CATCH

CATheter Infections in CHildren

SAP Report Shell

	ORIGINATED BY
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Date	16/08/2013
Protocol Version and Date	5.0 01/10/2012

Change Control

Updated shell version no.	Shell section changed	Description of change	Date changed	Initials
1.2	1	Addition of CONSORT diagrams split by prospective and deferred consent	07/07/2014	KD
1.1	4.1.2	PICANET primary reason for admission and PIMS2 SCORE included in table	15/05/2014	KD
1.2	4.3.1	Safety (inserted only) added to table	07/07/2014	KD
1.2	4.3.2	Section changed from protocol deviations to threats to validity	07/07/2014	KD
1.1	4.4.1	Adverse events grouped into fewer groups	15/05/2014	KD
1.2	4.4.3	Mortality by consent included	07/07/2014	KD
1.2	4.5.1	Issues of non proportional hazards, samples and competing risks analysis included	07/07/2014	KD
1.2	4.5.6	Mortality by 30 days analysed by ITT and safety populations, updated to include ONS data and mortality by discharge also presented	07/07/2014	KD
1.2	4.5.8	Resistance for cvc tip samples is not included due to quality of data.	07/07/2014	KD
1.2	4.5.11	Time to event (PICU discharge) analysis conducted as a post hoc analysis	07/07/2014	KD
1.2	4.5.12	Time to event (hospital discharge) analysis conducted as a post hoc analysis	07/07/2014	KD

Recorded deviations from SAP

Omission from SAP	Justification
Section on loss to follow up and inclusion of loss to follow up in flow diagram	The usual definition of loss to follow up doesn't apply in this trial. The only loss to follow up was due to samples not being taken in patients that were clinically indicated. The flow diagrams present the converse (the numbers of patients where samples were taken). This information is also presented within the section on threats to validity.
No graphical presentation of heterogeneity in primary outcome	This was not undertaken due to the large variation in the numbers recruited across sites and the low number of events.
Protocol deviations were not split by site	This was not presented due to the large variation in the numbers recruited across sites and the decision not to adjust analyses by site based on this being a logistical randomisation factor rather than being a clinical factor of interest.
Immune compromised and devices in situ were not included as covariates in the regression analysis. Type of admission was restricted to prospective vs. deferred consent.	There were insufficient events for all preplanned covariates to be included. The covariates included were based on prognostic importance.
Number needed to treat (NNT) not presented	Not applicable to survival outcome

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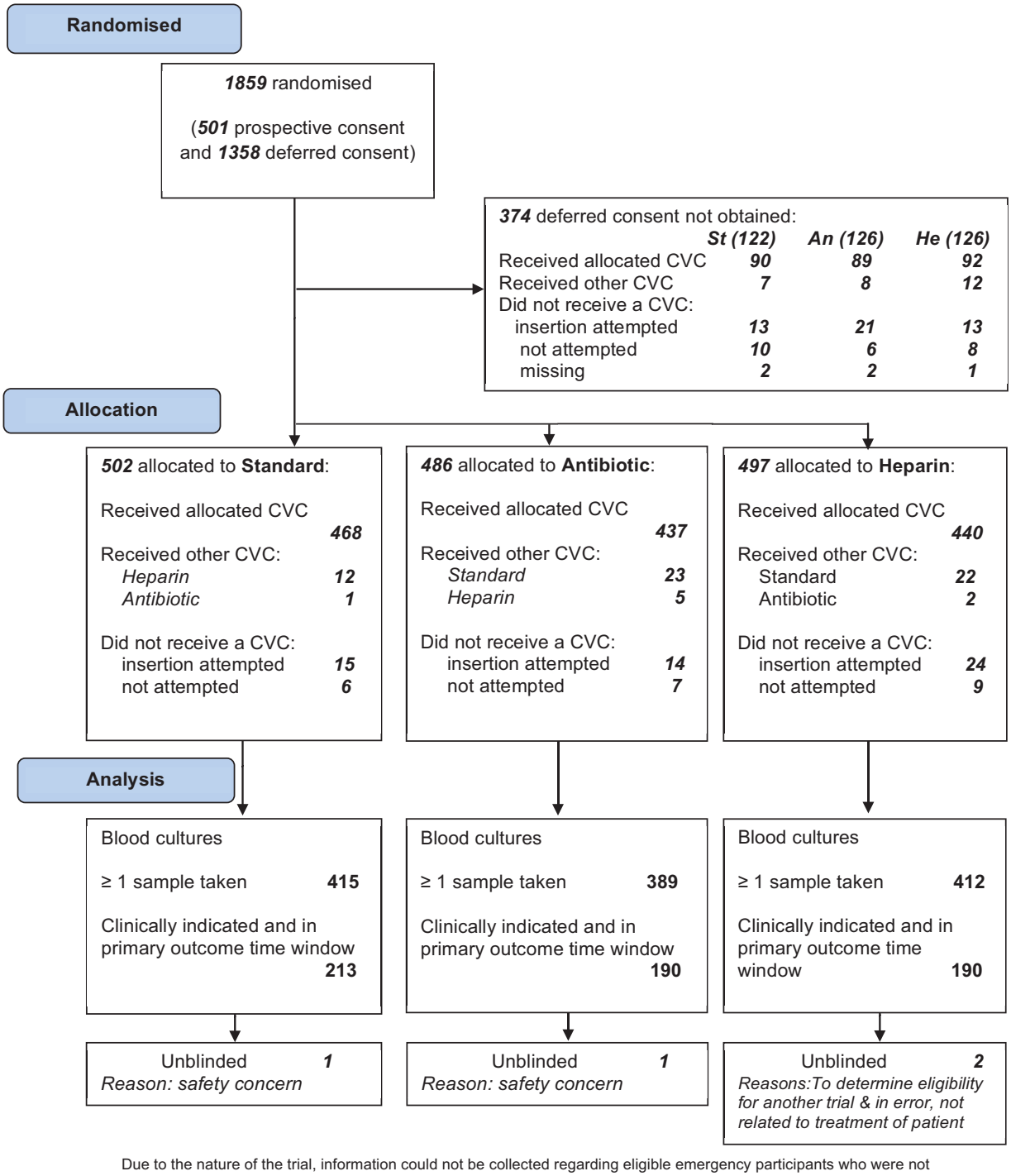
Figure 1: CONSORT 2010 Flow Diagram - Overall



Due to the nature of the trial, information could not be collected regarding eligible emergency participants who were not randomised.
No patients were withdrawn after randomisation

Figure 2: CONSORT 2010 Flow Diagram – Prospective consent

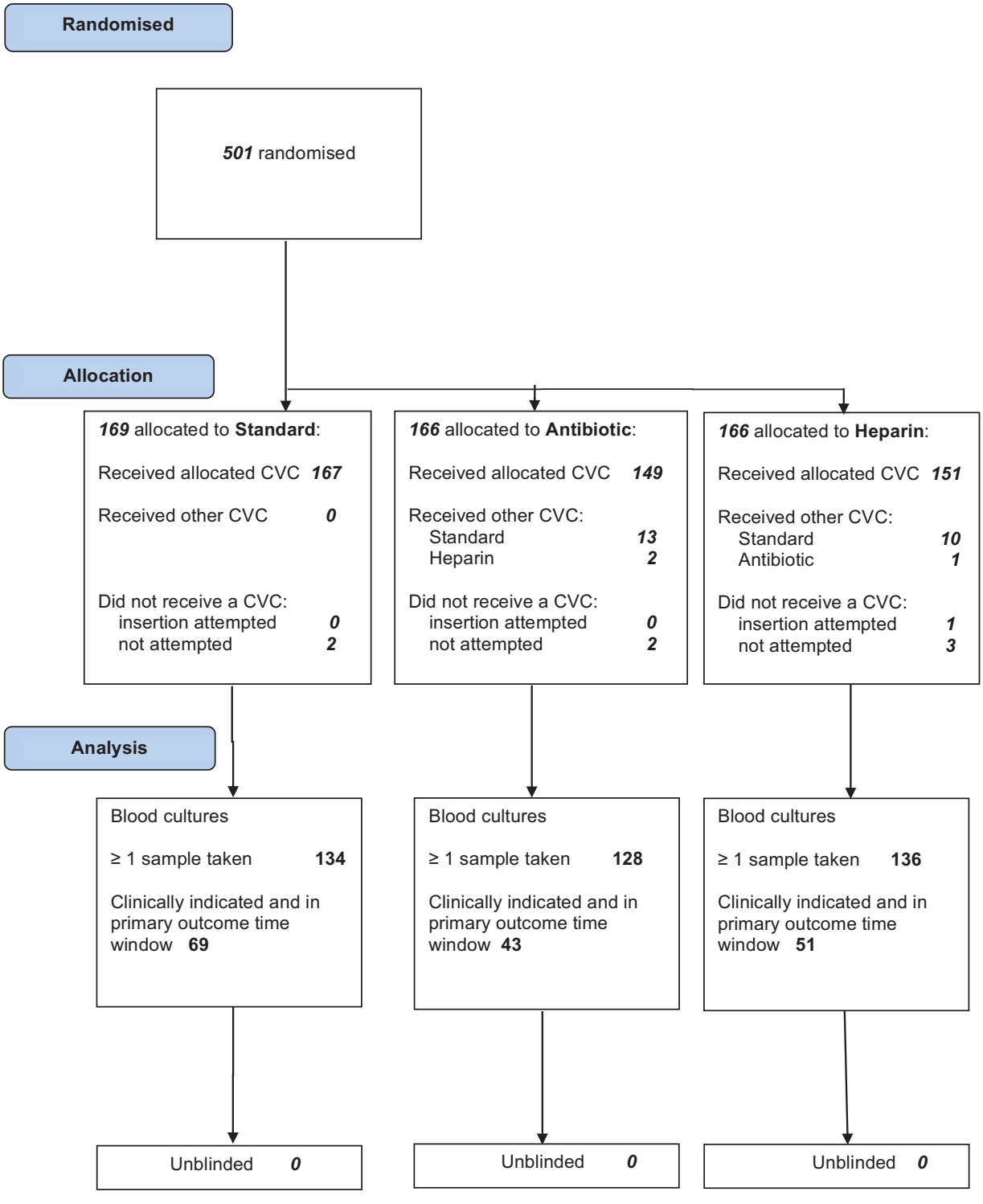
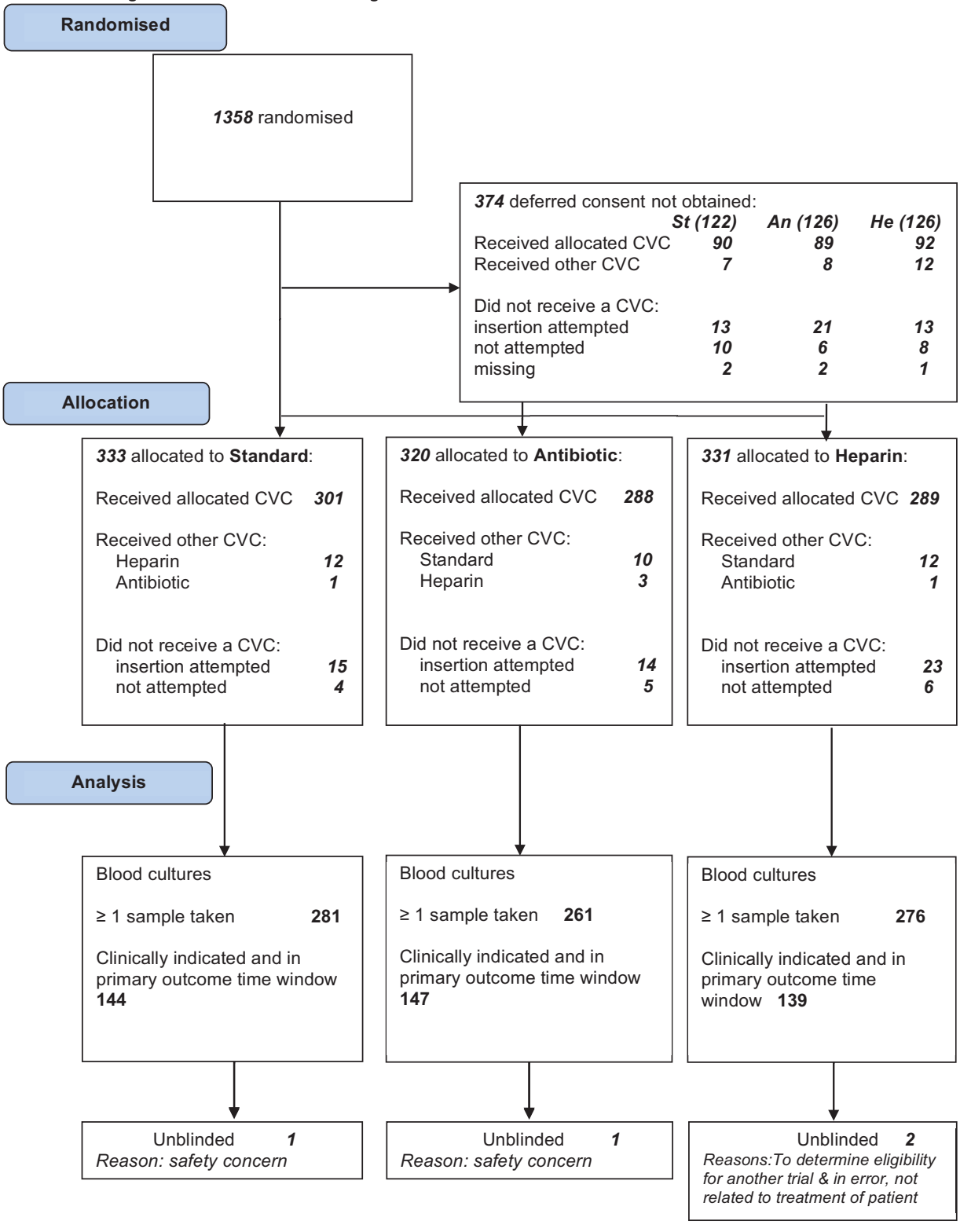


Figure 3: CONSORT 2010 Flow Diagram – Deferred consent



1 Randomisation checking

Checks to be conducted	✓
Randomisation numbers are sequential by date randomised	✓
No missing randomisation numbers	✓
Treatments balanced across strata where required	✓

Table 1: Missing randomisation numbers

Site	Randomisation numbers not used	N	Reason
Leeds General Infirmary	0030-1-2-020	1	Patient was randomised and the CVC was not inserted. CRF's were not completed. The patient was re-randomised (0030-1-2-024).
Leicester Royal Infirmary	0031-1-1-014	1	File note to state that envelope was missing or opened in error
Southampton General Hospital	0114-1-1-024	1	File note to state that envelope was missing or opened in error
Bristol Royal Hospital for Children	0116-1-1-060	1	File note to state that envelope was missing or opened in error
Nottingham General Hospital	0213-1-1-009	1	File note to state that envelope was missing or opened in error
St Mary's Hospital London	0214-1-1-028, 0214-1-1-038	2	File note to state that envelope was missing or opened in error
Alder Hey Children's Hospital	0243-1-1-044, 0243-1-2-004, 0243-1-2-017, 0243-1-2-019	4	File note to state that envelope was missing or opened in error
Great Ormond Street Hospital for Sick Children PICU/CICU	0249-1-5-048, 0249-1-5-167, 0249-1-5-239, 0249-1-5-259, 0249-1-5-295	5	File note to state that envelope was missing or opened in error
Evelina (Guy's & St. Thomas's)	5840-1-1-056, 5840-1-1-108, 5840-1-1-111, 5840-1-1-123	4	File note to state that envelope was missing or opened in error
Great Ormond Street Hospital for Sick Children Childrens' Acute Transport Service	7470-1-6-200	1	No file note
	7470-1-6-026, 7470-1-6-037, 7470-1-6-040, 7470-1-6-087, 7470-1-6-120, 7470-1-6-150, 7470-1-6-152, 7470-1-6-158, 7470-1-6-160, 7470-1-6-167, 7470-1-6-176, 7470-1-6-187	12	File note to state that envelope was missing or opened in error
Birmingham Children's Hospital	0133-1-2-001, 0133-1-2-002, 0133-1-2-003, 0133-1-2-004, 0133-1-2-005, 0133-1-2-006, 0133-1-2-007, 0133-1-2-008, 0133-1-2-009, 0133-1-2-010, 0133-1-2-011, 0133-1-2-012, 0133-1-2-013, 0133-1-2-014, 0133-1-2-015, 0133-1-2-016, 0133-1-2-017, 0133-1-2-018, 0133-1-2-019, 0133-1-2-020	20	Incorrect batch of envelopes sent to site, 0133/1/2/001 - 0133/1/2/020 never sent
	0133-0-1-034, 0133-1-1-064	2	File note to state that envelope was missing or opened in error
Total		55	

Table 2: Randomisation numbers used out of sequence

Site	Randomisation numbers used out of	N	Reason

	sequence*		
Great Ormond Street Hospital for Sick Children PICU/CICU	0249-1-5-237	1	File not states missing rather than out of sequence
	0249-1-5-070, 0249-1-5-074, 0249-1-5-146, 0249-1-5-238, 0249-1-5-147, 0249-1-5-280, 0249-1-5-299	7	File note received from site indicating they were used out of sequence. Training needs discussed
Southampton General Hospital	0114-0-1-101, 0114-1-1-007, 0114-1-1-008, 0114-1-1-031, 0114-1-1-032, 0114-1-1-060, 0114-1-1-063	7	File note received from site indicating they were used out of sequence. Training needs discussed
Bristol Royal Hospital for Children	0116-1-1-010, 0116-1-1-011, 0116-1-1-014, 0116-1-1-015, 0116-1-1-026, 0116-1-1-027, 0116-1-1-038, 0116-1-1-043, 0116-1-1-044, 0116-1-1-049, 0116-1-1-050	11	File note received from site indicating they were used out of sequence. Training needs discussed
Birmingham Children's Hospital	0133-1-1-103, 0133-1-1-104, 0133-1-1-109, 0133-1-1-110, 0133-1-1-112, 0133-1-1-113	6	File note received from site indicating they were used out of sequence. Training needs discussed
Royal Brompton Hospital	0211-1-1-008, 0211-1-1-009	2	File note received from site indicating they were used out of sequence. Training needs discussed
Nottingham General Hospital	0213-1-1-020, 0213-1-1-021, 0213-1-1-029, 0213-1-1-030	4	File note received from site indicating they were used out of sequence. Training needs discussed
St Mary's Hospital London	0214-1-1-011, 0214-1-1-012, 0214-1-1-013, 0214-1-1-042	4	File note received from site indicating they were used out of sequence. Training needs discussed
Evelina (Guy's & St. Thomas's)	5840-1-1-013, 5840-1-1-014, 5840-1-1-033, 5840-1-1-088, 5840-1-1-089, 5840-1-1-091, 5840-1-1-105, 5840-1-1-106, 5840-1-1-127, 5840-1-1-131, 5840-1-1-139, 5840-1-1-144, 5840-1-1-146	13	File note received from site indicating they were used out of sequence. Training needs discussed
Alder Hey Children's Hospital	0243-0-1-010	1	Due to the partial date and time indicated in 0243-0-1-010 patients notes this is why it looks out of sequence
	0243-0-1-009, 0243-0-1-026, 0243-0-1-044, 0243-1-2-003, 0243-1-2-005, 0243-1-2-006, 0243-1-2-010, 0243-1-2-011, 0243-1-2-012, 0243-1-2-013, 0243-1-2-014	11	File note received from site indicating they were used out of sequence. Training needs discussed
Total		67	

*CATS patients have not been listed here. They are randomised out of sequence due to the way the retrieval teams go out to a patient and take an envelope which may not be used while another team go out and take the next in sequence

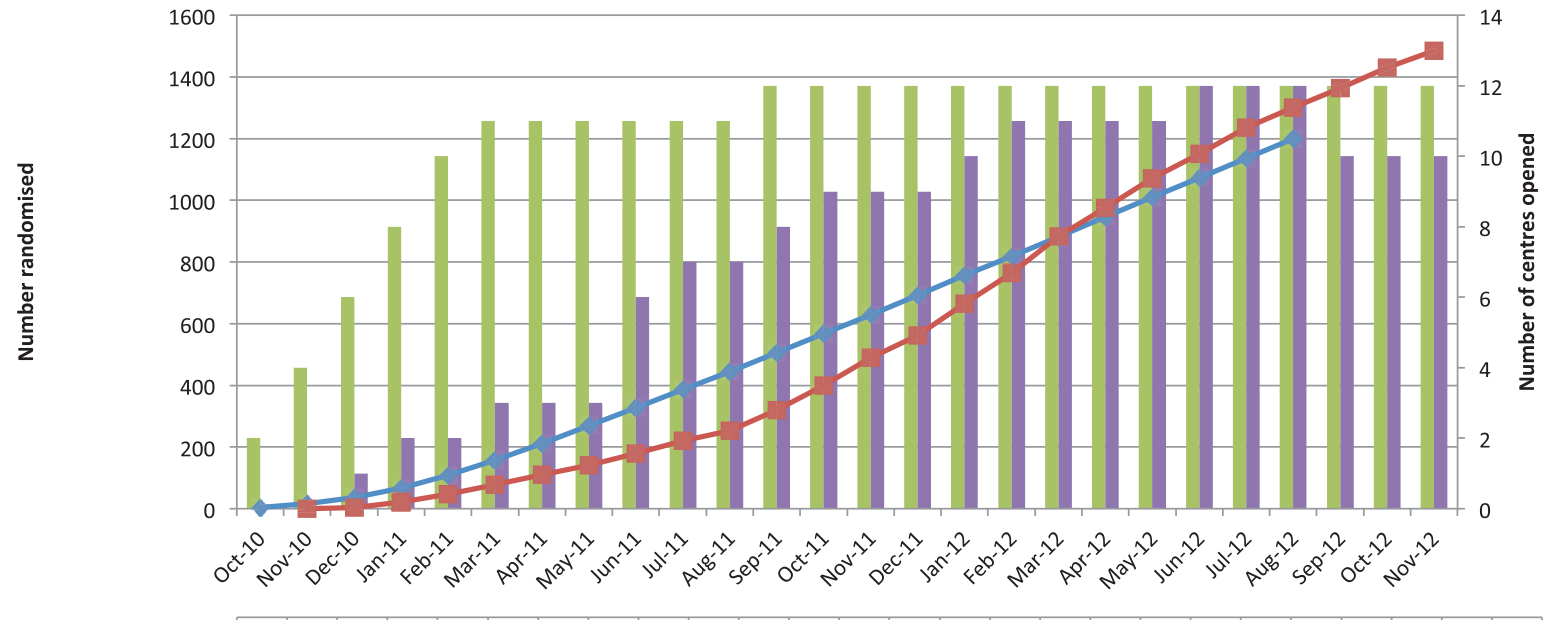
2 Recruitment

Table 3: Target and Actual Randomisation Numbers by Centre

Centre Code	Centre	Date site initiated	Date of first randomisation	Target recruitment	Number randomised and consented	Prospective	Deferred
0249	Great Ormond Street Hospital for Sick Children PICU/CICU	10/02/2011	25/02/2011	200	277	27	250
7470*	Great Ormond Street Hospital for Sick Children Childrens' Acute Transport Service	10/02/2011	15/04/2011		85	0	85
5840	Evelina (Guy's & St. Thomas's)	25/11/2010	06/01/2011	100	161	43	118
0211	Royal Brompton Hospital	17/06/2011	24/08/2011	100	49	29	20
0214	St Mary's Hospital London	01/02/2012	07/02/2012	100	26	0	26
0114	Southampton General Hospital	27/06/2011	11/07/2011	100	200	140	60
0116	Bristol Royal Hospital for Children	20/06/2011	24/06/2011	100	109	61	48
0243	Alder Hey Children's Hospital	05/07/2011	11/07/2011	100	113	69	44
0133	Birmingham Children's Hospital	22/08/2011	01/09/2011	100	150	34	116
0188	Glenfield Hospital	13/10/2011	22/10/2012	100	65	48	17
0031	Leicester Royal Infirmary	13/10/2011	11/01/2012		15	3	12
0072	Royal Victoria Infirmary	25/01/2012	03/02/2012	50	41	0	41
0069	Freeman Hospital	26/01/2012	10/02/2012		18	13	5
0030	Leeds General Infirmary	14/12/2010	22/12/2010	100	149	32	117
0213	Nottingham General Hospital	11/05/2012	16/05/2012	50	27	2	25
Total				1200	1485	501	984

*Great Ormond Street Hospital for Sick Children Childrens' Acute Transport Service retrieves and randomises patients which maybe sent to other sites. These patients are counted within the site that takes consent.

Figure 4: Overall recruitment graph



	Oct-10	Nov-10	Dec-10	Jan-11	Feb-11	Mar-11	Apr-11	May-11	Jun-11	Jul-11	Aug-11	Sep-11	Oct-11	Nov-11	Dec-11	Jan-12	Feb-12	Mar-12	Apr-12	May-12	Jun-12	Jul-12	Aug-12	Sep-12	Oct-12	Nov-12
Centres expected	2	4	6	8	10	11	11	11	11	11	11	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Centres opened	0	0	1	2	2	3	3	3	6	7	7	8	9	9	9	10	11	11	11	11	12	12	12	10	10	10
Expected	4	17	36	66	108	157	211	269	327	386	445	505	567	629	692	756	819	882	946	1009	1073	1136	1200			
Actual		0	4	22	47	77	111	140	178	221	252	320	399	489	561	665	764	884	975	1071	1151	1235	1300	1363	1430	1485

3 Table Shells

3.1 Baseline characteristics

3.1.1 Demographic details

Table 4: Demographic details

Baseline Characteristic	Standard	Antibiotic	Heparin	Impregnated (Heparin or Antibiotic)	Total (%)
Patients randomised	502 (33.80)	486 (32.73)	497 (33.47)	983 (66.20)	1485
Deferred strata					
Deferred consent taken[1]	333 (66.33)	320 (65.84)	331 (66.60)	651 (66.23)	984 (66.26)
Same hospital	118 (35.44)	120 (37.50)	112 (33.84)	232 (35.64)	350 (35.57)
Other hospital (retrieval)	215 (64.56)	200 (62.50)	219 (66.16)	419 (64.36)	634 (64.43)
Own PICU team	57 (26.51)	49 (24.50)	54 (24.66)	103 (24.58)	160 (25.24)
Other specialist team	7 (3.26)	5 (2.50)	10 (4.57)	15 (3.58)	22 (3.47)
Regional CAT	122 (56.74)	111 (55.50)	113 (51.60)	224 (53.46)	346 (54.57)
Other	29 (13.49)	34 (17.00)	41 (18.72)	75 (17.90)	104 (16.40)
Not known	0 (0.00)	1 (0.5)	1 (0.46)	2 (0.48)	2 (0.32)
Prospective strata					
Prospective consent taken[2]	169 (33.67)	166 (34.16)	166 (33.40)	332 (33.77)	501 (33.74)
Same hospital	163 (96.45)	158 (95.18)	157 (94.58)	315 (94.88)	478 (95.41)
Missing	1 (0.59)	0 (0.00)	2 (1.20)	2 (0.60)	3 (0.60)
Other hospital (retrieval)	5 (2.96)	8 (4.82)	7 (4.22)	15 (4.52)	20 (3.99)
Own PICU team	0 (0.00)	4 (50.00)	2 (28.57)	6 (40.00)	6 (30.00)
Other specialist team	1 (20.00)	1 (12.50)	3 (42.86)	4 (26.67)	5 (25.00)
Regional CAT	3 (60.00)	1 (12.50)	1 (14.29)	2 (13.33)	5 (25.00)
Other	1 (20.00)	1 (12.50)	1 (14.29)	2 (13.33)	3 (15.00)
Not known	0 (0.00)	1 (12.50)	0 (0.00)	1 (6.67)	1 (5.00)
Age (years)					
<3 months	159 (31.67)	159 (32.72)	175 (35.21)	334 (33.98)	493 (33.20)

	3 months-<1 year	129 (25.70)	123 (25.31)	116 (23.34)	239 (24.31)	368 (24.78)
	1-10 years	174 (34.66)	154 (31.69)	174 (35.01)	328 (33.37)	502 (33.80)
	11+ years	40 (7.97)	50 (10.29)	32 (6.44)	82 (8.34)	122 (8.22)
	Mean	2.58	2.86	2.46	2.66	2.63
	Standard deviation	4.00	4.36	3.84	4.11	4.07
	Median	0.70	0.62	0.66	0.63	0.66
	Interquartile Range	0.13, 3.10	0.09, 3.69	0.07, 2.74	0.08, 3.19	0.09, 3.15
	Minimum	0.001	0.002	0.002	0.002	0.001
	Maximum	16.84	18.21	15.66	18.21	18.21
Gender, n (%)						
	Male	285 (56.77)	291 (59.88)	277 (55.73)	568 (57.78)	853 (57.44)
	Female	217 (43.23)	195 (40.12)	220 (44.27)	415 (42.22)	632 (42.56)
Weight (kg)	N	502	484	497	981	1483
	<3kgs	41 (8.17)	38 (7.85)	56 (11.27)	94 (9.58)	135 (9.10)
	3-10kgs	278 (55.38)	280 (57.85)	273 (54.93)	553 (56.37)	831 (56.04)
	>10kgs	183 (36.45)	166 (34.30)	168 (33.80)	334 (34.05)	517 (34.86)
	Median	6.95	6.45	6.80	6.70	6.80
	Interquartile Range	3.80, 13.60	3.60, 14.75	3.70, 13.0	3.70, 13.90	3.7, 13.8

1. 12 were elective admissions (3 standard, 4 antibiotic and 5 heparin) but deferred consent was obtained.
2. 9 were emergency admissions (1 standard, 4 antibiotic and 4 heparin) but prospective consent was obtained.

3.1.2 Baseline disease characteristics

Table 5: Baseline disease characteristics

Baseline Characteristic	Standard	Antibiotic	Heparin	Impregnated (Heparin or Antibiotic)	Total
N	502 (33.80)	486 (32.73)	497 (33.47)	983 (66.20)	1485
Surgery	174 (34.66)	171 (35.19)	181 (36.42)	352 (35.81)	526 (35.42)
cardiac	162 (93.10)	155 (90.64)	166 (91.71)	321 (91.19)	483 (91.83)
Pre-existing CVC within 72 hours prior to time of randomisation:					
Yes	95 (18.92)	91 (18.72)	83 (16.70)	174 (17.70)	269 (18.11)
No	407 (81.08)	395 (81.28)	414 (83.30)	809 (82.30)	1216 (81.89)
Health status BEFORE the acute problem precipitated PICU admission:					
Healthy	155 (30.88)	140 (28.81)	150 (30.18)	290 (29.50)	445 (29.97)
Not Healthy	346 (68.92)	346 (71.19)	347 (69.82)	693 (70.50)	1039 (69.97)
Missing	1 (0.20)	0 (0.00)	0 (0.00)	0 (0.00)	1(0.07)
Anticoagulant medication within 72 prior to randomisation:					
Yes	50 (9.96)	59 (12.14)	61 (12.27)	120 (12.21)	170 (11.45)
No	452 (90.04)	427 (87.86)	436 (87.73)	863 (87.79)	1315 (88.55)
Antibiotic medication within 72 prior to randomisation:					
Yes	286 (56.97)	276 (56.79)	284 (57.14)	560 (56.97)	846 (56.97)
No	216 (43.03)	210 (43.21)	212 (42.66)	422 (42.93)	638 (42.96)
Missing	0 (0.00)	0 (0.00)	1 (0.20)	1 (0.10)	1 (0.07)
PICANET consent:					
Yes	479 (95.42)	456 (93.83)	473 (95.17)	929 (94.51)	1408 (94.81)
No	23 (4.58)	30 (6.17)	24 (4.83)	54 (5.49)	77 (5.19)
PIMS2 score:					
<1%	54 (11.27)	48 (10.53)	48 (10.15)	96 (10.33)	150 (10.65)
1-5%	264 (55.11)	236 (51.75)	247 (52.22)	483 (51.99)	747 (53.05)
5-15%	116 (24.22)	123 (26.97)	119 (25.16)	242 (26.05)	358 (25.43)
15-30%	34 (7.10)	31 (6.80)	39 (8.24)	70 (7.54)	104 (7.39)
30%+	11 (2.30)	18 (3.95)	20(4.23)	38 (4.09)	49 (3.48)
PICANET primary reason for admission:					

Cardiovascular	235 (49.06)	233 (51.10)	250 (52.85)	483 (51.99)	718 (50.99)
Endocrine/Metabolic	30 (6.26)	34 (7.46)	30 (6.34)	64 (6.89)	94 (6.68)
Infection	39 (8.14)	30 (6.58)	31 (6.55)	61 (6.57)	100 (7.10)
Oncology	9 (1.88)	6 (1.31)	8 (1.69)	14 (1.51)	23 (1.63)
Respiratory	102 (21.29)	86 (18.86)	84 (17.76)	170 (18.30)	272 (19.32)
Neurological	22 (4.59)	31 (6.80)	29 (6.13)	60 (6.46)	82 (5.82)
Trauma	18 (3.76)	10 (2.19)	18 (3.81)	28 (3.01)	46 (3.27)
Other	24 (5.01)	26 (5.70)	22 (4.65)	48 (5.16)	72 (5.11)
Unknown	0 (0.00)	0 (0.00)	1 (0.21)	1 (0.11)	1 (0.07)
Suspected Infection at time of randomisation:					
Yes	214 (42.63)	181 (37.24)	199 (40.04)	380 (38.66)	594 (40.00)
No	288 (57.37)	305 (62.76)	298 (59.96)	603 (61.34)	891 (60.00)
Immune compromised:					
Yes	44 (8.76)	31 (6.38)	29 (5.84)	60 (6.10)	104 (7.00)
No	450 (89.64)	449 (92.39)	463 (93.16)	912 (92.78)	1362 (91.72)
Not known	8 (1.59)	6 (1.23)	5 (1.01)	11 (1.12)	19 (1.28)
Positive blood culture within 72 hours prior to time of randomisation:					
Yes	40 (7.97)	25 (5.14)	36 (7.24)	61 (6.21)	101 (6.80)
No	462 (92.03)	459 (94.44)	458(92.15)	917 (93.29)	1379 (92.86)
Missing	0 (0.00)	2 (0.41)	3 (0.60)	5 (0.50)	5 (0.34)

3.1.3 Description of interventions

Table 6: Description of interventions

Baseline Characteristic	Standard	Antibiotic	Heparin	Impregnated (Heparin and Antibiotic)	Total
Randomised and consented	502 (33.80)	486 (32.73)	497 (33.47)	983 (66.20)	1485
Deferred consent:	333 (66.33)	320 (65.84)	331 (66.60)	651 (66.23)	984 (66.26)
CVC inserted	314 (94.29)	301 (94.06)	302 (91.24)	603 (92.63)	917 (93.19)
Same hospital	283 (90.13)	271 (90.03)	267 (88.41)	538 (89.22)	821 (89.53)
ICU (PICU/NICU/CICU)	276 (97.53)	264 (97.41)	259 (97.00)	523 (97.21)	799 (97.32)
Other ward (HDU or other ward)	1 (0.35)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.12)
Theatre	5 (1.77)	4 (1.48)	7 (2.62)	11 (2.04)	16 (1.95)
Other /A&E	1 (0.35)	3 (1.11)	1 (0.38)	4 (0.74)	5 (0.61)
Other hospital	31 (9.87)	30 (9.97)	33 (10.93)	63 (10.45)	94 (10.25)
ICU (PICU/NICU/CICU)	5 (16.13)	6 (20.00)	3 (9.09)	9 (14.28)	14 (14.89)
Other ward (HDU or other ward)	4 (12.90)	0 (0.00)	8 (24.24)	8 (12.70)	12 (12.77)
Theatre	3 (9.68)	8 (26.67)	7 (21.21)	15 (23.81)	18 (19.15)
Other /A&E	19 (61.29)	16 (53.33)	15 (45.45)	31 (49.21)	50 (53.19)
Missing	0 (0.00)	0 (0.00)	2 (0.66)	2 (0.33)	2 (0.22)
Prospective:	169 (33.67)	166 (34.16)	166 (33.40)	332 (33.77)	501 (33.74)
CVC inserted	167 (98.82)	164 (98.80)	162 (97.59)	326 (98.19)	493 (98.40)
Same hospital	167 (100.00)	164 (100.00)	161 (99.38)	325 (99.69)	492 (99.80)
ICU (PICU/NICU/CICU)	15 (8.98)	23 (14.02)	16 (9.94)	39 (12.00)	54 (10.98)
Other ward (HDU or other ward)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Theatre	152 (91.02)	141 (85.98)	144 (89.44)	285 (87.69)	437 (88.82)
Other /A&E	0 (0.00)	0 (0.00)	1 (0.62)	1 (0.31)	1 (0.20)
Missing	0 (0.00)	0 (0.00)	1 (0.62)	1 (0.31)	1 (0.20)
Size of line:					
4	28 (5.82)	45 (9.68)	39 (8.40)	84 (9.04)	112 (7.94)
5	421 (87.52)	384 (82.58)	391 (84.27)	775 (83.42)	1196 (84.82)
7	21 (4.37)	23 (4.95)	18 (3.88)	41 (4.41)	62 (4.40)
Missing	11 (2.29)	13 (2.79)	16 (3.45)	29 (3.12)	40 (2.84)
Number of lumens					
Triple	450 (93.55)	421 (90.54)	422 (90.95)	843 (90.74)	1293 (91.70)
Double	30 (6.24)	44 (9.46)	38 (8.19)	82 (8.83)	112 (7.94)

Missing	1 (0.21)	0 (0.00)	4 (0.86)	4 (0.43)	5 (0.36)
Site:					
Femoral	253 (52.60)	217 (46.67)	235 (50.65)	452 (48.65)	705 (50.00)
Other	228 (47.40)	247 (53.12)	225 (48.49)	472 (50.81)	700 (49.65)
Missing	0 (0.00)	1 (0.21)	4 (0.86)	5 (0.54)	5 (0.35)
Sterile Procedures used:					
Prospective consent:	167 (98.82)	164 (98.80)	162 (97.59)	326 (98.19)	493 (98.40)
Yes	166 (99.40)	163 (99.39)	161 (99.38)	324 (99.39)	490 (99.39)
No	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Not known	1 (0.60)	1 (0.61)	1 (0.62)	2 (0.61)	3 (0.61)
Deferred consent:	314 (94.29)	301 (94.06)	302 (91.24)	603 (92.63)	917 (93.19)
Yes	306 (97.45)	299 (99.34)	300 (99.34)	599 (99.34)	905 (98.69)
No	1 (0.32)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.11)
Not known	7 (2.23)	2 (0.66)	2 (0.66)	4 (0.66)	11 (1.20)

3.2 48 hours post randomisation

3.2.1 48 hours post randomisation

Table 7: 48 hours post randomisation

Characteristic	Standard	Antibiotic	Heparin	Impregnated (Heparin and Antibiotic)	Total
N	502 (33.80)	486 (32.73)	497 (33.47)	983 (66.20)	1485
Other devices in situ in addition to CVC:					
Less than 4	160 (31.87)	169 (34.77)	185 (37.22)	354 (36.01)	514 (34.61)
Greater than or equal to 4	340 (67.73)	311 (63.99)	311 (62.58)	622 (63.28)	962 (64.78)
Missing	2 (0.40)	6 (1.23)	1 (0.20)	7 (0.71)	9 (0.61)
Presence of an intrabody cavity device*:					
Yes	404 (80.48)	381 (78.40)	380 (76.46)	761 (77.42)	1165 (78.45)
No	96 (19.12)	100 (20.58)	116 (23.34)	216 (21.97)	312 (21.01)
Missing	2 (0.40)	5 (1.03)	1 (0.20)	6 (0.61)	8 (0.54)

* ET tube, tracheotomy tube, intracranial pressure monitor, chest drain, peritoneal dialysis catheter

3.3 Study population

3.3.1 Data sets analysed

Table 8: Data sets analysed

Population	Standard	Antibiotic	Heparin	Impregnated (Heparin and Antibiotic)	Total
Intention-to-treat (randomised and consented)	502 (33.80%)	486 (32.73%)	497 (33.47%)	983 (66.20%)	1485
Safety[1] (inserted and attempted)	533 (36.43%)	451 (30.83%)	479 (32.74%)	930 (63.57%)	1463
Safety (inserted only)	517 (36.67%)	437 (30.99%)	456 (32.34%)	893 (63.33%)	1410

1. For those where insertion was attempted or successful, the actual allocations used were unavailable for 61 (insertion attempted 45 and successful insertion 16) and therefore the randomised allocation was used.

Definitions for analysis populations:

Intention to treat: The principle of intention-to-treat, as far as is practically possible, will be the main strategy of the analysis adopted for the primary outcome and all the secondary outcomes. These analyses will be conducted on all patients randomised to the treatment groups, regardless of whether CVC insertion was attempted or not.

Safety: The safety analysis data set will contain all participants that were randomised and had CVC insertion attempted. Patients will be included in the treatment group that they actually received (the CVC that was actually inserted or the CVC that was attempted if no CVC was inserted).

3.2.2 Threats to validity

Table 9: Threats to validity

Threats to validity: n (%)	Standard	Antibiotic	Heparin	Impregnated (Heparin and Antibiotic)	Total
Randomised and consented	502 (33.80)	486 (32.73)	497 (33.47)	983 (66.20)	1485
Internal validity:					
Randomised multiple times[1]	15 (2.99%)	12 (2.47%)	11 (2.21%)	23 (2.34%)	38 (2.56%)
CVC inserted, clinical indication after 48h after randomisation, but no sample taken ever in POTW	183 (36.45%)	196 (40.33%)	196 (39.44%)	392 (39.88%)	575 (38.72%)
External validity:					
Child over 16	2 (0.40%)	4 (0.82%)	0 (0.00%)	4 (0.41%)	6 (0.40%)
CVC inserted but removed before 48h[2]	94 (18.73%)	96 (19.75%)	96 (19.32%)	192 (19.53%)	286 (19.26%)
CVC inserted >12hrs after randomisation	1 (0.20%)	1 (0.21%)	4 (0.80%)	5 (0.51%)	6 (0.40%)
Line not required following randomisation (post 12hrs) randomisation pack returned to CTU:					
CVC attempted but not inserted	15 (2.99%)	14 (2.88%)	24 (4.83%)	38 (3.87%)	53 (3.57%)
CVC insertion not attempted	6 (1.20%)	7 (1.44%)	9 (1.81%)	16 (1.63%)	22 (1.48%)
Incorrect randomisation envelope used[3]	4 (0.80%)	8 (1.65%)	9 (1.81%)	17 (1.73%)	21 (1.41%)

1. 7470-1-6-181 (antibiotic) Site do not know the other randomisation number and other details cannot be verified
2. This does not include those transferred or those that died, 5 were transferred before the CVC had been inserted 48 hours (2 standard, 2 heparin and 1 antibiotic) and follow up was missing for one (0249-1-5-204 – standard).
3. There were file notes for a further 5 patients to state the wrong envelope had been used, but the consent was checked and matched the randomisation number (one patient was emergency but file note stated elective 0243-1-1-007 (Heparin) but deferred consent obtained and four patients were elective but had a file note to state that they were emergency but had prospective consent 0188-0-2-039 - Antibiotic, 0114-0-1-021 - Heparin, 5840-0-1-007 - Heparin, 0069-0-1-002 - Antibiotic).

3.4 Safety data

3.4.1 Adverse events

Adverse events

Table 10: Adverse events

Adverse Event (Expected/ Unexpected)	Treatment				Total number of events (Total number of participants)
	Standard (n=533) Total number of events (number of participants)	Antibiotic (n=451) Total number of events (number of participants)	Heparin (n=479) Total number of events (number of participants)	Impregnated (Heparin or Antibiotic) (n=930) Total number of events (number of participants)	
Exit site infection (E)	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)
Hypersensitivity (E)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Unexplained thrombocytopenia defined as a low platelet count (<100,000 per mm3) (E)	0 (0)	1 (1)	1 (1)	2 (2)	2 (2)
Trauma from line insertion (E)	2 (2)	2 (2)	3 (3)	5 (5)	7 (7)
Line displacement (falling out/tip displaced) (E)	4 (4)	6 (6)	3 (3)	9 (9)	13 (13)
Line breakage/mechanical problem/ Line related (manufacture) complication (E)	2 (2)	3 (3)	2 (2)	5 (5)	7 (7)
Unclassifiable	0 (0)	1 (1)	0 (0)	1 (1)	1 (1)
Total	9 (9)	13 (13)	9 (9)	22 (22)	31 (31)

Blood stream infection, thrombosis and antibiotic resistance are outcomes and are included in Sections 0, 0 and 0.

Adverse events by severity

Table 11: Adverse events by severity

Adverse Event (Expected/ Unexpected)	Severity	Treatment				Total number of events (Total number of participants)
		Standard (n=533) Total number of events (number of participants)	Antibiotic (n=451) Total number of events (number of participants)	Heparin (n=479) Total number of events (number of participants)	Impregnated (Heparin or Antibiotic) (n=930) Total number of events (number of participants)	
Exit site infection (E)	Mild	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)
	Moderate	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Severe	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hypersensitivity (E)	Mild	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Moderate	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Severe	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Unexplained thrombocytopenia defined as a low platelet count (<100,000 per mm3) (E)	Mild	0 (0)	0 (0)	1 (1)	1 (1)	1 (1)
	Moderate	0 (0)	1 (1)	0 (0)	1 (1)	1 (1)
	Severe	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Trauma from line insertion (E)	Mild	1 (1)	2 (2)	2 (2)	4 (4)	5 (5)
	Moderate	1 (1)	0 (0)	1 (1)	1 (1)	2 (2)
	Severe	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Line displacement (falling out/tip displaced) (E)	Mild	3 (3)	4 (4)	1 (1)	5 (5)	8 (8)
	Moderate	1 (1)	1 (1)	2 (2)	3 (3)	4 (4)
	Severe	0 (0)	1 (1)	0 (0)	1 (1)	1 (1)
Line breakage/mechanical problem/ Line related (manufacture) complication	Mild	1 (1)	3 (3)	2 (2)	5 (5)	6 (6)
	Moderate	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

(E)	Severe	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)
Unclassifiable	Mild	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Moderate	0 (0)	1 (1)	0 (0)	1 (1)	1 (1)
	Severe	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Total	Mild	6 (6)	9 (9)	6 (6)	15 (15)	21 (21)
	Moderate	2 (2)	3 (3)	3 (3)	6 (6)	8 (8)
	Severe	1 (1)	1 (1)	0 (0)	1 (1)	2 (2)

Blood stream infection, thrombosis and antibiotic resistance are outcomes and are included in Sections 0, 0 and 0.

3.4.2 Serious adverse events

Two thrombosis events were reported in error on the serious adverse event CRF and should have been recorded on the thrombosis CRF. Therefore they have not been included as a serious adverse event and have instead been included as part of the outcome thrombosis.

No other serious adverse events were reported.

3.4.3 Overall mortality

The safety population has been used for overall mortality. There is no time limit for mortality presented in the tables below. The secondary outcome mortality by 30 days is presented in Section 3.2.3.

Table 12: Median time to death

Treatment	Number that were allocated intervention	Number where CVC insertion was attempted or successful	Number of deaths	Median days (Interquartile range)	Minimum	Maximum
Standard	539	533	66 (12.38)	15.30 (6.00, 38.96)	0.36	156.28
Antibiotic or Heparin combined	946	930	82 (8.82)	9.41 (4.14, 31.26)	0.35	296.15
Heparin	488	479	38 (7.93)	14.80 (5.26, 32.61)	0.35	296.15
Antibiotic	458	451	44 (9.76)	8.97 (2.60, 25.63)	0.40	187.95

Two patients have been included in the group they were randomised to (0188-1-1-009 as insertion was attempted but not successful so therefore the actual allocation was not available but the case report form states that an other CVC was used, 0214-1-1-040 was inserted but the allocation received was unobtainable and the case report form states that an other CVC was used).

There were a further 3 deaths (2 heparin, 1 antibiotic) but are not included here as CVC insertion was not attempted.

Table 13: Overall mortality split by deferred/prospective consent and treatment group

Deferred consent/ Prospective consent	Treatment				Total
	Standard (n=533)	Antibiotic (n=451)	Heparin (n=479)	Impregnated (Heparin or Antibiotic) (n=930)	
Prospective consent (n=494)	7 (3.65)	3 (2.03)	4 (2.60)	7 (2.32)	14 (2.83)
Deferred consent (n=969)	59 (17.30)	41 (13.53)	34 (10.46)	75 (11.94)	134 (13.83)
Total	66 (12.38)	44 (9.76)	38 (7.93)	82 (8.82)	148 (9.97)

The denominators used in this table are the number in the safety population for each intervention split by prospective/deferred.

Table 14: Overall mortality: Reasons

Related/Unrelated	Reason	Treatment				Total
		Standard (n=533)	Antibiotic (n=451)	Heparin (n=479)	Impregnated (Heparin and Antibiotic) (n=930)	
Unrelated	Related to co-morbidities at admission	58 (87.88)	37 (84.09)	35 (92.11)	72 (87.80)	130 (87.84)
	Cerebral Haemorrhage	0 (0.00)	0 (0.00)	1 (2.63)	1 (1.22)	1 (0.68)
	Multi organ failure due to calcification of the arteries	1 (1.515)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.68)
	Pneumonitis Multiorgan Failure	1 (1.515)	0 (0.00)	1 (2.63)	1 (1.22)	2 (1.35)
	Pseudomonas Septicaemia 2nd to peritonitis	0 (0.00)	1 (2.27)	0 (0.00)	1 (1.22)	1 (0.68)
	Severe Birth Asphyxia	1 (1.515)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.68)
	Complication of treatment	1 (1.515)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.68)
	Died of cerebral bleeding by ventricular assist device	1 (1.515)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.68)
	Group b strep infection/sepsis that was the initial	1 (1.515)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.68)

	cause					
	i) Multi organ failure. ii) Systemic inflamatory response syndrome.	0 (0.00)	0 (0.00)	1 (2.63)	1 (1.22)	1 (0.68)
	Multiorgan failure	0 (0.00)	1 (2.27)	0 (0.00)	1 (1.22)	1 (0.68)
	Not known exact cause	0 (0.00)	1 (2.27)	0 (0.00)	1 (1.22)	1 (0.68)
	Pulmonary hemorrhage	1 (1.515)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.68)
Unlikely	Related to co-morbidities at admission	0 (0.00)	2 (4.55)	0 (0.00)	2 (2.44)	2 (1.35)
Related	NA	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing	NA	1 (1.515)	2 (4.55)	0 (0.00)	2 (2.44)	3 (2.03)
Total		66 (44.59)	44 (29.73)	38 (25.68)	82 (55.41)	148

3.5 Efficacy data

3.5.1 Primary efficacy assessment - time to first blood stream infection

Table 15: Time to first blood stream infection: Hazard ratio

Analysis	Treatment	Hazard ratio (95% confidence interval)	p-value
Primary	Antibiotic or Heparin combined versus Standard	0.71 (0.37, 1.34)	0.29
Secondary	Heparin versus Standard	1.04 (0.53, 2.03)	0.90
Secondary	Antibiotic versus Standard	0.43 (0.20, 0.96)	0.04
Secondary	Antibiotic versus Heparin	0.42 (0.19, 0.93)	0.03

Table 16: Time to first blood stream infection: Median in days

Treatment	Number randomised	Number experiencing the primary outcome	Median days (Interquartile range)	Minimum	Maximum
Standard	502	18 (3.59)	7.53 (4.47, 11.17)	2.08	24.13
Antibiotic or Heparin combined	983	24 (2.44)	5.24 (3.15, 8.18)	2.01	18.60
Heparin	497	17 (3.42)	4.19 (3.13, 8.38)	2.01	13.55
Antibiotic	486	7 (1.44)	6.94 (5.99, 7.98)	2.37	18.60

Figure 5: Time to first blood stream infection

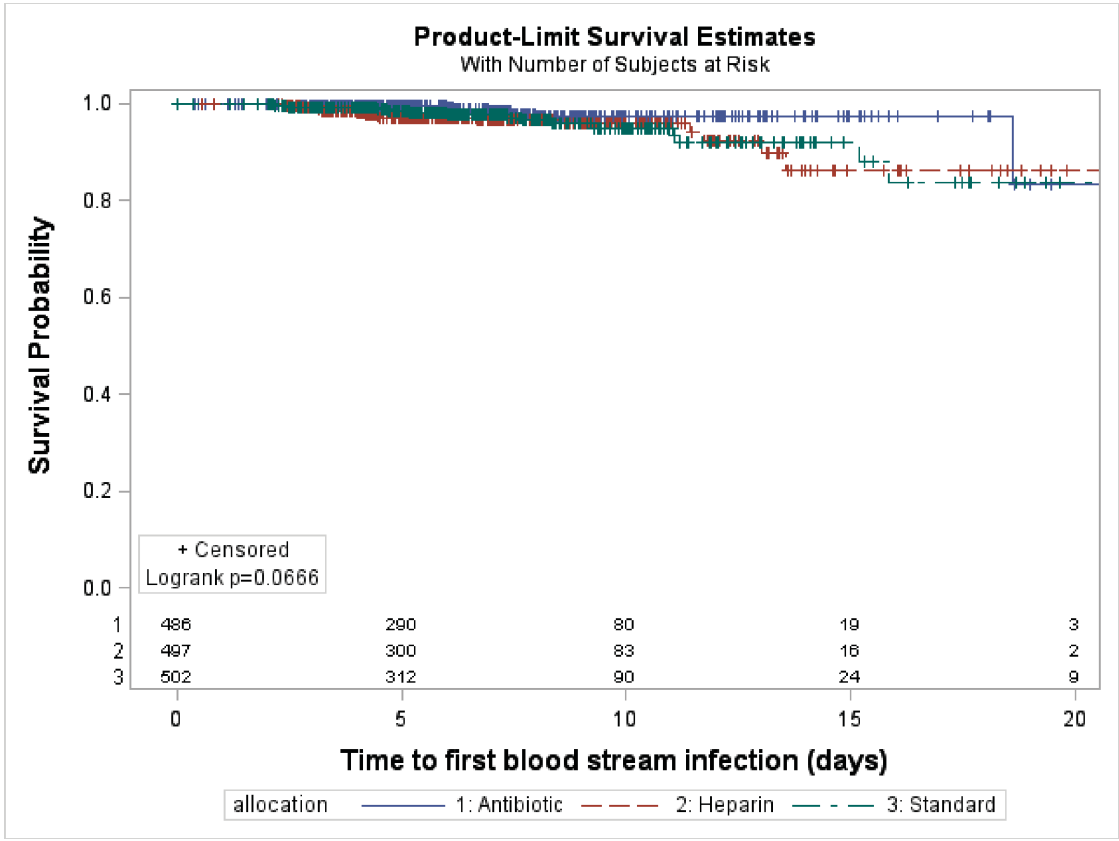


Figure 6: Time to first blood stream infection (y axis cut)

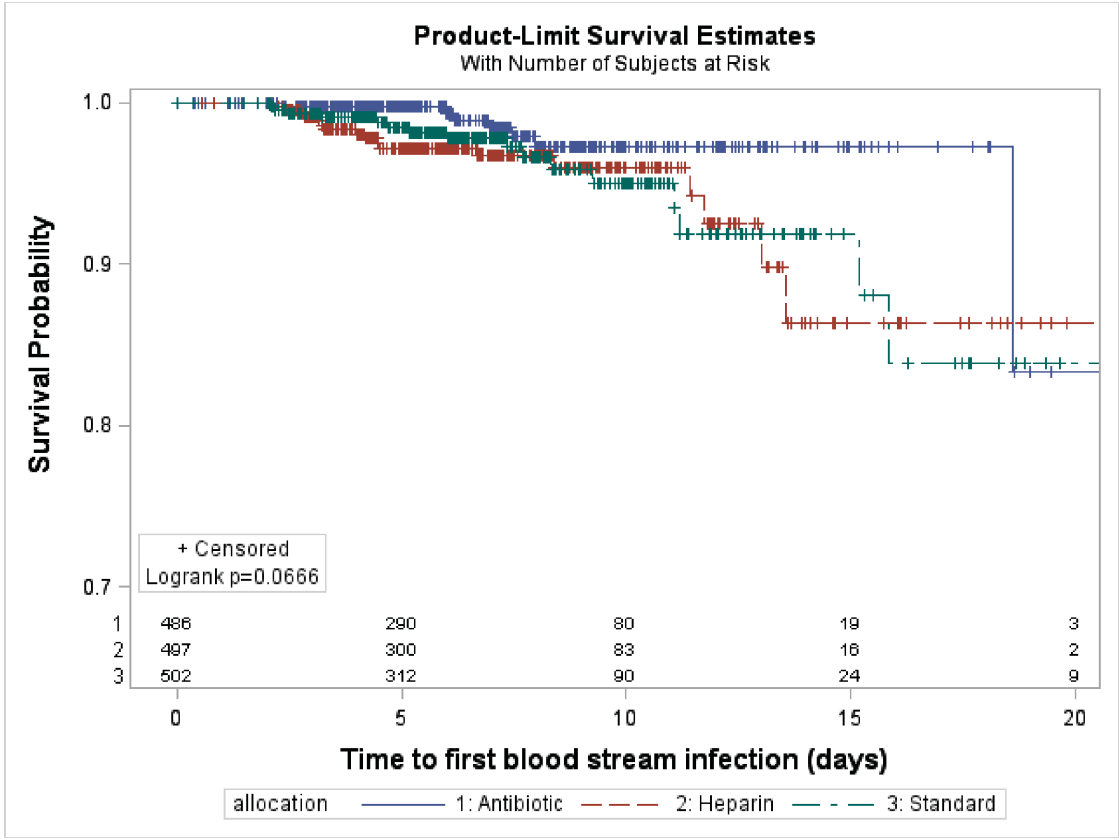


Table 17: Differences between date and time of randomisation and insertion

Treatment	Number randomised	Inserted*	Difference in hours between date and time of randomisation and insertion (median, IQR)
Standard	502	478	0.58 (0.25, 1.17)
Antibiotic or Heparin combined	983	921	0.50 (0.25, 1.13)
Antibiotic only	486	461	0.50 (0.25, 1.00)
Heparin only	497	460	0.50 (0.25, 1.25)
Total	1485	1399	0.50 (0.25, 1.25)

* Based on 1410 inserted. Partial time only available for 11, so these have been excluded from this table (3 standard, 4 heparin, 4 antibiotic)

Table 18: First blood stream infection

Non-skin/skin organism	Sample site of positive BSI												Total
	CVC lumen			Arterial			Peripheral			Multiple sites			
	Treatment												
	Standard	Antibiotic	Heparin	Standard	Antibiotic	Heparin	Standard	Antibiotic	Heparin	Standard	Antibiotic	Heparin	
Non-skin organism	8	3	7	1	1	3	1	0	1	4	2	5	36
Skin organism	1	1	0	0	0	0	0	0	0	2	0	1	5
Skin and non-skin	1	0	0	0	0	0	0	0	0	0	0	0	1*
Total	10	4	7	1	1	3	1	0	1	6	2	6	42

* The non-skin organism was from a sample taken at 47 hours and 55 minutes after randomisation.

Post hoc:
Combined versus Standard RR 0.67 (95% CI: 0.36, 1.25)
Antibiotic versus Standard RR 0.39 (95% CI: 0.16, 0.95)
Heparin versus Standard RR 0.95 (95% CI: 0.49, 1.87)
Antibiotic versus Heparin RR 0.41 (95% CI: 0.17, 1.00)

Combined versus Standard RD -0.01 (95% CI:-0.03, 0.01)
Antibiotic versus Standard RD -0.02 (95% CI:-0.04, -0.002)
Heparin versus Standard RD -0.002 (95% CI:-0.02, 0.02)
Antibiotic versus Heparin RD -0.02 (95% CI:-0.04, -0.001)

A further six patients had a blood stream infection in the primary outcome time window but had no clinical indication reported (4 standard, 1 antibiotic and 1 heparin).

Issue of non proportional hazards

In **Figure** and **Figure** the plots for the different CVCs appear to cross, therefore the assumption of proportional hazards should be considered. The plots were redone to consider the primary analysis of standard versus impregnated CVC (**Figure**, **Figure**) and appear to cross within the first 7 days when the majority of events occur. However, there are only a small number of events for the primary outcome (42/1485). A time varying coefficient was fitted to the model using STATA (version 11.2). The time varying coefficient was not statistically significant (p=0.306), therefore we can assume that assumption of proportional hazards holds.

Figure 7: Time to first blood stream infection: standard versus impregnated, days 0-21

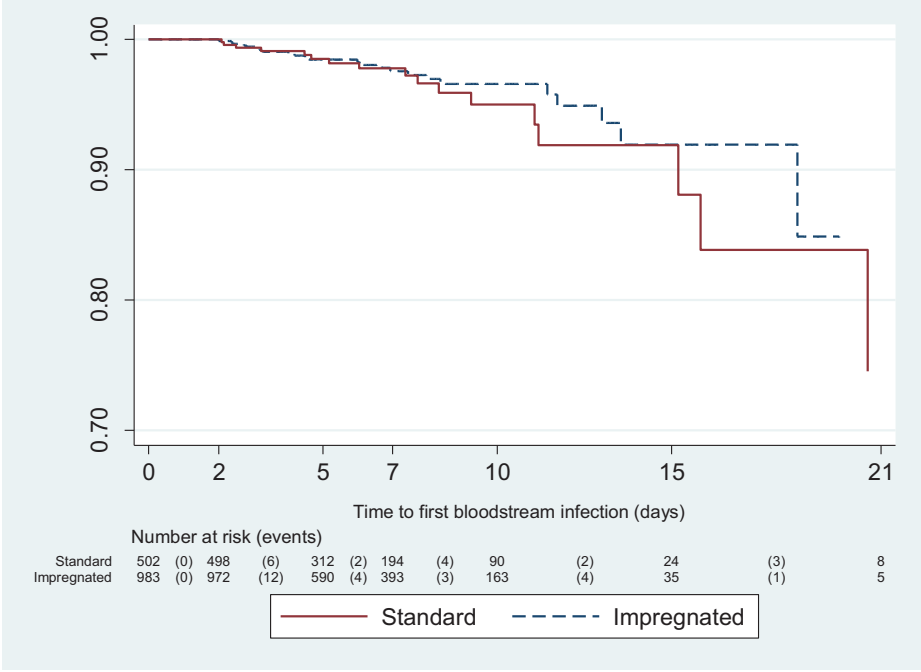
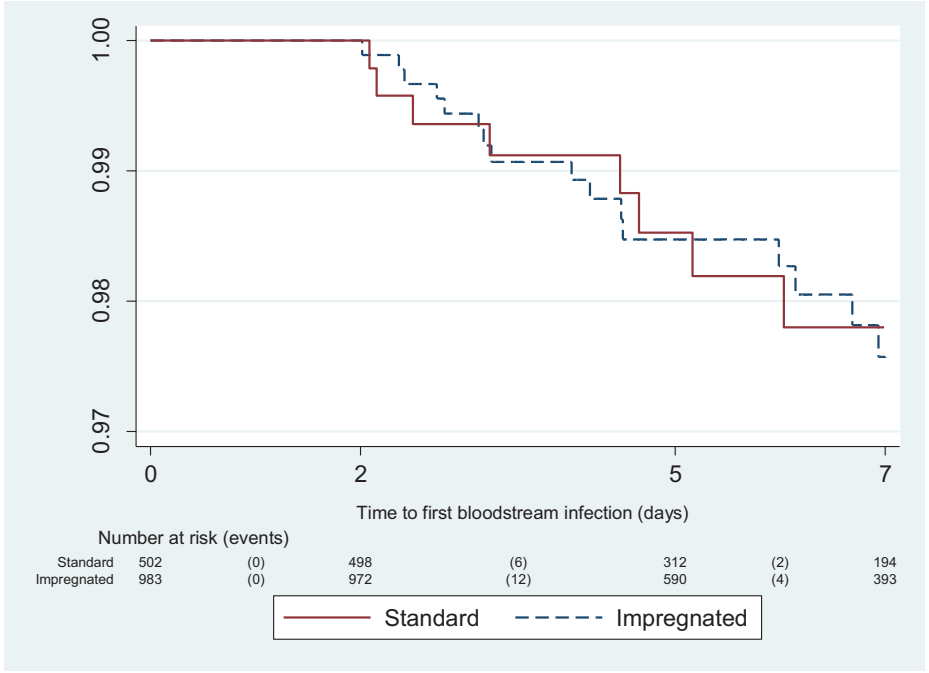


Figure 8: Time to first blood stream infection: standard versus impregnated, days 0-7



Samples

Table 19: Samples: Any blood culture at any time (by centre)

Centre Code	Centre	Standard (n=502) Number samples (number randomisations)	Antibiotic (n=486) Number samples (number randomisations)	Heparin (n=497) Number samples (number randomisations)	Impregnated (Heparin and Antibiotic) (n=983) Number samples (number randomisations)	Total (n=1485) Number samples (number randomisations)
0249	Great Ormond Street Hospital for Sick Children PICU/CICU	209 (84)	199 (68)	192 (72)	391 (140)	600 (224)
7470	Great Ormond Street Hospital for Sick Children Childrens' Acute Transport Service	64 (22)	61 (22)	112 (24)	173 (46)	237 (68)
5840	Evelina (Guy's & St. Thomas's)	163 (49)	110 (40)	123 (50)	233 (90)	396 (139)
0211	Royal Brompton Hospital	29 (11)	29 (11)	46 (13)	75 (24)	104 (35)
0214	St Mary's Hospital London	10 (5)	21 (9)	31 (9)	52 (18)	62 (23)
0114	Southampton General Hospital	162 (53)	143 (63)	162 (63)	305 (126)	467 (179)
0116	Bristol Royal Hospital for Children	71 (29)	91 (34)	88 (33)	179 (67)	250 (96)
0243	Alder Hey Children's Hospital	94 (33)	62 (29)	87 (28)	149 (57)	243 (90)
0133	Birmingham	128 (41)	124 (32)	123 (34)	247 (66)	375 (107)

	Children's Hospital					
0188	Glenfield Hospital	42 (15)	27 (14)	31 (13)	58 (27)	100 (42)
0031	Leicester Royal Infirmary	8 (4)	5 (3)	16 (5)	21 (8)	29 (12)
0072	Royal Victoria Infirmary	44 (13)	45 (13)	44 (13)	89 (26)	133 (39)
0069	Freeman Hospital	14 (5)	9 (3)	10 (4)	19 (7)	33 (12)
0030	Leeds General Infirmary	151 (44)	156 (41)	187 (46)	343 (87)	494 (131)
0213	Nottingham General Hospital	26 (7)	21 (7)	13 (5)	34 (12)	60 (19)
Total		1215 (415)	1103 (389)	1265 (412)	2368 (801)	3583 (1216)

Samples are descriptively summarised (number of samples and number of randomisations) for samples taken 48 hours after insertion and within 48 hours after removal that are clinically indicated.

Table 20: Samples: Blood cultures clinically indicated and in the primary outcome time window

	Standard (n=502) Number samples (number randomisations)	Antibiotic (n=486) Number samples (number randomisations)	Heparin (n=497) Number samples (number randomisations)	Impregnated (Heparin and Antibiotic) (n=983) Number samples (number randomisations)	Total (n=1485) Number samples (number randomisations)
Relevant to primary outcome					
Samples clinically indicated and in POTW	328 (213)	269 (190)	326 (190)	595 (380)	923 (593)
Type of sample					
arterial	55 (49)	44 (39)	55 (41)	99 (80)	154(129)
peripheral	22 (19)	33 (32)	39 (35)	72 (67)	94 (86)
CVC	226 (161)	167 (129)	208 (136)	375 (265)	601 (426)
Other	20 (17)	21 (18)	17 (11)	38 (29)	58 (46)
unknown	5 (5)	4 (4)	7 (7)	11 (11)	16 (16)

The numbers in brackets do not add up to the value in the first row as participants may have several types of samples.

Sensitivity analysis for missing microbiology

Those with no microbiology but with a clinical indication in the time frame for the primary outcome i.e. 48 hours after randomisation and within 48 hours after removal are included in the numerator for the primary outcome in this sensitivity analysis i.e. they are assumed to have experienced the primary outcome. The time point of the first clinical indication in the timeframe was used in this sensitivity analysis.

Table 21: Time to first blood stream infection: sensitivity analysis

Treatment	Number randomised	Number experiencing the primary outcome	Number to be included in the sensitivity analysis	Total
Standard	502	18 (3.59)	8 (1.59)	26 (5.18)
Antibiotic or Heparin	983	24 (2.44)	9 (0.92)	33 (3.36)
Antibiotic	486	7 (1.44)	6 (1.23)	13 (2.67)
Heparin	497	17 (3.42)	3 (0.60)	20 (4.02)
Total	1485	42 (2.83)	17 (1.14)	59 (3.97)

Table 22: Time to first blood stream infection: sensitivity analysis

Analysis	Treatment	Hazard ratio (95% confidence interval)	p-value
Primary	Antibiotic or Heparin combined versus Standard	0.67 (0.39, 1.15)	0.15
Secondary	Heparin versus Standard	0.83 (0.47, 1.49)	0.54
Secondary	Antibiotic versus Standard	0.54 (0.29, 1.02)	0.06
Exploratory	Antibiotic versus Heparin	0.64 (0.32, 1.27)	0.20

Those with a positive blood stream infection but no clinical indication in the time frame for the primary outcome i.e. 48 hours after randomisation and within 48 hours after removal are included in the numerator for the primary outcome in this sensitivity analysis i.e. they are assumed to have experienced the primary outcome. The time point of the positive blood stream infection was used in this sensitivity analysis.

Table 23: Time to first blood stream infection: sensitivity analysis (post-hoc)

Treatment	Number randomised	Number experiencing the primary outcome	Number to be included in the sensitivity analysis	Total
Standard	502	18 (3.59)	4 (0.80)	22 (4.38)
Antibiotic or Heparin	983	24 (2.44)	2 (0.20)	26 (2.64)
Antibiotic	486	7 (1.44)	1 (0.21)	8 (1.65)
Heparin	497	17 (3.42)	1 (0.20)	18 (3.62)
Total	1485	42 (2.83)	6 (0.40)	48 (3.23)

Table 24: Time to first blood stream infection: sensitivity analysis (post-hoc)

Analysis	Treatment	Hazard ratio (95% confidence interval)	p-value
Primary	Antibiotic or Heparin combined versus Standard	0.61 (0.34, 1.12)	0.11
Secondary	Heparin versus Standard	0.89 (0.48, 1.67)	0.72
Secondary	Antibiotic versus Standard	0.40 (0.20, 0.83)	0.01
Exploratory	Antibiotic versus Heparin	0.44 (0.20, 0.95)	0.04

Figure 9: Sensitivity analysis

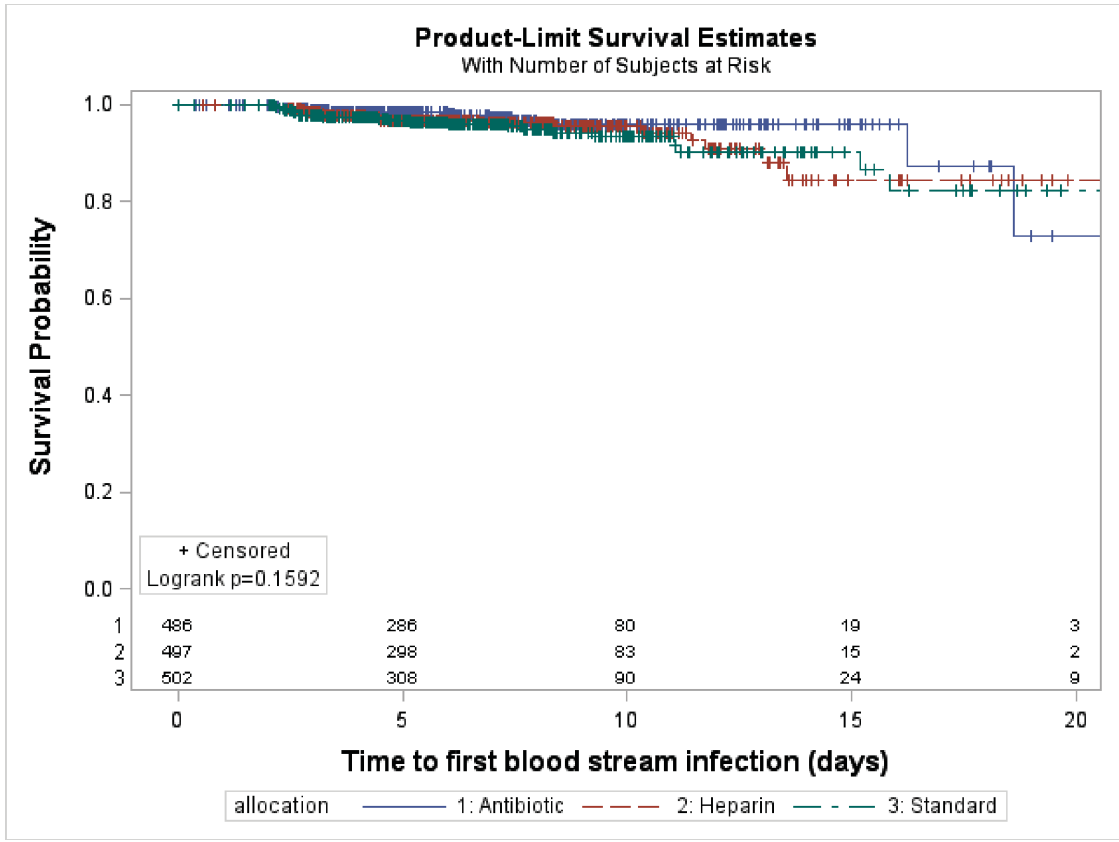
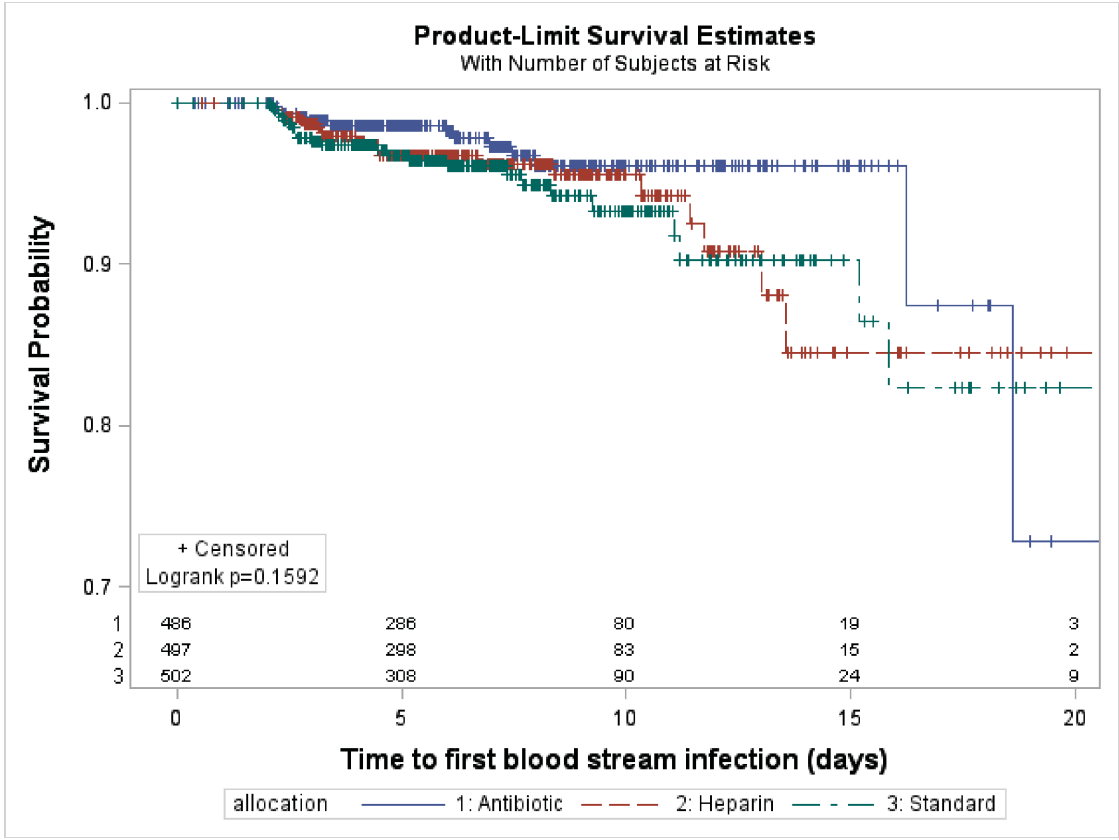


Figure 10: Sensitivity analysis (y axis cut)



Regression results

Regression models have been used to further investigate the outcomes between the groups, including an assessment of the potential modifying effect of deferred or prospective consent (stratification variable) and suspected infection at randomisation. A separate analysis was conducted considering deferred or prospective consent (stratification variable) and site for the primary comparison only.

Table 25: Time to first blood stream infection

Variable	Value	Hazard ratio (95% CI)	p-value
Baseline comparator: standard			
Treatment	Antibiotic or Heparin	0.71 (0.38, 1.33)	0.29
Consent	Prospective Deferred	- 0.87 (0.40, 1.90)	- 0.73
Suspected systemic infection at time of randomisation	No Yes	- 0.69 (0.33, 1.42)	- 0.31
Baseline comparator: standard			
Treatment	Heparin Antibiotic	1.05 (0.54, 2.05) 0.40 (0.17, 0.96)	0.89 0.04
Consent	Prospective Deferred	- 0.87 (0.40, 1.90)	- 0.35
Suspected systemic infection at time of randomisation	No Yes	- 0.68 (0.33, 1.40)	- 0.30
Baseline comparator: heparin			
Treatment	Antibiotic	0.39 (0.16, 0.95)	0.04
Consent	Prospective Deferred	- 0.85 (0.30, 2.45)	- 0.76
Suspected systemic infection at time of randomisation	No Yes	- 0.99 (0.40, 2.43)	- 0.98

Table 26: Number of deferred and prospective patients experiencing the primary outcome

Treatment	Number randomised			Number experiencing the primary outcome		
	Total	Deferred	Prospective	Total	Deferred	Prospective
Standard	502	333 (66.33)	169 (33.67)	18 (3.59)	12 (3.60)	6 (3.55)
Antibiotic or Heparin	983	651 (66.23)	332 (33.77)	24 (2.44)	18 (2.76)	6 (1.81)
Antibiotic	486	320 (65.84)	166 (34.16)	7 (1.44)	6 (1.88)	1 (0.60)
Heparin	497	331 (66.60)	166 (33.40)	17 (3.42)	12 (3.63)	5 (3.01)
Total	1485	984 (66.26)	501 (33.74)	42 (2.83)	30 (3.05)	12 (2.40)

Table 27: Number of patients with suspected infection

Treatment	Number randomised			Number experiencing the primary outcome		
	Total	Suspected infection	No suspected infection	Total	Suspected infection	No suspected infection
Standard	502	214 (42.63)	288 (57.37)	18 (3.59)	7 (3.27)	11 (3.82)
Antibiotic or Heparin	983	380 (38.66)	603 (61.34)	24 (2.44)	11 (2.89)	13 (2.16)
Antibiotic	486	181 (37.24)	305 (62.76)	7 (1.44)	3 (1.66)	4 (1.31)
Heparin	497	199 (40.04)	298 (59.96)	17 (3.42)	8 (4.02)	9 (3.02)
Total	1485	594 (40.00)	891 (60.00)	42 (2.83)	18 (3.03)	24 (2.69)

Table 28: Number of patients experiencing the primary outcome and site of CVC insertion

Treatment	Number randomised				Number experiencing the primary outcome		
	Total	CVC inserted	Femoral	Other	Total	Femoral	Other
Standard	502	481 (95.82)	253 (52.60)	228 (47.40)	18 (3.59)	9 (3.56)	9 (3.95)
Antibiotic or Heparin	983	929 (94.51)	452 (48.65)	477 (51.35)	24 (2.44)	14 (3.10)	10 (2.10)
Antibiotic	486	465 (95.68)	217 (46.67)	247 (53.33)	7 (1.44)	4 (1.84)	3 (1.21)
Heparin	497	464 (93.36)	235 (50.65)	229 (49.35)	17 (3.42)	10 (4.26)	7 (3.06)
Total	1485	1410 (94.95)	705 (50.00)	705 (50.00)	42 (2.83)	23 (3.26)	19 (2.70)

Table 29: Time to first blood stream infection

Variable	Value	Hazard ratio (95% CI)	p-value
Baseline comparator: standard			
Treatment	Antibiotic or Heparin	0.73 (0.39, 1.36)	0.33
Consent	Prospective	-	-
	Deferred	0.72 (0.35, 1.50)	0.38
Site	Femoral	-	-
	Other	1.01 (0.53, 1.94)	0.97

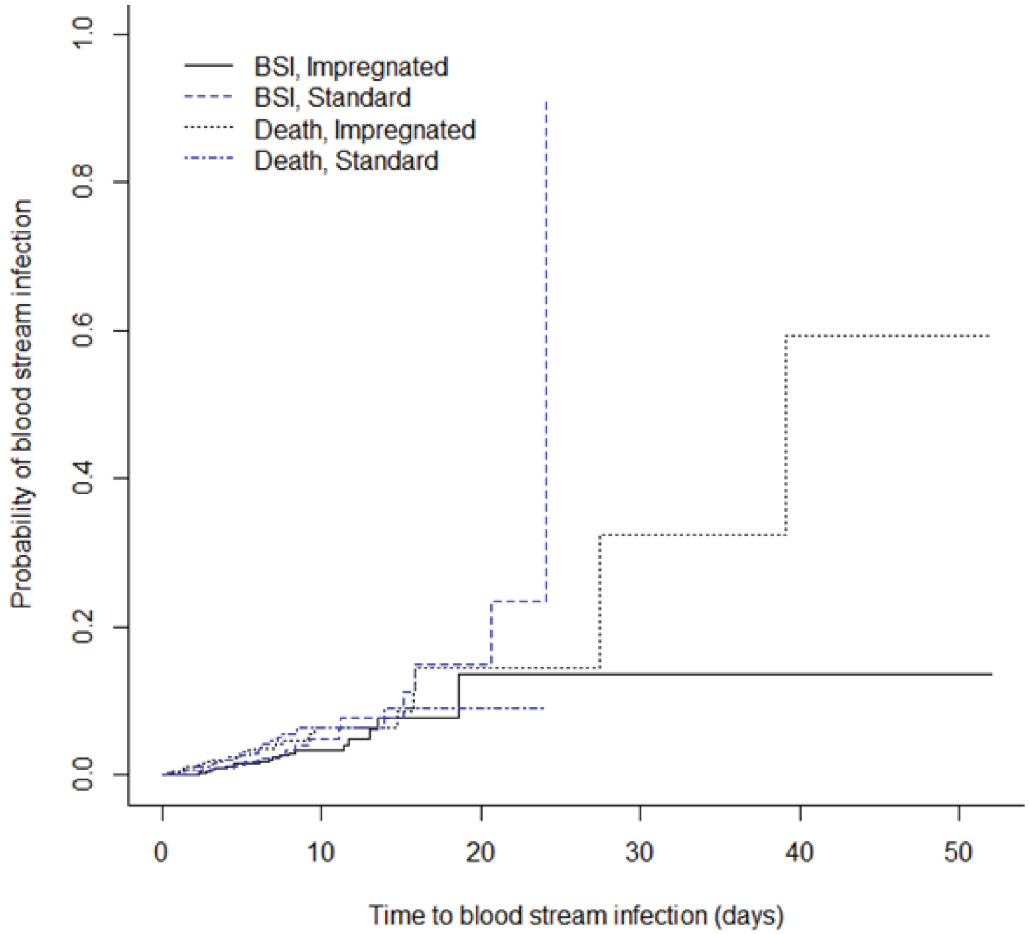
Competing risks exploratory analysis (post hoc)

After allocations were provided, a decision was made to undertake an exploratory analysis on competing risks of death and blood stream infection for the primary outcome time to first blood stream infection for the primary comparison of impregnated (antibiotic and heparin) versus standard CVCs.

Table 30: Competing risks exploratory analysis: impregnated versus standard CVCs

Outcome	**Hazard ratio** **(95% CI)** **Gray's test *p*-value**
blood stream infection	0.71 (0.39, 1.31) *p*=0.29
death	1.08 (0.63, 1.85) *p*=0.89

Figure 11: Time to first blood stream infection – cumulative incidence plot



3.5.2 Rate of blood stream infection during CVC insertion per 1000 CVC days

Where blood stream infection is defined as per primary outcome but without any criteria around the timing of the sample and the CVC must be in situ. A second episode of blood stream infection (defined as per primary outcome) is defined by a positive blood culture of a different isolate (in terms of species and antibiogram) from a sample taken whilst the cvc is in situ. Any positive blood cultures of the same isolate will be regarded as the same episode regardless of time since the first sample.

Table 31: Rate of blood stream infection during CVC insertion per 1000 CVC days

Analysis	Treatment	Number randomised	Number of participants with infections	Number of infections	Number of days CVC in situ	Number of infections standardised to 1000 CVC days	Rate ratio (95% confidence interval)	p-value
Baseline comparator: standard								
-	Standard	502	21	21	2547.30	8.24	-	-
Primary	Antibiotic or Heparin	983	29	29	4809.30	6.03	0.73 (0.40, 1.34)	0.31
Secondary	Antibiotic	486	8	8	2418.45	3.31	0.40 (0.17, 0.97)	0.04
Secondary	Heparin	497	21	21	2390.85	8.78	1.07 (0.55, 2.06)	0.85
Baseline comparator: heparin								
Secondary	Antibiotic	486	8	8	2418.45	3.31	0.38 (0.16, 0.89)	0.03
Total		1485	50	50	7356.60	6.80	-	-

3.5.3 Time to CVC thrombosis

Thrombosis is defined clinically by (any one or more of the following):

a. 2 records of difficulty drawing back blood from one or more lumen within 5 days;
b. 2 or more episodes of flushing to unblock within 5 days;
c. an episode of swollen limb;
d. positive ultrasound;
e. removal of CVC because of clinical evidence of a blocked CVC.

Table 32: Time to CVC thrombosis

Analysis	Treatment	Number randomised	Number experiencing a thrombosis	Hazard ratio (95% confidence interval)	p-value
Baseline comparator: standard					
-	Standard	502	125 (24.90)	-	-
Primary	Antibiotic or Heparin	983	231 (23.50)	0.98 (0.79, 1.22)	0.88
Secondary	Antibiotic	486	126 (25.93)	1.09 (0.85, 1.40)	0.49
Secondary	Heparin	497	105 (21.13)	0.88 (0.68, 1.14)	0.34
Baseline comparator: heparin					
Secondary	Antibiotic	486	126 (25.93)	1.24 (0.96, 1.60)	0.11
Total		1485	356 (23.97)	-	-

Post hoc:
Combined versus Standard RR 0.93 (95% CI:0.77, 1.13)
Antibiotic versus Standard RR 1.02 (95% CI:0.83, 1.27)
Heparin versus Standard RR 0.84 (95% CI:0.67, 1.06)
Antibiotic versus Heparin RR 1.22 (95% CI:0.97, 1.53)

Combined versus Standard RD -0.02 (95% CI:-0.06, 0.03)
Antibiotic versus Standard RD 0.01 (95% CI:-0.05, 0.06)
Heparin versus Standard RD -0.04 (95% CI:-0.09, 0.01)
Antibiotic versus Heparin RD 0.05 (95% CI:-0.01, 0.10)

Figure 12: Time to thrombosis

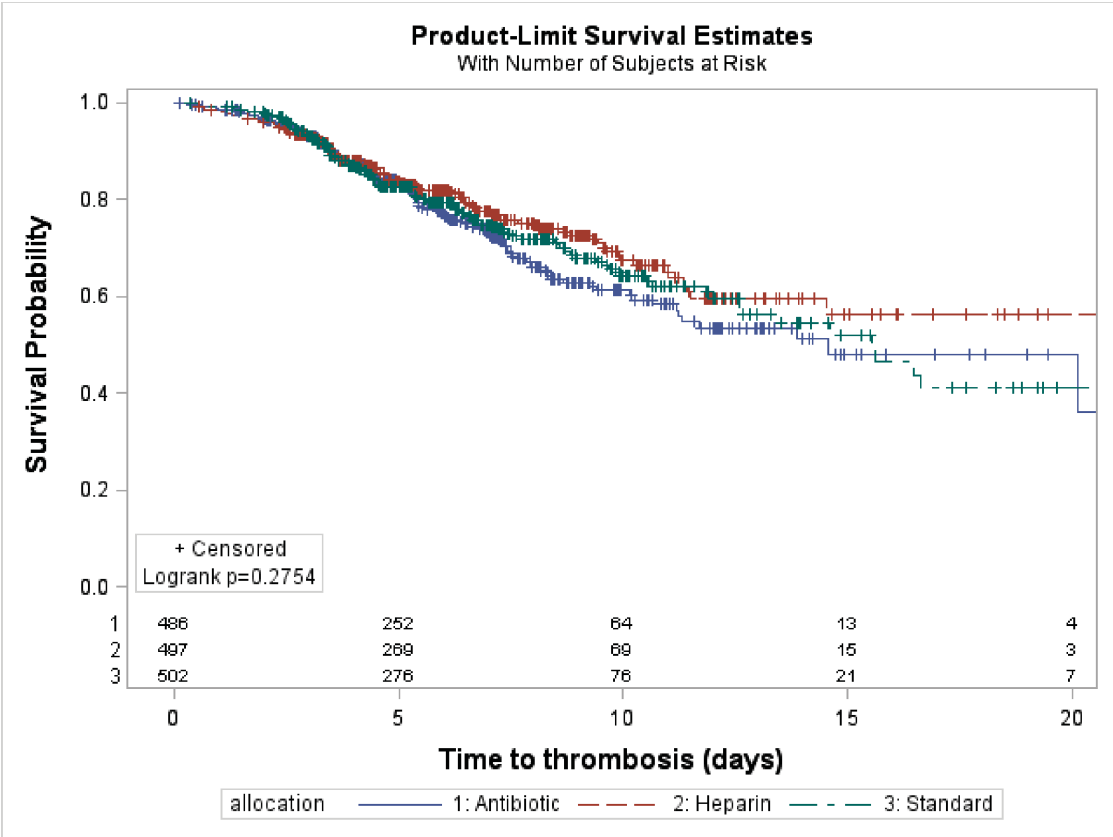
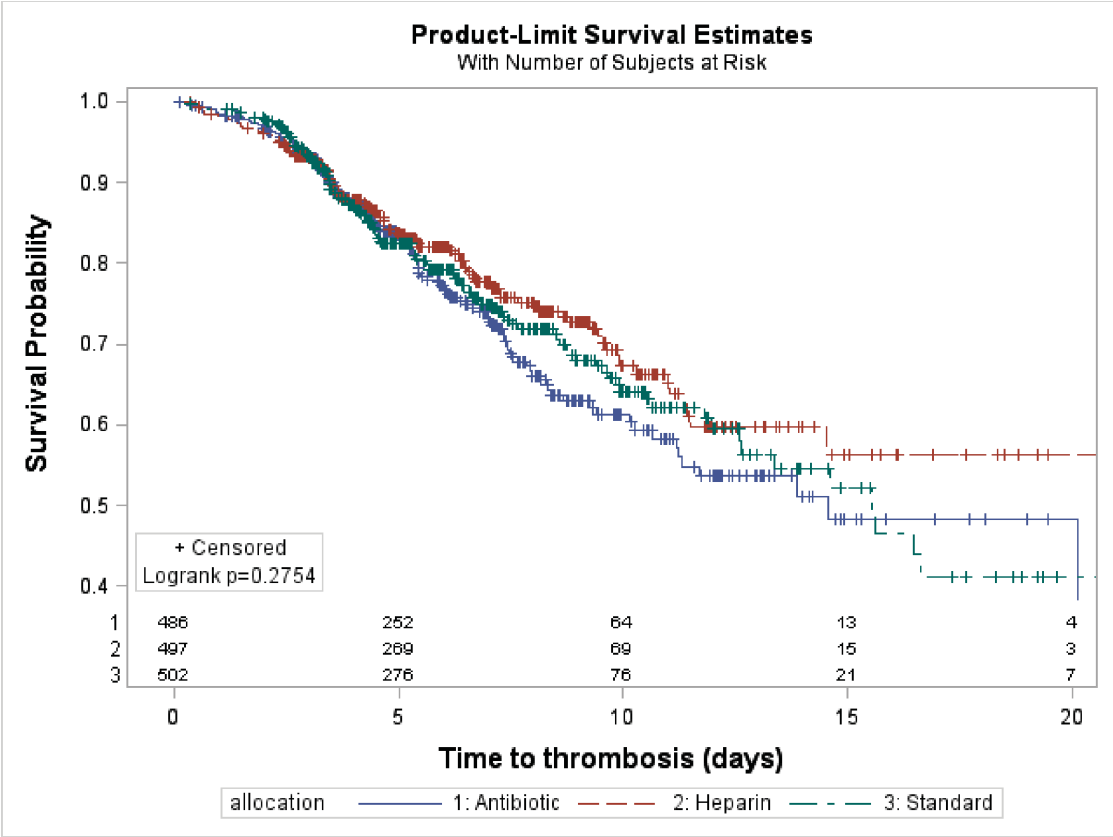


Figure 13: Time to thrombosis (y axis cut)



Sensitivity analysis for thrombosis (post hoc)

A sensitivity analysis was conducted, by considering a change in definition of thrombosis to include two occurrences of swollen limb compared to the original definition (see above) of only one occurrence of swollen limb (on the thrombosis case report form or adverse event case report form).

Table 33: Sensitivity analysis for time to CVC thrombosis (two occurrences of swollen limb)

Treatment	Number randomised	Number experiencing a thrombosis	Hazard ratio (95% confidence interval)	p-value
Baseline comparator: standard				
Standard	502	109 (21.71)	-	-
Antibiotic or Heparin	983	201 (20.45)	0.98 (0.78, 1.24)	0.88
Antibiotic	486	113 (23.25)	1.13 (0.87, 1.47)	0.36
Heparin	497	88 (17.71)	0.84 (0.64, 1.11)	0.23
Baseline comparator: heparin				
Antibiotic	486	113 (23.25)	1.34 (1.02, 1.77)	0.04
Total	1485	310 (20.88)	-	-

3.5.4 Time to a composite measure of clinically indicated blood stream infection based on the primary outcome or high bacterial DNA load or culture negative bloodstream infection based on clinical criteria

Defined as:

a. Primary outcome as defined above
b. Any of the clinical indicators of infection and blood culture taken and
    i. High bacterial DNA load from a PCR positive result or
    ii. change in antibiotic on same day or next day or
    iii. CVC removal for infection

Table 34: Time to a composite measure of clinically indicated blood stream infection

Analysis	Treatment	Hazard ratio (95% confidence interval)	p-value
Baseline comparator: standard			
Primary	Antibiotic or Heparin	0.95 (0.75, 1.20)	0.65
Secondary	Antibiotic	0.94 (0.72, 1.23)	0.67
Secondary	Heparin	0.95 (0.73, 1.25)	0.73
Baseline comparator: heparin			
Secondary	Antibiotic	0.99 (0.75, 1.30)	0.93

Figure 14: Time to composite measure

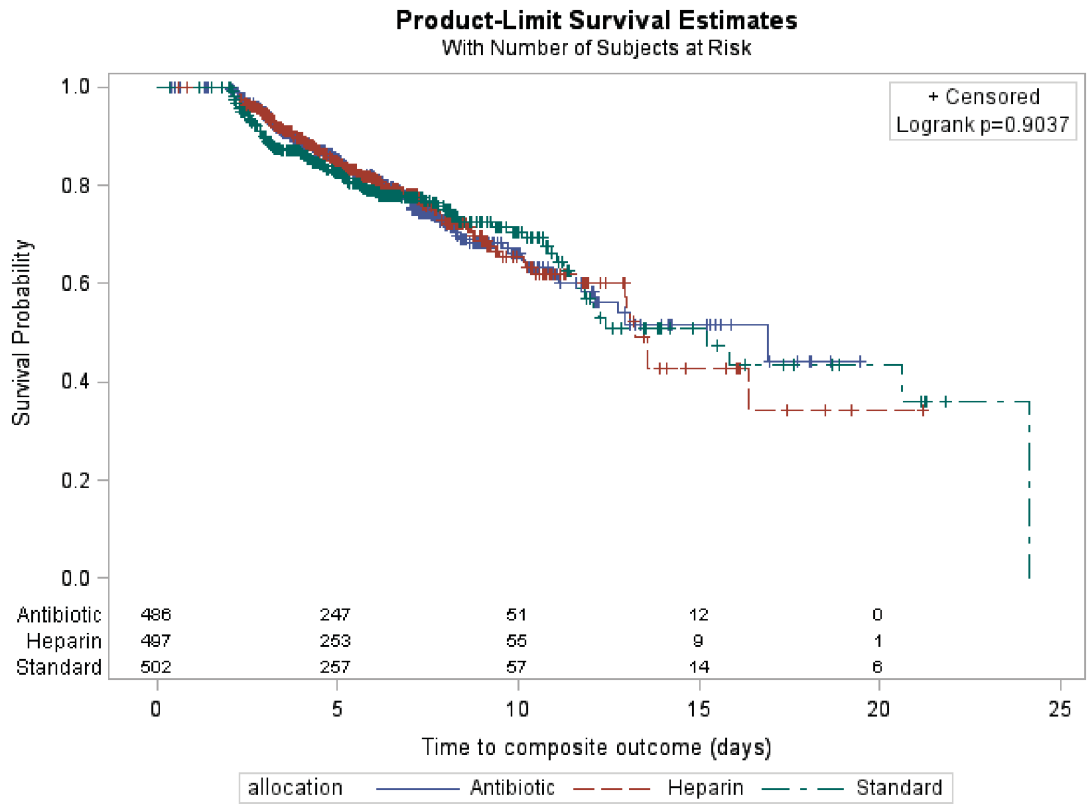


Table 35: Composite measure of clinically indicated blood stream infection

Treatment	Number randomised	Number experiencing a composite measure of clinically indicated blood stream infection											Total
		Primary outcome	Any of the clinical indicators of infection and (negative) blood culture taken and										
			High bacterial DNA load from a PCR positive result only	Change in antibiotic on same day or next day only	CVC removal for infection only	Primary outcome and removed for infection	Primary outcome and antibiotic change	Removed for infection and antibiotic change	PCR positive and antibiotic change	Primary outcome, removed for infection and antibiotic change	Removed for infection, PCR positive and antibiotic change	All 4 criteria	
Standard	502	2	2	79	6	1	8	7	1	6	0	1	113
Antibiotic or Heparin	983	4	2	135	19	0	12	24	1	7	0	1	205
Antibiotic	486	0	1	71	12	0	6	11	1	1	0	0	103
Heparin	497	4	1	64	7	0	6	13	0	6	0	1	102
Total	1485	6	4	214	25	1	20	31	2	13	0	2	318

Post hoc:
Combined versus Standard RR 0.93(95% CI:0.76, 1.15)
Antibiotic versus Standard RR 0.95 (95% CI:0.75, 1.20)
Heparin versus Standard RR 0.92 (95% CI:0.73, 1.17)
Antibiotic versus Heparin RR 1.03 (95% CI:0.81, 1.32)

3.5.5 A CVC related blood stream infection

Defined by:

a. the same isolate (species and antibiogram) from the CVC tip and from a blood culture sample taken from any site more than 48 hours after CVC insertion and within 48 hours following CVC removal;
b. differential positivity of the same isolate in blood cultures taken from multiple CVC lumens (i.e. not all positive or negative at the same sampling or the same skin commensal isolated from the same lumen but not all lumens on multiple occasions).
c. OR positive BSI AND CVC removed for infection
d. OR positive BSI AND CVC exit site infection

Table 36: CVC related blood stream infection

Treatment	Number randomised	Number experiencing a CVC related blood stream infection
Standard	502	12 (2.39)
Antibiotic or Heparin	983	13 (1.32)
Antibiotic	486	3 (0.62)
Heparin	497	10 (2.01)
Total	1485	25 (1.68)

Table 37: CVC related blood stream infection

Analysis	Treatment	Relative risk (95% confidence interval)	p-value
Primary	Antibiotic or Heparin combined versus Standard	0.55 (0.25, 1.21)	0.13
Secondary	Heparin versus Standard	0.84 (0.36, 1.96)	0.68
Secondary	Antibiotic versus Standard	0.25 (0.07, 0.90)	0.03
Secondary	Antibiotic versus Heparin	0.30 (0.08, 1.11)	0.09

3.2.3 Mortality by 30 days

Table 38: Mortality by 30 days (ITT)

Treatment	Number randomised	Number followed up for >30 days	Number followed up for <30 days	Unclear on length of follow up	Number of deaths by 30 days
Standard	502	102 (20.32)	397 (79.08)	3 (0.60)	41 (8.17)
Antibiotic or Heparin	983	171 (17.39)	808 (82.20)	4 (0.41)	65 (6.61)
Antibiotic	486	85 (17.49)	398 (81.89)	3 (0.62)	39 (8.02)
Heparin	497	86 (17.30)	410 (82.49)	1 (0.20)	26 (5.23)
Total	1485	273 (18.38)	1205 (81.14)	7 (0.47)	106 (7.14)

Table 39: Mortality by 30 days (ITT)

Analysis	Treatment	Relative risk (95% confidence interval)	p-value
Primary	Antibiotic or Heparin combined versus Standard	0.80 (0.53, 1.20)	0.27
Secondary	Heparin versus Standard	0.62 (0.37, 1.03)	0.06
Secondary	Antibiotic versus Standard	0.98 (0.62, 1.55)	0.93
Secondary	Antibiotic versus Heparin	1.58 (0.95, 2.64)	0.08

Table 40: Mortality by 30 days (ITT) – Updated to include ONS data

Treatment	Number randomised	Number of deaths by 30 days
Standard	502	42 (8.37)
Antibiotic or Heparin	983	67 (6.82)
Antibiotic	486	39 (8.02)
Heparin	497	28 (5.63)
Total	1485	109 (7.34)

Table 41: Mortality by 30 days (ITT) – Updated to include ONS data

Analysis	Treatment	Relative risk (95% confidence interval)	p-value
Primary	Antibiotic or Heparin combined versus Standard	0.80 (0.54, 1.20)	0.28
Secondary	Heparin versus Standard	0.65 (0.40, 1.07)	0.09
Secondary	Antibiotic versus Standard	0.96 (0.61, 1.51)	0.85
Secondary	Antibiotic versus Heparin	1.46 (0.88, 2.42)	0.14

Table 42: Mortality by 30 days (safety analysis)

Treatment	Number that were allocated intervention	Number where CVC insertion was attempted or successful	Number followed up for >30 days	Number followed up for <30 days	Unclear on length of follow up	Number of deaths by 30 days
Standard	539	533	109 (20.45)	422 (79.17)	2 (0.38)	44 (8.26)
Antibiotic or Heparin	946	930	161 (17.31)	765 (82.26)	4 (0.43)	59 (6.34)
Antibiotic	458	451	78 (17.29)	370 (82.04)	3 (0.67)	34 (7.54)
Heparin	488	479	83 (17.33)	395 (82.46)	1 (0.21)	25 (5.22)
Total	1485	1463	270 (18.46)	1187 (81.13)	6 (0.41)	103 (7.04)

Follow up based on 1463 patients where CVC insertion was attempted or successful. This analysis will be updated when HES data become available.

Table 43: Mortality by 30 days (safety analysis)

Analysis	Treatment	Relative risk (95% confidence interval)	p-value
Primary	Antibiotic or Heparin combined versus Standard	0.75 (0.50, 1.13)	0.17
Secondary	Heparin versus Standard	0.61 (0.37, 1.02)	0.06
Secondary	Antibiotic versus Standard	0.91 (0.57, 1.44)	0.68
Secondary	Antibiotic versus Heparin	1.48 (0.87, 2.52)	0.15

Table 44: Mortality by 30 days (safety analysis) – Updated to include ONS data

Treatment	Number that were allocated intervention	Number were CVC insertion was attempted or successful	Number of deaths by 30 days
Standard	539	533	45 (8.44)
Antibiotic or Heparin	946	930	64 (6.88)
Antibiotic	458	451	35 (7.76)
Heparin	488	479	29 (6.05)
Total	1485	1463	109 (7.45)

Table 45: Mortality by 30 days (safety analysis) – Updated to include ONS data

Analysis	Treatment	Relative risk (95% confidence interval)	p-value
Primary	Antibiotic or Heparin combined versus Standard	0.80 (0.54, 1.18)	0.26
Secondary	Heparin versus Standard	0.69 (0.43, 1.13)	0.14
Secondary	Antibiotic versus Standard	0.91 (0.57, 1.44)	0.68
Secondary	Antibiotic versus Heparin	1.31 (0.79, 2.18)	0.30

Table 46: Mortality by discharge (ITT – post hoc analysis)

Treatment	Number randomised	Number of deaths by discharge
Standard	502	59 (11.75)
Antibiotic or Heparin	983	89 (9.05)
Antibiotic	486	48 (9.88)
Heparin	497	41 (8.25)
Total	1485	148 (9.97)

Table 47: Mortality by discharge (ITT – post hoc analysis)

Analysis	Treatment	Relative risk (95% confidence interval)	p-value
Primary	Antibiotic or Heparin combined versus Standard	0.75 (0.53, 1.06)	0.10
Secondary	Heparin versus Standard	0.68 (0.44, 1.03)	0.07
Secondary	Antibiotic versus Standard	0.82 (0.55, 1.23)	0.34
Secondary	Antibiotic versus Heparin	1.22 (0.79, 1.89)	0.37

Table 48: Mortality by discharge (Safety – post hoc analysis)

Treatment	Number that were allocated intervention	Number were CVC insertion was attempted or successful	Number of deaths by discharge
Standard	539	533	64 (12.01)
Antibiotic or Heparin	946	930	81 (8.71)
Antibiotic	458	451	43 (9.53)
Heparin	488	479	38 (7.93)
Total	1485	1463	145 (9.91)

Table 49: Mortality by discharge (Safety – post hoc analysis)

Analysis	Treatment	Relative risk (95% confidence interval)	p-value
Primary	Antibiotic or Heparin combined versus Standard	0.70 (0.49, 0.99)	0.04
Secondary	Heparin versus Standard	0.63 (0.41, 0.96)	0.03
Secondary	Antibiotic versus Standard	0.77 (0.51, 1.16)	0.21
Secondary	Antibiotic versus Heparin	1.22 (0.77, 1.93)	0.39

3.5.7 Type of bacteria and fungi isolated from positive blood cultures

Bacteria and Fungi isolated from samples that meet the criteria for the primary outcome.

Table 50: Type of bacteria and fungi isolated from positive blood cultures

Category	Organism	Treatment				
		Standard	Antibiotic	Heparin	Antibiotic or Heparin	Total
Gram positive	Staphylococcus aureus	1	1	3	4	5
	Streptococcus spp.	1	0	0	0	1
	Meticillin-resistant Staphylococcus aureus	1	0	0	0	1
	Enterococcus spp.	2	0	2	2	4
	Enterococcus Faecium	0	0	1	1	1
	enterococcus faecalis	0	0	1	1	1
	Streptococcus mitis	1	0	1	1	2
	Streptococcus parasanguis & Streptococcus salivarius	0	1	0	1	1
Gram negative	Serratia marcescens	1	1	0	1	2
	Pseudomonas aeruginosa	2	1	1	2	4
	Gram negative bacillus	1	0	1	1	2
	Escherichia coli	0	1	0	1	1
	Escherichia coli And coliform	0	1	0	1	1
	Coliform	1	0	0	0	1
	Klebsiella spp.	0	0	1	1	1
	Cellulomas spp.	0	0	1	1	1
	Raoultella panticola and Enterobacter spp.	1	0	0	0	1
Gram positive and Gram negative	Enterococcus spp. And Klebsiella pneumonia	0	0	1	1	1
Fungi	Candida spp.	2	0	2	2	4
Fungi	Candida albicans	0	0	1	1	1
Skin bacteria and Gram positive	Coagulase-negative staphylococcus and Enterococcus spp.	1	0	0	0	1
Skin bacteria	Coagulase-negative staphylococcus	3	1	1	2	5
Total		18	7	17	24	42

Resistance to minocycline or rifampicin of blood culture or CVC tip isolates

Samples taken between randomisation and 48 hours after removal are included in this table. Testing for antibiotic resistance varied by centre. Only 12 (13 organisms) of the 42 children with the primary outcome had minocycline and rifampicin resistance reported using etest strips; 8/12 were resistant, in each case to both antibiotics (3/5 standard; 2/2 antibiotic; 3/5 heparin). Resistant organisms by trial arm are provided in **Table**.

Table 51: Resistance to minocycline or rifampicin of blood culture by CVC allocation

CVC allocation	Organism	E test result	
		Minocycline	Rifampicin
Standard	Colifom bacilli	Resistant	Resistant
	Enterococcus faecalis	Resistant	Resistant
	Serratia marcescens	Resistant	Resistant
	Staph aureus	Sensitive	Sensitive
	MRSA	Sensitive	Sensitive
Antibiotic	E.coli	Resistant	Resistant
	Staphylococcal species	Resistant	Resistant
Heparin	Klebsiella pneumoniae	Resistant	Resistant
	Klebsiella pneumoniae	Resistant	Resistant
	Staph aureus	Sensitive	Sensitive
	Coagulase negative staphylococci	Sensitive	Sensitive
	Enterococcus hirae and Coagulase negative staphylococci	Resistance Sensitive	Sensitive Resistant

Organisms resistant to Minocycline and Rifampicin

Standard

- Colifom bacilli
- Colifom bacilli
- Coag Neg Staph (Rifampicin only)
- Coag Neg Staph
- Enterococcus faecalis
- Coagulase (Rifampicin only)
- S. epi (Rifampicin only)
- Mixed coagulase negative Staphylococci (Rifampicin only)
- Enterococcus (minocycline only)
- S. viridans (minocycline only)
- Coagulase (Rifampicin only)
- P.aeruginosa (Rifampicin only)
- S.marcescens

Antibiotic

- Staph
- E. coli
- Enterococcus sp,Mixed coagulase negative Staphylococci (Rifampicin only)
- Mixed coagulase negative Staphylococci (Rifampicin only)
- Mixed coagulase negative Staphylococci,Enterococcus sp,Pseudomonas aeruginosa (Rifampicin only)
- Coag Neg Staph. 2 (Rifampicin only), Enterococcus (minocycline only)
- Enterococcus (minocycline only)
- Coag Neg Staph. (Rifampicin only)
- E.cloacae

Heparin

- Klebsiella pneumonia
- Enterococcus hirae (minocycline only), Enterococcus faecalis and CNS (Rifampicin only)
- K Pneumoniae & Ent Cloacae
- Coag Neg Staph (Rifampicin only)
- Coag Neg Staph (Rifampicin only)
- Pseudomonas aeruginosa
- Klebsiella spp
- Mixed coagulase negative Staphylococci (Rifampicin only)
- Coagulase negative Staphylococcus (minocycline only)
- Staphylococcus capitis (minocycline only)
- Enterococcus, P.aeruginosa, Coag Neg Staph. (Rifampicin only)

3.5.8 Unexplained thrombocytopenia after insertion of CVC- detected by routine laboratory monitoring

There were two occurrences of unexplained thrombocytopenia which were recorded as adverse events and are included in the adverse event table (Section 0).

3.5.9 Time to randomised CVC removal

Table 52: Time to randomised CVC removal

Analysis	Treatment	Number randomised	Number of participants with a successful CVC insertion	Hazard ratio (95% confidence interval)	p-value
Baseline comparator: standard					
-	Standard	502	481	-	-
Primary	Antibiotic or Heparin	983	929	1.04 (0.93, 1.16)	0.53
Secondary	Antibiotic	486	465	1.02 (0.90, 1.17)	0.67
Secondary	Heparin	497	464	1.05 (0.92, 1.19)	0.51
Baseline comparator: heparin					
Secondary	Antibiotic	486	465	0.99 (0.87, 1.13)	0.87

25 patients did not have a CVC removal date, of these, 16 had died and the line was left in and 9 were transferred. These dates were used in the analysis and patients were censored at these dates.

Table 53: Length of CVC insertion (post hoc)

Treatment	Number randomised	Number of participants with a successful CVC insertion	Length of CVC insertion in days, Median (IQR)
Standard	502	481	4.28 (2.30, 6.97)
Antibiotic or Heparin	983	929	4.25 (2.19, 6.97)
Antibiotic	486	465	4.31 (2.13, 7.0)
Heparin	497	464	4.20 (2.24, 6.97)

Figure 15: Time to CVC removal

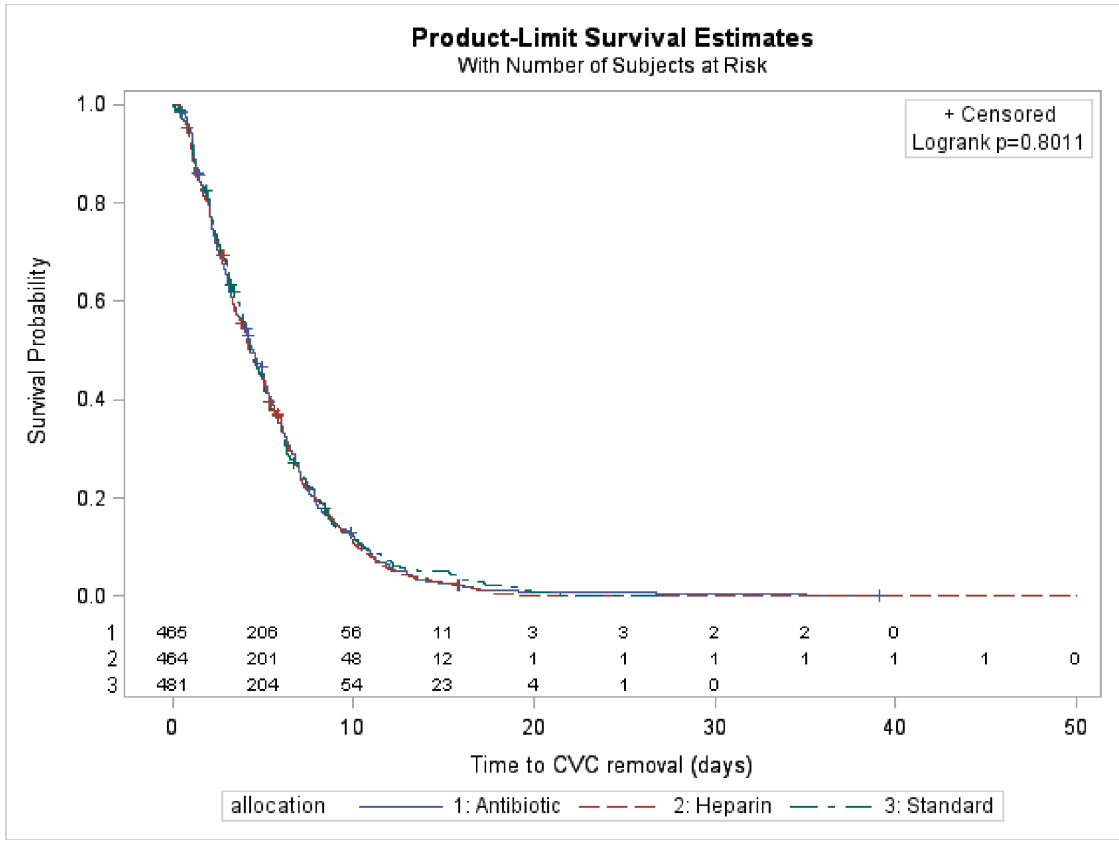
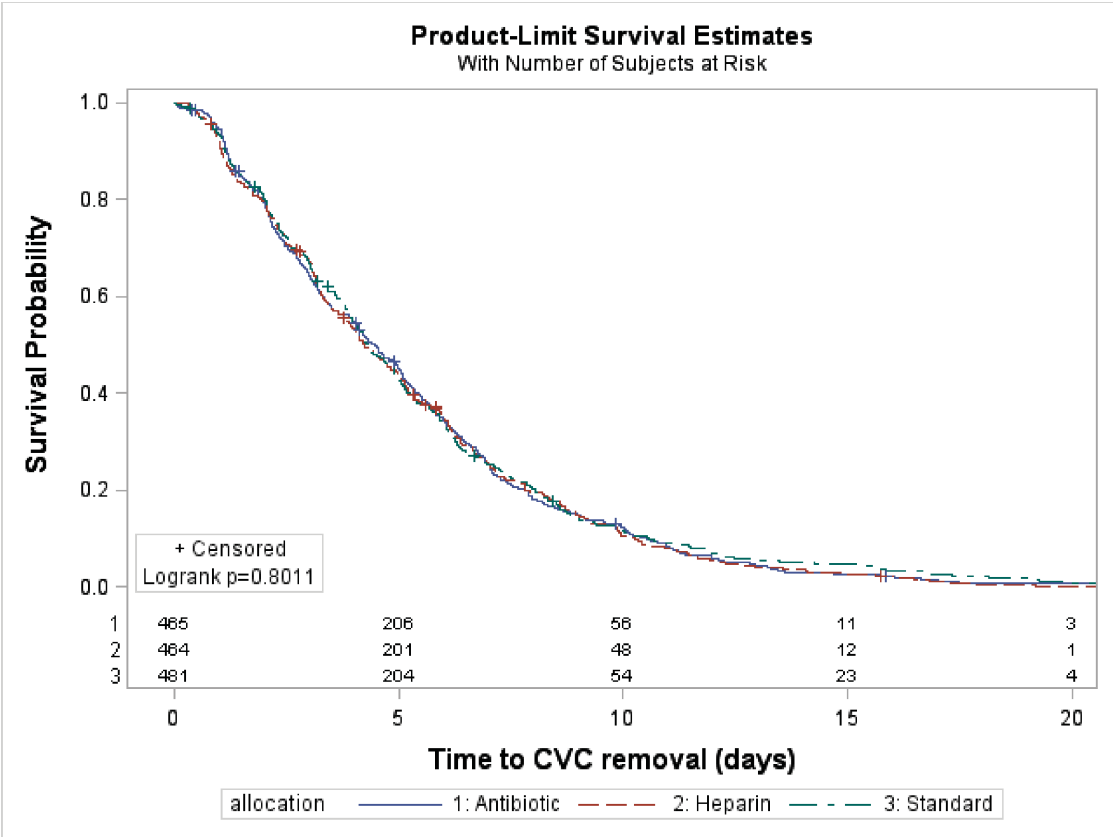


Figure 16: Time to CVC removal (x axis cut)



3.2.4 Length of stay requiring PICU/CICU/NICU

Table 54: Length of stay requiring PICU/CICU/NICU

Treatment	Number randomised	Number admitted to PICU/CICU/NICU	Number included in analysis	Length of stay requiring PICU/CICU/NICU in days, Median (IQR)	p-value
Baseline comparator: standard					
Standard	502	502	499	5.06 (2.78, 9.95)	-
Antibiotic or Heparin	983	980	976	4.71 (2.24, 9.07)	0.08
Antibiotic	486	485	482	4.43 (2.16, 9.31)	0.10
Heparin	497	495	494	4.88 (2.29, 8.92)	0.17
Baseline comparator: heparin					
Antibiotic	486	485	482	4.43 (2.16, 9.31)	0.80
Total	1485	1482	1475	4.90 (2.38, 9.24)	-

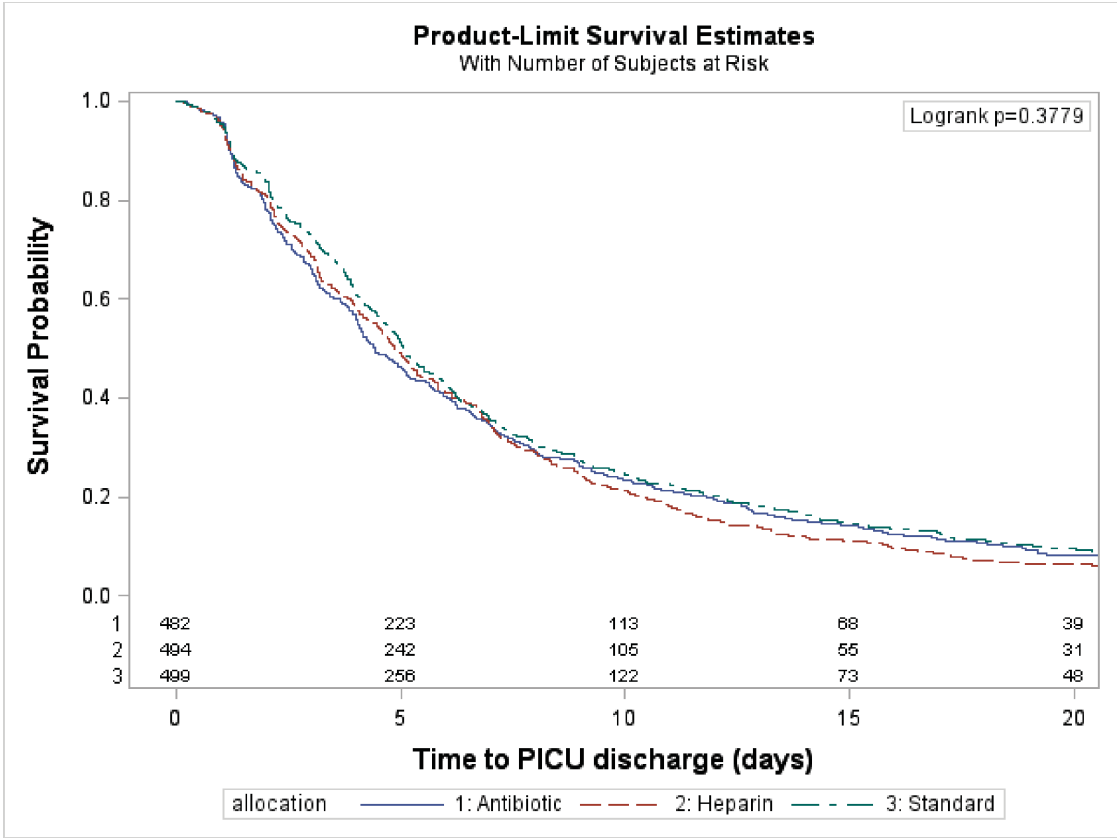
Three patients were not admitted to PICU/CICU/NICU (1 antibiotic and 1 heparin were admitted to theatre and a general pediatric ward, no information on the third patient). The date of transfer is not available for 7 patients (dates used instead of transfer date: CVC removal date for 4 patients and date on the progress log for 3 where CVC was not inserted: 3 standard, 3 antibiotic, 1 heparin). The admission date is missing or incorrect for three patients (2 standard, 1 heparin). The randomisation date has been used in this analysis.

Table 8: Time to PICU discharge (post hoc analysis)

Treatment	Hazard ratio (95% confidence interval)	p-value
Baseline comparator: standard		
Antibiotic or Heparin	1.08 (0.97, 1.20)	0.17
Antibiotic	1.07 (0.95, 1.22)	0.27
Heparin	1.08 (0.96, 1.23)	0.21
Baseline comparator: heparin		
Antibiotic	0.98 (0.86, 1.11)	0.73

N=1475 and no censoring involved.

Figure 17: Time to PICU discharge (post hoc analysis)



3.5.11 Total length of hospital stay for current episode (for up to 6 month post randomisation)

Table 56: Total length of hospital stay

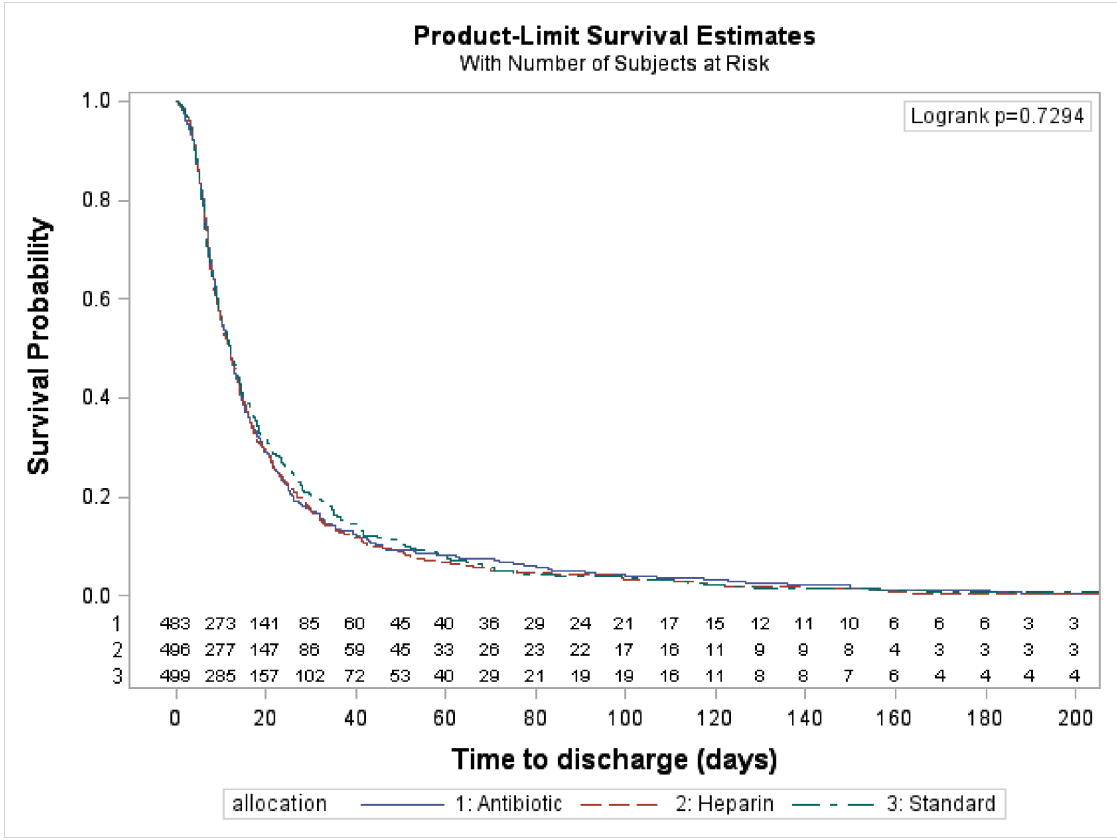
Treatment	Number randomised	Number included in analysis	Length of hospital stay in days, Median (IQR)	p-value
Baseline comparator: standard				
Standard	502	499	12.02 (6.37, 25.60)	-
Antibiotic or Heparin	983	979	12.03 (6.51, 22.54)	0.60
Antibiotic	486	483	12.03 (6.72, 22.68)	0.74
Heparin	497	496	12.05 (6.41, 22.45)	0.57
Baseline comparator: heparin				
Antibiotic	486	483	12.03 (6.72, 22.68)	0.83
Total	1485	1478	12.03 (6.44, 23.40)	-

1467 have time less than 6 months, 11 have time over 6 months, 7 have negative time as no transfer form and have been excluded from this analysis (4 have removal date, 3 not inserted).

Table 57: Time to discharge (post hoc analysis)

Treatment	Hazard ratio (95% confidence interval)	p-value
Baseline comparator: standard		
Antibiotic or Heparin	1.04 (0.93, 1.16)	0.47
Antibiotic	1.03 (0.91, 1.16)	0.68
Heparin	1.05 (0.93, 1.19)	0.42
Baseline comparator: heparin		
Antibiotic	0.98 (0.87, 1.11)	0.77

Figure 18: Time to discharge (post hoc analysis)



4 Plots and graphs

Plot number	Title	Section number of data to be included	Population	x-axis/y-axis
1	CONSORT 2010 Flow Diagram – Overall	1	ITT	-
2	CONSORT 2010 Flow Diagram – Prospective consent	1	ITT	-
3	CONSORT 2010 Flow Diagram – Deferred consent	1	ITT	-
4	Overall recruitment graph	3	-	-
5	Primary efficacy – Standard versus Antibiotic or Heparin: Time to first blood stream infection	4.5.1	ITT	Time to first blood stream infection (days) / Survival distribution function
6	Primary efficacy – Standard versus Antibiotic or Heparin: Time to first blood stream infection (y axis cut)	4.5.1	ITT	Time to first blood stream infection (days) / Survival distribution function
7	Time to first blood stream infection: standard versus impregnated, days 0-21	4.5.1	ITT	Time to first blood stream infection (days) / Survival distribution function
8	Time to first blood stream infection: standard versus impregnated, days 0-7	4.5.1	ITT	Time to first blood stream infection (days) / Survival distribution function
9	Sensitivity analysis – Standard versus Antibiotic or Heparin: Time to first blood stream infection	4.5.1	ITT	Time to first blood stream infection (days) / Survival distribution function
10	Sensitivity analysis – Standard versus Antibiotic or Heparin: Time to first blood stream infection (y axis cut)	4.5.1	ITT	Time to first blood stream infection (days) / Survival distribution

				function
11	Impregnated versus Standard Time to first blood stream infection – cumulative incidence plot	4.5.1	ITT	Time to first blood stream infection (days) / Survival distribution function
12	Standard versus Antibiotic or Heparin: Time to CVC thrombosis	4.5.3	ITT	Time to CVC thrombosis (days) / Survival distribution function
13	Standard versus Antibiotic or Heparin: Time to CVC thrombosis (y axis cut)	4.5.3	ITT	Time to CVC thrombosis (days) / Survival distribution function
14	Standard versus Antibiotic or Heparin: Time to a composite measure of clinically indicated blood stream infection based on the primary outcome or high bacterial DNA load or culture negative bloodstream infection based on clinical criteria	4.5.4	ITT	Time to composite outcome (days) / Survival distribution function
15	Standard versus Antibiotic or Heparin: Time to CVC removal	4.5.10	ITT	Time to CVC removal (days) / Survival distribution function
16	Time to CVC removal (x axis cut)	4.5.10	ITT	Time to CVC removal (days) / Survival distribution function
17	Standard versus Antibiotic or Heparin: Time to PICU discharge (post hoc analysis)	4.5.11	ITT	Time to PICU discharge (days) / Survival distribution function
18	Standard versus Antibiotic or Heparin: Time to discharge (post hoc analysis)	4.5.12	ITT	Time to discharge (days) / Survival distribution function
19	Flow of patients for the primary outcome	-	-	-

Approval and agreement

Statistical Analysis Report Version Number being approved:1.2

Trial Statistician

Name _____

Signed _____ Date _____

Senior Statistician or Head of Statistics

Name _____

Signed _____ Date _____

Chief Investigator

Name _____

Signed _____ Date _____

OR Electronic approval attached ☐

Figure 19: Flow of patients for the primary outcome