appendix 9. Preliminary results of our systematic review

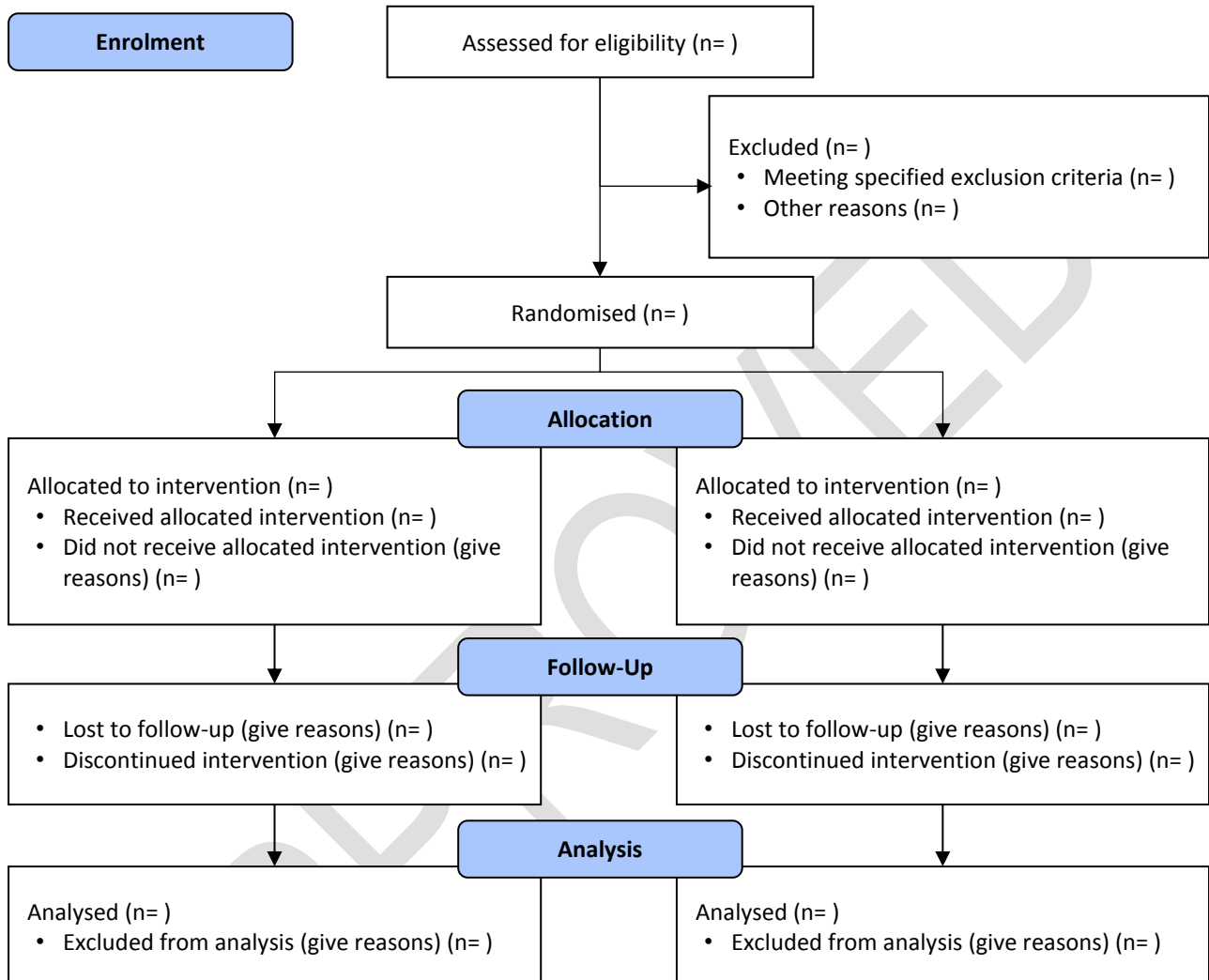
Preliminary results of our systematic review on restrictive vs. standard of care/more liberal fluid resuscitation in patients with septic shock.

Pending

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14.10 Appendix 10. Trial flow chart

Please refer to the Consort Statement for more information (<http://www.consort-statement.org/>). The flowchart should be modified to reflect the flow of participants in the trial. The flowchart (n=) will be filled in at the end of the trial.



14.11 Appendix 11. International Committee of Medical Journal Editors (ICMJE) form for potential conflict of interest



ICMJE INTERNATIONAL COMMITTEE of
MEDICAL JOURNAL EDITORS

SAVE

ICMJE Form for Disclosure of Potential Conflicts of Interest

Instructions

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form is designed to be completed electronically and stored electronically. It contains programming that allows appropriate data display. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in six parts.

- 1. Identifying information.**
- 2. The work under consideration for publication.**

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes".
- 3. Relevant financial activities outside the submitted work.**

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.
- 4. Intellectual Property.**

This section asks about patents and copyrights, whether pending, issued, licensed and/or receiving royalties.
- 5. Relationships not covered above.**

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.

Definitions.

<p>Entity: government agency, foundation, commercial sponsor, academic institution, etc.</p> <p>Grant: A grant from an entity, generally [but not always] paid to your organization</p> <p>Personal Fees: Monies paid to you for services rendered, generally honoraria, royalties, or fees for consulting, lectures, speakers bureaus, expert testimony, employment, or other affiliations</p> <p>Non-Financial Support: Examples include drugs/equipment supplied by the entity, travel paid by the entity, writing assistance, administrative support, etc.</p>	<p>Other: Anything not covered under the previous three boxes</p> <p>Pending: The patent has been filed but not issued</p> <p>Issued: The patent has been issued by the agency</p> <p>Licensed: The patent has been licensed to an entity, whether earning royalties or not</p> <p>Royalties: Funds are coming in to you or your institution due to your patent</p>
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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name)

2. Surname (Last Name)

3. Date

4. Are you the corresponding author? Yes No

5. Manuscript Title

6. Manuscript Identifying Number (if you know it)

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? Yes No

ADD

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the 'Add +' box. You should report relationships that were **present during the 36 months prior to publication**.

Are there any relevant conflicts of interest? Yes No

ADD

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? Yes No

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Section 5. Relationships not covered above

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

- Yes, the following relationships/conditions/circumstances are present (explain below):
- No other relationships/conditions/circumstances that present a potential conflict of interest

At the time of manuscript acceptance, journals will ask authors to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask authors to disclose further information about reported relationships.

Section 6. Disclosure Statement

Based on the above disclosures, this form will automatically generate a disclosure statement, which will appear in the box below.

Generate Disclosure Statement

Evaluation and Feedback

Please visit <http://www.icmje.org/cgi-bin/feedback> to provide feedback on your experience with completing this form.