# Clinical trial results:
# Conservative vs. Liberal Approach to fluid therapy of Septic Shock in Intensive Care

## Summary

| | |
|---|---|
| EudraCT number | 2014-000902-37 |
| Trial protocol | DK |
| Global end of trial date | 04 November 2015 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 12 August 2017 |
| First version publication date | 12 August 2017 |
| Summary attachment (see zip file) | main results and paper (Hjortrup et al - CLASSIC trial ICM 2016.pdf) |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | RH-ITA-005 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02079402 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Dept. of Intensive Care 4131, Copenhagen University Hospital, Rigshospitalet |
| Sponsor organisation address | Blegdamsvej 9, Copenhagen, Denmark, 2100 |
| Public contact | Prof. Anders Perner, Dept. of Intensive Care Rigshospitalet, 45 35458333, anders.perner@regionh.dk |
| Scientific contact | Prof. Anders Perner, Dept. of Intensive Care Rigshospitalet, 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 | 15 December 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 04 November 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 04 November 2015 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

to assess the feasibility of a trial comparing two approaches to fluid resuscitation of septic shock after initial resuscitation; a trigger guided approach vs. a target guided approach, the latter reflecting standard care

Protection of trial subjects:

All trial subjects received the highest standard of care with high degree of monitoring.
Also, fluid therapy is an intervention abundantly used across the world.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 08 August 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Finland: 8 |
| Country: Number of subjects enrolled | Denmark: 143 |
| Worldwide total number of subjects | 151 |
| EEA total number of subjects | 151 |

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 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 65 |
| From 65 to 84 years | 80 |
| 85 years and over | 6 |

## Subject disposition

### Recruitment

Recruitment details:

Recruitment was performed on schedule.

### Pre-assignment

Screening details:

Inclusion: adults with septic shock who had received the initial fluid management.
203 fulfilled inclusion criteria and were screened; 153 were randomised; 151 were analysed.

### Period 1

| | |
|---|---|
| Period 1 title | Intervention period (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Blinding implementation details:

Open-label trial.
Trial statistician was blinded to allocation

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Fluid restriction group |

Arm description:

isotonic crystalloid
(saline or Ringer's solutions) fluid boluses of 250–500 mL
could be given intravenously during ICU stay in the case
of severe hypoperfusion

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | pr1 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

patient specific

| | |
|---|---|
| **Arm title** | Standard Care |

Arm description:

isotonic crystalloid (saline
or Ringer's solutions) fluid boluses could be given intravenously
during ICU stay as long as haemodynamic variables
improved

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | pr1 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravascular use |

Dosage and administration details:

patient specific dosing

| **Number of subjects in period 1** | Fluid restriction group | Standard Care |
|---|---|---|
| Started | 75 | 76 |
| Completed | 75 | 76 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Fluid restriction group |
| Reporting group description: | |
| isotonic crystalloid (saline or Ringer's solutions) fluid boluses of 250–500 mL could be given intravenously during ICU stay in the case of severe hypoperfusion | |
| Reporting group title | Standard Care |
| Reporting group description: | |
| isotonic crystalloid (saline or Ringer's solutions) fluid boluses could be given intravenously during ICU stay as long as haemodynamic variables improved | |

| Reporting group values | Fluid restriction group | Standard Care | Total |
|---|---|---|---|
| Number of subjects | 75 | 76 | 151 |
| Age categorical<br>Units: Subjects | | | |
| In utero | | | 0 |
| Preterm newborn infants (gestational age < 37 wks) | | | 0 |
| Newborns (0-27 days) | | | 0 |
| Infants and toddlers (28 days-23 months) | | | 0 |
| Children (2-11 years) | | | 0 |
| Adolescents (12-17 years) | | | 0 |
| Adults (18-64 years) | | | 0 |
| From 65-84 years | | | 0 |
| 85 years and over | | | 0 |
| Age continuous<br>Units: years | | | |
| median | 69 | 73 | |
| inter-quartile range (Q1-Q3) | 61 to 76 | 67 to 77 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 23 | 29 | 52 |
| Male | 52 | 47 | 99 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Fluid restriction group |
| Reporting group description: | |
| isotonic crystalloid (saline or Ringer's solutions) fluid boluses of 250–500 mL could be given intravenously during ICU stay in the case of severe hypoperfusion | |
| Reporting group title | Standard Care |
| Reporting group description: | |
| isotonic crystalloid (saline or Ringer's solutions) fluid boluses could be given intravenously during ICU stay as long as haemodynamic variables improved | |

### Primary: resuscitation fluid first 5 days after rando

| | |
|---|---|
| End point title | resuscitation fluid first 5 days after rando |
| End point description: | |
| See other outcome measures in the attached published article | |
| End point type | Primary |
| End point timeframe: | |
| 5 days | |

| End point values | Fluid restriction group | Standard Care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 75 | 76 | | |
| Units: ml | | | | |
| median (inter-quartile range (Q1-Q3)) | 500 (0 to 2500) | 2000 (1000 to 4100) | | |

### Statistical analyses

| Statistical analysis title | primary analysis |
|---|---|
| Comparison groups | Fluid restriction group v Standard Care |
| Number of subjects included in analysis | 151 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Wilcoxon (Mann-Whitney) |

### Primary: resusciation fluid during entire ICU stay

| End point title | resusciation fluid during entire ICU stay |
|---|---|

End point description:

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

End point timeframe:

entire ICU stay

| **End point values** | Fluid restriction group | Standard Care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 75 | 76 | | |
| Units: ml | | | | |
| median (inter-quartile range (Q1-Q3)) | 500 (0 to 3250) | 2200 (1000 to 4750) | | |

**Statistical analyses**

| **Statistical analysis title** | co-primary analysis |
|---|---|
| Comparison groups | Fluid restriction group v Standard Care |
| Number of subjects included in analysis | 151 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Wilcoxon (Mann-Whitney) |

## Adverse events

### Adverse events information[1]

Timeframe for reporting adverse events:

During ICU stay up to 90 days from randomisation

Adverse event reporting additional description:

serious adverse events were predefined outcome measures in the trial. See the attached published paper for full description

| | |
|---|---|
| Assessment type | 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: Serious adverse events (SAEs) will not be recorded as an entity, because the majority of septic ICU patients will experience several SAEs during their critical illness. The most important SAEs will be captured in the exploratory outcome measures and in the daily SOFA-scoring. Patient charts will 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? Yes

| Date | Amendment |
|---|---|
| 19 June 2015 | Action: Promotion of a secondary outcome to a co-primary outcome.<br>Applied for: June 19th 2015<br>Approved by Ethics Committee and Medicines Agency: July 31st 2015<br>Outcome: Amount of resuscitation fluid during ICU stay |
| 25 September 2015 | Change: The definition of circulatory impairment in the inclusion criterion "Suspected or confirmed circulatory impairment (hypotension/hypoperfusion/hypovolemia) for no more than 12 hours including the hours preceding ICU admission" was revised.<br>Previous protocol version: 4.2 June 4th 2014<br>New (final) protocol version: 4.3 September 25th 2014<br>Applied for: September 25th 2014<br>Approved by Ethics Committee and Medicines Agency and effectuated: October 30th 2014 |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

### Online references

http://www.ncbi.nlm.nih.gov/pubmed/27686349