Clinical trial results:
Restrictive Fluid Administration vs. Standard of Care in Emergency Department Sepsis Patients - a Multicenter, Randomized Clinical Feasibility Trial

Summary

EudraCT number	2021-000224-35
Trial protocol	DK
Global end of trial date	18 March 2022

Results information

Result version number	v1 (current)
This version publication date	31 August 2022
First version publication date	31 August 2022
Summary attachment (see zip file)	REFACED Sepsis_AcademicEmergencyMedicine_Jessen et al_2022 (Academic Emergency Medicine - 2022 - Jessen - Restrictive Fluids Versus Standard Care in Adults with Sepsis in the.pdf)

Trial information

Trial identification

Sponsor protocol code	RECEM00001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05076435
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Research Center for Emergency Medicine, Department of Clinical Medicine, Aarhus University
Sponsor organisation address	Palle Juul-Jensens Boulevard 99, J103, Aarhus N, Denmark, 8200
Public contact	Research Center for Emergency Medic, Research Center for Emergency Medicine, Department of Clinical Medicine, Aarhus University, 0045 7846 6660, cfa@clin.au.dk
Scientific contact	Research Center for Emergency Medic, Research Center for Emergency Medicine, Department of Clinical Medicine, Aarhus University, 0045 7846 6660, cfa@clin.au.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	18 March 2022
Global end of trial reached?	Yes
Global end of trial date	18 March 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To test if an IV fluid restrictive protocol in ED patients with sepsis is feasible, i.e., if the protocol decreases the IV fluid volumes administered compared to standard care.

Protection of trial subjects:

Generally, fluid administration is considered safe and is very commonly used in clinical practice. In the restrictive fluid group protocol violations (i.e., giving fluids although no criteria are fulfillled) will be allowed if deamed needed by the treating physician. The clinical team will document any specific adverse events suspected to be related to the intervention.

Background therapy:

Standard Care fluid administration

Evidence for comparator:

Fluid restriction has been suggested to be beneficial in septic shock. No evidence in sepsis patients without shock exists. Although trials are currently exploring fluid strategies in patients with hypotension and septic shock, there are no studies on fluid administration in patients with early sepsis without shock/hypotension. Research within this field has been requested by experts. As fluid administration is very frequent, but not evidence-based, and carries potential risks, we consider it to be of great interest for society and patients to perform research in this area. Fluid resuscitation is a key intervention in sepsis, but the optimal amount of fluid to be given has not been established. The present trial is a feasibility trial, i.e., a trial assessing the feasibility of the proposed protocol in a clinical setting. The aim is to investigate the ability to reduce fluid volume using the given protocol. Should the trial prove feasible with separation between the two interventions, a large-scale trial assessing patient important outcomes is intended.

Actual start date of recruitment	03 November 2021
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	Denmark: 124
Worldwide total number of subjects	124
EEA total number of subjects	124

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)	20
From 65 to 84 years	75
85 years and over	29

Subject disposition

Recruitment

Recruitment details:

Nov 3rd, 2021, to Dec 18th 2021, Participants were recruited in the EDs at Aarhus University Hospital, the Regional Hospital Randers, and the Regional Hospital Viborg

Pre-assignment

Screening details:

inclusion criteria:1) Unplanned ED admission,2) age≥18 years,3) sepsis defined as a)infection suspected,b) blood cultures drawn,c) intravenous antibiotics administered/planned, d)SOFA-score ≥ 2, and 4) expected hospital stay>24 hours, Exclusion: see protocol: DOI: 10.1186/s40814-022-01034-y / refaced-sepsis.dk

Period 1

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

Blinding implementation details:

It was not possible to blind the intervention for neither the treating team, patients nor relatives.

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard care group

Arm description:

Fluids were administered by clinicians' choice

Arm type	Active comparator
Investigational medicinal product name	Sodium Chloride solution 0.9%
Investigational medicinal product code	13341
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Dose as per the treating physicians

Investigational medicinal product name	Sodium chloride 9mg/ml, indsusion "Fresenius Kabi"
Investigational medicinal product code	14043
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

As per treating physician

Investigational medicinal product name	Ringer-acetat "Fresenius Kabi", infusion
Investigational medicinal product code	12624
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Solution for injection

Dosage and administration details:

Per treating physician

Investigational medicinal product name	Ringer-lactat "Fresenius Kabi", infusion
Investigational medicinal product code	06756
Other name	
Pharmaceutical forms	Solution for infusion

Routes of administration	Solution for infusion

Dosage and administration details:

As per treating physician

Arm title	Restrictive fluid administration

Arm description:

In the restrictive fluid group, intravenous crystalloid fluids should not be given unless one of the below mentioned hypoperfusion criteria were met.

- Lactate concentration ≥ 4 mmol/l (arterial or venous)
- Hypotension (systolic blood pressure < 90 mmHg)
- Mottling beyond edge of kneecap (i.e., Mottling score >2)33
- Severe oliguria, i.e., diuresis < 0.1 ml/kg/h, during the first 4 hours of admission

If one or more of these criteria were met, a fluid bolus of 250 ml isotonic crystalloid (isotonic saline or Ringer's acetate/lactate) could be administered per protocol. It was not a requirement that a fluid bolus was administered.

Arm type	Experimental
Investigational medicinal product name	Sodium Chloride solution 0.9%
Investigational medicinal product code	13341
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Dose as per the restrictive protocol

Investigational medicinal product name	Sodium chloride 9mg/ml, indsusion "Fresenius Kabi"
Investigational medicinal product code	14043
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

As per treating physician or per trial protocol

Investigational medicinal product name	Ringer-acetat "Fresenius Kabi", infusion
Investigational medicinal product code	12624
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Solution for injection

Dosage and administration details:

Per treating physician or per restrictive protocol

Investigational medicinal product name	Ringer-lactat "Fresenius Kabi", infusion
Investigational medicinal product code	06756
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Solution for infusion

Dosage and administration details:

As per treating physician or per restrictive protocol

Number of subjects in period 1	Standard care group	Restrictive fluid administration
Started	62	62
Completed	59	58
Not completed	3	4
Adverse event, serious fatal	1	-
Consent withdrawn by subject	1	-
Discharge within 24 hours	1	4

Baseline characteristics

Reporting groups	
Reporting group title	Standard care group
Reporting group description:	
Fluids were administered by clinicians' choice	
Reporting group title	Restrictive fluid administration
Reporting group description:	

In the restrictive fluid group, intravenous crystalloid fluids should not be given unless one of the below mentioned hypoperfusion criteria were met.

- Lactate concentration ≥ 4 mmol/l (arterial or venous)
- Hypotension (systolic blood pressure < 90 mmHg)
- Mottling beyond edge of kneecap (i.e., Mottling score >2)33
- Severe oliguria, i.e., diuresis < 0.1 ml/kg/h, during the first 4 hours of admission

If one or more of these criteria were met, a fluid bolus of 250 ml isotonic crystalloid (isotonic saline or Ringer's acetate/lactate) could be administered per protocol. It was not a requirement that a fluid bolus was administered.

Reporting group values	Standard care group	Restrictive fluid administration	Total
Number of subjects	62	62	124
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	10	10	20
From 65-84 years	39	36	75
85 years and over	13	16	29
Age continuous			
Units: years			
median	76	75	
inter-quartile range (Q1-Q3)	68 to 83	67 to 85	-
Gender categorical			
Units: Subjects			
Female	28	25	53
Male	34	37	71

End points

End points reporting groups

Reporting group title	Standard care group
Reporting group description:	
Fluids were administered by clinicians' choice	
Reporting group title	Restrictive fluid administration
Reporting group description:	
In the restrictive fluid group, intravenous crystalloid fluids should not be given unless one of the below mentioned hypoperfusion criteria were met. • Lactate concentration ≥ 4 mmol/l (arterial or venous) • Hypotension (systolic blood pressure < 90 mmHg) • Mottling beyond edge of kneecap (i.e., Mottling score >2)33 • Severe oliguria, i.e., diuresis < 0.1 ml/kg/h, during the first 4 hours of admission If one or more of these criteria were met, a fluid bolus of 250 ml isotonic crystalloid (isotonic saline or Ringer's acetate/lactate) could be administered per protocol. It was not a requirement that a fluid bolus was administered.	

Primary: Crystalloid fluid volumes (24 h)

End point title	Crystalloid fluid volumes (24 h)
End point description:	
(NaCl and Ringers administered in 24 hours)	
End point type	Primary
End point timeframe:	
24 hours	

End point values	Standard care group	Restrictive fluid administration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	61		
Units: ml				
median (inter-quartile range (Q1-Q3))	1000 (80 to 2000)	0 (0 to 600)		

Statistical analyses

Statistical analysis title	Quantile regression
Comparison groups	Standard care group v Restrictive fluid administration
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Quantile regression (median regression)
Parameter estimate	Median difference (final values)
Point estimate	-1000

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1392
upper limit	-607
Variability estimate	Standard deviation

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: 90 days	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	eddra

Reporting groups	
Reporting group title	Restrictive fluid administration
Reporting group description: -	
Reporting group title	Standard Care
Reporting group description: -	

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: We experienced no adverse events as defined by the protocol

Serious adverse events	Restrictive fluid administration	Standard Care	
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 61 (27.87%)	18 / 62 (29.03%)	
number of deaths (all causes)	3	1	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Acute myocardial ischemia/infarction			
subjects affected / exposed	1 / 61 (1.64%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart failure or cardiogenic shock or cardiac arrest/death			
subjects affected / exposed	3 / 61 (4.92%)	2 / 62 (3.23%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Hypervolemia			
subjects affected / exposed	4 / 61 (6.56%)	4 / 62 (6.45%)	
occurrences causally related to treatment / all	0 / 4	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
New onset of severe acute kidney injury			

subjects affected / exposed	9 / 61 (14.75%)	10 / 62 (16.13%)	
occurrences causally related to treatment / all	0 / 9	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Restrictive fluid administration	Standard Care	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 61 (0.00%)	0 / 62 (0.00%)	

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.

None to report

Notes: