



Clinical trial results:

A multi-centre, randomised, double blind, placebo-controlled trial evaluating the effects of early administration of fibrinogen concentrate in adults with major traumatic haemorrhage. E-FIT 1 Study

Summary

EudraCT number	2015-000875-28
Trial protocol	GB
Global end of trial date	15 December 2016

Results information

Result version number	v1 (current)
This version publication date	25 March 2020
First version publication date	25 March 2020
Summary attachment (see zip file)	Published paper (Curry_et_al-2018-Critical_Care.pdf)

Trial information

Trial identification

Sponsor protocol code	2.0 28/10/2015
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Additional study identifiers

ISRCTN number	ISRCTN67540073
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	NHS Blood & Transplant
Sponsor organisation address	Long Road, Cambridge, United Kingdom, cb20pt
Public contact	Claire Foley, NHS Blood and Transplant, +44 1223588110, claire.foley@nhsbt.nhs.uk
Scientific contact	Claire Foley, NHS Blood and Transplant, +44 01223588110, claire.foley@nhsbt.nhs.uk

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	19 December 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	15 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study will investigate the following:

- feasibility of administration FgC within 45 minutes of admission to ED, where the aim will be to administer the FgC at the earliest possible time
- effects of early FgC supplementation on laboratory biomarkers during major traumatic haemorrhage

Protection of trial subjects:

Participants screened and enrolled to the EFIT study, were incapacitated at the point of study entry due to the nature of their traumatic injuries. Participants were therefore incapable of giving consent at the point of study entry. Patients were enrolled to the study using an emergency waiver due to the emergency nature of the trial, with subsequent assent sought from a patient/professional legal representative and/or full informed consent obtained when capacity was re-gained. The process for consent was approved by an approved Research Ethics Committee in the UK.

Background therapy:

Trauma patients who present to hospital with major haemorrhage are treated using an integrated approach known as damage control resuscitation (DCR). This focuses on 1) diagnostic and treatment pathways aimed at identifying and stopping on-going bleeding e.g. emergency surgery or interventional radiology and 2) best supportive care, known as haemostatic resuscitation (HR) which includes blood transfusion (using major haemorrhage protocols (MHP), reversal of blood acidosis and active re-warming of patients. HR is defined by the early (empiric) and simultaneous delivery of RBCs and FFP with platelets in high ratios and in conjunction with Tranexamic acid.

Evidence for comparator:

The comparator arm involved IV administration of a matching placebo - 300ml isotonic saline.

Actual start date of recruitment	01 October 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 48
Worldwide total number of subjects	48
EEA total number of subjects	48

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)	48
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment commenced (FPFV): 20/02/2016

Recruitment completed (LP recruited): 18/11/2016

UK only

Pre-assignment

Screening details:

166 patients were screened for eligibility against the inclusion/exclusion criteria.

88 were classed as not eligible. 78 were considered eligible, of which 30 were not randomised (due to other factors). 48 participants were randomised. See attached paper for further details.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor

Blinding implementation details:

Blinded study kits using unique identifier and blinded administration kits.

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention

Arm description:

Receipt of IMP

Arm type	Experimental
Investigational medicinal product name	RiaSTAP
Investigational medicinal product code	B02BB01
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

6g in total

Arm title	Placebo
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Arm description:

placebo arm - IV administration of solution for injection

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo (normal saline - sodium chloride 0.9%w/v).

Placebo will be 50 mL normal saline for each 1g fibrinogen concentrate and will be infused as a slow bolus over 5 minutes.

Number of subjects in period 1	Intervention	Placebo
Started	24	24
Completed	20	19
Not completed	4	5
Physician decision	4	5

Baseline characteristics

Reporting groups

Reporting group title	Intervention
Reporting group description: Receipt of IMP	
Reporting group title	Placebo
Reporting group description: placebo arm - IV administration of solution for injection	

Reporting group values	Intervention	Placebo	Total
Number of subjects	24	24	48
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)	24	24	48
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
median age			
Units: years			
median	38	36	
inter-quartile range (Q1-Q3)	31 to 47	22 to 56	-
Gender categorical			
Units: Subjects			
Female	4	5	9
Male	20	19	39

End points

End points reporting groups

Reporting group title	Intervention
Reporting group description:	
Receipt of IMP	
Reporting group title	Placebo
Reporting group description:	
placebo arm - IV administration of solution for injection	

Primary: Feasibility - primary outcome 1

End point title	Feasibility - primary outcome 1
End point description:	
Proportion of participants who received the study intervention within 45 minutes of admission	
End point type	Primary
End point timeframe:	
Within 45 minutes from admission	

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: subjects	20	19		

Statistical analyses

Statistical analysis title	Feasibility - Primary outcome 1
Statistical analysis description:	
The feasibility of administering an intervention within 45 minutes of admission will be assessed for all participants. For the trial to be considered feasible, at least 90% of the participants must achieve this target.	
Comparison groups	Intervention v Placebo
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other ^[1]
Parameter estimate	proportion (%)
Point estimate	69
Confidence interval	
level	95 %
sides	2-sided
lower limit	52
upper limit	83

Notes:

[1] - Feasibility - intention to treat

Primary: Feasibility - primary outcome 2

End point title	Feasibility - primary outcome 2
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End point description:

Proportion of participants with at least one Clauss fibrinogen level ≥ 2 g/L, at 2 hours from admission, during first active haemorrhage

End point type	Primary
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End point timeframe:

2 hours from admission, during first active haemorrhage

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: subjects	20	17		

Statistical analyses

Statistical analysis title	Feasibility - Primary outcome 2
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Statistical analysis description:

The proportion (and exact Binomial 95% confidence interval) of participants with at least one Fg blood level ≥ 2 g/L, at 2 hours from admission, during first active haemorrhage will be calculated overall and for each treatment arm. Fisher's exact test will be used to examine if the proportion of participants with at least one Fg blood level ≥ 2 g/L during first active haemorrhage is significantly different between the two treatment arms.

Comparison groups	Intervention v Placebo
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1014
Method	Fisher exact
Parameter estimate	Proportion
Point estimate	62
Confidence interval	
level	95 %
sides	2-sided
lower limit	45
upper limit	78

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

15th October 2015- 15th December 2016

Adverse event reporting additional description:

Site reported SAEs

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22
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Reporting groups

Reporting group title	Active arm
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Reporting group description:

SAEs reported for all participants in the treatment arm

Reporting group title	Placebo group
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Reporting group description:

SAEs reported for participants in the placebo group

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: Total number of subject reporting at least one AE in the treatment arm: 12

Total number of subject reporting at least one AE in the placebo arm: 11

Serious adverse events	Active arm	Placebo group	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 20 (65.00%)	11 / 19 (57.89%)	
number of deaths (all causes)	8	3	
number of deaths resulting from adverse events	8	3	
Injury, poisoning and procedural complications			
surgical emphysema			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Ischaemia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	3 / 19 (15.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	

uncontrolled haemorrhage subjects affected / exposed	2 / 20 (10.00%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 20 (5.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac contusion			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulseless electrical activity			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Intracranial pressure increased			
subjects affected / exposed	2 / 20 (10.00%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Ischaemic stroke			
subjects affected / exposed	1 / 20 (5.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	4 / 20 (20.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 4	0 / 1	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal injury			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal sepsis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 20 (10.00%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tension pneumothorax			

subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventilator associated pneumonia			
subjects affected / exposed	0 / 20 (0.00%)	2 / 19 (10.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 20 (20.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Compartment syndrome			
subjects affected / exposed	3 / 20 (15.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			

subjects affected / exposed	4 / 20 (20.00%)	2 / 19 (10.53%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	

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

Non-serious adverse events	Active arm	Placebo group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)	0 / 19 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 October 2015	Updates to Protocol - approved by Research Ethics Committee.

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/29914530>