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Long-term patient-important outcomes after septic shock: a protocol for 1-year follow-up of the CLASSIC-trial

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Abstract

Background: In patients with septic shock mortality is high, and survivors experience long-term physical, mental and social impairments. The ongoing Conservative vs Liberal Approach to fluid therapy of Septic Shock in Intensive Care (CLASSIC) trial assesses the benefits and harms of a restrictive versus (vs) standard-care intravenous (IV) fluid therapy. The hypothesis is that IV fluid restriction improves patient-important long-term outcomes.

Aim: To assess the predefined patient-important long-term outcomes in patients randomised into the CLASSIC trial.

Methods: In this pre-planned follow-up study of the CLASSIC trial, we will assess all-cause mortality, Health-Related Quality of Life (HRQoL) and cognitive function one year after randomisation in the two intervention groups. The 1-year mortality will be collected from electronic patient records or central national registries in most participating countries. We will contact survivors and assess EuroQol 5-Dimension, -5-Level (EQ-5D-5L) and EuroQol-Visual Analogue Scale and Montreal Cognitive Assessment 5-minute protocol score. We will analyse mortality by logistic regression and use general linear models to assess HRQoL and cognitive function.

Discussion: With this pre-planned follow-up study of the CLASSIC trial, we will provide patient-important data on long-term survival, HRQoL and cognitive function of restrictive vs standard-care IV fluid therapy in patients with septic shock.

Introduction

Sepsis is a syndrome with a dysregulated host response to an infection; in the most severe cases septic shock, multiple organ failure and death are frequent.¹ Sepsis contributes to every third hospital death.² Patients surviving septic shock often have long-term physical, psychological and cognitive disabilities with health-related and social implications.³⁻⁷ Any improvement in the treatment of septic shock is estimated to have a significant impact on public health and health economy.³

Intravenous (IV) fluid therapy is a recommended key intervention in septic shock, however, the evidence on how to manage fluids in these ICU settings is of low quality.^{6,8,9} Therefore, the ongoing multi-centre, randomised clinical trial (RCT) “The Conservative vs Liberal Approach to fluid therapy of Septic Shock in Intensive Care” (CLASSIC) assesses the benefits and harms of IV fluid restriction vs standard care in adult intensive care unit (ICU) patients with septic shock.¹⁰

Health-related quality of life

Health-related quality of life (HRQoL) is the most frequently used patient-reported outcome measure (PROM) for patients surviving critical illness in ICU.¹¹⁻¹³ HRQoL instruments offer a comprehensive multidimensional approach assessing physical, mental, and social domains and an overall perceived health state.^{14,15} The HRQoL measure is, therefore, an important outcome measure in addition to survival.¹⁵

Most often HRQoL is assessed in ICU survivors using generic, non-disease-specific instruments, most frequently the Short Form 36-item questionnaire or the EuroQol 5 dimension scale (EQ-5D).¹³ The EQ-5D is a short HRQoL questionnaire including domains on mobility, self-care, usual activities, pain/discomfort and anxiety/depression.¹⁶ The EQ-5D is considered validated to be used for follow-up in ICU trials to assess self-perceived HRQoL¹⁷⁻²⁰ and is recommended as a core outcome measure in this setting.²¹ The EQ-5D comes in two versions: a 3-level and a 5-level version. The EQ-5D in five levels (EQ-5D-5L) is to be answered together with an EQ-Visual Analogue Scale (EQ-VAS), the latter being a range for worst- to best imaginable health state.¹⁶

Cognitive function

Long-term cognitive impairment after critical illness is defined as the neuro-psychological changes that tend to persist and cause deficits of a magnitude that impair daily function.²² The incidence of cognitive impairment after sepsis has been reported to range from 4% to 62%.^{23,24} Both physical and cognitive impairment after intensive care are likely modifiable outcomes²⁵ as well as being outcomes reported as important to patients who survived acute respiratory failure.²⁶

The Montreal Outcome Assessment (MoCA) is a validated tool to assess cognitive function.²⁷ The full MoCA score is based on face-to-face interviews, but these are challenging to perform in large trials. The Mini MoCA refers to the MoCA 5-minute protocol,²⁸ previously validated in stroke-patients, consisting of five cognitive domains from the full MoCA for assessing mild cognitive impairment.²⁸ The five domains are attention, verbal learning and memory, executive function/language and orientation covered by four subtests.²⁸

Fluid trials for patients with septic shock measuring 1-year follow-up

A systematic review and meta-analysis, assessing lower vs higher fluid volumes in patients with septic shock, including nine trials, is in review.²⁹ None of these nine trials assessed long-term patient-important outcomes like HRQoL or cognitive function.

In the Fluid and Catheters Treatment Trial (FACTT) patients with acute lunge injury were randomised to conservative vs standard fluid therapy after the initial management.³⁰ In an adjunct study to the FACTT trial, a potential association between the conservative fluid-management strategy and long-term cognitive impairment was found in survivors²⁵ when assessed after 12 months by a validated neurocognitive telephone test at 12 months.^{25,31} The authors could not explain the result by reduced cerebral perfusion (e.g. cardiac index, systolic blood pressure) and encouraged further research to validate this result.²⁵

At least two ongoing restricted vs standard IV fluid trials in patients with sepsis/septic shock are on ongoing; The Crystalloid Liberal Or Vasopressor Early Resuscitation in Sepsis (CLOVERS) trial

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follows patients until day 90 with in-hospital mortality as primary outcome,³² and the CLASSIC trial follows patients until one year, assessing mortality, HRQoL and cognitive function.¹⁰ The CLASSIC trial seems to be the only trial measuring long-term patient-important-outcomes.¹⁰

Aim

To assess the predefined patient-important, long-term outcomes in patients randomised in the CLASSIC trial.

Hypothesis

The hypothesis is that IV fluid restriction will improve survival, HRQoL and cognitive function after septic shock.

Method

The CLASSIC trial

CLASSIC is an ongoing investigator-initiated, international, parallel-grouped, randomised 1:1 by a computer-generated allocation sequence list, stratified, analyst-blinded trial (NCT03668236). In the CLASSIC trial we assess benefits and harms of restricted vs standard-care IV fluid therapy in adult ICU patients with septic shock, stratified for haematological or metastatic cancer (yes/no) and trial site.¹⁰ The protocol and statistical analysis plan for the 90-day follow-up have been published.¹⁰ The planned sample size is 1554 patients. The first patient was enrolled November 27th, 2018, and the last patient is expected November 27th, 2020, with 1-year follow-up of the last patient by November 27th, 2021.

The primary outcome is mortality at day 90 and secondary outcomes are serious adverse events, serious adverse reactions, days alive at day 90 without life support, days alive and out of hospital at day 90, and mortality, HRQoL and cognitive function at one year.

Study design

This is a pre-planned long-term follow-up study assessing secondary outcomes of the CLASSIC trial. The staff assessing HRQoL and cognitive function and the statistician will be blinded to the trial allocation.

Study population

All patients randomised in the CLASSIC trial for whom there is obtained consent to carry out 1-year follow-up.

Inclusion criteria

All the following criteria must be met:

- 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:¹
 - Suspected or confirmed site of infection or positive blood culture AND
 - Ongoing infusion of vasopressor/inotrope agent to maintain a mean arterial blood pressure of 65 mmHg or above AND
 - Lactate of 2 mmol/L or above in any plasma sample performed within the last 3 hours
- Have received at least 1 L of IV fluid (crystalloids, colloids or blood products) in the last 24 hours prior to screening.

Exclusion criteria

Patients who meet any of the following criteria will be excluded:

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

Outcomes at 1-year follow-up

- All-cause mortality
- HRQoL measured by the EQ-5D-5L and EQ-VAS
- Cognitive function as assessed by the Mini MoCA

Ethical approval

The CLASSIC trial is registered at the European Clinical Trials Database (2018-000404-42) and www.clinicaltrials.gov (NCT03668236), is approved by the Danish Medicines Agency (2018020596), the Ethics Committee of the Capital Region (H-18006255), and the Danish Data Protection Agency (VD-2018-392) and by the relevant authorities for all participating sites. Written informed consent will be obtained for all patients when regained mental capacity.

Protection of data

At enrolment each patient receives a unique trial identification number in the electronic case report form (eCRF). All data will be obtained from patient files and national registers and recorded in a secured web-based eCRF. Data are managed electronically in the eCRF by trained trial personnel and will be handled according to the National Data Protection Agency and protected by the Danish national laws.^{33,34}

Workflow

We will introduce a Standard Operating Procedure (SOP) to be followed for all patients to motivate a high response rate and uniform data collection.^{35,36} Patients withdrawn from the intervention who have accepted further data registration will be contacted for the 1-year follow-up.

Obtaining survival status

We will obtain 1-year survival status for all patients. One-year mortality post randomisation will be obtained by registry for all Danish patients. At the sites in other countries it will be obtained as feasible. If the patient has deceased, date of death will be registered.

Telephone interviews

Each site will conduct telephone interviews with all survivors at 1-year post randomisation (allowing four additional weeks to increase the likelihood of response). Each site must secure that the personnel, who contacts the patients is blinded to the trial allocation.

Obtaining Mini MoCA

Every site will receive a version of the Mini MoCA in their language and the SOP on how to obtain the Mini MoCA. To increase consistency, all assessors will obtain training and certification according to the recommendations of MoCA Clinic & Institute. It is important to start the

interview with the Mini MoCA to ensure this is completed, in case the patient gets tired. Also, it is important that the patient is placed in a quiet room with no other people (to avoid noise and help) and not facing a calendar due to a question concerning orientation in the cognitive function score.³⁷ The Mini MoCA²⁸ can only be answered by the patient directly by phone and not by proxy. If the Mini MoCA has not been released for use at the time of the first assessment (one year after randomisation of the first patient), we will adapt the Mini MoCA from the MoCA full v. 7.1 with acceptance from the author.

Obtaining EQ-5D-5L

Every participating site will receive a version of the questionnaire in their language and the SOP on how to obtain the EQ-5D-5L. The EQ-5D-5L and the EQ-VAS scores can be obtained by phone, as we recommend, or by mail, if the patient prefers this. If the patient is not cognitively able to participate, we will ask a relevant proxy to answer.¹⁵ There is a proxy version of the EQ-5D-5L in all languages needed for the trial. In this version the proxy is asked to rate the patients' HRQoL in their (the proxies) opinion.

Statistical analyses

We will conduct all analyses in the intention-to-treat (ITT) population defined as all randomised patients for whom there is consent for the use of data. If the distribution of HRQoL and Mini MoCA deviates substantially from the normal distribution the primary analysis will be adjusted for the stratification variable of sites using Van Elteren test for differences of medians between groups. If the distribution of HRQoL and Mini MoCA comes close to a normal distribution or if the distribution of the Log transformed data comes close to a normal distribution, we perform multiple linear regression adjusted for both the stratification variable of sites and haematological malignancy.

In the two intervention groups we will assess any differences in:

- One-year mortality using two-tailed logistic regression adjusted for the stratification variables. Odds ratio will be converted to relative risks (computed using generalised linear

model (GLM) with appropriate link functions and binomial error-distribution) to consistently report the latter. We will present a Kaplan-Meier curve for the crude data.

- EQ-5D-5L, EQ-VAS and Mini MoCA scores using a generalised linear model or nonparametric test stratified for site (the rating and calculation is described in a Supplemental File S1). We have considered the challenge of handling patients “truncated due to death” when analysing functional outcomes in trials.³⁸ In consensus, we decided to assume that death is worse than a low HRQoL or low cognitive function score. Patients who are dead at 1-year follow-up will therefore be assigned the worst possible value (a value of zero). This will make these data non-normally distributed. We will, therefore, compare the groups using the method of Lange and Kryger Jensen; the probability of having a zero will be modelled using a logistic regression while the mean value among the non-zero values will be modelled using linear regression.³⁹ A joint test for no treatment effect will be reported.
- The scores of the single sub-domains of the EQ-5D-5L and the Mini MoCA will be presented in a supplement.

With 2 x 777 patients and a control event rate of 55% for the mortality at 1-year,^{40,41} we will have an 80% statistical power to detect a 15% relative risk reduction in the fluid restriction group vs the standard-care group with a type 1 error level of 1% . The estimates of the control event rates originate from data of previous septic shock trials.^{40,41} We expect HRQoL and cognitive function at 1-year to be highly skewed (non-normally distributed). As we lack knowledge on the details of the distribution, no realistic power analysis can be provided. We therefore refrain from this to avoid creating a false impression of precision. We will also conduct sensitivity analyses of EQ-5D-5L and Mini MoCA in the survivors only.

Significance

We will provide 99% confidence intervals (CI) between means (if data are nearly normally distributed) or otherwise between medians (by bootstrapping). We will present the results as adjusted absolute and relative risk differences, computed using generalised linear models with

appropriate link functions and binomial error-distribution, using 99% CIs for the secondary outcomes (P-value 0.01) due the multiplicity of these as stated in the CLASSIC protocol.¹⁰

Patients with missing data

Patients who die before 1-year follow-up will not create missingness. There are the following reasons for having missing data:

- Lost to follow-up (missing vital status and the EQ-5D-5L, EQ-VAS and the Mini MoCA data)
- Patients known to be alive who cannot be contacted or do not respond (missing EQ-5D-5L and Mini MoCA data).

We will obtain the reasons for missing data (Supplemental file S2); these will be described in the main manuscript and presented in supplementary material. If data in the completed questionnaires are missing exclusively for the outcome of EQ-5D-5L and the Mini MoCA in less than 5% or more than 40% of patients, or data are Missing Completely At Random (MCAR) with a negative Little's test ($P > 0.05$), we will not impute missing data.⁴²

If data are missing for outcomes in more than 5% and less than 40% of the patients, data will be imputed using multiple imputation (MI) assuming data missing at random (MAR); 50 imputed datasets will be generated. If MI is considered necessary, aggregated analyses of the imputed datasets will be calculated. However, assuming data missing not at random (MNAR) we will conduct analyses as best-worse and worse-best scenarios where data from missing response from survivors will be imputed using the mean \pm 1 standard deviation of the EQ-5D-5L and Mini MoCA in patients with complete data.⁴²

Discussion

With this long-term follow-up study, we aim to establish how restrictive vs standard-care IV fluid therapy affects long-term patient-important outcomes in adult patients with septic shock. The strength of our study includes being based on a large international RCT, which aims to provide us with high-quality evidence and with lowest possible risk of bias. The protocol for the CLASSIC trial, including the long-term follow-up after 1 year, and statistical analysis plan (SAP) was defined and published prior to the end of the trial.¹⁰

The limitations of our long-term follow-up include lack of a baseline EQ-5D-5L or MoCA score, which can lead to a potential baseline imbalance in HRQoL and cognitive function, which may be present but un-detected. The Mini MoCA is not validated for critically ill patients and it only detects mild cognitive impairment. Patients surviving sepsis may have long-term moderate to severe cognitive impairment.⁴ Therefore, cognitive impairment could potentially be underestimated with the Mini MoCA score. We will evaluate the use of the Mini MoCA tool, which to our knowledge has not previously been used in a RCT as long-term outcome in critically ill patients. Furthermore, evaluation of a simple and short tool measuring an important patient outcome will add significant value for future research.

Conclusion

We will assess HRQoL and cognitive function one year after patients with septic shock have been included in the CLASSIC trial. This will provide us with essential knowledge of long-term benefits and/or harms of restrictive IV fluid therapy versus standard-care.

Declarations

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Publication

The results of the long-term follow-up of the CLASSIC trial will be published in a peer-reviewed journal.

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Conflict of interest

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References

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche J-D, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, Poll T van der, Vincent J-L, Angus DC. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; 315: 801–10.
2. Vincent J-L, Jones G, David S, Olariu E, Cadwell KK. Frequency and mortality of septic shock in Europe and North America: a systematic review and meta-analysis. *Crit Care* 2019; 23: 196.
3. Hajj J, Blaine N, Salavaci J, Jacoby D. The “Centrality of Sepsis”: A Review on Incidence, Mortality, and Cost of Care. *Healthcare* 2018 Jul 30; 6. doi: 10.3390/healthcare6030090
4. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term Cognitive Impairment and Functional Disability Among Survivors of Severe Sepsis. *JAMA* 2010; 304: 1787–94.
5. Prescott HC, Angus DC. Enhancing Recovery From Sepsis: A Review. *JAMA* 2018; 319: 62–75.
6. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, Rochweg B, Rubenfeld GD, Angus DC, Annane D, Beale RJ, Bellinghan GJ, Bernard GR, Chiche J-D, Coopersmith C, De Backer DP, French CJ, Fujishima S, Gerlach H, Hidalgo JL, Hollenberg SM, Jones AE, Karnad DR, Kleinpell RM, Koh Y, Lisboa TC, Machado FR, Marini JJ, Marshall JC, Mazuski JE, McIntyre LA, McLean AS, Mehta S, Moreno RP, Myburgh J, Navalesi P, Nishida O, Osborn TM, Perner A, Plunkett CM, Ranieri M, Schorr CA, Seckel MA, Seymour CW, Shieh L, Shukri KA, Simpson SQ, Singer M, Thompson BT, Townsend SR, Van der Poll T, Vincent J-L, Wiersinga WJ, Zimmerman JL, Dellinger RP. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Med* 2017; 43: 304–77.
7. Prescott HC, Langa KM, Liu V, Escobar GJ, Iwashyna TJ. Increased 1-year healthcare use in survivors of severe sepsis. *Am J Respir Crit Care Med* 2014; 190: 62–9.
8. Perner A, Cecconi M, Cronhjort M, Darmon M, Jakob SM, Pettilä V, van der Horst ICC. Expert statement for the management of hypovolemia in sepsis. *Intensive Care Med* 2018; 44: 791–8.
9. Silversides JA, Perner A, Malbrain MLNG. Liberal versus restrictive fluid therapy in critically ill patients. *Intensive Care Med* 2019 Aug 9. doi: 10.1007/s00134-019-05713-y

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10. Meyhoff TS, Hjortrup PB, Møller MH, Wetterslev J, Lange T, Kjaer M-BN, Jonsson AB, Hjortsø CJS, Cronhjort M, Laake JH, Jakob SM, Nalos M, Pettilä V, van der Horst I, Ostermann M, Mouncey P, Rowan K, Cecconi M, Ferrer R, Malbrain MLNG, Ahlstedt C, Hoffmann S, Bestle MH, Nebrich L, Russell L, Vang M, Rasmussen ML, Sjølling C, Rasmussen BS, Brøchner AC, Perner A. Conservative vs liberal fluid therapy in septic shock (CLASSIC) trial-Protocol and statistical analysis plan. *Acta Anaesthesiol Scand* 2019 Jul 5. doi: 10.1111/aas.13434
 11. Oeyen SG, Vandijck DM, Benoit DD, Annemans L, Decruyenaere JM. Quality of life after intensive care: a systematic review of the literature. *Crit Care Med* 2010; 38: 2386–400.
 12. Winters BD. Long-term mortality and quality of life in sepsis: a systematic review. *Crit Care Med* 2010; 38: 1276–83.
 13. Turnbull AE, Rabiee A, Davis WE, Nasser MF, Venna VR, Lolitha R, Hopkins RO, Bienvenu OJ, Robinson KA, Needham DM. Outcome Measurement in ICU Survivorship Research From 1970 to 2013: A Scoping Review of 425 Publications. *Crit Care Med* 2016; 44: 1267–77.
 14. Fayers PM, Machin D. *Quality of Life. Assessment, Analysis and Interpretation*. England: Wiley, 2001. .
 15. Badia X, Diaz-Prieto A, Gorriz M, Herdman M, Torrado H, Farrero E, Cavanilles J. Using the EuroQol-5D to measure changes in quality of life 12 months after discharge from an intensive care unit. *Intensive Care Med* 2001; 27: 1901–7.
 16. Brooks R. EuroQol: the current state of play. *Health Policy* 1996; 37: 53–72.
 17. Angus DC, Carlet J, 2002 Brussels Roundtable Participants. Surviving intensive care: a report from the 2002 Brussels Roundtable. *Intensive Care Med* 2003; 29: 368–77.
 18. Kaarlola A, Tallgren M, Pettilä V. Long-term survival, quality of life, and quality-adjusted life-years among critically ill elderly patients. *Crit Care Med* 2006; 34: 2120–6.
 19. Khoudri I, Belayachi J, Dendane T, Abidi K, Madani N, Zekraoui A, Zeggwagh AA, Abouqal R. Measuring quality of life after intensive care using the Arabic version for Morocco of the EuroQol 5 Dimensions. *BMC Res Notes* 2012; 5: 56.
 20. Badia X, Díaz-Prieto A, Rué M, Patrick DL. Measuring health and health state preferences among critically ill patients. *Intensive Care Med* 1996; 22: 1379–84.

21. Needham DM, Sepulveda KA, Dinglas VD, Chessare CM, Friedman LA, Bingham CO, Turnbull AE. Core Outcome Measures for Clinical Research in Acute Respiratory Failure Survivors: An International Modified Delphi Consensus Study. *Am J Respir Crit Care Med* N Y 2017; 196: 1122–30.
22. Morandi A, Pandharipande PP, Jackson JC, Bellelli G, Trabucchi M, Ely EW. Understanding terminology of delirium and long-term cognitive impairment in critically ill patients. *Best Pract Res Clin Anaesthesiol* 2012; 26: 267–76.
23. Patel MB, Morandi A, Pandharipande PP. What's new in post-ICU cognitive impairment? *Intensive Care Med* 2015; 41: 708–11.
24. Calsavara AJC, Nobre V, Barichello T, Teixeira AL. Post-sepsis cognitive impairment and associated risk factors: A systematic review. *Aust Crit Care Off J Confed Aust Crit Care Nurses* 2018; 31: 242–53.
25. Mikkelsen ME, Christie JD, Lanken PN, Biester RC, Thompson BT, Bellamy SL, Localio AR, Demissie E, Hopkins RO, Angus DC. The adult respiratory distress syndrome cognitive outcomes study: long-term neuropsychological function in survivors of acute lung injury. *Am J Respir Crit Care Med* 2012; 185: 1307–15.
26. Turnbull AE, Sepulveda KA, Dinglas VD, Chessare CM, Bingham CO, Needham DM. Core Domains for Clinical Research in Acute Respiratory Failure Survivors: An International Modified Delphi Consensus Study. *Crit Care Med* 2017; 45: 1001–10.
27. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H. The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool For Mild Cognitive Impairment. *J Am Geriatr Soc* 2005; 53: 695–9.
28. Wong A, Nyenhuis D, Black SE, Law LSN, Lo ESK, Kwan PWL, Au L, Chan AYY, Wong LKS, Nasreddine Z, Mok V. Montreal Cognitive Assessment 5-Minute Protocol Is a Brief, Valid, Reliable, and Feasible Cognitive Screen for Telephone Administration. *Stroke* 2015; 46: 1059–64.
29. Meyhoff TS, Møller MH, Hjortrup PB, Cronhjort M, Perner A, Wetterslev J. Lower vs. higher fluid volumes in sepsis-protocol for a systematic review with meta-analysis. *Acta Anaesthesiol Scand* 2017; 61: 942–51.

30. The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Comparison of Two Fluid-Management Strategies in Acute Lung Injury. *N Engl J Med* 2006; 354: 2564–75.
31. Taichman DB, Christie J, Biester R, Mortensen J, White J, Kaplan S, Hansen-Flaschen J, Palevsky HI, Elliott CG, Hopkins RO. Validation of a brief telephone battery for neurocognitive assessment of patients with pulmonary arterial hypertension. *Respir Res* 2005; 6: 39.
32. Self WH, Semler MW, Bellomo R, Brown SM, deBoisblanc BP, Exline MC, Ginde AA, Grissom CK, Janz DR, Jones AE, Liu KD, Macdonald SPJ, Miller CD, Park PK, Reineck LA, Rice TW, Steingrub JS, Talmor D, Yealy DM, Douglas IS, Shapiro NI. Liberal Versus Restrictive Intravenous Fluid Therapy for Early Septic Shock: Rationale for a Randomized Trial. *Ann Emerg Med* 2018; 72: 457–66.
33. Lov om supplerende bestemmelser til forordning om beskyttelse af fysiske personer i forbindelse med behandling af personoplysninger og om fri udveksling af sådanne oplysninger (databeskyttelsesloven) - retsinformation.dk [Internet]. [cited 2019 Aug 8]. Available from: <https://www.retsinformation.dk/Forms/r0710.aspx?id=201319>
34. Ansvar og regler - Sundhedsdatastyrelsen [Internet]. [cited 2019 Aug 8]. Available from: <https://sundhedsdatastyrelsen.dk/da/borger-og-offentlighed/sikkerhed-om-dine-data/ansvar-og-regler>
35. Brueton VC, Tierney JF, Stenning S, Meredith S, Harding S, Nazareth I, Rait G. Strategies to improve retention in randomised trials: a Cochrane systematic review and meta-analysis. *BMJ Open* 2014; 4: e003821.
36. Robinson KA, Dinglas VD, Sukrithan V, Yalamanchilli R, Mendez-Tellez PA, Dennison-Himmelfarb C, Needham DM. Updated systematic review identifies substantial number of retention strategies: Using more strategies retains more study participants. *J Clin Epidemiol* 2015; 68: 1481–7.
37. Wong A, Nyenhuis D, Black SE, Law LSN, Lo ESK, Kwan PWL, Au L, Chan AY, Wong LK, Nasreddine Z, Mok V. The MoCA 5-min protocol is a brief, valid, reliable and feasible cognitive screen for telephone administration. *Stroke J Cereb Circ* 2015; 46: 1059–64.

38. Colantuoni E, Scharfstein DO, Wang C, Hashem MD, Leroux A, Needham DM, Girard TD. Statistical methods to compare functional outcomes in randomized controlled trials with high mortality. *BMJ* 2018; 360: j5748.
39. Jensen AK, Lange T. A novel high-power test for continuous outcomes truncated by death. *ArXiv191012267 Stat [Internet]* 2019 Oct 27 [cited 2019 Oct 30]. Available from: <http://arxiv.org/abs/1910.12267>
40. Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Åneman A, Madsen KR, Møller MH, Elkjær JM, Poulsen LM, Bendtsen A, Winding R, Steensen M, Berezowicz P, Sjøe-Jensen P, Bestle M, Strand K, Wiis J, White JO, Thornberg KJ, Quist L, Nielsen J, Andersen LH, Holst LB, Thormar K, Kjældgaard A-L, Fabritius ML, Mondrup F, Pott FC, Møller TP, Winkel P, Wetterslev J. Hydroxyethyl Starch 130/0.42 versus Ringer's Acetate in Severe Sepsis. *N Engl J Med* 2012; 367: 124–34.
41. Holst LB, Haase N, Wetterslev J, Wernerman J, Guttormsen AB, Karlsson S, Johansson PI, Åneman A, Vang ML, Winding R, Nebrich L, Nibro HL, Rasmussen BS, Lauridsen JRM, Nielsen JS, Oldner A, Pettilä V, Cronhjort MB, Andersen LH, Pedersen UG, Reiter N, Wiis J, White JO, Russell L, Thornberg KJ, Hjortrup PB, Müller RG, Møller MH, Steensen M, Tjäder I, Kilsand K, Odeberg-Wernerman S, Sjøbø B, Bundgaard H, Thyø MA, Lodahl D, Mærkedahl R, Albeck C, Illum D, Kruse M, Winkel P, Perner A. Lower versus Higher Hemoglobin Threshold for Transfusion in Septic Shock. *N Engl J Med* 2014; 371: 1381–91.
42. Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials - a practical guide with flowcharts. *BMC Med Res Methodol* 2017; 17: 162.