# 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 |

**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

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| 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.

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| 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.

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|---|---|
| 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]** | 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 |
|---|---|

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 values** | Standard fluid group | Restrictive fluid group | Total |
|---|---|---|---|
| Number of subjects | 776 | 755 | 1531 |
| Age categorical<br>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<br>Units: years | | | |
| median | 70 | 71 | |
| inter-quartile range (Q1-Q3) | 60 to 77 | 62 to 77 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 324 | 303 | 627 |
| Male | 452 | 452 | 904 |

## End points

### End points reporting groups

| 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).

| 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 |
|---|---|

End point description:

| End point type | Primary |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 hypernatremia, 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 |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

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 |
|---|---|

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 |
|---|---|

End point description:

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

| End point type | Secondary |
|---|---|

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. Ajusted 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 |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 1 |

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: