Early fibrinogen concentrate therapy for major haemorrhage in trauma (E-FIT 1). Results from a UK multi-centre, randomised, double blind, placebo-controlled pilot trial.

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Running Title

E-FIT 1 : fibrinogen concentrate in trauma haemorrhage.

ABSTRACT

Background: There is increasing interest in the timely administration of concentrated sources of fibrinogen to patients with major traumatic bleeding. Following evaluation of early cryoprecipitate in the CRYOSTAT 1 trial, we explored the use of fibrinogen concentrate, which may have advantages of more rapid administration in acute haemorrhage. The aims of this pragmatic study were to: assess feasibility of fibrinogen concentrate administration within 45 minutes of hospital admission and to quantify efficacy in maintaining fibrinogen levels ≥ 2 g/L during active haemorrhage..

Methods: This was a blinded, randomised, placebo-controlled trial conducted at five UK major trauma centres in adult trauma patients with active bleeding and who required activation of the major haemorrhage protocol. Participants were randomised to standard major haemorrhage therapy plus 6g fibrinogen concentrate or placebo.

Results: 27 of 39 participants (69%, 95% CI: 52 – 83%) across both arms received study intervention within 45 minutes of admission. There was some evidence of a difference in the proportion of participants with fibrinogen levels ≥ 2g/L between arms (p = 0.10). Fibrinogen levels in the fibrinogen concentrate (FgC) arm rose by a mean of 0.9 g/L (SD: 0.5) compared to a reduction of 0.2 g/L (SD: 0.5) in the placebo arm and were significantly higher in the FgC arm (p < 0.0001) at 2 hours. Secondary endpoints: Fibrinogen levels were not different at day 7. Transfusion use and thromboembolic events were similar between arms. All-cause mortality at 28 days was 35.5 % (95% CI: 23.8-50.8%) overall, with no difference between arms.

Conclusions: In this trial, early delivery of fibrinogen concentrate within 45 minutes of admission was not feasible. Although evidence points to a key role for fibrinogen in the treatment of major bleeding, researchers need to recognize the challenges of timely delivery in the emergency setting. Future studies must explore barriers to rapid fibrinogen therapy, focusing on methods to reduce times to randomization; using 'off the shelf' fibrinogen therapies (such as extended shelf-life cryoprecipitate held in ED or fibrinogen concentrates with very rapid reconstitution times) and limiting the need for coagulation test based transfusion triggers.

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BACKGROUND

Uncontrolled bleeding is the most common preventable cause of death in major trauma [1] and affects up to 40% of patients with severe injury. Trauma haemorrhage is exacerbated by a complex interplay of clotting abnormalities and may result in a trauma-induced coagulopathy (TIC). Activation of protein C is central to TIC [2] and associated with increased fibrinolysis [3] and loss of fibrinogen [4]. Hypofibrinogenaemia occurs early after injury and is an independent predictor of death [5]. Augmentation of blood fibrinogen levels necessitates the use of a concentrated form of fibrinogen supplementation (e.g. cryoprecipitate or fibrinogen concentrate; FgC) since fresh frozen plasma (FFP) alone is ineffective [4,6].

There is continued debate about the comparative effectiveness of the two concentrated fibrinogen treatments [7,8] despite two recent feasibility randomised controlled trials (RCTs) in trauma haemorrhage (CRYOSTAT 1 [9] and FiiRST [10]). The aim of this paper is to report the findings of a second feasibility study in adult trauma haemorrhage using FgC. The primary objectives of the E-FIT 1 study were to determine whether it was possible to deliver FgC therapy early (within 45 minutes) to adult trauma patients and the proportion of participants whose fibrinogen levels were maintained ≥ 2 g/L during active haemorrhage.

MATERIALS AND METHODS

Study Design E-FIT 1 trial

The E-FIT 1 study was a multi-centre, double blind, placebo-controlled RCT, conducted in five UK major trauma centres. The study is registered with www.controlled-trials.com (ISRCTN67540073).

Eligibility criteria and randomisation

Trauma patients were eligible if they were adults (judged to be 16 years or older); were actively bleeding and in haemorrhagic shock; and therefore required activation of the major haemorrhage protocol (MHP) or had already received a transfusion of emergency red blood cells (RBC). Exclusion criteria included: patient transferred from another hospital; the trauma team leader deemed the injury incompatible with life; more

than 3 hours had elapsed from time of injury; pregnant women and severe isolated or unsalvageable head injury. Women of child bearing age had a point of care blood test performed to rule out pregnancy (Abbott, Princeton, NJ, USA).

Participants were block randomised in a 1:1 ratio of placebo:active arm. An independent statistician produced the allocation sequence using a computer generated random sequence and randomisation lists were produced centrally. Allocation concealment was maintained by the labelling of study packs prior to release to sites. Identical study packs containing either FgC or placebo were sequentially labelled and participants were allocated to the next available study pack. All research site staff, participants and trial management staff were blinded to study allocation.

Consent

An emergency waiver with independent agreement process was used. Written, informed consent from the participant was sought as soon as practically possible after study entry for continuation in the trial. If the participant did not regain capacity, agreement was sought from next of kin or other appropriate representative. The protocol and consent process was approved by NRES Committee South Central Oxford C ethics committee (15/S3/0316) and MHRA (25224/0003/001-0001).

Study Intervention

Participants were randomised equally to treatment or placebo. All randomised participants received MHP and the study intervention was started as soon as possible and within 45 minutes of hospital arrival. Typically an MHP constituted two transfusion packs; pack 1 followed by repeated use of pack 2, until bleeding was controlled. Pack 1 included 4 RBC and 4 FFP; pack 2 included 4 RBC, 4 FFP, 10 units cryoprecipitate (approximately 300 mL, 4g fibrinogen), 1 pool platelets. (Specifications for blood components are found in the UK ‘red book’) [10]. Standard laboratory clotting tests were taken throughout active bleeding and a fibrinogen of < 1.5 g/L was the trigger for additional cryoprecipitate, where necessary.

The dose of fibrinogen concentrate was chosen using data from CRYOSTAT 1 [9]. In this trial, two pools of UK cryoprecipitate, containing approximately 4g fibrinogen, constituted study intervention and fibrinogen levels were maintained above 1.8 g/L during active bleeding. Modelling data from a multi-centre European study have reported that a fibrinogen of 2.3 g/L is associated with the lowest mortality rates [12]. A dose of 6g FgC was therefore chosen, since 2g fibrinogen raises the blood level in patients with major bleeding by approximately 0.5 g/L [13].

In the treatment arm, an infusion of 6g FgC (RiaSTAP, CSL Behring, King of Prussia, PA, USA) was administered as soon as possible and an equivalent volume (300 mL) 0.9% saline in the placebo arm. FgC and placebo were blinded interventions. Study intervention packs were held in the emergency department (ED). Blinding was maintained by research staff following a validated protocol [14,15]. Reconstitution of study intervention was completed at the patient bedside by research staff. The intervention was drawn into black syringes and infused as anIV bolus over 5 minutes. Participants were deemed to have received the study intervention if at least five whole syringes were infused.

Outcomes

The primary outcome was the feasibility of administering the study intervention within 45 minutes of admission, defined by the proportion of all participants randomised who started their infusion within that time. For this trial to be successful, at least 90% of the participants were required to achieve this target. An additional primary outcome was to determine the proportion of participants whose fibrinogen level remained at 2g/L or above during active haemorrhage.

Secondary outcome measures were clinical and laboratory measures of efficacy and safety. Clinical outcomes included: mortality at 3, 6 and 24 hours, and 28 days from admission; transfusion requirements, in numbers of units, at 3, 6 and 24 hours; duration of organ support; in-patient stay, including the intensive care unit

(ICU)/high dependency unit (HDU); and quality of life. Safety was measured by symptomatic thrombotic events; arterial (e.g. myocardial infarction (MI), stroke) and venous (e.g. pulmonary embolism (PE), deep venous thrombosis (DVT)) during hospital stay. Laboratory measures included Clauss fibrinogen at 2 hours after admission and at day 7 from admission. Standard MHP protocols in the UK recommend frequent blood samples every 30 – 60 minutes during trauma haemorrhage [16] and were taken as standard measurements.

Sample and Data Collection

Blood samples were drawn immediately upon admission to the resuscitation room. Clauss fibrinogen measures were analysed in the hospital coagulation laboratories, according to standard operating procedures. Patient characteristics, mechanism and severity of injury and admission physiology were collected and scored using AIS, ISS and GCS scales. Tranexamic acid and other haemostatic drug administrations were recorded. Organ support was defined using the CTCOFR score [17]. Organ failure was defined using the SOFA score. Data on timing of transfusions, clear fluids and mortality were collected in the first 24 hours. Measures to mitigate venous thromboembolic risk were recorded weekly to day 28. Symptomatic thromboembolic disease was categorised according to standard clinical and/or radiological measures. Quality of life (EQ-5D-5L) questionnaires were completed upon discharge or day 28, whichever was the sooner. The EQ-5D-5L descriptive systems index value was calculated, allowing the five health dimensions to be converted into a single numeric measure[18].

Sample Size and Data Analysis

If the proportion of participants who received the study intervention within 45 minutes from admission was 90%, a sample size of 40 would yield a 95% confidence interval for this estimate of between 76% and 97%. To allow for 20% drop out, the final sample size was chosen to be 48 participants in total, with 24 participants per arm. All analyses were performed according to the ITT principle and included all randomised participants.

Clinical and laboratory measures were compared using Fisher's exact test or Mann-Whitney test for categorical or continuous data, as appropriate. Normal linear regression was used to assess whether fibrinogen at 2 hours from admission was different between the two arms, adjusting for values at admission. Normal linear regression, unadjusted for any other factors, was used to assess whether fibrinogen at 7 days from admission was different between arms. Residual plots from each normal linear regression were examined for evidence of non-linearity, skew or non-constant variance. Log-transformed fibrinogen would be used in the regression model(s) if any evidence was found. All-cause mortality was estimated using the Kaplan-Meier method and compared using the log-rank test. Duration of organ support and hospital stay were estimated using competing risks methods and compared using Gray's test. Death prior to the event of interest was considered the competing risk.

Sensitivity analyses were conducted for the primary outcomes, treating cases with missing time of administration of the study intervention as administration within 45 minutes (best-case scenario) or as administration beyond 45 minutes (worst-case scenario) and treating cases with missing fibrinogen at 2 hours from admission as achieving (best-case scenario) or not achieving (worst-case scenario) a level of at least 2 g/L. Except where specified, all analyses were unadjusted and there was no adjustment for multiple testing. All statistical tests were two-sided. All analyses were undertaken using the SAS/STAT software version 9.4 (SAS Institute Inc., Cary, NC, USA).

An Independent Data Monitoring Committee (IDMC) monitored all safety events throughout the study. All serious adverse events were evaluated and classified independently by the co-chief investigators, and any disagreements were resolved by consensus. The study manuscript was produced according to CONSORT recommendations for the reporting of randomised clinical trials [19].

RESULTS

Recruitment and Baseline Characteristics

166 adult trauma patients with major trauma haemorrhage were admitted and screened between January 2016 and November 2016. 78 met eligibility criteria and 48 were randomised to the trial. The main reasons for ineligibility are set out in the CONSORT flow diagram (Figure 1). Of the 48 participants randomised, 39 received study intervention. Of the nine who did not receive study intervention no intravenous access could be established in two participants and seven participants initially deemed eligible were subsequently found not to meet eligibility criteria: three had no ongoing haemorrhagic shock (stabilisation of BP and HR) and four were found to have unsalvageable traumatic brain injury. No participant withdrew consent or was lost to follow-up. One participant was screened and was ineligible due to concerns regarding potential pregnancy.

Baseline characteristics were similar in the two study arms (Table 1) although participants in the FgC arm had a lower systolic blood pressure (86mmHg vs. 95mmHg), higher injury severity (34 vs. 29), and lower EXTEM CA5 (26mm vs. 35mm) on admission. 100% participants received a 1g bolus of tranexamic acid either pre-admission or at arrival to hospital. Mean admission fibrinogen level was 1.6 g/L (standard deviation (SD) 0.7) in the FgC arm and 2.1 g/L (SD 0.9) in the placebo arm (Table 2). No participant received platelets, cryoprecipitate or colloid pre-admission.

Table 1. Baseline characteristics.

	FIBRINOGEN CONCENTRATE ARM	PLACEBO ARM
SUBJECTS		
N	24	24
Age	38 (31 – 47)	36 (22 – 56)
Male	20 (83)	19 (79)
TIMELINES		
Injury to hospital[1] (min)	98 (77 – 118)	87 (66 – 116)
INJURIES & ADMISSION PHYSIOLOGY		
Blunt	21 (88)	18 (75)
ISS	34 (24 – 43)	29 (22 – 34)
Systolic blood pressure (mmHg)	86 (72 – 124)	95 (82 – 128)
Heart rate (min^{-1})	101 (88 – 116)	112 (93 – 126)
GCS	3 (3 – 14)	3 (3 – 15)
Clauss Fibrinogen (g/L)	1.9 (0.9 – 2.2)	2.3 (1.6-2.5)
EXTEM CA5	26 (15 – 28)	35 (26 – 42)

FIBTEM CA5	4 (3 – 7)	7 (4 – 12)
PRE RANDOMISATION		
TXA administered pre-admission	18 (75)	20 (83)
RBC (units)	1 (0-2)	1 (0-2)
FFP (units)	0 (0-1)	0 (0-2)
Crystalloid (mL)	0 (0 – 475)	0 (0 – 625)

Key: CA5 – clot amplitude at 5 minutes; FFP – fresh frozen plasma; GCS – Glasgow Coma Score; ISS – injury severity score; RBC – red blood cell; TXA – tranexamic acid

Data are number (%) for categorical variables and median (IQR) for continuous variables.

[1] One participant was admitted to hospital>3 hours after injury (subsequently defined as a protocol deviation)

Primary Outcomes

27/39 participants (69%, 95% confidence interval; CI 52 – 83%) across both arms received study intervention within 45 minutes of admission. It was not feasible to deliver study intervention within 45 minutes of hospital admission, and the pre-defined target of 90% compliance was not met. The median time to delivery of study intervention was 39 mins (interquartile range, IQR: 28.0 – 54.0) across all participants and similar in each arm (p=0.56); FgC arm 37.5 minutes (IQR: 31.0 – 43.5) vs. placebo arm 40.0 minutes (IQR: 23.0 – 76.0) respectively. Twelve participants did not receive study intervention within 45 minutes for the following reasons: awaiting pregnancy results (n = 2); inability to administer treatment whilst participant was in CT scan (n = 4); lack of IV access (n = 2); transfusion not commenced immediately upon admission (n = 3); clerical error with time a participant booked in to ED (n = 1).

75% (95% CI: 51 – 91%) of participants in the FgC arm (15 /20 participants) had a fibrinogen blood level of 2 g/L or more during the first 2 hours of admission compared with 47% (95% CI: 23 – 72%) in the placebo arm (8 /17 participants) (p=0.10). The levels changed over time, as shown in Table 2. The mean fibrinogen level was higher in the FgC arm when compared with the placebo arm (p <0.0001) at two hours from admission during active haemorrhage. In the placebo group, the fibrinogen level fell by 0.2 g/L (SD: 0.5), compared with a rise of 0.9 g/L (SD: 0.5) in the active arm. Sensitivity analyses of primary outcome measures concluded that the results presented were not sensitive to the missing data. There was no evidence of a difference in Clauss fibrinogen levels at day 7 between arms (p=0.28). There was no evidence of non-linearity, skew or non-constant variance in any of the normal linear regression residual plots.

Table 2. Fibrinogen levels over time by treatment arm

Outcome	FIBRINOGEN CONCENTRATE ARM (n=24)	PLACEBO ARM (n=24)	Overall (n=48)	P-value
Mean (SD) Fibrinogen				
At admission	1.6 (0.7)	2.1 (0.9)	1.9 (0.8)	n/a
At 2 hours from admission during first active haemorrhage[1]	2.8 (1.3)	1.8 (0.6)	2.3 (1.1)	<0.0001
7 days from admission	6.7 (1.8)	7.5 (1.9)	7.1 (1.9)	0.2843

[1] P-value adjusted for value at admission

Secondary Outcomes Including Safety

There was no difference in transfusion requirements between arms (Table 3) in the first 24 hours for red cells, FFP and platelets but we observed a trend towards more cryoprecipitate use in the FgC arm at 24 hours (p=0.06).

Table 3. Transfusion requirements during the first 24 hours.

	FIBRINOGEN CONCENTRATE ARM (n=24)	PLACEBO ARM (n=24)	P value
UNITS AT 3 HOURS			
RBC	4 (2 – 6)	2 (2 – 6)	0.73
FFP	3 (2 – 6)	3 (0 – 7)	0.92
Platelets	0 (0 - 1)	0 (0 - 1)	0.98
Cryoprecipitate	0 (0 - 2)	0 (0 – 1)	0.46
UNITS AT 6 HOURS			
RBC	3 (2 – 6)	2 (2 – 5)	0.62
FFP	4 (2 – 6)	3 (0 – 7)	0.77
Platelets	0 (0 – 1)	0 (0 – 1)	0.85
Cryoprecipitate	0 (0 – 2)	0 (0 – 0)	0.12
UNITS AT 24 HOURS			
RBC	4 (2 – 8)	2 (2 – 5)	0.38
FFP	5 (2 – 8)	3 (0 – 6)	0.39
Platelets	1 (0 – 1)	0 (0 – 1)	0.59
Cryoprecipitate	2 (0 – 2)	0 (0 – 0)	0.06

Key: FFP – fresh frozen plasma; RBC – red blood cell

Data are median IQR. At each time point blood component use was analysed for patients who were still alive within the specified time frame. One participant died within 2 hours (+/-30 mins) of admission, two within 3 hours (+/-30 mins) of admission, five within 6 hours (+/-1 hr) of admission and seven within 24 hours (+/-4 hrs) of admission.

There were 10 deaths in the FgC arm and 7 in the placebo arm (Figure 2) and six participants died prior to receipt of study intervention (two in the FgC arm and four in the placebo arm). All-cause mortality at 28 days was 35.5 % (95% CI: 23.8-50.8%) overall; 42.0% (95% CI: 25.2-64.0%) in the FgC arm and 29.2% (95% CI: 15.1-51.6%) in the placebo arm. Of the 11 participants who died after receiving the study intervention, three died from uncontrolled bleeding (two FgC); five from multiple organ failure (MOF) (four FgC); one from single organ failure (FgC); one from TBI (FgC) and one from polytrauma (placebo). The times to death for the participants who died from haemorrhage were 1.9 and 4.9 hours (FgC) and 8.1 hours (placebo).

We did not observe any difference in duration of organ support (median 17 days in both arms, p=0.63), overall hospital length of stay (lower quartile 27 and 18 days (FgC vs placebo), p = 0.49) or quality of life (median self-evaluated health score 48 and 55 (FgC vs placebo), p=0.39 and median index value 0.16 and 0.21 (FgC vs placebo), p=0.92). 83% participants (39 /47) received venous thromboembolism (VTE) prevention therapy by day 7 of their hospital admission, rising to 100% by day 28 (15 /15). Serious adverse events are described in Table 4 with five patients suffering a thromboembolic event – two of the three arterial events were in the placebo arm and two pulmonary embolic events in the FgC arm.

Table 4. Serious adverse events.

	FIBRINOGEN CONCENTRATE ARM	**PLACEBO ARM**
SUBJECTS		
Number of participants in receipt of the study intervention	20	19
Number of participants experiencing at least one SAE[1]	13	11
Number of SAEs	29	21
Symptomatic thrombotic events	3	2
Arterial		
MI	0	0
Stroke	1	1
Other (arterial thrombus)	0	1
Venous		
DVT	0	0
PE	2	0
Sepsis	4	6

Organ Failure	10	2
Multiple organ failure	4	1
Single organ failure	6	1
New onset major bleeding	1	3
Uncontrolled major bleeding[2]	2	1
Other SAEs	9	7
Death		
All deaths[3]	8	3
Death due to bleeding	2 (25%)	1 (33%)

Key: DVT – deep venous thrombosis; MI – myocardial infarction; PE – pulmonary embolus; SAE – serious adverse event
Safety data were only collected for the 39 participants who were administered the study intervention.
[1] 11 participants experienced more than one SAE
[2] Major bleeding that was not controlled at any time from admission
[3] Includes all cases of multi organ failure, all cases of uncontrolled bleeding, one case of single organ failure in the active treatment arm and two other SAEs (one in the active treatment arm and one in the placebo arm).

DISCUSSION

This is the second randomised controlled trial evaluating administration of FgC in trauma. Despite median administration times approximating 40 minutes, the range varied widely (10 to 82 minutes) and only 69% of participants received study intervention within 45 minutes of admission. There was some evidence of a difference in the proportion of participants with fibrinogen levels ≥ 2g/L between arms ($p = 0.10$). However, the FgC group had a fibrinogen level of 1.6 g/L on admission (0.7 g/L lower than the placebo arm) which likely reflects the trends towards higher injury severity and greater degree of shock in the intervention arm. Importantly, the fibrinogen level in the FgC arm rose by a mean of 0.9 g/L (SD: 0.5) compared to a reduction of 0.2 g/L (SD: 0.5) in the placebo arm and average fibrinogen level at 2 hours from admission was significantly higher in the FgC arm ($p < 0.0001$). Fibrinogen levels did not remain elevated by 7 days, a finding also shown in the two other feasibility RCTs [9,10], suggesting no long-term effect of fibrinogen replacement.

Transfusion requirements were not different between arms, however it was notable there was a trend to increased cryoprecipitate use in the FgC arm. Transfusion needs were greater for all blood components in the FgC arm, again a difference likely reflecting the higher injury burden and shock, the empiric nature of

transfusion administration and the lower admission level of fibrinogen. The proportion of patients achieving haemostasis at 3 hours however was identical in both arms, suggesting that duration of bleeding does not fully explain the need for greater cryoprecipitate use in the FgC arm (data not shown).

No safety signal for thrombotic events was detected in this study. Venous thromboembolism was reported only in the FgC arm and was under 10%, a rate similar to a recent FgC trauma study, which also used 6g FgC as their intervention [10]. More deaths were recorded in the FgC arm (n = 8 vs. n = 3), with no difference in deaths from bleeding between arms, although the study was not powered for mortality. Differences in death rates may represent the variability in baseline characteristics between groups i.e., higher injury severity and worse organ failure in the FgC arm.

Rapid reconstitution is often cited as an important benefit of fibrinogen concentrate. Our study, and that of Nascimento, reported similar median FgC reconstitution times; 23 minutes (SD: 9) (E-FIT1) and 26 minutes (SD: 5) (FiiRST) [10]. In a non-RCT setting, dissolution of fibrinogen for *in vitro* testing has been reported within 30 seconds [20], although it most commonly takes 10 minutes [21]. The longer reconstitution times in our study were due to the need to dissolve the fibrinogen whilst maintaining allocation concealment. The study vials were kept in cardboard tamper-proof boxes meaning dissolution of fibrinogen powder (or placebo) could not be visually assessed and each vial needed to 'rest' for 3 minutes prior to drawing into a syringe [14]. In an unblinded RCT, time to factor concentrate administration was shorter at 10 minutes (IQR: 10 – 16) [22]. A future alternative source of concentrated fibrinogen may be extended shelf-life cryoprecipitate [23] which could be pre-thawed and held in ED avoiding reconstitution times, but this has yet to be tested in an RCT setting.

The inclusion criteria for this trial did not use fibrinogen level. Goal-directed transfusion therapy, using viscoelastic haemostatic assays (VHA) (TEG or ROTEM), is standard practice in many trauma centres in Europe and US [22, 24, 25] and is advocated for guiding transfusion therapy. In a retrospective European study, VHA

guided therapy has led to a 50% reduction in the incidence of massive transfusion for trauma compared with that predicted by the TASH score, with an associated reduction in mortality from 33 to 22% [26]. However, delays to first results are incurred (on average 15 – 20 mins [21,22]) and empiric, immediate transfusion therapy for patients with uncontrolled haemorrhage is a standard of care [27]. To date, in trauma haemorrhage, there are no evidence-based thresholds to guide fibrinogen treatment, only expert consensus [28]. A small RCT, which was terminated early, used dual ROTEM measures to guide transfusion (FIBTEM A10 >8 mm, EXTEM CT <78 s) and these data may support the use of ROTEM to direct transfusion therapy [22] but need validation in a larger study. A large European study is due to complete in 2018 (iTACTIC – NCT02593877) which will compare the efficacy of VHA and standard clotting tests for transfusion in trauma.

Our study was designed to include participants with the clinical phenotype of severe bleeding, not those exclusively with a low fibrinogen level. The authors did not use VHA or Clauss fibrinogen for two reasons (1) to minimize delay to randomisation (VHA testing incurs 10 – 15 minute delays – when speed of delivery of transfusion is known to be important [27,29,30] and (2) to include participants with the broader clinical entity of bleeding. The recent RETIC trial used FIBTEM A10 for eligibility and randomisation took approximately 35 – 38 minutes, compared to 15-16 minutes in our study [22].

This is one of the first published multi-centre UK trauma transfusion studies and it provides evidence that the delivery and conduct of RCTs in the challenging environment of ED is possible. Prior to study start it was predicted that the recruitment would take 18 months. Recruitment was completed within 10 months, facilitated both by the research infrastructure and the ability of research teams to recruit outside core hours. Rapid recruitment has been recently seen in another transfusion trauma study (FEISTY, NCT02745041) showing an encouraging appetite for the collection of high quality collaborative study data.

This study has several limitations. It is a small feasibility study and large differences were seen between treatment groups, in particular shock parameters and fibrinogen levels, which will alter treatment effects. Treatments for trauma haemorrhage are more effective when given earlier in the time course of major

bleeding, as demonstrated by the CRASH-2 data [29], and it is possible that a time delay incurred in the delivery of FgC in this study may have attenuated potential clinical benefits. This study was designed to test the ability of the research teams to administer fibrinogen concentrate rapidly and secondary endpoints should be viewed cautiously as it was not powered for evaluation of clinical outcomes.

CONCLUSION

E-FIT 1 shows that it was not feasible to administer the study intervention within 45 minutes of admission consistently, and the pre-defined target of 90% participants was not met. Although the proportion of participants with fibrinogen levels above 2 g/L was not statistically different between arms, the rise in fibrinogen levels was greater in the active arm. There was no safety signal for thrombotic events in this study. This trial has highlighted the need for future studies to focus on the barriers to rapid delivery of concentrated fibrinogen therapies by examining each step in the trial process including times taken to confirm eligibility and subsequent randomization, as well as the specifics of speed of drug reconstitution and delivery.

List of abbreviations

CI – confidence interval; CONSORT - Consolidated Standards of Reporting Trials; CTCOFR - Composite Time to Complete Organ Failure Resolution score; DVT – deep venous thrombosis; FgC – fibrinogen concentrate; FFP – fresh frozen plasma; HDU – high dependency unit; ICU – intensive care unit; ITT – intention to treat; MHP – major haemorrhage protocol; MI – myocardial infarction; PE – pulmonary embolus; RBC – red blood cells; RCT – randomized controlled trial; SOFA – sequential organ failure assessment score; TIC – trauma induced coagulopathy; VTE – venous thromboembolic event.

DECLARATIONS

Ethics approval and consent: An emergency waiver with independent agreement process was used. The protocol and consent process was approved by NRES Committee South Central Oxford C (15/S3/0316) and MHRA (25224/0003/001-0001). Written, informed consent from the participant was sought as soon as practically possible after study entry for continuation in the trial. If the participant did not regain capacity, agreement was sought from next of kin or other appropriate representative.

Consent for publication: Not applicable

Availability of data: trial data for EFIT 1 is held within the NHSBT Clinical Trials Unit.

Competing interests: NC has received support for conference attendance from CSL Behring and is a Consultant for LFB; RD has received consultancy from LFB; all other authors have no competing interests to declare.

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Author's contributions: NC, SS designed the study, wrote the protocol, analysed data and wrote the manuscript. CF led the CTU running of the trial, analysed data and wrote the manuscript. HW, AM, RH, VH, AD conducted the study, conducted CTU trial work, read and approved the final manuscript. EC, AZ designed and conducted the statistical analysis for the trial, wrote and approved the final manuscript. JR, PM, MJR, SZ, RD led recruitment at sites and read and approved the final manuscript.

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Figure Legends.

Figure 1. CONSORT flow diagram.

Key: TBI – traumatic brain injury
Overall recruitment rate was 62% and ranged between 22% - 100% across the five centres.

Figure 2. Survival to day 28 by treatment arm.