



## Clinical trial results:

### Fibrinogen concentrate versus placebo for treatment of postpartum haemorrhage: a prospective double blind randomised control trial

#### Summary

EudraCT number	2012-005511-11
Trial protocol	GB
Global end of trial date	26 November 2015

#### Results information

Result version number	v1 (current)
This version publication date	29 December 2018
First version publication date	29 December 2018
Summary attachment (see zip file)	BJA paper (PIIS000709121753754X.pdf)

#### Trial information

##### Trial identification

Sponsor protocol code	SPON1155-12
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##### Additional study identifiers

ISRCTN number	ISRCTN46295339
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Cardiff University
Sponsor organisation address	Heath Park, Cardiff, United Kingdom, CF14 4YS
Public contact	Julia Townson, Centre for Trials Research (CTR, Cardiff University, 044 02920687606, townson@cf.ac.uk
Scientific contact	Julia Townson, Centre for Trials Research (CTR, Cardiff University, 044 02920687606, townson@cf.ac.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	26 November 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 November 2015
Global end of trial reached?	Yes
Global end of trial date	26 November 2015
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

This study aims to establish whether giving fibrinogen (one of the body's blood clotting factors and it plays an important role in forming a strong clot) to women who are bleeding during childbirth and who have a low fibrinogen, reduces blood loss and reduces the amount of blood transfusion that women require.

Protection of trial subjects:

IDMC reviewed the accumulating data

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 May 2013
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: 57
Worldwide total number of subjects	57
EEA total number of subjects	57

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)	57
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

In order to recruit 57 women to the RCT, we estimated we would need to enrol 1050 into the observational study. However, we only needed 663 women to be recruited into the observational study to randomise 57 women.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Placebo

Arm description:

normal saline

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

Dosage and administration details:

Placebo will be 50 mL of normal saline for each 1 gm of fibrinogen. Black opaque syringes will also be supplied.

Placebo treatment will be a blinded empty bottle (identical to the fibrinogen bottle) and 50ml normal saline in a diluent bottle.

<b>Arm title</b>	Fibrinogen
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Arm description:

fibrinogen concentrate

Arm type	Active comparator
Investigational medicinal product name	Fibrinogen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

The fibrinogen concentrate was supplied as vials of 1 gm per bottle by CSL Behring to St Mary's Pharmaceutical Unit (SMPU), Cardiff.

Active treatment will be 1 gm fibrinogen concentrate as a lyophilised powder in a blinded bottle and 50ml sterile water for injection in a diluent bottle.

The dose of fibrinogen/placebo will be rounded to use complete vials and the maximum dose of fibrinogen or placebo will not exceed 8 gm.

A clinician, who is managing the major obstetric haemorrhage and trained in study procedures, will draw up and give the fibrinogen/placebo.

Number of subjects in period 1 <sup>[1]</sup>	Placebo	Fibrinogen
Started	27	28
Completed	27	28

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Notes:

[1] - 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: 2 subjects (1 in each arm) were enrolled but were ineligible and thus did not start treatment

## Baseline characteristics

### Reporting groups

Reporting group title	Placebo
Reporting group description: normal saline	
Reporting group title	Fibrinogen
Reporting group description: fibrinogen concentrate	

Reporting group values	Placebo	Fibrinogen	Total
Number of subjects	27	28	55
Age categorical			
Age at recruitment			
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)	27	28	55
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Age at recruitment			
Units: years			
arithmetic mean	33.5	30.8	
standard deviation	± 6.37	± 5.45	-
Gender categorical			
Units: Subjects			
Female	27	28	55
Male	0	0	0

## End points

### End points reporting groups

Reporting group title	Placebo
Reporting group description:	
normal saline	
Reporting group title	Fibrinogen
Reporting group description:	
fibrinogen concentrate	

### Primary: number of allogeneic blood products (RBC, FFP, cryoprecipitate, platelets) infused after study medication until hospital discharge

End point title	number of allogeneic blood products (RBC, FFP, cryoprecipitate, platelets) infused after study medication until hospital discharge
End point description:	
End point type	Primary
End point timeframe:	
after study medication under hospital discharge	

End point values	Placebo	Fibrinogen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	28		
Units: Number of allogeneic units				
number (not applicable)	75	58		

### Statistical analyses

Statistical analysis title	Negative binomial regression model
Comparison groups	Fibrinogen v Placebo
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.45
Method	Negative Binomial regression
Parameter estimate	Incidence rate ratio
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	1.7

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**Secondary: Number of units of red blood cells (RBC) transfusions**

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End point title	Number of units of red blood cells (RBC) transfusions
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End point description:

End point type	Secondary
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End point timeframe:

study medication to date of discharge

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End point values	Placebo	Fibrinogen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	28		
Units: Units	38	37		

**Statistical analyses**

Statistical analysis title	Number of RBC transfusions (units)
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Statistical analysis description:

Incidence rate ratio (IRR) of the fibrinogen arm compared with placebo arm for the number of RBC units transfused. An IRR <1 indicating a higher incidence rate of transfusions in placebo compared with the fibrinogen arm and an IRR >1 indicating a higher incidence rate of transfusions in the fibrinogen arm compared with the placebo.

Comparison groups	Placebo v Fibrinogen
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.88
Method	Negative binomial regression model
Parameter estimate	Incidence rate ratio
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	2.67

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**Secondary: Number of Fresh Frozen Plasma (FFP) units transfused**

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End point title	Number of Fresh Frozen Plasma (FFP) units transfused
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End point description:

Incidence rate ratio (IRR) of the fibrinogen arm compared with placebo arm for the number of FFP units transfused. An IRR <1 indicating

a higher incidence rate of transfusions in placebo compared with the fibrinogen arm and an IRR >1 indicating a higher incidence rate of transfusions in the fibrinogen arm compared with the placebo.

End point type	Secondary
End point timeframe: study medication to date of discharge	

End point values	Placebo	Fibrinogen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	28		
Units: Units	33	18		

### Statistical analyses

<b>Statistical analysis title</b>	Number of FFP units transfused
Comparison groups	Placebo v Fibrinogen
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.37
Method	Negative Binomial regression model
Parameter estimate	Incidence rate ratio
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.13
upper limit	2.16

### Secondary: Measured abnormal blood loss (ml)

End point title	Measured abnormal blood loss (ml)
End point description:	
End point type	Secondary
End point timeframe: within 24 hours of study medication	



End point values	Placebo	Fibrinogen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	28		
Units: ml				
median (inter-quartile range (Q1-Q3))	300 (60 to 800)	225 (100 to 341.25)		

## Statistical analyses

Statistical analysis title	Measured abnormal blood loss
Statistical analysis description:	
Data were log transformed due to skewed distribution. The estimate should be interpreted as a ratio of logs (fibrinogen:placebo) rather than a difference	
Comparison groups	Placebo v Fibrinogen
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.66
Method	Regression, Linear
Parameter estimate	ratio of logs
Point estimate	-0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.35
upper limit	0.85

## Secondary: Invasive procedures

End point title	Invasive procedures
End point description:	
End point type	Secondary
End point timeframe:	
within 24 hours of study medication	

End point values	Placebo	Fibrinogen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	28		
Units: number	5	4		

## Statistical analyses

<b>Statistical analysis title</b>	Number of women with invasive procedures
Comparison groups	Fibrinogen v Placebo
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.67
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	3.08

## Secondary: Level 2 care

End point title	Level 2 care
End point description:	
End point type	Secondary
End point timeframe:	
from study medication to date of discharge	

<b>End point values</b>	Placebo	Fibrinogen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	28		
Units: Number of women	24	27		

## Statistical analyses

<b>Statistical analysis title</b>	Level 2 care
Comparison groups	Placebo v Fibrinogen
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.31
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.38

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	34.65

## Secondary: Number of women ever breastfed

End point title	Number of women ever breastfed
End point description:	
End point type	Secondary
End point timeframe:	
6 weeks post partum	

End point values	Placebo	Fibrinogen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	28		
Units: number of women	19	17		

## Statistical analyses

Statistical analysis title	Ever breastfed
Comparison groups	Fibrinogen v Placebo
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.38
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	2.04

## Adverse events

### Adverse events information<sup>[1]</sup>

Timeframe for reporting adverse events:

All serious adverse events were reported following randomisation up until 6 weeks.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	10.0
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### Reporting groups

Reporting group title	Placebo
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Reporting group description:

normal saline

Reporting group title	Fibrinogen
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Reporting group description:

fibrinogen concentrate

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: There were no non-serious adverse events recorded for these results

Serious adverse events	Placebo	Fibrinogen	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 27 (0.00%)	9 / 28 (32.14%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Pregnancy, puerperium and perinatal conditions			
Postpartum haemorrhage	Additional description: Reported as ESUSAR reference number 213230038001-00097031		
subjects affected / exposed	0 / 27 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postpartum thrombosis	Additional description: Labour induced 20/09/13. On 30th September 2013 the participant arrived in medical assessment unit, she complained of 5 days of shortness of breath, with a cough and chest pain. A CT revealed she had a thrombosis of the right ovarian vein.		
subjects affected / exposed	0 / 27 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postpartum disorder	Additional description: Developed shortness of breath and pulmonary oedema whilst FFP was being administered.		
subjects affected / exposed	0 / 27 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pre-eclampsia			

subjects affected / exposed	0 / 27 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 27 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine infection			
subjects affected / exposed	0 / 27 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	0 / 27 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hospital admission			
subjects affected / exposed	0 / 27 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometritis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

<b>Non-serious adverse events</b>	Placebo	Fibrinogen	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 April 2013	Allow infusion of fibrinogen at any rate at the discretion of the clinician. Clearly state that FFP can be given as soon as it arrives. State that the IDMC will meet after fewer patients have been randomised. The IDMC will also be asked to focus on thrombotic episodes and infusion reactions.
25 April 2013	The use of A5 instead of MCF to enter the interventional phase. The primary and secondary outcomes. Originally the primary outcome was 'Total number of allogeneic blood products transfused within 24 hours after study medication'. This has now been changed to 'Total number of allogeneic blood products transfused after study medication until discharge' A FIBTEM test at 24 hours has been added. Data is collected electronically as oppose to paper based. In the event death: the unblinding procedure has now been changed; approval has to be sought from SEWTU prior to carrying out unblinding Intention to Treat (ITT) added to statistical section. Additional FIBTEM and coagulation screen will be taken at 24 hours after the study medication. Minor wording change in section 8.2 exclusion criteria, "stated" is changed to "documented". Wording change section 11 withdrawal and loss to follow-up. "The patient may withdraw or be withdrawn from the observational phase and do not proceed to the interventional phase" The following sentence has been removed "If placenta accreta is diagnosed during the surgery, the patient will not be included in the efficacy analysis." Section 14.2: Previous PPH has been added to the list of data to be collected in the study and to the CRF
01 August 2013	Substantial amendment/clarification to the inclusion criteria: Women can be included in the observational phase before delivery but cannot be randomised in the interventional phase until after delivery.  For ease of use Fibrinogen concentrate to treat postpartum haemorrhage is referred to as OBS2 (Obstetrics Bleeding Study 2) Addition of co-investigators and change in some of trial team's details.

27 August 2013	<p>Secondary outcomes clarified:</p> <p>1) The total number of units of red blood cells, FFP, platelets and cryoprecipitate transfused within 24 hours after study medication.</p> <p>The volume of cell salvaged blood transfused within 24 hours and until discharge (250 mL cell salvaged blood will be considered equivalent to 1 unit of red blood cells.)</p> <p>The total number of units of red blood cells, FFP, platelets and cryoprecipitate plus 1 unit for every 250 mL cell salvage transfused within 24 hours after study medication and until discharge</p> <p>Change definitions of invasive procedures.</p> <p>2) Withhold FFP if bleeding stopping</p> <p>3) Inclusion criteria. Gestation <math>\geq 24+0</math> weeks</p> <p>4) Informed consent. If the woman has received the antenatal leaflet but didn't indicate whether she would wish to participate in the study or not, she may be approached to enter the study.</p> <p>5) Tranexamic acid may be infused at any time during the observational phase according to the treating clinicians' discretion.</p> <p>6) Allocation of study medication. If, in the opinion of the treating clinician, it would not be safe to administer placebo at the time of randomisation, the woman will not enter the interventional phase but will be treated at the discretion of the clinician. This may include the use of fibrinogen concentrate from routine stocks. All data will continue to be collected and the reason for not randomising will be recorded.</p> <p>7) Unblinding in the event of death or adverse event. Unblinding can be done through the OBS2 online database.</p> <p>8) Study treatments. The study centres can request an appropriate number of study medication pack when the study medication level reaches 3 study medication packs.</p> <p>9) Pre-medication. Tranexamic acid should be given before or as soon as practical after study treatment.</p> <p>10) SAEs reporting to CSL (within 24 hours of the sponsor being made aware of them).</p> <p>11) Flow chart for adverse event reporting procedure has been amended.</p>
14 November 2013	<p>Pharmacovigilance:</p> <ul style="list-style-type: none"> <li>- Day zero is defined as the day an SAE form is received at SEWTU.</li> <li>- The assignment of the causality should be made by the Investigator responsible for the care of the participant. The Chief Investigator (Clinical Reviewer Delegate) will also be responsible for making an assessment of causality.</li> <li>- The assessment of whether or not an adverse reaction is an expected reaction from the administration of the IMP will be provided by the Chief Investigator (or Clinical Reviewer Delegate), it will not be provided by the Investigator responsible for the care of the participant.</li> <li>- The responsible investigator should sign the causality of the event. No assessment of expectedness will be provided by the Investigator responsible for the care of the participant.</li> </ul>
17 December 2013	<p>Further information has been provided by the manufacturer (CSL Behring) in relation to temperature storage of IMP. Hence section 12.1 has been amended: Fibrinogen concentrate and placebo in study packs will be stored according to manufacturer's instructions (Investigator's Brochure 2011 &amp; communication with CSL Behring, December 2013).</p>
17 December 2013	<p>Further information has been provided by the manufacturer (CSL Behring) in relation to temperature storage of IMP. Hence section 12.1 has been amended: Fibrinogen concentrate and placebo in study packs will be stored according to manufacturer's instructions (Investigator's Brochure 2011 &amp; communication with CSL Behring, December 2013).</p>
14 April 2014	<ul style="list-style-type: none"> <li>- Number of participants in the observational arm amended to approximately 450 women.</li> <li>- Minor amendments to section 15.2 (sample size).</li> <li>- Withdrawal: form completed on the online database</li> <li>- 6 week follow-up: telephone or face to face</li> </ul>

15 August 2014	<ul style="list-style-type: none"> <li>-SAE: form completed on the online database</li> <li>-Contingency plan in the event of a system failure (online database)</li> <li>-Procedure to obtain outcome data in the event of non-contact at 6 weeks (interventional phase)</li> </ul>
26 September 2014	<ul style="list-style-type: none"> <li>-Planned trial period changed to December 2014 (was September 2014)</li> <li>- Section 12.1: Minimum and maximum temperature will be monitored weekly (was daily)</li> </ul>
05 March 2015	<ul style="list-style-type: none"> <li>-Planned trial period changed to October 2015 (was December 2014).</li> <li>- Minimum stock level at sites changed to 2 IMP packs</li> <li>- Adding an expression of interest form to ask participants whether they would be interested in taking part in other studies related to post-partum haemorrhage, including their experience in the Obstetrics Bleeding Study (OBS2).</li> </ul>
23 November 2015	<ul style="list-style-type: none"> <li>-Planned trial period changed to October 2016 (was December 2014).</li> <li>- Inclusion of a qualitative sub-study to explore participants, legal representatives and health professionals' experiences and attitudes towards the consent process in the Obstetric Bleeding Study (OBS2).</li> </ul>

Notes:

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## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported