



Clinical trial results:

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

Summary

EudraCT number	2018-000404-42
Trial protocol	DK SE CZ ES BE FI IT
Global end of trial date	16 November 2022

Results information

Result version number	v1 (current)
This version publication date	13 October 2023
First version publication date	13 October 2023

Trial information

Trial identification

Sponsor protocol code	RH-ITA-007
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03668236
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Department of Intensive Care, Rigshospitalet
Sponsor organisation address	Blegdamsvej 9, Copenhagen, Denmark, 2100
Public contact	Anders Perner, Dept. of Intensive Care, Copenhagen University Hospital - Rigshospitalet, DK. , +45 35458333, anders.perner@regionh.dk
Scientific contact	Anders Perner, Dept. of Intensive Care, Copenhagen University Hospital - Rigshospitalet, DK. , +45 35458333, anders.perner@regionh.dk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 March 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 February 2022
Global end of trial reached?	Yes
Global end of trial date	16 November 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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.

Protection of trial subjects:

Parts of the protocol were tested in a feasibility RCT which included safety measures (NCT02079402).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 November 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 951
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Sweden: 130
Country: Number of subjects enrolled	Switzerland: 117
Country: Number of subjects enrolled	Italy: 54
Country: Number of subjects enrolled	Norway: 233
Country: Number of subjects enrolled	Czechia: 50
Country: Number of subjects enrolled	United Kingdom: 18
Worldwide total number of subjects	1554
EEA total number of subjects	1419

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	1554
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

We recruited patients from November 27, 2018 to November 16, 2021.

Pre-assignment

Screening details:

We screened 2223, excluded 669, randomized 1554 and included 1545 patients in the primary analysis.

Period 1

Period 1 title	Intervention period (overall period)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Treatment allocation was concealed for the Data Monitoring and Safety Committee, the trial statistician, and for the management committee until the first version of the abstract had been drafted.

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard fluid group

Arm description:

No upper limit for the use of IV fluid.

1) 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.

2) IV fluids should be given as maintenance if the ICU has a protocol recommending maintenance fluid

3) IV fluids should be given to substitute expected or observed loss, dehydration or electrolyte derangements

Arm type	Experimental
Investigational medicinal product name	Sodium chloride
Investigational medicinal product code	B05BB01
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

As specified in the protocol

Investigational medicinal product name	Ringers Acetate
Investigational medicinal product code	B05BB01
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

As specified in the protocol.

Investigational medicinal product name	Plasmalyte
Investigational medicinal product code	B05BB01
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

As specified in the protocol.

Investigational medicinal product name	Ringers Lactate
Investigational medicinal product code	B05BB01
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion
Dosage and administration details: As specified in the protocol.	
Arm title	Restrictive fluid group

Arm description:

No IV fluids unless one of the below extenuating circumstances occurs;

1)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.

2)In case of overt fluid losses (e.g. aspirates) IV fluid may be given to correct for the loss, but not above the volume lost.

3)In case the oral for water or electrolyte solutions is contraindicated , 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 count as input).

Arm type	Experimental
Investigational medicinal product name	Sodium chloride
Investigational medicinal product code	B05BB01
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

As specified in the protocol

Investigational medicinal product name	Ringers Acetate
Investigational medicinal product code	B05BB01
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

As specified in the protocol.

Investigational medicinal product name	Plasmalyte
Investigational medicinal product code	B05BB01
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

As specified in the protocol.

Investigational medicinal product name	Ringers Lactate
Investigational medicinal product code	B05BB01
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

As specified in the protocol.

Number of subjects in period 1	Standard fluid group	Restrictive fluid group
Started	784	770
Completed	781	764
Not completed	3	6
Consent withdrawn by subject	2	3
Lost to follow-up	1	3

Period 2

Period 2 title	Baseline period
Is this the baseline period?	Yes ^[1]
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard fluid group

Arm description:

No upper limit for the use of IV fluid.

1) 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.

2) IV fluids should be given as maintenance if the ICU has a protocol recommending maintenance fluid

3) IV fluids should be given to substitute expected or observed loss, dehydration or electrolyte derangements

Arm type	Experimental
Investigational medicinal product name	Sodium chloride
Investigational medicinal product code	B05BB01
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

As specified in the protocol

Investigational medicinal product name	Ringers Acetate
Investigational medicinal product code	B05BB01
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

As specified in the protocol.

Investigational medicinal product name	Plasmalyte
Investigational medicinal product code	B05BB01
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

As specified in the protocol.

Investigational medicinal product name	Ringers Lactate
Investigational medicinal product code	B05BB01
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion
Dosage and administration details: As specified in the protocol.	
Arm title	Restrictive fluid group

Arm description:

No IV fluids unless one of the below extenuating circumstances occurs;

1)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.

2)In case of overt fluid losses (e.g. aspirates) IV fluid may be given to correct for the loss, but not above the volume lost.

3)In case the oral for water or electrolyte solutions is contraindicated , 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 count as input).

Arm type	Experimental
Investigational medicinal product name	Sodium chloride
Investigational medicinal product code	B05BB01
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

As specified in the protocol

Investigational medicinal product name	Ringers Acetate
Investigational medicinal product code	B05BB01
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

As specified in the protocol.

Investigational medicinal product name	Plasmalyte
Investigational medicinal product code	B05BB01
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

As specified in the protocol.

Investigational medicinal product name	Ringers Lactate
Investigational medicinal product code	B05BB01
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

As specified in the protocol.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 is the total number of patients randomised in the trial minus those who withdrew

consent for the use of their data.

Number of subjects in period 2 ^[2] 3 ^[3]	Standard fluid group	Restrictive fluid group
Started	776	755
Completed	776	755

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: All baseline values were missing in 15 patients in the restrictive-fluid group and 8 patients in the standard-fluid group.

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: A total of 3 patients in the restrictive-fluid group and 2 in the standard-fluid group withdrew consent for the use of data. For additional 11 patients in the restrictive fluid group and 6 in the standard-fluid group, consent was only granted for the use of allocation and 90-day follow-up. Thus, all baseline values were missing in 15 patients in the restrictive-fluid group and 8 patients in the standard-fluid group.

Baseline characteristics

Reporting groups

Reporting group title	Standard fluid group
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Reporting group description:

No upper limit for the use of IV fluid.

1) 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.

2) IV fluids should be given as maintenance if the ICU has a protocol recommending maintenance fluid

3) IV fluids should be given to substitute expected or observed loss, dehydration or electrolyte derangements

Reporting group title	Restrictive fluid group
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Reporting group description:

No IV fluids unless one of the below extenuating circumstances occurs;

1) 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.

2) In case of overt fluid losses (e.g. aspirates) IV fluid may be given to correct for the loss, but not above the volume lost.

3) In case the oral for water or electrolyte solutions is contraindicated, 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 count as input).

Reporting group values	Standard fluid group	Restrictive fluid group	Total
Number of subjects	776	755	1531
Age categorical Units: Subjects			
Adults (18-64 years)	280	243	523
From 65-84 years	442	455	897
85 years and over	54	57	111
Age continuous Units: years			
median	70	71	
inter-quartile range (Q1-Q3)	60 to 77	62 to 77	-
Gender categorical Units: Subjects			
Female	324	303	627
Male	452	452	904

End points

End points reporting groups

Reporting group title	Standard fluid group
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Reporting group description:

No upper limit for the use of IV fluid.

1) 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.

2) IV fluids should be given as maintenance if the ICU has a protocol recommending maintenance fluid

3) IV fluids should be given to substitute expected or observed loss, dehydration or electrolyte derangements

Reporting group title	Restrictive fluid group
-----------------------	-------------------------

Reporting group description:

No IV fluids unless one of the below extenuating circumstances occurs;

1) 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.

2) In case of overt fluid losses (e.g. aspirates) IV fluid may be given to correct for the loss, but not above the volume lost.

3) In case the oral for water or electrolyte solutions is contraindicated, 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 count as input).

Reporting group title	Standard fluid group
-----------------------	----------------------

Reporting group description:

No upper limit for the use of IV fluid.

1) 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.

2) IV fluids should be given as maintenance if the ICU has a protocol recommending maintenance fluid

3) IV fluids should be given to substitute expected or observed loss, dehydration or electrolyte derangements

Reporting group title	Restrictive fluid group
-----------------------	-------------------------

Reporting group description:

No IV fluids unless one of the below extenuating circumstances occurs;

1) 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.

2) In case of overt fluid losses (e.g. aspirates) IV fluid may be given to correct for the loss, but not above the volume lost.

3) In case the oral for water or electrolyte solutions is contraindicated, 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 count as input).

Primary: 90-day mortality

End point title	90-day mortality
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End point description:

End point type	Primary
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End point timeframe:

After randomisation up to a maximum of 90 days.

End point values	Standard fluid group	Restrictive fluid group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	781	764		
Units: number of patients	329	323		

Statistical analyses

Statistical analysis title	Adjusted absolute difference
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Statistical analysis description:

Logistic regression analysis adjusted for the stratification variables (site and hematologic or metastatic cancer) in the intention-to-treat population.

Comparison groups	Restrictive fluid group v Standard fluid group
Number of subjects included in analysis	1545
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Absolute difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.7
upper limit	4.9

Secondary: Serious adverse events

End point title	Serious adverse events
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End point description:

*Number of patients with one or more serious adverse events (SAEs). Composite outcome defined by cerebral ischemia, myocardial ischemia, intestinal ischemia, limb ischemia and severe acute kidney injury. The single components of the composite outcome are reported in the primary publication (PMID: 35709019).

All secondary outcome data were missing for 23 patients (15 in restrictive group, 8 in standard group). For SAEs, 4 patients (in addition to the 23) had missing data in the composite outcome.

End point type	Secondary
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End point timeframe:

During ICU stay until a maximum of 90 days.

End point values	Standard fluid group	Restrictive fluid group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	772	751		
Units: number of patients*	238	221		

Statistical analyses

Statistical analysis title	Adjusted absolute difference
Statistical analysis description:	
Logistic regression analysis adjusted for the stratification variables (site and metastatic or hematologic cancer) in the ITT population. The parameter estimate with corresponding confidence interval is for the comparison of the restrictive fluid group vs standard fluid group.	
Comparison groups	Standard fluid group v Restrictive fluid group
Number of subjects included in analysis	1523
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Absolute difference, percentage points
Point estimate	-1.7
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-7.7
upper limit	4.3

Secondary: Number of days alive without life support

End point title	Number of days alive without life support
End point description:	
Number of days alive without the use of invasive mechanical ventilation, circulatory support, or any form of renal replacement therapy. All secondary outcome data were missing for 23 patients (15 in restrictive group, 8 in standard group).	
End point type	Secondary
End point timeframe:	
After randomisation until a maximum of 90 days.	

End point values	Standard fluid group	Restrictive fluid group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	776	755		
Units: days				
median (inter-quartile range (Q1-Q3))	77 (1 to 87)	77 (1 to 87)		

Statistical analyses

Statistical analysis title	Adjusted absolute difference
Statistical analysis description: The parameter estimate with corresponding confidence interval is for the comparison of the restrictive fluid group vs standard fluid group.	
Comparison groups	Standard fluid group v Restrictive fluid group
Number of subjects included in analysis	1531
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-11
upper limit	11

Notes:

[1] - Calculated by Van Elteren test after adjustment for site.

Secondary: Serious adverse reactions

End point title	Serious adverse reactions
End point description: Number of patients with one or more serious adverse reactions (SARs). Composite outcome defined by severe hyponatremia, generalised tonic-clonic seizures, anaphylactic reactions, central pontine myelinolysis, severe hyperchloremic acidosis, or severe metabolic alkalosis. All secondary outcome data were missing for 23 patients (15 in restrictive group, 8 in standard group). The single components of the composite outcome are reported in the primary publication (PMID: 35709019).	
End point type	Secondary
End point timeframe: During ICU stay until a maximum of 90 days.	

End point values	Standard fluid group	Restrictive fluid group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	776	755		
Units: number of patients	32	31		

Statistical analyses

Statistical analysis title	Adjusted absolute difference
Statistical analysis description: Logistic regression analysis adjusted for the stratification variables (site and metastatic or hematologic cancer) in the ITT population. The parameter estimate with corresponding confidence interval is for the comparison of the restrictive fluid group vs standard fluid group.	
Comparison groups	Standard fluid group v Restrictive fluid group

Number of subjects included in analysis	1531
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Absolute difference, percentage points
Point estimate	-0.1
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-2.8
upper limit	2.6

Secondary: Number of days alive and out of hospital

End point title	Number of days alive and out of hospital
End point description:	Including any readmissions during the 90-day follow-up period. All secondary outcome data were missing for 23 patients (15 in restrictive group, 8 in standard group).
End point type	Secondary
End point timeframe:	After randomisation until a maximum of 90 days.

End point values	Standard fluid group	Restrictive fluid group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	776	755		
Units: days				
median (inter-quartile range (Q1-Q3))	33 (0 to 70)	21 (0 to 69)		

Statistical analyses

Statistical analysis title	Adjusted absolute difference
Statistical analysis description:	The parameter estimate with corresponding confidence interval is for the comparison of the restrictive fluid group vs standard fluid group.
Comparison groups	Standard fluid group v Restrictive fluid group
Number of subjects included in analysis	1531
Analysis specification	Pre-specified
Analysis type	superiority ^[2]
Parameter estimate	Median difference (final values)
Point estimate	-12
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-30
upper limit	6

Notes:

[2] - Calculated by Van Elteren test after adjustment for site.

Secondary: 1-year mortality

End point title	1-year mortality
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End point description:

End point type	Secondary
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End point timeframe:

After randomisation up to a maximum of 1 year.

End point values	Standard fluid group	Restrictive fluid group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	767 ^[3]	750 ^[4]		
Units: Number of patients	383	385		

Notes:

[3] - 2 patients withdrew consent for 90-day follow-up and 15 patients for 1-year follow-up.

[4] - 3 patients withdrew consent for 90-day follow-up and 17 patients for 1-year follow-up.

Statistical analyses

Statistical analysis title	Adjusted risk difference
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Statistical analysis description:

Adjusted absolute risk difference for 1-year mortality in the restrictive group versus standard group. Adjusted for stratification variables (site and hematologic malignancy or metastatic cancer).

Comparison groups	Standard fluid group v Restrictive fluid group
Number of subjects included in analysis	1517
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk difference (RD)
Point estimate	1.5
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-4.8
upper limit	7.8

Secondary: Health related quality of life

End point title	Health related quality of life
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End point description:

EQ-5D-5L: EuroQol 5 domains 5 levels health-related quality of life scale with non-survivors at 1 year included with the value 0. Index values calculated using country-specific value sets.

End point type	Secondary
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End point timeframe:

Collected 1 year after randomisation.

End point values	Standard fluid group	Restrictive fluid group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	712 ^[5]	704 ^[6]		
Units: EQ-5D-5L index values				
median (inter-quartile range (Q1-Q3))	0 (0 to 0.81)	0 (0 to 0.82)		

Notes:

[5] - 2 and 15 patients withdrew consent for 90-day and 1-year follow-up, and 55 had missing data.

[6] - 3 and 17 patients withdrew consent for 90-day and 1-year follow-up, and 46 had missing data.

Statistical analyses

Statistical analysis title	Adjusted mean difference
Statistical analysis description:	
Adjusted mean difference with 99% CI for Eq-5D-5L index values in the restrictive fluid group versus the standard fluid group.	
Comparison groups	Standard fluid group v Restrictive fluid group
Number of subjects included in analysis	1416
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-0.06
upper limit	0.05

Secondary: Cognitive function

End point title	Cognitive function
End point description:	
Cognitive function assessed by Mini MoCA Montreal cognitive assessment. Non-survivors at 1 year included with the worst possible values.	
End point type	Secondary
End point timeframe:	
1 year after randomisation.	

End point values	Standard fluid group	Restrictive fluid group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	669 ^[7]	668 ^[8]		
Units: Mini MoCA values				
median (inter-quartile range (Q1-Q3))	0 (0 to 22)	0 (0 to 22)		

Notes:

[7] - 2 and 15 patients withdrew consent for 90-day and 1-year follow-up and 98 had missing data.

[8] - 3 and 17 patients withdrew consent for 90-day and 1-year follow-up and 82 had missing data.

Statistical analyses

Statistical analysis title	Adjusted mean difference
Statistical analysis description: Adjusted mean difference for the Mini Moca values in the restrictive fluid group versus standard fluid group. Adjusted for stratification variables.	
Comparison groups	Standard fluid group v Restrictive fluid group
Number of subjects included in analysis	1337
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Mean difference (final values)
Point estimate	-0.14
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-1.59
upper limit	1.31

Secondary: Health related quality of life

End point title	Health related quality of life
End point description: EuroQol EQ visual analogue scale (VAS)	
End point type	Secondary
End point timeframe: Collected 1 year after randomisation. Non-survivors at 1 year included with the worst possible values.	

End point values	Standard fluid group	Restrictive fluid group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	690 ^[9]	687 ^[10]		
Units: EQ-VAS				
median (inter-quartile range (Q1-Q3))	0 (0 to 70)	0 (0 to 70)		

Notes:

[9] - 2 and 15 patients withdrew consent for 90-day and 1-year follow-up, and 77 had missing values.

[10] - 3 and 17 patients withdrew consent for 90-day and 1-year follow-up, and 63 had missing values.

Statistical analyses

Statistical analysis title	Adjusted mean difference
Statistical analysis description: Adjusted mean difference with 99% CI for EQ VAS values in the restrictive fluid group versus the	

standard fluid group.

Comparison groups	Standard fluid group v Restrictive fluid group
Number of subjects included in analysis	1377
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.65
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-5.4
upper limit	4.08

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

While the patient was in the ICU. From randomisation to a maximum of 90-days

Adverse event reporting additional description:

Any serious adverse reaction/event not covered in the secondary outcomes adjudicated to be related to the intervention by the investigator, was to be reported within 24 hours to the Sponsor. If deemed a SUSAR by the Sponsor, it was to be reported to the Danish Medicine Agency.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	1
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Frequency threshold for reporting non-serious adverse events: 0 %

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: No non-serious adverse events were recorded, but the patient charts contain daily registrations of clinical data, which can be obtained on request from the medical authorities.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Patients and personnel were aware of group assignments. Protocol violations occurred in 21.5% in the restrictive fluid group and 13.0% in the standard group. Different results may be obtained in settings where more IV fluid is used in standard care.

Notes: