

**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
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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
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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
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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
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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			
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			
Units: years			
median	69	73	
inter-quartile range (Q1-Q3)	61 to 76	67 to 77	-
Gender categorical			
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: resuscitation fluid during entire ICU stay

End point title	resuscitation 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
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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: 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. Applied for: June 19th 2015 Approved by Ethics Committee and Medicines Agency: July 31st 2015 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. Previous protocol version: 4.2 June 4th 2014 New (final) protocol version: 4.3 September 25th 2014 Applied for: September 25th 2014 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>