Figure 1 Summary of trial entry, randomisation and treatment

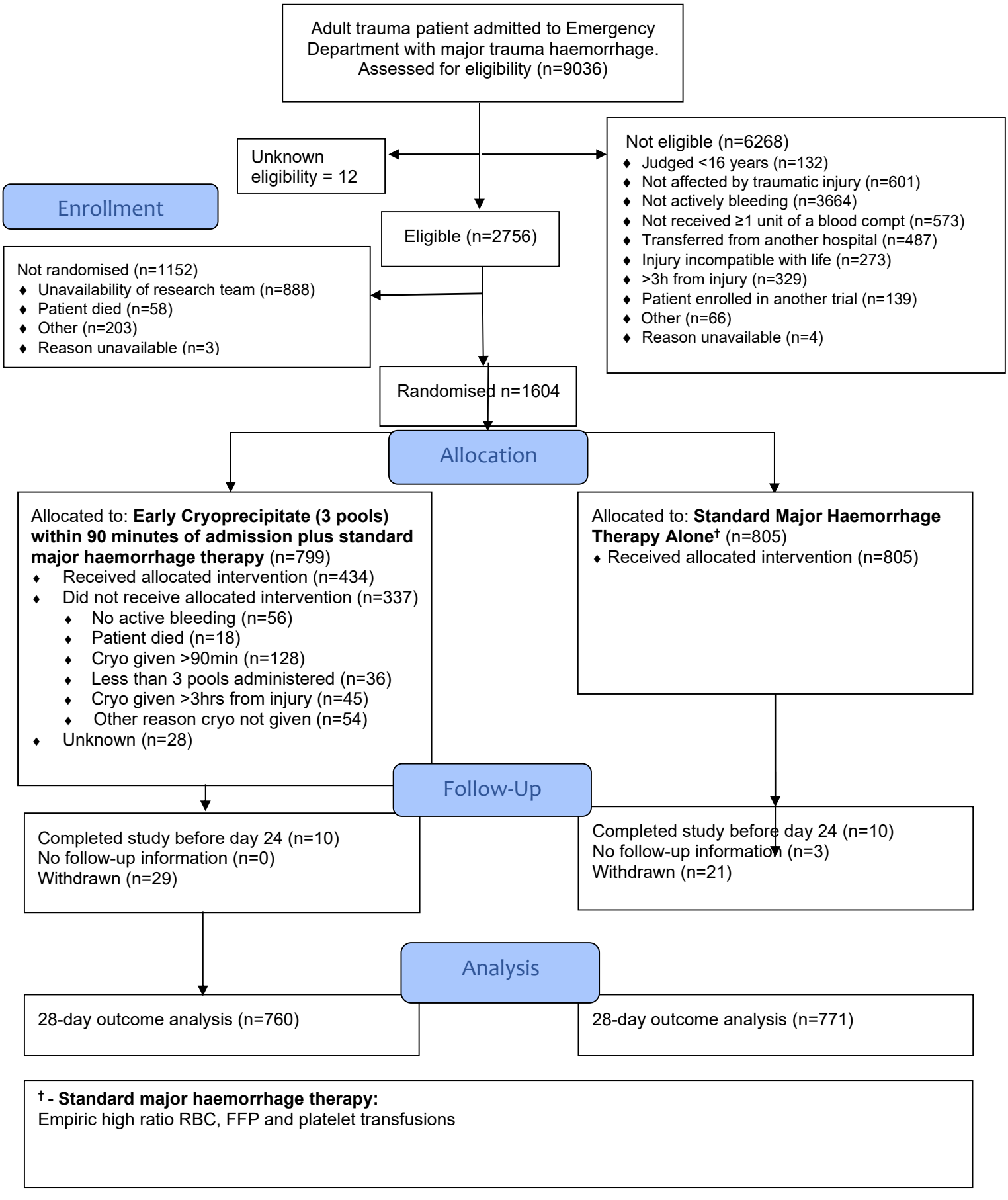

Table 1 **Baseline characteristics – data are number/total number (%) for categorical variables, and median (IQR) for continuous variables**

	Std MHP arm (n=805)	Early cryo arm (n=799)	Overall (n=1604)
Subjects			
Male	633/796 (80)	618/785 (79)	1251/1581 (79)
Age (years)	40 (26-55)	38 (25-55)	39 (26-55)
Time from injury to admission to emergency department (mins)	77 (55-100)	75 (55-99)	76 (55-100)
Injuries and physiology at admission to emergency department			
Blunt injury	519/796 (65)	495/785 (63)	1014/1581 (64)
Injury Severity Score	29 (18-43)	29 (17-43)	29 (18-43)
Head AIS ≥ 4	191/664 (29)	157/665 (24)	348/1329 (26)
Systolic blood pressure (mm Hg)	103 (83-126)	102 (84-124)	103 (83-125)
Heart rate (per min)	108 (88-127)	108 (88-126)	108 (88-127)
In cardiac arrest	17/735 (2)	12/717 (2)	29/1452 (2)
Glasgow Coma Score	13 (3-15)	14 (3-15)	14 (3-15)
Pre hospital			
RBC (units)	0 (0-2)	0 (0-2)	0 (0-2)
FFP (units)	0 (0-1)	0 (0-1)	0 (0-1)
Crystalloids (ml)	0 (0-250)	0 (0-250)	0 (0-250)
Colloids (ml)	0 (0-0)	0 (0-0)	0 (0-0)
TXA administered	639/796 (80)	615/783 (79)	1254/1579 (79)
Race and ethnicity (US participants only)			
White	6/24 (25)	10/24 (42)	16/48 (33)
Black	8/24 (33)	5/24 (21)	13/48 (27)
Other race	10/24 (42)	9/24 (38)	19/48 (40)
Hispanic ethnicity	1/24 (4)	0/24 (0)	1/48 (2)
Not Hispanic ethnicity	14/24 (58)	16/24 (67)	30/48 (63)
Unknown ethnicity	9/24 (38)	8/24 (33)	17/48 (35)

Summary of missing data: Data on all characteristics were missing for 23 participants. In addition, ISS, cardiac arrest and blood pressure were missing for 246, 129 and 119 participants respectively. There was a small amount of missing data for other items.

Table 2 All-cause mortality at 28 days by arm

Outcome	Std MHP arm (n=805)	Early cryo arm (n=799)	Overall (n=1604)	P-value
Participants who died on or before day 28 from admission – n/N (%)	201/771 (26.1)	192/760 (25.3)	393/1531 (25.7)	
Relative risk[1] (95% CI)	0.97 (0.81-1.17)			
Odds ratio[2] (95% CI)	0.96 (0.75-1.23)			0.7406
Odds ratio also adjusted for participant factors[3] (95% CI)	1.15 (0.93-1.42)			
Participants for whom 28 day vital status was not available from any source – n/N (%)	34/805 (4.2)	39/799 (4.9)	73/1604 (4.6)	

[1] Early Cryo arm relative to Standard arm, adjusted for centre
[2] Early Cryo arm relative to Standard arm, adjusted for centre, p-value for treatment term in mixed logistic regression model.
[3] Early Cryo arm relative to Standard arm adjusted for centre and significant participant factors.
Note: Participants for whom 28 day vital status was not available were not included in this analysis. No participants were excluded for other reasons.

Table 3 Transfusion requirements

Outcome	Std MHP arm (n=805)	Early cryo arm (n=799)	Overall (n=1604)	P-value
Median (IQR) products transfused per participant from injury to 24 hours				
RBC (units)	5 (3-8)	5 (3-9)	5 (3-9)	
Platelets (units)	0 (0-1)	0 (0-1)	0 (0-1)	
FFP (units)	4 (2-8)	4 (2-8)	4 (2-8)	
Cryoprecipitate (units)	0 (0-2)	3 (3-3)	2 (0-3)	
Total blood products (units)	10 (5-18)	12 (7-21)	11 (6-20)	
Crystalloids (ml)	1600 (250-3200)	2000 (700-3500)	1958 (500-3384)	
Colloids (ml)	0 (0-0)	0 (0-0)	0 (0-0)	
Median (IQR) products transfused per participant from injury to 24 hours, for those who survived at least 24 hours				
RBC (units)	4 (3-8)	4 (3-8)	4 (3-8)	
Platelets (units)	0 (0-1)	0 (0-1)	0 (0-1)	
FFP (units)	4 (2-7)	4 (2-7)	4 (2-7)	
Cryoprecipitate (units)	0 (0-2)	3 (3-3)	2 (0-3)	
Total blood products (units)	9 (5-16)	11 (7-19)	10 (6-18)	
Crystalloids (ml)	2000 (500-3500)	2000 (1000-3620)	2000 (750-3500)	
Colloids (ml)	0 (0-0)	0 (0-0)	0 (0-0)	
Mean products transfused per participant per hour over the first 24 hours				
RBC (units)[1]	0.65	0.63	0.64	0.7588
Platelets (units)[1]	0.05	0.05	0.05	0.8475
FFP (units)[1]	0.47	0.48	0.48	0.9963
Cryoprecipitate (units)[1]	0.06	0.17	0.11	<0.0001
Total blood products (units)[1]	1.23	1.33	1.28	0.4364
Crystalloids (ml)[2]	101.94	123.71	112.73	0.0802
Colloids (ml)[2]	4.39	7.60	5.98	0.8326
Participants who received cryoprecipitate – n/N (%)	256/795 (32)	665/785 (85)	921/1580 (58)	
Median time from admission to start of first cryoprecipitate for those who received it[3] (mins)	120	68	74	<0.0001
IQR	79-184	53-85	56-102	
Range	8-1535	2-1032	2-1535	

Participants who received their first infusion within 90 mins of admission – n/N (%)				
Overall[4]	70/747 (9)	521/769 (68)	591/1516 (39)	<0.0001
Study year 1 (Jul 17 - 18)	4/71 (6)	54/75 (72)	58/146 (40)	
Study year 2 (Jul 18 - 19)	20/219 (9)	166/238 (70)	186/457 (41)	
Study year 3 (Jul 19 - 20)	24/177 (14)	119/185 (64)	143/362 (40)	
Study year 4 (Jul 20 - 21)	15/178 (8)	110/170 (65)	125/348 (36)	
Study year 5 (Jul 21 – Nov 21)	7/102 (7)	72/101 (71)	79/203 (39)	
p-value for change over time[5]	0.9671			
Participants who received 3 or more pools of early cryoprecipitate– n/N (%)		604/785 (77)		
Participants who received 3 or more pools of cryoprecipitate in 24h – n/N (%)	92/795 (12)	612/785 (78)	704/1580 (45)	
Participants who received tranexamic acid from injury up to 24 hours from admission – n/N (%)				
Overall[4]	764/794 (96)	758/784 (97)	1522/1578 (96)	0.2740
UK centres[6]	759/770 (99)	750/760 (99)	1509/1530 (99)	<0.0001
International Centres[6]	5/24 (21)	8/24 (33)	13/48 (27)	

[1] P-value from negative binomial regression model, adjusted for centre
[2] P-value from linear regression model, adjusted for centre
[3] P-value from Mann-Whitney test
[4] P-value from logistic regression model, adjusted for centre
[5] P-value for linear study year term in logistic regression model, adjusted for centre, standard MHP participants only
[6] P-value from logistic regression, adjusted for centre, for difference in overall use between countries

Table 4 **Secondary Outcomes**

	CRYO group (n=799)	**STD group (n=805)**	**Absolute difference (95% CI)**	**Odds or hazard ratio (95% CI)**	**p-value**
***Mortality at 6 hours from admission* n/N (%)**	56/784 (7.1)	68/795 (8.6)	-1.4% (-4.1-1.2)	OR: 0.82 (0.58-1.17)	*0.26*
***Mortality at 24 hours from admission* n/N (%)**	88/783 (11.2)	97/794 (12.2)	-1.0% (-4.2-2.2)	OR: 0.91 (0.63-1.31)	0.61
Kaplan-Meier estimated mortality rate at 6 months from admission % (95% CI)	26.1 (23.2-29.4)	27.3 (24.3-30.7)	-1.2% (-5.7-3.3)	HR: 0.96 (0.79-1.17)	0.67
Kaplan-Meier estimated mortality rate at 12 months from admission % (95% CI)	26.6 (23.6-30.0)	27.7 (24.6-31.1)	-1.0% (-5.5-3.5)	HR: 0.96 (0.79-1.17)	0.71
Critical care outcomes					
Ventilator days	1 (0-6)	1 (0-7)	0 (-0.3-0.3)		0.90
Critical care days (first episode)	4 (1-12)	4 (1-13)	0 (-0.9-0.9)		0.85
Hospital outcomes					
Length of stay	11 (3-27)	11 (3-27)	0 (-2.4-2.4)		0.88
Destination at discharge					
Home	280/375 (75)	278/374 (74)			
Nursing home/Rehab facility	9/375 (2)	8/374 (2)			
Other hospital	63/375 (17)	72/374 (19)			
Other	23/375 (6)	16/374 (4)			

Quality of Life					
Median EQ-5D-5L[g] index value at discharge	0.51 (0.26-0.72)	0.50 (0.20-0.73)	0 (-0.1-0.1)		0.80[l]
GOS[h] at discharge/day 28					0.55[m]
Low disability	226/705 (32)	221/712 (31)			
Moderate disability	129/705 (18)	129/712 (18)			
Severe disability	155/705 (22)	153/712 (21)			
Severe disability	155/705 (22)	153/712 (21)			
Persistent vegetative state	21/705 (3)	27/712 (4)			
Death	174/705 (25)	182/712 (26)			

Abbreviations: GOS, Glasgow Outcome Score; OR, odds ratio; HR, hazard ratio.

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

Table 5 Safety outcomes

Outcome	Std MHP arm (n= 805	Early cryo arm (n=799)	Overall (n=1604)	P-value
Thrombotic events – N	85	85	170	
Venous thromboembolism	59	58	117	
Pulmonary embolus	36	38	74	
DVT	23	20	43	
Participants affected – n/N (%)	57/805 (7.1)	55/799 (6.9)	112/1604 (7.0)	
Mean number of events per participant per week	0.0387	0.0386	0.0387	
Arterial thrombotic events	26	27	53	
Myocardial infarction	4	4	8	
Stroke	11	11	22	
Other occlusion of any other artery	11	12	23	
Participants affected – n/N (%)	26/805 (3.2)	26/799 (3.3)	52/1604 (3.2)	
Mean number of events per participant per week	0.0171	0.0180	0.0175	
Cumulative incidence of thrombotic events at day 28 – % (95% CI) [1]	12.9 (10.2-15.8)	12.7 (10.1-15.6)	12.8 (10.9-14.8)	0.8852
Serious transfusion related adverse events - n/N (%) [2]	0/805 (0)	3/799 (0.4)	3/1604 (0.2)	0.1234
Thromboprophylaxis measures used – n/N (%)	606/769 (78.8)	590/760 (77.6)	1196/1529 (78.2)	
Anticoagulants given – n/N (%)	34/788 (4.3)	12/776 (1.5)	46/1564 (2.9)	
Antidotes administered for those on anticoagulants – n/N (%)	19/34 (55.9)	8/12 (66.7)	27/46 (58.7)	

[1] P-value from Fine and Gray model
[2] P-value for Fisher's exact test