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Abstract

CATheter Infections in CHildren (CATCH): a randomised controlled trial and economic evaluation comparing impregnated and standard central venous catheters in children

Katie Harron,[1] Quen Mok,[2] Kerry Dwan,[3] Colin H Ridyard,[4] Tracy Moitt,[3] Michael Millar,[5] Padmanabhan Ramnarayan,[2] Shane M Tibby,[6] Berit Muller-Pebody,[7] Dyfrig A Hughes,[4] Carrol Gamble[3] and Ruth E Gilbert[1]*

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Background: Impregnated central venous catheters (CVCs) are recommended for adults to reduce bloodstream infection (BSI) but not for children.

Objective: To determine the effectiveness of impregnated compared with standard CVCs for reducing BSI in children admitted for intensive care.

Design: Multicentre randomised controlled trial, cost-effectiveness analysis from a NHS perspective and a generalisability analysis and cost impact analysis.

Setting: 14 English paediatric intensive care units (PICUs) in England.

Participants: Children aged < 16 years admitted to a PICU and expected to require a CVC for ≥ 3 days.

Interventions: Heparin-bonded, antibiotic-impregnated (rifampicin and minocycline) or standard polyurethane CVCs, allocated randomly (1 : 1 : 1). The intervention was blinded to all but inserting clinicians.

Main outcome measure: Time to first BSI sampled between 48 hours after randomisation and 48 hours after CVC removal. The following data were used in the trial: trial case report forms; hospital administrative data for 6 months pre and post randomisation; and national-linked PICU audit and laboratory data.

Results: In total, 1859 children were randomised, of whom 501 were randomised prospectively and 1358 were randomised as an emergency; of these, 984 subsequently provided deferred consent for follow-up. Clinical effectiveness – BSIs occurred in 3.59% (18/502) of children randomised to standard CVCs, 1.44% (7/486) of children randomised to antibiotic CVCs and 3.42% (17/497) of children randomised to heparin CVCs. Primary analyses comparing impregnated (antibiotic and heparin CVCs) with standard CVCs showed no effect of impregnated CVCs [hazard ratio (HR) 0.71, 95% confidence interval (CI) 0.37 to 1.34]. Secondary analyses showed that antibiotic CVCs were superior to standard CVCs (HR 0.43, 95% CI 0.20 to 0.96) but heparin CVCs were not (HR 1.04, 95% CI 0.53 to 2.03). Time to thrombosis, mortality by 30 days and minocycline/rifampicin resistance did not differ by CVC. Cost-effectiveness – heparin CVCs were not clinically effective and therefore were not cost-effective. The incremental cost of antibiotic CVCs compared with standard CVCs over a 6-month time horizon was £1160 (95% CI –£4743 to £6962), with an incremental cost-effectiveness ratio of £54,057 per BSI avoided. There was considerable uncertainty in costs: antibiotic CVCs had a probability of 0.35 of being dominant. Based on index hospital stay costs only, antibiotic CVCs were associated with a saving of £97,543 per BSI averted. The estimated value of health-care resources associated with each BSI was £10,975 (95% CI –£2801 to £24,751). Generalisability and cost-impact – the baseline risk of BSI in 2012 for PICUs in England was 4.58 (95% CI 4.42 to 4.74) per 1000 bed-days. An estimated 232 BSIs could have been averted in 2012 using antibiotic CVCs. The additional cost of purchasing antibiotic CVCs for all children who require them (£36 per CVC) would be less than the value of resources associated with managing BSIs in PICUs with standard BSI rates of > 1.2 per 1000 CVC-days.

Conclusions: The primary outcome did not differ between impregnated and standard CVCs. However, antibiotic-impregnated CVCs significantly reduced the risk of BSI compared with standard and heparin CVCs. Adoption of antibiotic-impregnated CVCs could be beneficial even for PICUs with low BSI rates, although uncertainty remains whether or not they represent value for money to the NHS. Limitations – inserting clinicians were not blinded to allocation and a lower than expected event rate meant that there was limited power for head-to-head comparisons of each type of impregnation. Future work – adoption of impregnated CVCs in PICUs should be considered and could be monitored through linkage of electronic health-care data and clinical data on CVC use with laboratory surveillance data on BSI.

Trial registration: ClinicalTrials.gov NCT01029717.

Funding: This project was funded by the NIHR Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 20, No. 18. See the NIHR Journals Library website for further project information.

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Glossary

Bundled Healthcare Resource Group Healthcare Resource Group referring to a patient pathway of care such as a ward stay.

Unbundled Healthcare Resource Group A high-cost or specialist service Healthcare Resource Group in addition to a patient pathway of care.

List of abbreviations

A&E	accident and emergency
AIC	Akaike information criterion
BIC	Bayesian information criterion
BSI	bloodstream infection
CEAC	cost-effectiveness acceptability curve
CHiP	Control of Hypoglycaemia in Paediatric Intensive Care
CI	confidence interval
CR-BSI	catheter-related bloodstream infection
CRF	case report form
CVC	central venous catheter
DNA	deoxyribonucleic acid
HDU	high-dependency unit
HES	Hospital Episode Statistics
HQIP	Healthcare Quality Improvement Partnership
HR	hazard ratio
HRG	Healthcare Resource Group
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
IDSMC	Independent Data and Safety Monitoring Committee
ln	natural logarithm
NCA	National Clinical Audit
NICU	neonatal intensive care unit
ONS	Office for National Statistics
PAS	Patient Administration System
PCR	polymerase chain reaction
PHE	Public Health England
PICANet	Paediatric Intensive Care Audit Network
PICU	paediatric intensive care unit
PIM2	Paediatric Index of Mortality
QALY	quality-adjusted life-year
RCT	randomised controlled trial
ROC	receiver operating characteristic
RR	relative risk
rRNA	ribosomal ribonucleic acid

Plain English summary

Children who are admitted to hospital for intensive care often need to have medicines given directly into their veins, through a small plastic tube called a central venous catheter (CVC). CVCs avoid the need for repeated injections, but their disadvantage is an increased risk of bloodstream infection (BSI), which can result in prolonged treatment and time in hospital.

In adults, CVCs coated with medicine to kill bacteria (antibiotics) or prevent clots (heparin) help reduce the risk of BSI. However, we do not know if coating the much narrower CVCs used for children would work in the same way. The only way to find out which type of CVC (standard non-coated, antibiotic coated or heparin coated) works best was to carry out a randomised controlled trial.

Children aged < 16 years who needed a CVC for intensive care treatment participated within 14 hospitals in England. Consent was provided for all participants in the trial. Each child had an equal chance of receiving one of the three CVC types.

Bloodstream infection occurred in 4% of children with standard CVCs and 2% of those with impregnated CVCs. Rates of BSI were lowest in the antibiotic CVC group (1%) but these children had slightly higher health-care costs for the 6 months after trial participation. Although doubt remains whether or not antibiotic CVCs would result in cost savings for the NHS in England, our results suggest that using antibiotic CVCs could help reduce BSI rates for children in intensive care.

Scientific summary

Background

Bloodstream infection (BSI) is an important cause of adverse clinical outcomes and costs to the NHS in the UK. Paediatric intensive care units (PICUs) have one of the highest reported rates of hospital-acquired BSI of any clinical specialty.

Nine systematic reviews, two cost-effectiveness analyses and at least 48 randomised controlled trials (RCTs; 11,586 patients) have demonstrated substantial benefits of impregnated central venous catheters (CVCs) for reducing catheter-related BSI (CR-BSI) in adults. The best evidence to date shows that antibiotic-impregnated or heparin-bonded CVCs are most effective, producing similar reductions in risk of CR-BSI (70–80%). However, there is a lack of child-specific evidence for impregnated CVCs and they are not recommended for children in UK or US guidance. We compared both types of impregnated CVC (antibiotic and heparin) with standard CVCs to determine their effectiveness in children. Secondary analyses were conducted to investigate the effectiveness of each type of impregnation.

Objectives

1. To determine the clinical effectiveness of impregnated compared with standard CVCs for reducing BSI in children admitted for intensive care.
2. To determine the cost-effectiveness of impregnated CVCs from a NHS perspective.
3. To inform purchasing by assessing the generalisability and the cost impact of adopting impregnated CVCs for all children who need them.

Randomised controlled trial: clinical effectiveness

Methods

We conducted a three-arm RCT to compare the effect of heparin-bonded, antibiotic-impregnated and standard polyurethane CVCs on BSI in children requiring intensive care. The RCT is registered at ClinicalTrials.gov (reference number NCT01029717).

Design, study population and intervention

Children admitted to 14 PICUs in England between December 2010 and November 2012 were randomised to heparin-bonded, antibiotic-impregnated or standard CVCs manufactured by Cook Medical Incorporated (Bloomington, IN, USA).

Children aged < 16 years were eligible if they were admitted or being prepared for admission to a participating PICU and were expected to require a CVC for ≥ 3 days. For children admitted to a PICU following elective surgery, we sought prospective parental consent during preoperative assessment. For children who required a CVC as an emergency, we sought parental consent after randomisation and stabilisation (deferred consent) to avoid delaying treatment.

Randomisation and masking

Children were randomised at the bedside or in theatre immediately before CVC insertion. Randomisation sequences were computer generated in a 1 : 1 : 1 ratio, stratified by method of consent, site and envelope storage location within the site.

The clinician responsible for inserting the CVC was not blinded to CVC allocation (because of different colour strips for impregnated CVCs) but, as the CVCs looked identical whilst in situ, allocation was concealed from patients, their parents and PICU personnel responsible for their care.

Comparisons and end points

The primary analysis in the trial compared antibiotic or heparin CVCs with standard CVCs. Secondary analyses consisted of three-way comparisons between standard, antibiotic and heparin CVCs.

The primary outcome was time to the first BSI based on blood cultures taken between 48 hours after randomisation and 48 hours after CVC removal (or prior to death). All blood culture samples were clinically indicated, defined by recorded evidence of infection (one or more of temperature instability, change in inotrope requirements, haemodynamic instability or poor perfusion) or removal of the CVC because of suspected infection. Any positive blood culture was accepted for a non-skin organism, but for skin organisms two or more positive cultures within 48 hours of each other were required.

Secondary BSI-related outcomes were:

1. CR-BSI: the same organisms cultured from blood and the CVC tip between 48 hours after randomisation and 48 hours after CVC removal; or differential positivity of cultures from multiple CVC lumens on two or more occasions; or BSI and exit site infection or BSI and CVC removed for suspected infection
2. rate of BSI per 1000 CVC-days: number of BSIs between randomisation and CVC removal
3. time to a composite measure of BSI consisting of the primary outcome or a negative blood culture combined with a positive 16S polymerase chain reaction result for bacterial ribosomal ribonucleic acid, removal of the CVC because of suspected infection or a start of antibiotics or change in type of antibiotics on the same or next day.

We also compared time to CVC removal, CVC thrombosis, PICU discharge, hospital discharge and mortality within 30 days. Safety analyses compared CVC-related adverse events, mortality and antibiotic resistance to minocycline (> 0.5 µg/ml) or rifampicin (> 1.0 µg/ml).

Sample size

In total, 1200 children were required to achieve 80% power to detect a relative risk of 0.5 at a 5% level of significance, based on an estimated BSI rate of 10% and allowing for 5% loss to follow-up.

Statistical analysis

Outcome data were analysed according to the intention-to-treat principle. Safety analyses included the subset of children for whom CVC insertion was attempted, grouped by CVC actually received or, if insertion was not successful, the type used in the attempt.

The statistical analysis plan was developed prior to analysis and is available in *Appendix 1*. Time-to-event outcomes were analysed using Kaplan–Meier curves and the log-rank test. Cox regression was used to adjust the primary analysis of time to BSI for the use of prospective or deferred consent and suspected infection at baseline. Poisson regression was used to analyse the rate of BSI. All analyses were conducted using SAS software (version 9.2; SAS Institute Inc., Cary, NC, USA).

Results

Study population

In total, 1859 children were randomised, of whom 501 children were randomised prospectively and 1358 were randomised as an emergency; of those randomised as an emergency, 984 subsequently provided deferred consent for follow-up.

Baseline characteristics

In total, 58% of the children were aged < 12 months at admission and 33% were aged < 3 months. One-third had surgery prior to admission to the PICU and half had cardiovascular problems as their primary diagnosis at admission. CVC insertion took place in theatre for 437 out of 493 (89%) in the prospective consent (elective) group but in only 34 out of 917 (4%) of the deferred consent (emergency) group.

End points

Primary outcome

Bloodstream infection was recorded for 42 children [standard group 18/502 (3.59%); antibiotic group 7/486 (1.44%); heparin group 17/497 (3.42%)]. There was no significant difference in the primary outcome of time to first BSI comparing any impregnated CVC with the standard CVC [hazard ratio (HR) 0.71, 95% confidence interval (CI) 0.37 to 1.34; $p = 0.29$]. BSI risk was reduced for antibiotic compared with standard CVCs (HR 0.43, 95% CI 0.20 to 0.96; $p = 0.04$) and for antibiotic compared with heparin CVCs (HR 0.42, 95% CI 0.19 to 0.93; $p = 0.03$) but not for heparin compared with standard CVCs (HR 1.04, 95% CI 0.53 to 2.03; $p = 0.90$). The risk difference in BSI comparing any impregnated CVC with standard CVCs was –1.14 (95% CI –3.04 to 0.75) (heparin vs. standard CVCs –0.17, 95% CI –2.45 to 2.12; antibiotic vs. standard CVCs –2.15, 95% CI –4.09 to –0.20; antibiotic vs. heparin CVCs –1.98, 95% CI –3.90 to –0.06).

Secondary outcomes

For CR-BSI there was no significant difference between any impregnated CVC and standard CVCs ($p = 0.13$) but the risk of CR-BSI was significantly lower for antibiotic CVCs than for standard CVCs ($p = 0.03$). There was no significant difference in the risk of CR-BSI between antibiotic CVCs and heparin CVCs ($p = 0.09$) or between heparin CVCs and standard CVCs ($p = 0.68$). The BSI rate per 1000 CVC-days was lowest in the antibiotic group. The composite measure of BSI or culture-negative infection did not differ by CVC. No other secondary outcomes were associated with type of CVC.

Safety

No CVC-related adverse events (31 events) or mortality (148 events) were attributed to type of CVC. Only 12 out of 42 children with the primary outcome BSI had minocycline and rifampicin resistance reported using Etest® strips [see www.biomerieux-diagnostics.com/etest (accessed 20 November 2015)]; 8 out of 12 were resistant, in each case to both antibiotics (3/5 standard group; 2/2 antibiotic group; 3/5 heparin group).

Cost-effectiveness

We determined the cost-effectiveness of type of CVC per BSI averted using individual-level data on hospital use captured for study participants.

Methods

Resource use and costs

We assumed that inpatient hospital costs would capture the main cost drivers and the greatest proportion of direct medical costs. The time horizon aimed to include costs associated with managing BSI and was defined as 6 months post randomisation (or death).

Resource use was evaluated using:

i. trial case report forms (CRFs) recording admission and transfer/discharge dates for PICUs, high-dependency units (HDUs) and paediatric wards within participating hospitals
ii. Hospital Episode Statistics (HES) containing Healthcare Resource Groups (HRGs) for admissions to NHS hospitals in England

iii. the Paediatric Intensive Care Audit Network (PICANet), containing length of stay and HRGs for HDU and PICU admissions
iv. Hospital Patient Administration Systems (PASs) of participating hospitals, capturing length of stay and HRGs in PICUs and wards

The primary cost analysis was based on CRFs and PASs, with 6-month costs taken from HES, supplemented with HDU and intensive care unit (ICU) data from PICANet. Total individual patient costs were calculated from the sum of their bundled (ward) HRGs coded from the national tariff and their unbundled (ICU/HDU) codes taken from the national schedule.

Incremental analysis

The cost-effectiveness of each type of CVC was evaluated by (1) ranking type of CVC according to decreasing effectiveness and (2) eliminating ineffective or dominated interventions (those that are less effective but more costly than others). The incremental cost-effectiveness ratio (ICER) for the remaining CVCs was calculated as the difference in adjusted total costs divided by the difference in risk of BSI.

A cost-effectiveness acceptability curve was generated, using bootstrapping to account for the joint uncertainty in costs and outcomes.

Value of health-care resources associated with bloodstream infection

The value of health-care resources associated with BSI was estimated using generalised linear regression to model total post-randomisation costs, adjusting for significant prespecified baseline variables.

All analyses were performed using Stata version 10 (StataCorp LP, College Station, TX, USA).

Results

The average post-randomisation stay in the PICU was 10.5 days (95% CI 9.2 to 11.9 days) for standard CVCs, 10.8 days (95% CI 9.3 to 12.5 days) for antibiotic CVCs and 9.9 days (95% CI 8.6 to 11.4 days) for heparin CVCs. There were no significant differences in length of stay by CVC in PICUs ($p = 0.61$), HDUs ($p = 0.73$) or wards ($p = 0.54$).

The mean 6-month unadjusted costs per patient were £44,503 (95% CI £40,554 to £48,776) for standard CVCs, £45,663 (95% CI £41,600 to £49,994) for antibiotic CVCs and £42,065 (95% CI £38,220 to £46,246) for heparin CVCs. Costs were not significantly different by CVC type ($p = 0.46$). The 6-month incremental costs were positive (£1160, 95% CI –£4743 to £6962) for antibiotic CVCs and negative (–£2439, 95% CI –£8164 to £3359) for heparin CVCs compared with standard CVCs.

As heparin CVCs were shown not to be clinically effective compared with standard CVCs, the incremental analysis was limited to antibiotic CVCs compared with standard CVCs. The ICER for the 6-month time frame was £54,057 per BSI averted for antibiotic CVCs compared with standard CVCs, with a probability of 0.35 of antibiotic CVCs being cost saving or dominant.

Costs were very sensitive to the time horizon of analysis. Limiting the analysis to costs associated with the index stay only resulted in antibiotic CVCs dominating standard CVCs with a saving of £97,543 per BSI averted. The costs of antibiotic and standard CVCs became equal when the time horizon of analysis was 122 days.

The value of health-care resources associated with each BSI averted (adjusted cost per BSI estimated from the regression analysis) was £10,975 (95% CI –£2801 to £24,751).

Generalisability and cost impact

The generalisability and cost impact analysis aimed to inform the adoption of antibiotic CVCs for all children who need them during admission to PICUs in England.

Methods

Generalisability analysis

We determined the generalisability of the CATCH findings to the baseline risk of BSI in children with a CVC across PICUs in England. Rates of BSI in all children requiring a CVC in the PICU were estimated from a data linkage study using detailed information from PICANet and national laboratory surveillance data co-ordinated by Public Health England. Rates of BSI per 1000 bed-days were modelled using multilevel Poisson regression, adjusting for significant patient risk factors ($p < 0.05$).

Cost impact analysis

The baseline risk was defined as the number of BSIs per 1000 bed-days in children using standard CVCs in English PICUs during 2012. We estimated the BSI rate using antibiotic CVCs by applying the rate ratio from the trial to the baseline BSI rate, assuming that, irrespective of baseline risk, the relative effect of impregnated CVCs would be the same in all children. The number of BSIs averted using antibiotic CVCs was estimated by applying the respective BSI rates to the total number of bed-days in 2012. We estimated the number of admissions requiring CVCs from responses to a PICU survey on the percentage of emergency and elective admissions receiving CVCs in 2012.

We determined the budget and cost impacts of adopting antibiotic-impregnated CVCs by synthesising the following evidence: (1) the estimated risk of BSI using standard CVCs (derived from the data linkage study); (2) the number of BSIs potentially averted by using antibiotic-impregnated CVCs (based on the relative treatment effect in the trial); (3) the additional £36 associated with purchasing each impregnated CVC for all children expected to require one (numbers of CVCs based on PICU survey data); and (4) the value of the health-care resources associated with each averted BSI (from the trial economic analysis).

Results

The additional cost of purchasing antibiotic CVCs for all children in English PICUs in 2012 corresponded to an estimated budget impact of £317,916 (8831 CVCs). Based on 2012 BSI rates, the cost impact of managing BSIs occuring with standard compared with antibiotic CVCs in all PICUs was £2.5M per year (95% uncertainty interval –£66,544 to £5,557,451). The BSI rate using standard CVCs was 4.58 (95% CI 4.42 to 4.74) per 1000 estimated CVC-days in 2012. Applying the rate ratio gave an estimated 232 BSIs averted using antibiotic CVCs. The additional costs of antibiotic CVCs would be less than the value of resources associated with managing BSIs in PICUs with a standard BSI rate > 1.2 per 1000 CVC-days.

Conclusions

Implications for practice

The primary outcome, time to BSI, did not differ between impregnated and standard CVCs. Secondary analyses showed that antibiotic CVCs reduced the risk of BSI compared with standard or heparin CVCs. Therefore, use of impregnated CVCs for children admitted to PICUs could result in clinically important reductions in BSI rates. The benefits of antibiotic-impregnated CVCs apply even for PICUs with low BSI rates, although uncertainty remains whether or not they are cost-effective for the NHS.

Recommendations for research

- Adoption of impregnated CVCs in PICUs should be considered. Implementation strategies could be monitored through linkage of electronic health-care data and clinical data on CVC use with laboratory surveillance data on BSI.
- Further trials comparing antibiotic-impregnated or heparin-bonded CVCs with standard CVCs for children or adults in intensive care are not recommended.
- The NHS should work with industry to evaluate different types of impregnation for specific patient groups (e.g. neonates or patients requiring long-term CVCs).
- Use of linked administrative data should be considered for future trials to determine the generalisability of interventions when the event rate is likely to change substantially over the lifetime of the trial and to monitor implementation of effective interventions.

Trial registration

This trial is registered as ClinicalTrials.gov NCT01029717.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Introduction

Use in practice

Central venous catheters (CVCs) are widely used for patients of all ages who need intensive or high-dependency care to provide venous access for resuscitation, drug delivery, intravenous feeding, monitoring and blood sampling. CVCs are associated with an increased risk of bloodstream infection (BSI), which is hypothesised to be caused by organisms tracking along the CVC from the skin or from the external parts of the CVC to colonise the CVC tubing and tip.[1–5]

Risk factors for BSI include catheter dwell time, the frequency of 'breaching' the line for medication or sampling, multiple compared with single-lumen CVCs and infusion of lipid solution as part of parenteral nutrition.[6–10] The risk of BSI is reduced by strict adherence to aseptic procedures during CVC insertion and whenever the CVC is breached.[11–13] To help ensure staff follow aseptic procedures, audited checklists (called CVC bundles) have been introduced in several countries.[14–19]

In this report we focus on children who need a CVC as part of their intensive care treatment. Paediatric intensive care units (PICUs) have one of the highest reported rates of hospital-acquired BSI of any clinical specialty[20–23] and BSI is an important cause of adverse clinical outcome and health-care costs in critically ill children.[21,24–26] We estimate that approximately 60% of the 16,000 children admitted to 23 PICUs each year in England require insertion of a CVC as part of their acute care.[27] We do not include CVCs used for very preterm babies in neonatal intensive care or long-term CVCs, which are widely used to administer medication or parenteral nutrition for children with conditions such as cancer, cystic fibrosis, renal failure or short gut syndrome.

Rationale

Central venous catheter impregnation with anti-infective substances has been used for over 25 years.[28] Recent systematic review evidence from 48 randomised controlled trials (RCTs) and cost-effectiveness analyses including 11,586 patients demonstrated substantial benefits of impregnated compared with standard CVCs for catheter-related BSI (CR-BSI).[2,5,28–30] One of the most recent systematic reviews included a meta-analysis of direct and indirect comparisons of different types of impregnated and standard CVCs.[28] Heparin-bonded or antibiotic-impregnated CVCs were found to be the most effective options, being associated with similar reductions (70–80%) in the risk of CR-BSI. Heparin bonding acts by reducing thrombus formation and bacterial adherence to thrombi, but the bonding agent, benzalkonium chloride, also has anti-infective properties. Antibiotic-impregnated CVCs act by preventing biofilm formation and thereby prevent bacterial colonisation.

Despite the large number of RCTs and the substantial reductions seen in the risk of BSI in adults, impregnated CVCs have not been recommended for children in US or UK guidelines and their use in UK practice has been limited.[3,15,31,32] A recent survey showed that impregnated CVCs had been adopted for some or all children by less than half of British PICUs surveyed.[32] Lack of implementation in PICUs relates to (1) gaps in the evidence relating to children; (2) concerns about the quality of previous trials; and (3) uncertainty about the generalisability of RCT findings to settings where improved infection control strategies have been associated with steep declines in BSI rates.[33,34]

In children, there is a lack of evidence on the most effective type of CVC and on the expected effect size. According to the network meta-analysis by Wang *et al.*,[28] heparin-bonded and antibiotic-impregnated CVCs are the most effective options, having similar effects compared with standard CVCs. However, there is a lack of evidence on which type of CVCs would be most effective as there have been no adequately powered, direct 'head-to-head' comparisons of these options.[28] In the UK, the additional costs of heparin-bonded or antibiotic-impregnated CVCs are similar and so the decision on which type to adopt depends on their relative benefits and adverse effects. Only one of the eight RCTs comparing antibiotic-impregnated CVCs with standard CVCs ($n = 2073$ patients) included children and this study was terminated early because of a lower than expected event rate.[35–42] As CVCs for children are much narrower than adult CVCs and the risk of thrombus formation, bacterial adhesion and infection is much higher, it is hypothesised that the relative effect of antibiotic-impregnated compared with standard CVCs may differ in children and adults. Evidence is stronger for the benefits of heparin-bonded CVCs, as two of the three RCTs comparing heparin-bonded CVCs with standard CVCs ($n = 472$) included children.[43–45]

Several systematic reviews have raised concerns that the poor quality of previous studies means that the benefits of impregnated CVCs may have been overestimated.[5,29,46,47] First, few trials have reported good concealment of treatment allocation or blinding of clinicians to the intervention and many have failed to account for losses or withdrawals, all factors that could lead to overestimation of the effect.[5,29] Second, all previous trials relied on CR-BSI as the primary outcome measure, which requires positive cultures from the blood and catheter tip. This measure is highly susceptible to bias, as the tip can be easily contaminated during removal and residual antibiotic in the catheter tip may inhibit culture in the laboratory. Aside from the potential biases in measuring CR-BSI, impregnated CVCs may impact on all BSIs after CVC insertion, not just on CR-BSIs, and on the risks of mortality, complications and increased length of stay associated with BSI.

Few trials have determined the effect of impregnated CVCs on all BSIs in PICU in the context of ongoing reductions in BSI rates associated with the introduction of CVC care bundles.[11,13,14,33,48] Neither of the two trials of heparin-bonded CVCs in children and few of the trials of antibiotic-impregnated CVCs in adults have been conducted in the context of these strenuous efforts to reduce BSI. It is not known whether or not the relatively large reductions in relative risk (RR) and absolute risk seen in trials predating CVC care bundles would be sustained in PICUs where rates of infection have already been reduced by improved CVC care.[34] Even though a UK cost-effectiveness analysis estimated that impregnated CVCs would be cost-effective given baseline rates of CR-BSI as low as 0.2%,[29] there remains the question of whether or not the relative effect of impregnation would be less given improved catheter care.

Risks and benefits

Prevention of BSI is undoubtedly a clinically important outcome. Although evidence on attributable mortality varies, BSI is clearly associated with a longer stay in hospital and more intensive support.[20,21,24–26,49] For children in intensive care, CR-BSI has been associated with an additional 9–21 days' stay in hospital (6.5–15 days in PICU).[24–26] In adults, the additional acute health-care costs attributable to a BSI are an estimated £9148 per patient and could range between £2500 and £71,000.[29] The few studies of the costs of BSIs in PICU patients have found a difference of US$33,039–39,219 in PICU direct costs between infected and uninfected patients.[21,25] However, quantifying the effects of BSI are complicated by the time-dependent exposure: BSI increases hospital stay; increased length of stay is a risk factor for BSI.[50] Estimates of the attributable length of stay are subject to this time-dependent bias, leading to potentially overestimated BSI costs in previous studies.[51,52] On the other hand, no study has taken into account the long-term costs associated with BSI in children.

Potential adverse effects of CVCs are rare. Heparin bonding could theoretically trigger an allergic response, leading to heparin-induced thrombocytopenia, although no case has been reported to the manufacturers. Antibiotic impregnation could potentially lead to antibiotic resistance, although a systematic review showed no increased risk of resistant organisms isolated from blood cultures.[1]

Overview of aims and research questions

From a policy perspective, there could potentially be significant gains in terms of children's health and health-care costs across the NHS if impregnated CVCs could be confirmed to substantially reduce rates of BSI. We compared both types of impregnated CVC previously shown to be most effective (antibiotic and heparin) with standard CVCs to determine the effectiveness of CVC impregnation in children. Secondary analyses were conducted to evaluate the effectiveness of each type of CVC.

We aimed to inform NHS policy regarding impregnated CVCs for intensive care of children by undertaking a large pragmatic RCT to determine (1) clinical effectiveness; (2) cost-effectiveness of impregnated compared with standard CVCs; and (3) the generalisability and cost impact of adopting impregnated CVCs for all children who need them.

The main objectives and data sources for the three parts of the study were:

1. Clinical effectiveness:

    - to determine the effectiveness of impregnated compared with standard CVCs for reducing BSI in children admitted to intensive care
    - to determine which type of CVC is most effective, based on three-way comparisons of measures of BSI, mortality and adverse events
    - data source: clinical outcomes captured on case report forms (CRFs) in the RCT.

2. Cost-effectiveness:

    - to determine the cost-effectiveness of impregnated compared with standard CVCs for reducing BSIs, based on incremental acute health-care costs per BSI avoided
    - data sources: clinical outcomes captured on CRFs in the RCT and records of health-care use captured by linkage of RCT data with hospital administrative data.

3. Generalisability and cost impact:

    - to estimate the net cost impact to NHS PICUs given a policy to adopt impregnated CVCs for all children who need them
    - data sources: national data on PICU admissions (Paediatric Intensive Care Audit Network; PICANet) linked with infection surveillance data collated by Public Health England (PHE) and costs from the economic evaluation.

The specific objectives, methods and results for each of the three phases of the study are reported in *Chapters 2–5*. We discuss the implications of our findings for policy and recommendations for future research in *Chapter 6*.

Chapter 2 Clinical effectiveness: methods

Trial design

We conducted a parallel, three-arm RCT.[53] Children admitted to 14 PICUs in England between December 2010 and November 2012 were randomised to CVCs impregnated with antibiotics or heparin or to standard CVCs in a ratio of 1 : 1 : 1.

Setting and participants

Children aged < 16 years were eligible if they were admitted to a participating PICU or were being prepared for PICU admission by an emergency retrieval team and were expected to require a CVC for ≥ 3 days. Children who had already participated in the trial were ineligible.

Interventions

We used polyurethane CVCs manufactured by Cook Medical Incorporated (Bloomington, IN, USA). Sizes used were French gauge 4 (double lumen), 5 or 7 (triple lumen). Both types of impregnation involve internal and external surfaces. Cook Medical Inc. reports a concentration of 503 μg/cm of minocycline and 480 μg/cm of rifampicin for their antibiotic-impregnated CVC, which reduces biofilm formation.[54] Heparin bonding reduces thrombus and thereby biofilm formation and uses benzalkonium chloride as an anti-infective bonding agent.[5,55]

Randomisation and consent

For children admitted to the PICU following elective surgery, we sought prospective parental consent during preoperative assessment. Randomisation took place in theatre or in the anaesthetic room prior to entry into theatre. For children who required a CVC as an emergency, we sought parental consent after randomisation and stabilisation (deferred consent) to avoid delaying treatment, which was usually within 48 hours of randomisation. Children who required a CVC as part of their emergency care or resuscitation were randomised at the bedside in the PICU or at another hospital, where they were randomised by the PICU retrieval team prior to transfer to the PICU. Further details are given in the protocol [see www.nets.nihr.ac.uk/projects/hta/081347 (accessed 20 November 2015)].

At randomisation, the clinician or research nurse opened a pressure-sealed, sequentially numbered opaque envelope containing the CVC allocation. Randomisation sequences were computer generated by an independent statistician in random blocks of three and six, stratified by method of consent (deferred or prospective), site and envelope storage location within the site to facilitate easy access to envelopes (e.g. for insertion in theatre and in the PICU).

Parents consented to the use of their child's data for the trial, to follow-up using routinely recorded clinical data and to 0.5 ml of blood being collected whenever a blood culture was clinically required.[56] Samples were sent for polymerase chain reaction (PCR) testing for 16S ribosomal ribonucleic acid (rRNA) of bacterial ribosome protein to detect bacterial infection.

We also sought consent to link data from PICANet[57] to the child's study data to categorise the primary reason for admission and the Paediatric Index of Mortality (PIM2)[58] score on admission and to link to administrative hospital data for the economic analyses and death registration data from the Office for National Statistics (ONS) [see www.ons.gov.uk (accessed 4 January 2016)] to determine mortality after discharge from the PICU.

Blinding

Central venous catheter allocation was not blinded to the clinician responsible for inserting the CVC (because of the different colour strips for antibiotic and heparin CVCs) but, as the CVCs looked identical whilst in situ, allocation was concealed from patients, their parents and PICU personnel responsible for their care. Labels identifying the type of CVC were held securely in a locked drawer in case unblinding was required. Participant inclusion in analyses and occurrence of outcome events were established prior to release of the randomisation sequence for analysis.

Comparisons and outcomes

The primary analysis for the trial compared antibiotic or heparin CVCs with standard CVCs. Secondary analyses compared antibiotic with standard CVCs, heparin with standard CVCs and antibiotic with heparin CVCs.

The primary outcome was time to the first BSI based on blood cultures taken between 48 hours after randomisation and 48 hours after CVC removal (or prior to death). We used time to event analyses as the risk of BSI increases the longer a CVC is in place. This time interval was intended to capture BSIs related to the type of CVC. All blood culture samples were clinically indicated, defined by removal of the CVC because of suspected infection or other recorded evidence of infection (one or more of temperature instability, change in inotrope requirements, haemodynamic instability or poor perfusion). Any positive blood culture was accepted for a non-skin organism, but for skin organisms two or more positive cultures of the same organism were required within 48 hours of each other. A clinical committee reviewed all primary outcomes involving positive cultures.

We conducted a sensitivity analysis for potentially missing microbiology data by assuming that children with a record of clinical indication but no sample taken in the primary outcome time window did actually experience the primary outcome.

The main secondary outcomes were:

- CR-BSI: based on the same organisms cultured from blood and the CVC tip between 48 hours after randomisation and 48 hours after CVC removal; or differential positivity of cultures from multiple CVC lumens on two or more occasions; or BSI and exit site infection or BSI and CVC removed for suspected infection
- rate of BSI per 1000 CVC-days, based on one or more BSI between randomisation and CVC removal
- time to a composite measure of BSI consisting of the primary outcome or a negative blood culture combined with (1) a positive 16S PCR result for bacterial rRNA; (2) removal of the CVC because of suspected infection; or (3) start of antibiotics or change in type of antibiotics on the same or next day.

Other secondary outcomes were:

- time to CVC thrombosis (defined by two episodes within 5 days of each other of difficulty flushing the CVC or drawing back blood from the CVC, one episode of swollen limb, CVC removal because of thrombosis or a positive ultrasound indicating thrombosis)
- time to CVC removal
- mortality by 30 days
- length of PICU admission
- length of hospital stay (up to 6 months post randomisation)
- type of bacteria or fungi isolated from the BSI included in the primary outcome.

CVC-related outcomes evaluated in the safety analyses were:

- CVC-related adverse events (unexplained thrombocytopenia after insertion of the CVC, exit site infection, hypersensitivity, trauma from line insertion, line displacement, line breakage/mechanical problem/manufacture complication)
- mortality recorded up until hospital discharge
- antibiotic resistance to minocycline (> 0.5 µg/ml) or rifampicin (> 1.0 µg/ml).

Antibiotic resistance outcomes were based on Etest® strips [see www.biomerieux-diagnostics.com/etest (accessed 20 November 2015)] applied to organisms isolated from the BSI included in the primary outcome. Incomplete laboratory testing and reporting prevented analysis of resistance in cultures from the CVC tip (as specified in the protocol).

Sample size

We based the sample size calculation for the primary analysis on a RR. We assumed that detection of a RR of 0.5 in patients with a baseline risk of 10% would change policy. We assumed that the RR would remain relatively constant across baseline risks whereas the absolute risk difference would be more variable. A total of 1200 children were required in a 2 : 1 ratio (impregnated : standard) to achieve 80% power to detect a RR of 0.5 at a 5% level of significance, based on an estimated BSI rate of 10% and allowing for 5% loss to follow-up. A lower than expected BSI rate of 5% would have 62% power to detect a RR of 0.5 or 80% power for a RR of 0.32.

The Independent Data and Safety Monitoring Committee (IDSMC) recommended continuation of the study after (1) reviewing the first 209 children; (2) an interim analysis of 650 children using the Peto–Haybittle stopping rule for the primary outcome; and (3) recruitment had reached the original target of 1200 pre schedule in June 2012, before exhausting available funding (see *Acknowledgements*, *Trial Oversight Committees* and *Table 23*).

Statistical methods

Outcome data were analysed according to the intention-to-treat principle, meaning that children who were consented and randomised were analysed according to the type of CVC randomised, regardless of whether or not CVC insertion was attempted or the type of CVC received. Safety analyses included the subset of children for whom CVC insertion was attempted, grouped by CVC actually received.

The statistical analysis plan was developed prior to analysis and is available in *Appendix 1*. A 5% level of statistical significance and 95% confidence intervals (CIs) were used throughout. Absolute risk differences were calculated for proportions. Time-to-event outcomes were analysed using Kaplan–Meier curves and the log-rank test. Cox regression was used to adjust the primary analysis of time to BSI for the use of prospective or deferred consent and suspected infection at baseline. Poisson regression was used to analyse the secondary outcome of rate of BSIs (defined as the total number of BSIs per 1000 CVC-days occurring between randomisation and CVC removal). All analyses were conducted using SAS software version 9.3 (SAS Institute Inc., Cary, NC, USA).

Post hoc analyses evaluated competing risks from death or time to first BSI, using cumulative incidence curves. We applied Gray's test to detect whether or not there was a difference between impregnated and standard CVCs for the primary outcome.[59] This analysis was conducted using R statistical software (The R Foundation for Statistical Computing, Vienna, Austria).

Study oversight and role of funders

The Research Ethics Committee for South West England approved the study protocol. The manufacturer Cook supplied CVCs to participating units at a 20% discounted price. Neither the manufacturer nor the funder (the National Institute for Health Research) had any role in the design of the study, the collection or interpretation of the data or the reporting of the results. The CATCH trial is registered with ClinicalTrials.gov (NCT01029717). The protocol is available at www.nets.nihr.ac.uk/projects/hta/081347 (accessed 20 November 2015) and the statistical analysis plan is provided in *Appendix 1*.

Chapter 3 Clinical effectiveness: results

Study population

In total, 1859 children were randomised, of whom 501 children were randomised prospectively and 1358 were randomised as an emergency. Of those randomised as an emergency, 984 subsequently provided deferred consent for inclusion in the analyses (*Figure 1*; see *Appendix 2*, *Figures 11* and *12* for participant flow by emergency/elective randomisation). Reasons for non-consent in the deferred consent group included not approached [$n = 180$ (48%), mainly because of transfer to a non-participating unit or early discharge from the PICU], no response [$n = 17$ (4.5%)] or consent refused [$n = 177$ (47%)]. Detailed reasons for non-consent are reported elsewhere.[60] Numbers enrolled by site and by month are provided in *Appendix 2* (see *Table 24* and *Figure 13*).

Comparison of interventions

The intention-to-treat sample included 1485 children, of whom 1345 children received the allocated CVC. Threats to validity because of protocol deviations are provided in *Appendix 2* (see *Table 26*). Very few children had a clinical indication but no blood culture taken in the primary outcome time window (see *Figure 1*). Timings of samples for positive BSIs included in the primary and secondary outcomes are provided in *Table 1*.

Baseline characteristics

Table 2 shows that baseline characteristics were similar between the randomised groups. Over half (58%) of children were aged < 12 months at admission, with one-third aged < 3 months. One-third of children had surgery prior to admission to the PICU and half of all children randomised had cardiovascular problems as their primary diagnosis at admission.

During follow-up

Table 3 provides details of the CVC insertion and characteristics at 48 hours post randomisation. CVC insertion took place in the operating room for 437 out of 493 (89%) in the prospective consent (elective) group, but in only 34 out of 917 (4%) of the deferred consent (emergency) group.

Table 4 shows the number of arterial, peripheral and CVC samples taken by trial arm. Overall, 3583 blood samples were taken and 1216 out of 1485 (81.9%) of children had a sample taken. Sampling was similar by trial arm and site (see *Appendix 2*, *Table 25*).

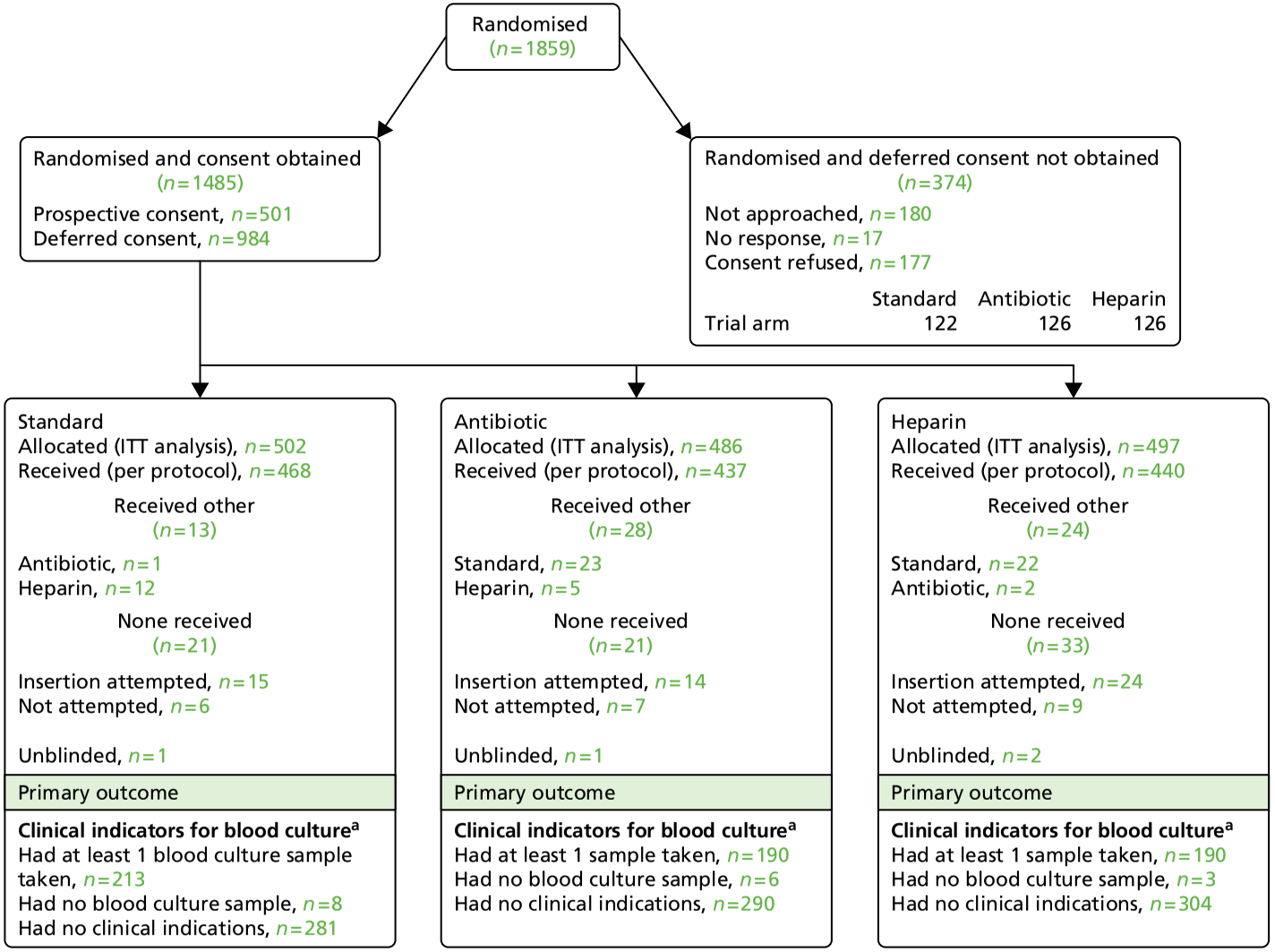

FIGURE 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram for all trial participants. a, Based on clinically indicated blood culture sample taken ≥48 hours after randomisation and <48 hours after CVC removal. ITT, intention to treat.

TABLE 1 Numbers of children included in the primary outcome, the rate of BSI and the rate of CR-BSI according to time since randomisation

Randomisation	48 hours after randomisation to CVC removal	48 hours after CVC removal
	Primary outcome of BSI	
	$n = 40$	$n = 2$
Rate of BSI per 1000 CVC-days		
$n = 10$	$n = 40$	
	CR-BSI	
	$n = 24$	$n = 1$

Shading indicates time window for outcome measure.

TABLE 2 Baseline characteristics and clinical condition before randomisation

	Standard		Antibiotic		Heparin	
Variable	*n*[a]	%	*n*[a]	%	*n*[a]	%
Patient characteristics	***502***	***100***	***486***	***100***	***497***	***100***
Emergency (deferred consent)	333	66.3	320	65.8	331	66.6
Elective (prospective consent)	169	33.7	166	34.2	166	33.4
Male	285	56.8	291	59.9	277	55.7
Age						
< 3 months	159	31.7	159	32.7	175	35.2
3–12 months	129	25.7	123	25.3	116	23.3
1–10 years	174	34.7	154	31.7	174	35.0
11+ years	40	8.0	50	10.3	32	6.4
Weight at admission						
< 3 kg	41	8.2	38	7.8	56	11.3
3–10 kg	278	55.4	280	57.6	273	54.9
> 10 kg	183	36.5	166	34.2	168	33.8
Missing	0	0.0	2	0.4	0	0.0
Admitted for surgery	174	34.7	171	35.2	181	36.4
PICU assessment (from linked PICANet data)	***479***	***95.4***	***456***	***93.8***	***473***	***95.2***
Primary reason for admission						
Cardiovascular	235	49.1	233	51.1	250	52.9
Endocrine/metabolic	30	6.3	34	7.5	30	6.3
Infection	39	8.1	30	6.6	31	6.6
Cancer	9	1.9	6	1.3	8	1.7
Respiratory	102	21.3	86	18.9	84	17.8
Neurological	22	4.6	31	6.8	29	6.1
Trauma	18	3.8	10	2.2	18	3.8
Other	24	5.0	26	5.7	22	4.7
Unknown	0	0.0	0	0.0	1	0.2

continued

TABLE 2 Baseline characteristics and clinical condition before randomisation (*continued*)

Variable	Standard		Antibiotic		Heparin	
	n[a]	%	*n*[a]	%	*n*[a]	%
PIM2						
< 1%	54	11.3	48	10.5	48	10.1
1 to < 5%	264	55.1	236	51.8	247	52.2
5 to < 15%	116	24.2	123	27.0	119	25.2
15 to < 30%	34	7.1	31	6.8	39	8.2
30%+	11	2.3	18	3.9	20	4.2
Clinical condition at randomisation	***502***	***100.0***	***486***	***100.0***	***497***	***100.0***
< 72 hours before randomisation						
Other CVC in situ	95	18.9	91	18.7	83	16.7
Anticoagulants received	50	10.0	59	12.1	61	12.3
Antibiotics received	286	57.0	276	56.8	284	57.1
Positive blood culture	40	8.0	25	5.1	36	7.2
At randomisation						
Infection suspected	214	42.6	181	37.2	199	40.0
Immunocompromised	44	8.8	31	6.4	29	5.8

a *n* = number of participants by randomised CVC.

TABLE 3 Details of the intervention and characteristics at 48 hours post randomisation

Variable	Standard		Antibiotic		Heparin	
	n[a]	%	*n*[a]	%	*n*[a]	%
CVC details (inserted CVCs)	***481***	***95.8***	***465***	***95.7***	***464***	***93.4***
Deferred consent, CVC inserted	314	65.3	301	64.7	302	65.1
Inserted at same hospital						
ICU	276	57.4	264	56.8	259	55.8
Theatre	5	1.0	4	0.9	7	1.5
Other	2	0.4	3	0.6	1	0.2
Inserted at other hospital[b]						
ICU	5	1.0	6	1.3	3	0.6
Theatre	3	0.6	8	1.7	7	1.5
Other	23	4.8	16	3.4	23	5.0
Missing	0	0.0	0	0.0	2	0.4
Prospective consent, CVC inserted	167	34.7	164	35.3	162	34.9
Inserted at same hospital						
ICU	15	3.1	23	4.9	16	3.4
Theatre	152	31.6	141	30.3	144	31.0
Other	0	0.0	0	0.0	1	0.2
Missing	0	0.0	0	0.0	1	0.2

TABLE 3 Details of the intervention and characteristics at 48 hours post randomisation (*continued*)

Variable	Standard		Antibiotic		Heparin	
	n[a]	%	*n*[a]	%	*n*[a]	%
Size of line						
4	28	5.8	45	9.7	39	8.4
5	421	87.5	384	82.6	391	84.3
7	21	4.4	23	4.9	18	3.9
Missing	11	2.3	13	2.8	16	3.4
Triple-lumen CVC	450	93.6	421	90.5	422	90.9
CVC inserted into femoral vein	253	52.6	217	46.7	235	50.6
48 hours post randomisation	***502***	***100.0***	***486***	***100.0***	***497***	***100.0***
Number of devices in situ						
< 4	160	31.9	169	34.8	185	37.2
≥ 4	340	67.7	311	64.0	311	62.6
Missing	2	0.4	6	1.2	1	0.2
Presence of an intrabody cavity device[c]						
Yes	404	80.5	381	78.4	380	76.5
No	96	19.1	100	20.6	116	23.3
Missing	2	0.4	5	1.0	1	0.2

ICU, intensive care unit.
a *n* = number of participants by randomised CVC.
b CVCs were inserted by the retrieval team prior to transfer to the PICU.
c Endotracheal tube, tracheotomy tube, intracranial pressure monitor, chest drain or peritoneal dialysis catheter.

TABLE 4 Samples taken in the primary outcome time window

Sample	Standard (*n* = 502)		Antibiotic (*n* = 486)		Heparin (*n* = 497)	
	n randomised[a]/ *n* samples[b]	%	*n* randomised[a]/ *n* samples[b]	%	*n* randomised[a]/ *n* samples[b]	%
Samples clinically indicated and in the primary outcome time window	213/328	42.4	190/269	39.1	190/326	38.2
Type of sample						
Arterial	49/55	9.8	39/44	8.0	41/55	8.2
Peripheral	19/22	3.8	32/33	6.6	35/39	7.0
CVC	161/226	32.1	129/167	26.5	136/208	27.4

a *n* randomised = number of participants by randomised CVC.
b Columns do not sum to total as sample types recorded as 'other' or that were missing are excluded.

Primary outcome

The number of blood samples contributing to the primary outcome is shown in *Appendix 2* (see *Figure 14*). Blood cultures were taken between 48 hours after randomisation and CVC removal for 40% of those randomised (593/1485; see *Figure 1*). BSI was recorded for 42 children [standard 18/502 (3.6%); antibiotic 7/486 (1.4%); heparin 17/497 (3.4%)]. Gram-positive organisms accounted for the majority of BSIs (*Table 5*).

Figure 2 shows the Kaplan–Meier curve for the primary outcome of time to first BSI. There was no significant difference in time to first BSI when comparing any impregnated CVC (antibiotic or heparin) with standard CVCs (*Table 6*). However, the risk of BSI was significantly lower for antibiotic compared with standard CVCs [hazard ratio (HR) 0.43, 95% CI 0.20 to 0.96] and for antibiotic compared with heparin CVCs (HR 0.42, 95% CI 0.19 to 0.93). The direction of these results was robust to the sensitivity analysis (see *Appendix 2*, *Table 27*). Regression analysis showed no significant effect of prespecified variables (type of consent and suspected infection at randomisation) and the effect of type of CVC was similar after adjusting for these variables (*Table 7*).

Competing risk analysis using Gray's test indicated no difference between the treatments for either competing risk (*p*-values of $p = 0.29$ for BSI and $p = 0.89$ for death; *Table 8*).

TABLE 5 Primary outcome (absolute measures) and type of organism isolated, according to CVC allocation

	Standard ($n = 502$)		Antibiotic ($n = 486$)		Heparin ($n = 497$)	
Outcome	*n*[a]	%	*n*[a]	%	*n*[a]	%
BSI	18	3.6	7	1.4	17	3.4
Median time to first BSI in days (IQR)	7.5	(4.5–11.2)	6.9	(6.0–8.0)	4.2	(3.1–8.4)
Organism type						
Non-skin	15[b]	2.99	6	1.23	16	3.22
Skin	3	0.60	1	0.21	1	0.20
Organism group[c]						
Gram positive[d]	10	1.99	3	0.62	10	2.01
Gram negative	6	1.20	4	0.82	5	1.01
Candida	2	0.40	0	0.00	3	0.60

IQR, interquartile range.
a *n* number of participants by randomised CVC unless otherwise stated.
b Includes one mixed BSI pathogen and skin organism.
c Subtotals add to more than the total in the heparin group because of multiple types of organisms isolated on the same occasion in some patients.
d Includes skin bacteria.

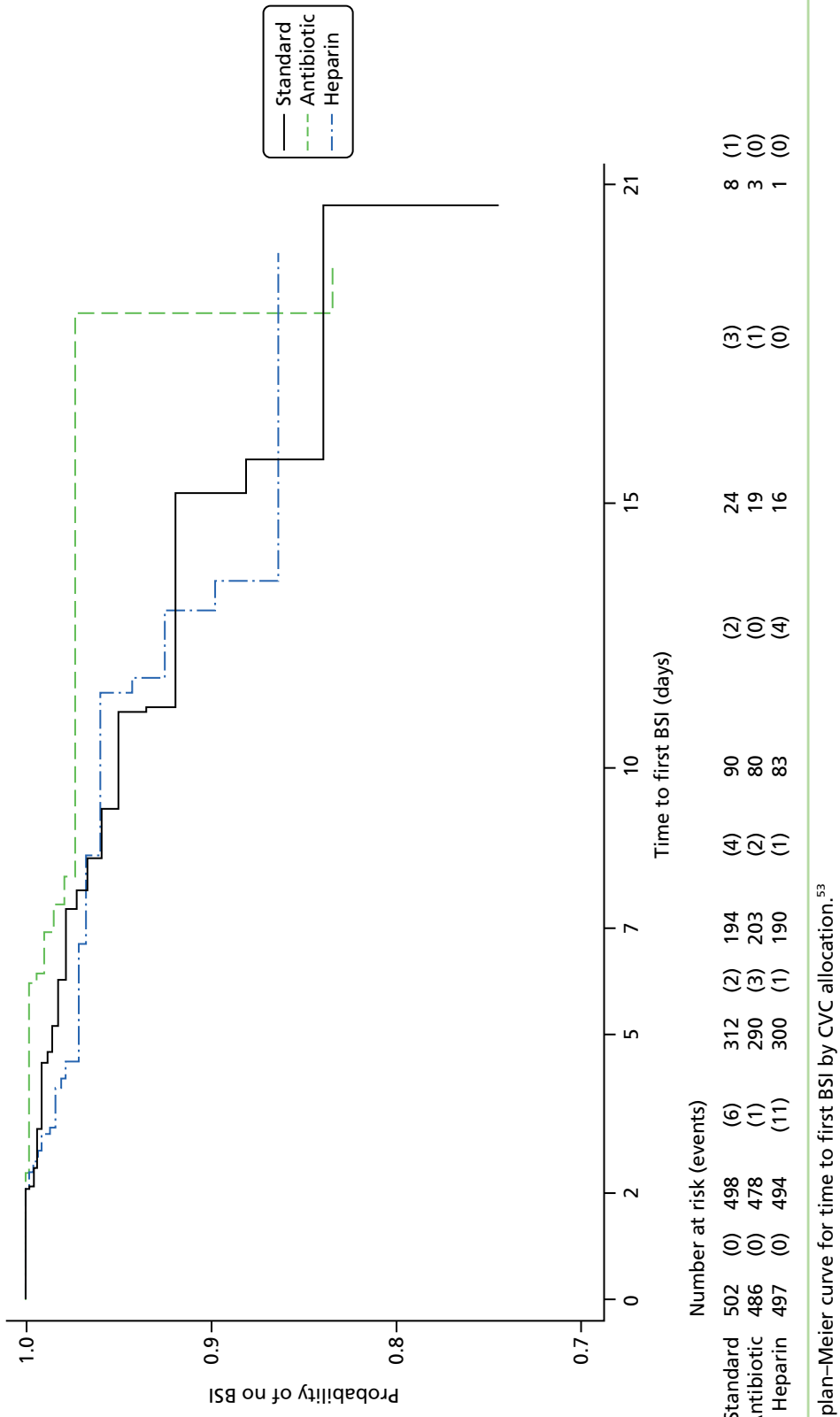

FIGURE 2 Kaplan–Meier curve for time to first BSI by CVC allocation.[53]

TABLE 6 Risk difference for first BSI and HR for time to first BSI according to CVC allocation

Analysis	Comparison	Risk difference (95% CI)	HR (95% CI)	*p*-value
Primary	Any impregnated ($n = 983$) vs. standard ($n = 502$) CVC	–1.14 (–3.04 to 0.75)	0.71 (0.37 to 1.34)	0.29
Secondary	Antibiotic ($n = 486$) vs. standard ($n = 502$) CVC	–2.15 (–4.09 to –0.20)	**0.43 (0.20 to 0.96)**	0.04
	Heparin ($n = 497$) vs. standard ($n = 502$) CVC	–0.17 (–2.45 to 2.12)	1.04 (0.53 to 2.03)	0.90
	Antibiotic ($n = 486$) vs. heparin ($n = 497$) CVC	–1.98 (–3.90 to –0.06)	**0.42 (0.19 to 0.93)**	0.03

Bold indicates differences that are significant at the 5% level.

TABLE 7 Regression results for the primary outcome

Analysis	Variable (*n* with outcome)	Comparator (*n* with outcome)	HR[a] (95% CI)	*p*-value
Primary	Antibiotic or heparin CVC (24)	Standard CVC (18)	0.71 (0.38 to 1.33)	0.29
	Deferred consent[b] (30)	Prospective consent[b] (12)	0.87 (0.40 to 1.90)	0.73
	Suspected infection(18)	No suspected infection (24)	0.69 (0.33 to 1.42)	0.31
Secondary	Antibiotic CVC (7)	Standard CVC (18)	**0.40 (0.17 to 0.96)**	0.04
	Heparin CVC (17)	Standard CVC (18)	1.05 (0.54 to 2.05)	0.89
	Deferred consent[b] (30)	Prospective consent[b] (12)	0.87 (0.40 to 1.90)	0.35
	Suspected infection (18)	No suspected infection (24)	0.68 (0.33 to 1.40)	0.30
Secondary	Antibiotic CVC (7)	Heparin CVC (17)	**0.39 (0.16 to 0.95)**	0.04
	Deferred consent[b] (30)	Prospective consent[b] (12)	0.85 (0.30 to 2.45)	0.76
	Suspected infection (18)	No suspected infection (24)	0.99 (0.40 to 2.43)	0.98

a HRs at $p < 0.05$ are in bold.
b Participants with prospective consent were admitted electively and participants with deferred consent were admitted as an emergency.

TABLE 8 Competing risk analysis for primary outcome of time to first BSI

Outcome	HR (95% CI)	Gray's test *p*-value
Time to first BSI (hours)	0.71 (0.39 to 1.31)	0.29
Time to death (hours)	1.08 (0.63 to 1.85)	0.89

Secondary outcomes

No children had more than one BSI whilst the trial CVC was in situ. The relationship between BSI outcomes and time since randomisation is shown in *Table 1*.

Overall, 25 (1.7%) children experienced a CR-BSI (*Table 9*). There was no significant difference between any impregnated CVC and standard CVCs ($p = 0.13$), but the risk of CR-BSI was significantly lower for antibiotic than for standard CVCs ($p = 0.03$). There was no significant difference between antibiotic and heparin CVCs ($p = 0.09$) or between heparin and standard CVCs ($p = 0.68$).

The rate of BSI per 1000 CVC-days did not differ in the primary comparison between any impregnated and standard CVCs (see *Table 9*). However, the rate of BSI was significantly lower for antibiotic compared with standard ($p = 0.04$) and heparin ($p = 0.03$; *Table 10*) CVCs. There was no significant difference in the rate of BSI between heparin and standard CVCs ($p = 0.85$).

A change in antibiotics on the same day as a negative blood culture or the next day made the largest contribution to the composite measure of BSI (see *Appendix 2*, *Table 28*). Overall, 317 (21%) children experienced the composite measure of BSI and this outcome did not differ by CVC type (see *Table 10*).

There was no difference in any other secondary outcome by CVC allocation (see *Table 10*). The types of bacteria and fungi isolated from positive blood cultures are provided in *Appendix 2* (see *Table 29*).

TABLE 9 Secondary outcomes (absolute measures) by CVC allocation

	Standard ($n = 502$)		Antibiotic ($n = 486$)		Heparin ($n = 497$)	
Outcome	n[a]	%	n[a]	%	n[a]	%
CR-BSI	12	2.4	3	0.6	10	2.0
Rate of BSI per 1000 CVC-days [number of BSIs/(number of days at risk/1000 days)] (95% CI)	8.2 [21/2.547]	(4.7 to 11.8)	3.3 [8/2.418]	(1.0 to 5.6)	8.8 [21/2.391]	(5.0 to 12.6)
Composite measure of BSI	112	22.3	103	21.2	102	20.5
CVC thrombosis	125	24.9	126	25.9	105	21.1
Median time to CVC removal in days (IQR)	4.28	(2.3–7.0)	4.3	(2.1–7.0)	4.20	(2.2–7.0)
Mortality by 30 days	42	8.4	39	8.0	28	5.6
Median time to PICU discharge in days (IQR)	5.1	(2.8–10.0)	4.4	(2.2–9.3)	4.9	(2.3–8.9)
Median time to hospital discharge in days (IQR)	12.0	(6.4–25.6)	12.0	(6.7–22.7)	12.1	(6.4–22.5)

IQR, interquartile range.
a n = number of participants by randomised CVC who experienced the outcome.

TABLE 10 Risk difference and/or HRs for secondary outcomes according to CVC allocation

	Any impregnated vs. standard CVCs (primary analysis)			Antibiotic vs. standard CVCs (secondary analysis)			Heparin vs. standard CVCs (secondary analysis)			Antibiotic vs. heparin CVCs (secondary analysis)		
Outcome	Risk difference (95% CI)	HR[a] (95% CI)	*p*-value	Risk difference (95% CI)	HR[a] (95% CI)	*p*-value	Risk difference (95% CI)	HR[a] (95% CI)	*p*-value	Risk difference (95% CI)	HR[a] (95% CI)	*p*-value
CR-BSI	–1.07 (–2.58 to 0.45)	0.55[b] (0.25 to 1.21)	0.13	–1.77 (–3.28 to -0.27)	**0.25[b] (0.07 to 0.90)**	0.03	–0.38 (–2.20 to 1.44)	0.84[b] (0.36 to 1.96)	0.68	–1.39 (–2.81 to 0.02)	0.30[b] (0.08 to 1.11)	0.09
Rate of BSI per 1000 CVC-days	–2.21 (–6.36 to 1.94)	0.73[b] (0.40 to 1.34)	0.31	–4.94 (–9.14 to -0.73)	**0.40[b] (0.17 to 0.97)**	0.04	0.55 (–4.60 to 5.70)	1.07[b] (0.55 to 2.06)	0.85	–5.49 (–9.89 to –1.08)	**0.38[b] (0.16 to 0.89)**	0.03
Composite measure of BSI	–1.46 (–5.90 to 2.98)	0.95 (0.75 to 1.20)	0.65	–1.12 (–6.26 to 4.03)	0.94 (0.72 to 1.23)	0.67	–1.79 (–6.87 to 3.30)	0.95 (0.73 to 1.25)	0.73	0.67 (–4.41 to 5.75)	0.99 (0.75 to 1.30)	0.93
CVC thrombosis	–1.40 (–6.02 to 3.22)	0.98 (0.79 to 1.22)	0.88	1.03 (–4.40 to 6.46)	1.09 (0.85 to 1.40)	0.49	–3.77 (–8.99 to 1.44)	0.88 (0.68 to 1.14)	0.34	4.80 (–0.50 to 10.10)	1.24 (0.96 to 1.60)	0.11
CVC removal		1.04 (0.93 to 1.16)	0.53		1.02 (0.90 to 1.17)	0.67		1.05 (0.92 to 1.19)	0.51		0.99 (0.87 to 1.13)	0.87
Mortality by 30 days	0.80 (0.54 to 1.20)			0.96 (0.61 to 1.51)			0.65 (0.40 to 1.07)			1.46 (0.88 to 2.42)		0.14
Time to PICU discharge		1.08 (0.97 to 1.20)	0.17		1.07 (0.95 to 1.22)	0.27		1.08 (0.96 to 1.23)	0.21		0.98 (0.86 to 1.11)	0.73
Time to hospital discharge		1.04 (0.93 to 1.16)	0.47		1.03 (0.91 to 1.16)	0.68		1.05 (0.93 to 1.19)	0.42		0.98 (0.87 to 1.11)	0.77

a HRs at $p < 0.05$ are in bold.
b Primary analyses compared time to event for all secondary outcomes except CR-BSI (risk ratio) and rate of BSI (rate ratio).

Safety analyses

More children in the cohort for the safety analyses were in the standard group ($n = 533$) than in the antibiotic ($n = 451$) or heparin ($n = 479$) groups. As standard CVCs were the default option in the majority of PICUs, more children received the allocated CVC in the standard arm (93%) than in the antibiotic (90%) or heparin (89%) arms.

No serious adverse events (e.g. intervention causing death or prolonging hospitalisation) were reported. CVC-related adverse events (i.e. unable to perform routine activity) were reported for 31 children ($n = 21$ mild, $n = 8$ moderate and $n = 2$ severe) (*Table 11*). No children had more than one adverse event and no events were attributed to the type of CVC.

Of the 1463 children whose CVC insertion was attempted, 148 (10%) died before discharge from the PICU (see *Table 11*). The majority of deaths were the result of related comorbidities at admission (see *Appendix 2*, *Table 30*).

Testing for antibiotic resistance varied by centre. Only 12 of the 42 children with the primary outcome had minocycline and rifampicin resistance reported using Etest strips; 8 out of 12 were resistant, in each case to both antibiotics (3/5 standard group; 2/2 antibiotic group; 3/5 heparin group). Resistant organisms by trial arm are provided in *Appendix 2* (see *Table 31*).

Post hoc analyses

A total of 1573 valid PCR samples were taken from 715 (48%) of the children. Of these children, 11 (1.5%) had a positive PCR result based on any detectable deoxyribonucleic acid (DNA) (12 samples) (*Table 12*). Positive PCR results were observed for two (8.3%) children with the primary outcome compared with nine (1.3%) children without the primary outcome. Values of the positive PCR results are provided in *Appendix 2* (see *Table 32*).

TABLE 11 Safety analyses of CVC-related adverse events and mortality

	Standard ($n = 533$)		Antibiotic ($n = 451$)		Heparin ($n = 479$)		Total ($n = 1463$)	
Adverse event	*n*[a]	%	*n*[a]	%	*n*[a]	%	*n*[a]	%
Unexplained thrombocytopenia	0	0.0	1	0.2	1	0.2	2	0.1
Exit site infection	1	0.2	0	0.0	0	0.0	1	0.1
Hypersensitivity	0	0.0	0	0.0	0	0.0	0	0.0
Trauma from line insertion	2	0.4	2	0.4	3	0.6	7	0.5
Line displacement	4	0.8	6	1.3	3	0.6	13[b]	0.9
Line breakage/mechanical problem/ manufacture complication	2	0.4	3	0.7	2	0.4	7[b]	0.5
Unclassifiable	0	0.0	1	0.2	0	0.0	1	0.1
Total	9	1.7	13	2.9	9	1.9	31	2.1
Mortality								
Deaths[c]	66	12.4	44	9.8	38	7.9	148	10.1
Median time to death in days (IQR)	15.3	(6.0–39.0)	9.0	(2.6–25.6)	14.8	(5.3–32.6)		

IQR, interquartile range.
a n = number by type of CVC received or, if not inserted, type of CVC insertion attempted.
b One event reported as severe.
c Measured on CRF as an adverse event before discharge.

TABLE 12 Polymerase chain reaction results for bacteria in blood samples taken during the primary outcome time window by CVC type

Group	Sample taken from child with primary outcome	*n* randomised	*n* (%) with PCR sample	*n* (%) with positive PCR result
Standard	No	484	239 (49.4)	4 (1.7)
	Yes	18	12 (66.7)	1 (8.3)
Antibiotic	No	479	221 (46.1)	3 (1.4)
	Yes	7	5 (71.4)	0 (0.0)
Heparin	No	480	231 (48.1)	2 (0.9)
	Yes	17	7 (41.2)	1 (14.3)
Total	No	1443	691 (47.9)	9 (1.3)
	Yes	42	24 (57.1)	2 (8.3)
		1485	715 (48.1)	11 (1.5)

Chapter 4 Cost-effectiveness analysis

Introduction

Central venous catheter infections are a substantial and preventable cause of iatrogenic morbidity, mortality, excess length of stay and health-care costs. In the setting of the PICU, BSIs related to CVCs have been reported to occur in 3–8% of all CVC insertions. As approximately two-thirds of the 16,000 admissions to English PICUs each year[57] require CVCs, the overall impact represents a major burden to patients and the NHS.[20,21]

Impregnated CVCs are nearly twice as expensive as standard CVCs, requiring decisions on their use to be informed by evidence of their cost-effectiveness. However, current economic evaluations are limited in their transferability to the PICU setting in the UK as they all relate to adult populations and, with one exception,[29] apply to different health-care systems (Australia,[61] Germany[62] and the USA[63–65]). Although care pathways and costs may differ in the UK setting, these studies consistently demonstrated antibiotic-impregnated CVCs to be cost saving while yielding improved outcomes.

Hockenhull *et al.*[29] modelled the cost-effectiveness of impregnated CVCs compared with standard CVCs in adult patients. The cost of managing CR-BSIs, estimated as £9148, was taken from a systematic review of economic studies. Based on a systematic review of RCTs, impregnated CVCs were estimated to reduce the incidence of CR-BSIs from 3% to 1.4%. The incremental cost-effectiveness ratio (ICER) of £8530 saved for each CR-BSI averted was calculated as the additional cost of the impregnated CVC less the expected cost per patient of managing excess CR-BSIs divided by the absolute risk reduction. Although intuitively simple, the model did not consider mortality effects or discriminate between different types of impregnated CVCs and the authors recommended that decision-makers interpret the results with caution.

Halton *et al.*[61] used a Markov decision model to compare the cost-effectiveness of a range of antimicrobial-coated CVCs, including minocycline- and rifampicin-coated catheters, relative to uncoated catheters in adult intensive care unit patients. Simulations suggested that antibiotic CVCs prevented 15 CR-BSIs per 1000 CVCs placed, with a corresponding gain of 1.6 quality-adjusted life-years (QALYs). The model predicted that 32 intensive care unit (ICU) bed-days and 95 general ward bed-days would be released, with a cost saving of AU$130,289 per 1000 CVCs.

Frank *et al.*[62] performed a case–control analysis of resource use and costs among 30 adults who developed a CR-BSI and 108 control subjects, each in an ICU setting. The marginal cost per infectious episode was estimated as €231, but the calculation and meaning of the ICER presented for silver-impregnated CVCs were unclear.

Marciante *et al.*[63] developed a series of decision models with patient-level clinical trial data to determine whether or not minocycline- and rifampin-impregnated CVCs are cost-effective in adults. Cost-effectiveness was indeterminable for CVCs inserted for ≤ 1 week as no infections had occurred during this time. Antibiotic CVCs were modelled to be cost-effective for longer periods of insertion, with expected savings of US$67 and gains of 0.009 QALYs per patient.

Shorr *et al.*[64] presented another decision-analytic model based on a hypothetical cohort of 1000 adult patients requiring a CVC. The incidence of CR-BSIs, excess lengths of ICU and ward stays and associated costs were selected from published studies. Compared with standard CVCs, minocycline- and rifampin-impregnated CVCs were estimated to reduce the incidence of CR-BSIs from 3.3% to 1.4%, resulting in a saving of US$9605 for each CR-BSI averted.

Veenstra *et al.*[65] used data from RCTs, meta-analyses, and case–control studies within a decision-analytic modelling framework to estimate the incremental cost-effectiveness of antiseptic-impregnated CVCs in a hypothetical cohort of hospitalised patients at high risk for CR-BSIs. Modelling the use of chlorhexidine/silver sulfadiazine-impregnated compared with standard CVCs resulted in a 2.2% decrease in the incidence of CR-BSIs, a 0.33% decrease in the incidence of death and a saving of US$196 per CVC used.

An important limitation of these studies was that each analysis modelled the costs and consequences of BSIs using data from disparate sources and as such relied heavily on assumptions relating to attribution of hospital lengths of stay (the main cost driver) and mortality to BSIs. The only UK-based economic evaluation considered an adult population and assumed that a patient with a CR-BSI spends 6 additional days in the ICU and 5 additional days in a general medical ward.[29] A recent study of 1339 cases of CR-BSI sampled from a US paediatric population and matched to control subjects by propensity score revealed a higher mean attributable length of stay of 19 days.[66] Although this is comparable with the 21-day excess length of stay estimated for paediatric haematology/oncology patients,[67] these estimates are reliant on retrospective observational data and are susceptible to bias.

Aim

We aimed to assess the cost-effectiveness of antibiotic, heparin and standard CVCs in an English PICU setting using data from the CATCH RCT. Although the primary comparison showed no evidence that impregnated CVCs (antibiotic or heparin) were more effective than standard CVCs, important differences in secondary comparisons among the three CVCs suggested that an economic evaluation was warranted to inform decisions on resource allocation. This would be especially relevant if one type of CVC were to reduce total costs, be associated with shorter periods in the PICU or reduce the length of ward stays.

Methods

Although cost–utility analyses, based on QALYs, are more appropriate for informing decisions concerning allocative efficiency, there are practical and methodological challenges in estimating utility values in children, especially very young children in the PICU setting. These include difficulties in responding to or understanding questions on health-related quality of life, whether for reasons of age, illness or consciousness; the limitations of using proxy utilities; the low event rate for the primary end point; and the inclusion of a wide range of clinical conditions. A cost-effectiveness analysis was therefore performed, which allowed for an assessment of technical efficiency (i.e. determination of the most efficient CVC for reducing the incidence of BSIs). The study methods were consistent with those used in other economic evaluations of CVCs.[62]

Resource use

The perspective of the analysis was that of the NHS in England, with the expectation that the main cost driver of inpatient hospital care would represent the greatest proportion of direct medical costs. The principal cost components were PICU, high-dependency unit (HDU) and ward stays (including readmissions), outpatient clinic visits, accident and emergency (A&E) admissions and the CVCs. The time horizon of the base-case analysis was selected to include the costs associated with managing BSIs and any sequelae within the 6-month period from randomisation. Shorter time horizons were examined in sensitivity analyses.

The measurement of resource use required complementary approaches using data collected as part of the trial and as part of routine care. Patients' use of hospital services was obtained from the following sources (*Figure 3*):

1. *The trial CRFs*. Research nurses completed the relevant sections of the CRF to record the dates during which patients were in neonatal intensive care units (NICUs) or PICUs, HDUs and paediatric wards within the hospitals participating in the CATCH trial. Data recorded on CRFs were used for the dates of hospital discharge, transfer to another hospital and CVC removal.
2. *Hospital Episode Statistics (HES) data from the Health and Social Care Information Centre*.[68] HES data contain details of all admissions to NHS hospitals in England and provide Healthcare Resource Groups (HRGs) for the type of care patients receive at a ward level, outpatient visits and A&E admissions, but do not provide details on ICU and HDU stays. HES data were used for estimating HRGs for ward stays, outpatient and A&E attendances.

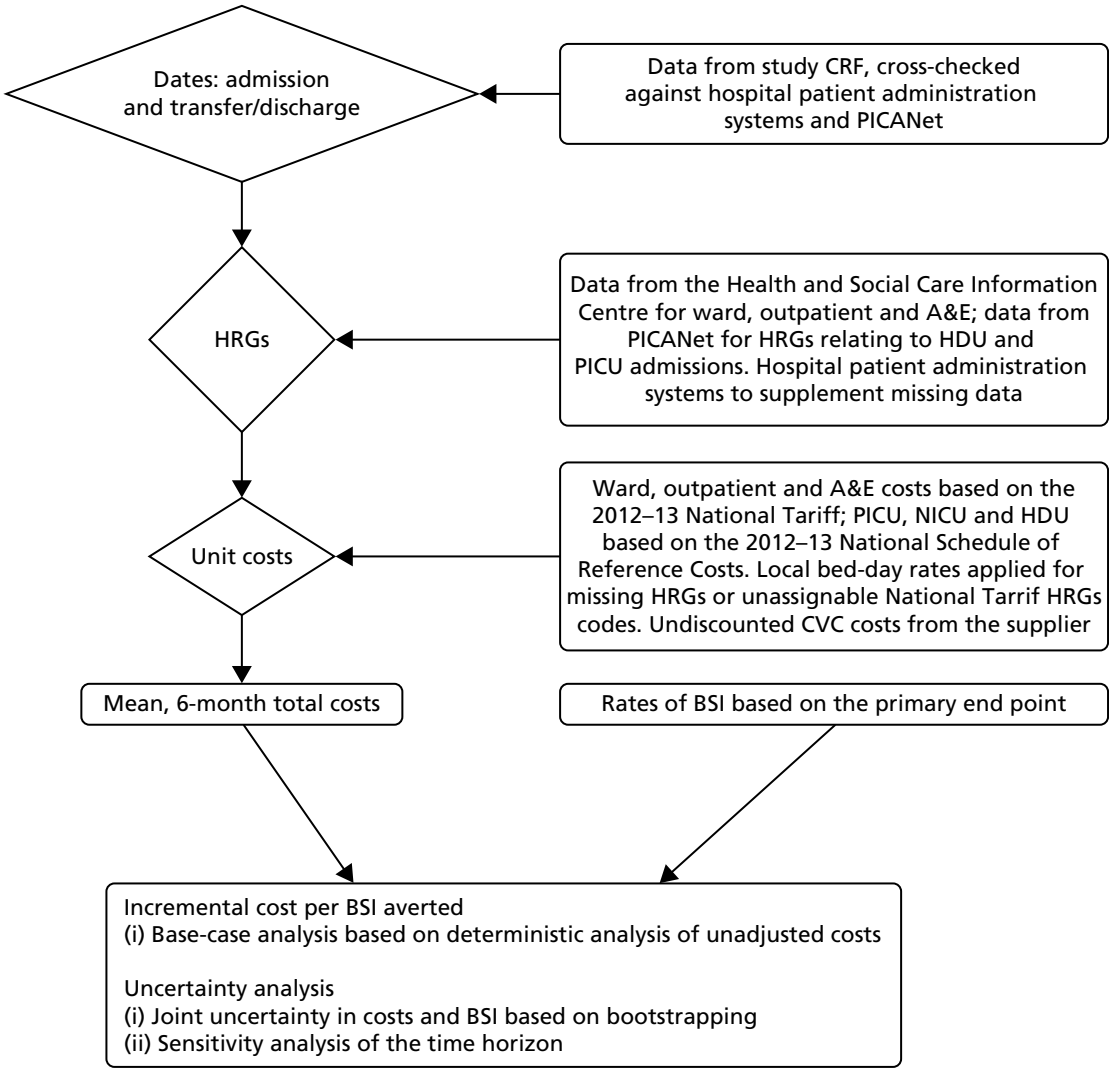

FIGURE 3 Flow diagram of the methods employed for the economic evaluation.

3. *The PICANet data set*.[57] This data set includes all ICU length of stays for paediatric patients in the UK and allows for the tracking over time of patients who have been transferred between ICUs in different hospitals. PICANet data were used for the national schedule of reference costs HRGs for HDU and ICU stays[69] and for checking hospital admission, transfer and discharge dates.
4. *Hospital Patient Administration Systems (PASs) of CATCH-participating hospitals*. These were accessed for patient lengths of stay on ICUs and wards and for relevant HRGs. These were used to supplement data that were missing from other sources.

Unit costs

Healthcare Resource Groups were chosen as the main currency of the economic analysis as these most closely reflect payments relating to patient stays. Cost codes based on the 2012–13 national tariff were applied to ward, outpatient and A&E codes.[70] These are bundled care packages, that is, they are reimbursed at a national level according to the NHS Payment by Results scheme[71] (see *Appendix 3*, *Table 33*). The 2012–13 national schedule of reference costs[69] was applied to PICU, NICU and HDU codes. These are unbundled care packages as they are locally reimbursed services (*Table 13*). Obsolete national tariff and schedule codes and hospital bed-day rates used between 2010 and 2012 were inflated using the Consumer Price Index (4.3% for 2010–11 and 2.7% for 2011–12). The preferred Hospital Price Index was available only for 2010–11, but was similar to the Consumer Price Index at 4.1%. The list prices of CVC devices were obtained from the supplier (Cook Medical Inc.).

TABLE 13 Unit costs for intensive care and high-dependency care based on HRGs from the national schedule tariff (2012–13)[69]

HRG code	HRG name	Primary description	Secondary description	Cost per day (£)
XB01Z	Paediatric Critical Care, Intensive Care, ECMO/ECLS	Highly specialised intensive care treatment, e.g. by ECMO	ECMO, ventricular assist devices and other highly complex procedures	4391
XB02Z	Paediatric Critical Care, Intensive Care, Advanced Enhanced		Unstable multisystem failure with other complications	2409
XB03Z	Paediatric Critical Care, Intensive Care, Advanced	Intensive nursing supervision at all times, undergoing complex monitoring and/or therapeutic procedures and including advanced respiratory support	Invasive ventilation with multisystem failure	2017
XB04Z	Paediatric Critical Care, Intensive Care, Basic Enhanced		Intensive ventilation with more than one system failure	2110
XB05Z	Paediatric Critical Care, Intensive Care, Basic	Continuous nursing supervision	Invasive ventilation with single system failure *or* non-invasive ventilation with more than one system failure	1743
XB06Z	Paediatric Critical Care, High Dependency, Advanced	Requiring closer observation and monitoring than is usually available on an ordinary children's ward, with higher than usual staffing levels	Non-invasive ventilation (e.g. CPAP and BIPAP by mask with intravenous drugs)	1335
XB07Z	Paediatric Critical Care, High Dependency		Close monitoring, oxygen by mask, no invasive ventilation	886

TABLE 13 Unit costs for intensive care and high-dependency care based on HRGs from the national schedule tariff (2012–13)[69] (*continued*)

HRG code	HRG name	Primary description	Secondary description	Cost per day (£)
XB08Z	Paediatric Critical Care, Transportation	As paediatric critical care facilities are centralised in a small number of hospitals providing expert specialist care, specialist transport teams are required to deliver clinical management during transfer of patients		2799
XA01Z	Neonatal Critical Care, Intensive Care	Care provided for babies who are the most unwell or unstable and have the greatest needs in relation to staff skills and staff to patient ratios	Baby receives any form of mechanical respiratory support via a tracheal tube and/or parenteral nutrition	1118

BIPAP; bilevel positive airway pressure; CPAP, continuous positive airway pressure; ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation.

Cost analysis

Bundled national tariff costs were based on the hospital spell and incorporated excess ward-days, a market forces factor and whether the case was elective or emergency. Tariff codes were obtained primarily from HES data (see *Appendix 3*) or, when unavailable, PAS data. If bundled HRGs were missing from both of these sources, ward costs were assigned from the ward bed-day rates supplied by hospital finance departments (*Table 14*). Similarly, bed-day rates were applied to stays with unassignable national tariff HRG codes (such as UZ01C and WA14Z) appearing in the HES and PAS data. These bed-day rates were needed for < 1% of admissions.

TABLE 14 Hospital ward bed-day rates as provided by hospital finance departments and adjusted for inflation (UK pounds sterling, 2013)

Hospital	HES hospital ID	Market forces factor[a]	Ward rate (£)[b]
Birmingham Children's Hospital	RQ3	1.05	290
Bristol Royal Hospital for Children	RA7	1.08	366
Evelina London Children's Hospital (Guy's and St Thomas')	RJ1	1.28	595[c]
Freeman Hospital	RTD	1.04	595[c]
Alder Hey Children's Hospital	RBS	1.04	364[d]
Glenfield Hospital	RWE	1.04	751
Great Ormond Street Hospital	RP4	1.29	2157
Leeds General Infirmary	RR8	1.05	542
Leicester Royal Infirmary	RWE	1.04	751
Queen's Medical Centre	RX1	1.04	374
Royal Brompton Hospital	RT3	1.25	370
Royal Victoria Infirmary	RTD	1.25	342
Southampton General Hospital	RHM	1.09	212
St Mary's Hospital, London	RYJ	1.24	394

a Used with HRGs only.
b Ward rate excludes ICU or HDU costs.
c Mean of series of wards provided by all hospitals except Alder Hey.
d Mean of series of wards provided by hospital.

Unbundled, locally reimbursed costs were calculated from the national schedule 'per day' codes taken from PICANet (see *Table 13*) or were assigned as XA01C in the cases in which neonatal critical care was indicated in CRF data. In the 10% of cases in which unbundled codes were missing, CRF data were consulted to determine whether the patient stay was in a PICU or a HDU. In addition, PICANet database entries (such as patient note summaries) were examined for any evidence of advanced and/or enhanced care. In the absence of any higher cost code indicators, a basic HDU code (XB07Z) or a basic ICU code (XB05Z) was applied from the national schedule of reference costs.[69]

Baseline costs, relating to the 6 months preceding randomisation, were calculated from HES and PICANet data on ward, PICU and HDU costs.

For the 6 months subsequent to randomisation, an adjustment was necessary to apportion costs given that ward, PICU and HDU costs related to episodes of care could start prior to randomisation. Patients admitted to hospital n days before randomisation and spending N days in hospital after randomisation had their total costs calculated as:

$$\text{Total cost} = (N/n + N) \times (\text{ward cost} + \text{PICU cost} + \text{HDU cost}) + (\text{outpatient costs} + \text{A\&E costs} + \text{CVC costs}). \quad (1)$$

Patients' use of health-care resources and total costs were calculated for the intention-to-treat population, with summary statistics generated by intervention group.

Outcomes

The clinical outcome for the cost-effectiveness analysis was the presence of a first BSI defined by a positive blood culture from a sample that was clinically indicated and taken more than 48 hours after CVC insertion and up to 48 hours after CVC removal. The likelihood of a BSI was estimated using a logistic regression analysis with intervention group as the explanatory variable.

Incremental analysis

The cost-effectiveness of each CVC was evaluated by (1) ranking CVCs according to decreasing effectiveness and (2) eliminating dominated interventions (those that were less effective or ineffective) or any extendedly dominated interventions. The ICER for the remaining CVCs was consequently calculated according to the following equation:

$$\text{ICER} = \Delta\text{costs}/\Delta\text{BSIs}, \quad (2)$$

where Δcosts is the difference in mean total costs between interventions and ΔBSIs is the difference in the risk of BSIs between interventions.

Uncertainty analysis

Non-parametric bootstrapping (10,000 replicates) was used to calculate bias-adjusted 95% central ranges for differences in costs and BSIs and their joint distributions. Uncertainty was represented using a cost-effectiveness acceptability curve (CEAC), which presented the probability of CVCs being cost-effective for given ceiling thresholds of costs per BSI averted.[72]

Uncertainty in total costs was further explored by adjusting for the contribution of independent baseline factors to overall variability.[73]

The following predefined explanatory variables were tested for independent associations with total costs: age group, body weight, 6-month pre-randomisation costs (all log-transformed), gender, pre-existing CVC 72 hours prior to randomisation, health status before PICU admission, reason for admission (cardiovascular, endocrine or metabolic, infection, neurological, oncology, respiratory, trauma, other), suspected infection at randomisation, immunocompromised, positive blood culture within 72 hours prior to randomisation, numbers of devices in situ, intervention group and admission type (elective or emergency). Assumptions were necessary to account for missing data with respect to some variables: patients were assumed to be

healthy ($n = 1$), not immunocompromised ($n = 19$) and to have no positive blood cultures ($n = 5$). Missing data for weight ($n = 2$) were imputed with the mean participant weight (11.95 kg). Missing reasons for admission ($n = 20$) were cross-checked against PICANet, PAS and available HES data. All were correctly assigned as cardiovascular patients.

Independent variables were tested in univariate analyses for their association with total costs, with risk factors that were significant at the 5% level selected for the multivariable regression using a stepwise approach. Given the non-normality of the cost data, generalised linear models were specified using a range of families and links. Assessment of goodness of fit using the Akaike information criterion (AIC) and the modified Park test was inconclusive, but the best-fitting link function, determined from the Pearson correlation, Pregibon link and modified Hosmer and Lemeshow tests, was the identity link. Although the underlying true distributions of costs are not normal, the analysis depends only on sample means and variances. Based on the comparatively large sample size, the central limit theorem was assumed to guarantee near normality of sample means and an ordinary least squares regression was considered appropriate.[73]

Bias-corrected CIs for costs and BSIs were estimated from bootstrapped data generated using the recycled predictions method.[74]

Sensitivity analysis

The prespecified time horizon of 6 months in the base-case analysis was selected to capture longer-term costs resulting from potential complications of BSIs but was somewhat arbitrary. The sensitivity of total costs and the ICERs to the time horizon of analysis was therefore considered by limiting costs to those incurred during the index hospitalisation (i.e. excluding any subsequent readmissions that may have occurred during the 6 months) and by analysing their relationship with time, from 1 month (when all BSIs had occurred) to 6 months.

Value of health-care resources associated with bloodstream infection

In an exploratory analysis, a variable representing the presence of a BSI was included in the cost regression to estimate the value of the health-care resources associated with managing a BSI. To avoid collinearity, the variable representing intervention group was omitted from this regression.

All analyses were performed using Stata version 10 (StataCorp LP, College Station, TX, USA) and the economic evaluation was reported according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.[75]

Results

Resource use and total costs

Complete cost data were available for all patients. In the 6 months preceding randomisation, the mean costs (length of stay) of ICU/HDU admissions were £6026 (3.19 days) for the standard CVC group, £5188 (2.76 days) for the antibiotic CVC group and £6616 (3.47 days) for the heparin CVC group. The mean total hospital costs for the corresponding period were £15,588, £16,933 and £16,722, respectively. Neither ICU/HDU costs nor total hospital costs differed by intervention group.

Patients randomised to antibiotic-impregnated CVCs spent a mean of 10.8 days (95% CI 9.3 to 12.5) in the PICU in the 6 months following randomisation compared with 9.9 days (95% CI 8.6 to 11.4) for those in the heparin-bonded CVC group and 10.5 days (95% CI 9.2 to 11.9) for those in the standard CVC group (*Table 15*). There were no significant differences between groups in length of stay in the PICU ($p = 0.70$), HDU ($p = 0.43$) or ward ($p = 0.52$). The mean total hospital stay in the 6 months after randomisation was 34.8 days (95% CI 31.2 to 38.5 days) for antibiotic CVCs, 31.4 days (95% CI 28.2 to 34.7 days) for heparin-bonded CVCs and 31.7 (95% CI 28.8 to 34.8 days) for standard CVCs. The six most significant HRGs (of 349 in total) accounted for 50% of ward costs. These related to surgical correction of congenital malformations, cardiac surgery or disorders of the lower respiratory tract.

TABLE 15 Patient length of stay and count of dominant HRGs relating to inpatient stays from randomisation to 6 months (including readmissions) according to place and intensity of care and intervention group

	Antibiotic		Heparin		Standard	
Unit	Mean (median)	95% CI	Mean (median)	95% CI	Mean (median)	95% CI
Days on ICU	10.79 (5.00)	9.28 to 12.48	9.91 (5.00)	8.57 to 11.44	10.50 (5.00)	9.17 to 11.93
Paediatric Critical Care, Intensive Care, ECMO/ ECLS (XB01Z)	0.31 (0.00)	0.07 to 0.72	0.39 (0.00)	0.09 to 0.80	0.41 (0.00)	0.17 to 0.72
Paediatric Critical Care, Intensive Care, Advanced Enhanced (XB02Z)	0.16 (0.00)	0.09 to 0.26	0.12 (0.00)	0.09 to 0.15	0.16 (0.00)	0.10 to 0.26
Paediatric Critical Care, Intensive Care, Advanced (XB03Z)	0.77 (0.00)	0.51 to 1.05	0.62 (0.00)	0.43 to 0.83	0.65 (0.00)	0.46 to 0.87
Paediatric Critical Care, Intensive Care, Basic Enhanced (XB04Z)	2.30 (0.49)	1.92 to 2.72	2.69 (0.78)	2.09 to 3.44	2.76 (0.00)	2.14 to 3.54
Paediatric Critical Care, Intensive Care, Basic (XB05Z)	6.96 (2.00)	5.65 to 8.45	5.63 (2.00)	4.75 to 6.59	6.40 (2.95)	5.42 to 7.47
Neonatal Critical Care, Intensive Care (XA01C)	0.29 (0.00)	0.10 to 0.55	0.46 (0.00)	0.13 to 1.03	0.11 (0.00)	0.04 to 0.20
Days on HDU	2.00 (0.59)	1.48 to 2.62	1.60 (0.59)	1.28 to 1.99	1.73 (0.00)	1.44 to 2.05
Paediatric Critical Care, High Dependency, Advanced (XB06Z)	1.28 (0.00)	0.94 to 1.70	1.09 (0.00)	0.80 to 1.45	1.22 (0.00)	0.98 to 1.49
Paediatric Critical Care, High Dependency (XB07Z)	0.72 (0.00)	0.42 to 1.16	0.51 (0.00)	0.40 to 0.64	0.51 (0.00)	0.40 to 0.64
Days on ward	22.01 (9.13)	19.26 to 24.80	19.85 (9.00)	17.40 to 22.40	19.48 (8.57)	17.12 to 21.94
Total days in hospital	34.80 (20.00)	31.21 to 38.48	31.36 (17.00)	28.18 to 34.65	31.72 (17.97)	28.75 to 34.81
Count of non-PICU/-HDU inpatient HRGs						
Complex Congenital Surgery (EA24Z)	100		103		109	
Intermediate Congenital Surgery (EA25Z)	68		70		72	
Major Complex Congenital Surgery (EA23Z)	45		39		37	
Cardiac Conditions with Complication and Comorbidity (PA23A)	109		102		74	
Lower Respiratory Tract Disorders without Acute Bronchiolitis with Length of Stay ≥ 1 day with Complication and Comorbidity (PA14C)	95		78		105	
Implantation of Prosthetic Heart or Ventricular Assist Device (EA43Z)	2		2		4	
Other inpatient HRGs	1103		1055		964	

ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation.

Total and disaggregated costs are presented in *Table 16*. The mean 6-month cost was £44,503 (median £28,952, range £1786–360,983, 95% CI £40,619 to £48,666) for standard CVCs, £45,663 (median £29,793, range £2189–442,365, 95% CI £41,647 to £50,009) for antibiotic-impregnated CVCs and £42,065 (median £27,621, range £2638–382,431, 95% CI £38,322 to £46,110) for heparin CVCs (*Figure 4*). These costs were not statistically significantly different between intervention groups ($p = 0.46$) or when disaggregated according to bundled costs ($p = 0.43$) and unbundled costs ($p = 0.73$).

TABLE 16 Disaggregated and total costs (£) by intervention group from randomisation to the end of the 6-month time frame

	Antibiotic		Heparin		Standard	
Unit	Mean (median)	95% CI	Mean (median)	95% CI	Mean (median)	95% CI
Paediatric critical care, intensive care						
ECMO/ECLS (XB01Z)	1358 (0)	310 to 3159	1703 (0)	386 to 3509	1796 (0)	723 to 3156
Advanced Enhanced (XB02Z)	388 (0)	207 to 636	289 (0)	216 to 371	395 (0)	228 to 620
Advanced (XB03Z)	1545 (0)	1031 to 2124	1250 (0)	872 to 1674	1318 (0)	933 to 1752
Basic Enhanced (XB04Z)	4861 (1023)	4060 to 5738	5675 (1646)	4418 to 7260	5822 (0)	4512 to 7460
Basic (XB05Z)	12,137 (3486)	9855 to 14,730	9822 (3486)	8274 to 11,489	11,159 (5133)	9440 to 13,025
Neonatal Critical Care, Intensive Care (XA01C)	325 (0)	113 to 613	517 (0)	142 to 1150	125 (0)	42 to 225
Paediatric critical care, high dependency						
High Dependency, Advanced (XB06Z)	1709 (0)	1254 to 2271	1450 (0)	1972 to 1940	1629 (0)	1301 to 1992
High Dependency (XB07Z)	635 (0)	372 to 1025	454 (0)	354 to 567	456 (0)	356 to 566
Transportation (XB08Z)	1158 (0)	1022 to 1293	1258 (0)	1109 to 1413	1208 (0)	1068 to 1353
Subtotal (PICU/HDU/NICU)[a]	24,115 (12,201)	20,824 to 27,764	22,417 (11,903)	19,429 to 25,771	23,907 (12,495)	20,989 to 27,049
Inpatient stay[b]						
Complex Congenital Surgery (EA24Z)	3011 (0)	2445 to 3593	2908 (0)	2363 to 3481	3144 (0)	2565 to 3753
Intermediate Congenital Surgery (EA25Z)	2166 (0)	1670 to 2699	1934 (0)	1470 to 2440	2044 (0)	1583 to 2545
Major Complex Congenital Surgery (EA23Z)	1865 (0)	1315 to 2481	1915 (0)	1310 to 2603	1466 (0)	1013 to 1960
Cardiac Conditions with Complication and Comorbidity (PA23A)	1277 (0)	818 to 1845	1173 (0)	831 to 1558	739 (0)	495 to 1025

continued

TABLE 16 Disaggregated and total costs (£) by intervention group from randomisation to the end of the 6-month time frame (*continued*)

Unit	Antibiotic		Heparin		Standard	
	Mean (median)	95% CI	Mean (median)	95% CI	Mean (median)	95% CI
Lower Respiratory Tract Disorders without Acute Bronchiolitis with Length of Stay ≥ 1 day with Complication and Comorbidity (PA14C)	858 (0)	593 to 1157	668 (0)	454 to 913	943 (0)	657 to 1268
Implantation of Prosthetic Heart or Ventricular Assist Device (EA43Z)	273 (0)	0 to 684	298 (0)	0 to 762	548 (0)	103 to 1155
Other inpatient HRG costs	10,316 (4017)	8616 to 12,231	8803 (3058)	7524 to 10,106	9930 (3259)	7860 to 12,409
Subtotal (inpatient)	19,766 (14122)	17,934 to 21,755	17,700 (13,716)	16,308 to 19,182	18,814 (13,748)	16,649 to 21,327
Other						
A&E cost[c]	89 (0)	76 to 104	85 (0)	73 to 99	91 (0)	78 to 104
Outpatient cost[c]	1615 (883)	1412 to 1838	1784 (837)	1496 to 2109	1648 (881)	1453 to 1871
CVC cost[d]	78.28	78 to 78	78.25	78 to 78	42.91	43 to 43
Total cost (full 6 months)	45,663 (29,793)	41,647 to 50,009	42,065 (27,621)	38,322 to 46,110	44,503 (28,952)	40,619 to 48,666

ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation.
a *National Schedule of Reference Costs 2012–13*.[69]
b Top six (of 349) HRGs ranked by cost, together contributing 50% of overall inpatient costs.
c 2012–13 national tariff HRGs: < 1% taken from bed-day rates.
d Costs supplied by CVC provider (Cook Medical Inc.).

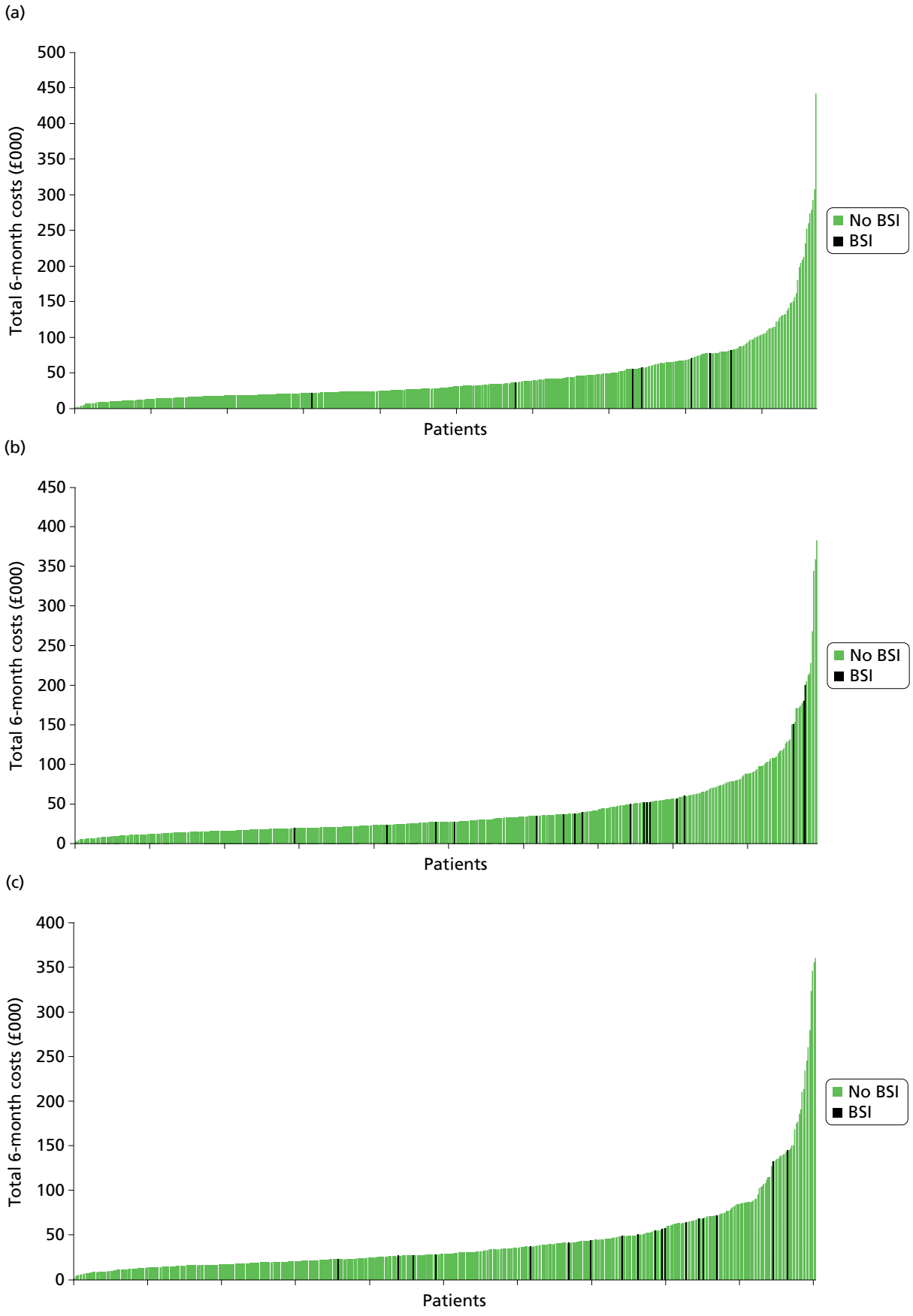

FIGURE 4 Ranking of 6-month total costs by intervention group, indicating patients who experienced a BSI. (a) Antibiotic CVCs; (b) heparin CVCs; and (c) standard CVCs.

Incremental costs

Mean unadjusted costs over the 6-month time frame were not significantly different by CVC but tended to be higher (by £1160, 95% CI –£4743 to £6962) for antibiotic CVCs than for standard CVCs and lower (–£2439, 95% CI –£8164 to £3359) for heparin CVCs compared with standard CVCs.

Randomisation ensured that all variables tested for the cost regression were well balanced between intervention groups. Only a small proportion (< 10%) of the residual variability in total cost could be explained by the significant independent predictor variables: natural logarithm (ln) of age (in days), ln of 6-month pre-randomisation costs, health status before PICU admission, reason for admission, whether or not immunocompromised and admission type (elective or emergency; *Table 17*). The adjusted incremental costs associated with the antibiotic and heparin CVC groups in relation to the standard CVC group were £1220 (95% CI –£4332 to £6773) and –£2399 (95% CI –£7914 to £3120), respectively, resulting in small improvements in precision.

Value of health-care resources associated with bloodstream infection

Over 6 month, patients who had experienced a BSI ($n = 42$) experienced 6.5 more days (95% CI 1.4 to 11.6 days) in the PICU than those with no BSI ($n = 1443$) and 15.1 additional total days (95% CI 4.0 to 26.2 days) of hospitalisation. The unadjusted mean 6-month cost for patients with a BSI was £60,481 (95% CI £47,873 to £73,809) and for patients without a BSI was £43,578 (95% CI £41,185 to £45,970), a difference of £17,263 (95% CI –£3076 to £31,450). The regression-derived adjusted difference in cost, representing the value of the resources used to manage BSI, was £10,975 (95% CI –£2801 to £24,751) (*Table 18*).

TABLE 17 Adjusted total (6-month) costs: results of the ordinary least squares regression of total costs based on significant baseline variables

Variable	Coefficient (£)	95% CI (£)	*p*-value
Ln of pre-randomisation cost	1444	602 to 2287	< 0.001
Admission type	27,423	20,993 to 33,853	< 0.001
Intervention group (antibiotic)	1221	–4332 to 6773	0.67
Intervention group (heparin)	–2399	–7917 to 3120	0.39
Prior health status (0 = not healthy; 1 = healthy)	–9974	–15,807 to –4140	< 0.001
Reason for admission (endocrine/metabolic)	–1921	–11,889 to 8048	0.71
Reason for admission (infection)	–22,300	–32,609 to –11,992	< 0.001
Reason for admission (neurological)	–21,854	–32,780 to –10,927	< 0.001
Reason for admission (oncology)	2641	–16,052 to 21,333	0.78
Reason for admission (other)	–3510	–14,355 to 7335	0.53
Reason for admission (respiratory)	–8289	–15,609 to –968	0.03
Reason for admission (trauma)	–12,144	–26,764 to 2477	0.1
Compromised immunity (yes/no)	8476	–1246 to 18,198	0.09
Ln of age in days	–236	–1300 to 828	0.66
Constant	24,086	13,255 to 34,916	< 0.001

BIC, Bayesian information criterion.
AIC = 24.25; BIC = 2.89×10^{12}; $R^2 = 0.092$.

TABLE 18 Value of health-care resources associated with managing a BSI: results of the ordinary least squares regression for estimating the cost of BSI, with total costs as the dependent variable and univariately significant baseline explanatory variables

Variable	Coefficient (£)	95% CI (£)	*p*-value
Ln of pre-randomisation cost	1439	598 to 2281	0.001
Admission type	27,341	20,916 to 33,767	< 0.001
Prior health status (0 = not healthy; 1 = healthy)	–9593	–15,440 to –3745	0.001
Reason for admission (endocrine/metabolic)	–2005	–11,968 to 7959	0.693
Reason for admission (infection)	–22,585	–32,896 to –12,274	< 0.001
Reason for admission (neurological)	–21,648	–32,559 to –10,736	< 0.001
Reason for admission (oncology)	2335	–16,347 to 21,017	0.806
Reason for admission (other)	–2948	–13,789 to 7894	0.594
Reason for admission (respiratory)	–8170	–15,484 to –856	0.029
Reason for admission (trauma)	–12,412	–27,016 to 2192	0.096
Compromised immunity (yes/no)	7965	–1770 to 17,700	0.109
Ln of age (in days)	–178	–1243 to 885	0.742
BSI (0 = no; 1 = yes)	10,975	–2801 to 24,751	0.118
Constant	23,064	12,759 to 33,369	< 0.001

$R^2 = 0.092$.

Outcomes

Seven of 486 children randomised to antibiotic CVCs experienced a BSI compared with 17 out of 497 in the heparin CVC group and 18 out of 502 in the standard CVC group. A statistically significant absolute risk difference was found only for antibiotic CVCs compared with standard CVCs (–2.15%, 95% CI –4.09% to –0.20%). Compared with standard CVCs, the unadjusted odds of acquiring a BSI with an antibiotic CVC was 0.39 (95% CI 0.16 to 0.95; $p = 0.04$) and with a heparin CVC was 0.95 (95% CI 0.49 to 1.87; $p = 0.89$).

Incremental and uncertainty analysis

As heparin CVCs were shown not to be clinically effective compared with standard CVCs there is no case for an incremental analysis: a clinically ineffective intervention cannot be cost-effective according to the same measure of BSI. The calculation of the ICER was therefore limited to the comparison between antibiotic and standard CVCs, which resulted in an ICER of £54,057 per BSI averted (*Table 19*).

The CEAC yielded probabilities of 0.38, 0.49 and 0.62 of antibiotic CVCs being cost-effective at (arbitrary) thresholds of £10,000, £50,000 and £100,000 per BSI averted respectively (*Figure 5*). The probability of antibiotic CVCs dominating standard CVCs was estimated as 0.35.

Sensitivity analysis

The mean number of days in hospital during the index hospitalisation was substantially shorter (e.g. 22.1 days for antibiotic CVCs) than the mean number of days in hospital during the 6 months from randomisation (e.g. 34.8 days for antibiotic CVCs; *Table 20* and see *Table 15*). Considering only the index hospitalisation, total costs tended to be lower in the antibiotic CVC group (£33,073, 95% CI £30,047 to £36,337) and in the heparin CVC group (£32,245, 95% CI £29,013 to £35,823) than in the standard CVC group (£35,165, 95% CI £31,864 to £38,670). The unadjusted incremental cost saving for antibiotic compared with standard CVCs was –£2093 (95% CI –£6919 to £2583) and for heparin compared with standard CVCs was –£2920 (95% CI –£7833 to £2180).

TABLE 19 Incremental analysis of unadjusted costs (mean values with 95% central range)

Analysis	Antibiotic	Heparin	Standard
Base-case analysis (6-month time horizon)			
Total cost (£)	45,663 (41,647 to 50,009)	42,064 (38,322 to 46,110)	44,503 (40,619 to 48,666)
Incremental cost (vs. standard) (£)	1160 (–4743 to 6692)	–2438 (–8164 to 3359)	–
BSI (%)	1.44 (0.4 to 2.5)	3.42 (1.8 to 5.0)	3.59 (2.0 to 5.2)
Incremental BSI (vs. standard) (%)	–2.15 (–4.1 to –0.2)	–0.17 (–2.5 to 2.1)	–
ICER (vs. standard) (£)	54,057 per BSI averted	–[a]	–
Sensitivity analysis (index hospitalisation)			
Total cost (£)	33,073 (30,047 to 36,337)	32,245 (29,013 to 35,823)	35,165 (31,864 to 38,670)
Incremental cost (vs. standard) (£)	–2093 (–6919 to 2583)	–2920 (–7833 to 2180)	–
BSI (%)	1.44 (0.4 to 2.5)	3.42 (1.8 to 5.0)	3.59 (2.0 to 5.2)
Incremental BSI (vs. standard) (%)	–2.15 (–4.1 to –0.2)	–0.17 (–2.5 to 2.1)	–
ICER (vs. standard) (£)	–97,543 per BSI averted[b]	–[a]	–

a As heparin CVCs were not deemed to be clinically effective in reducing BSI rates, they cannot be cost-effective for the same outcome measure.
b Cost saving.

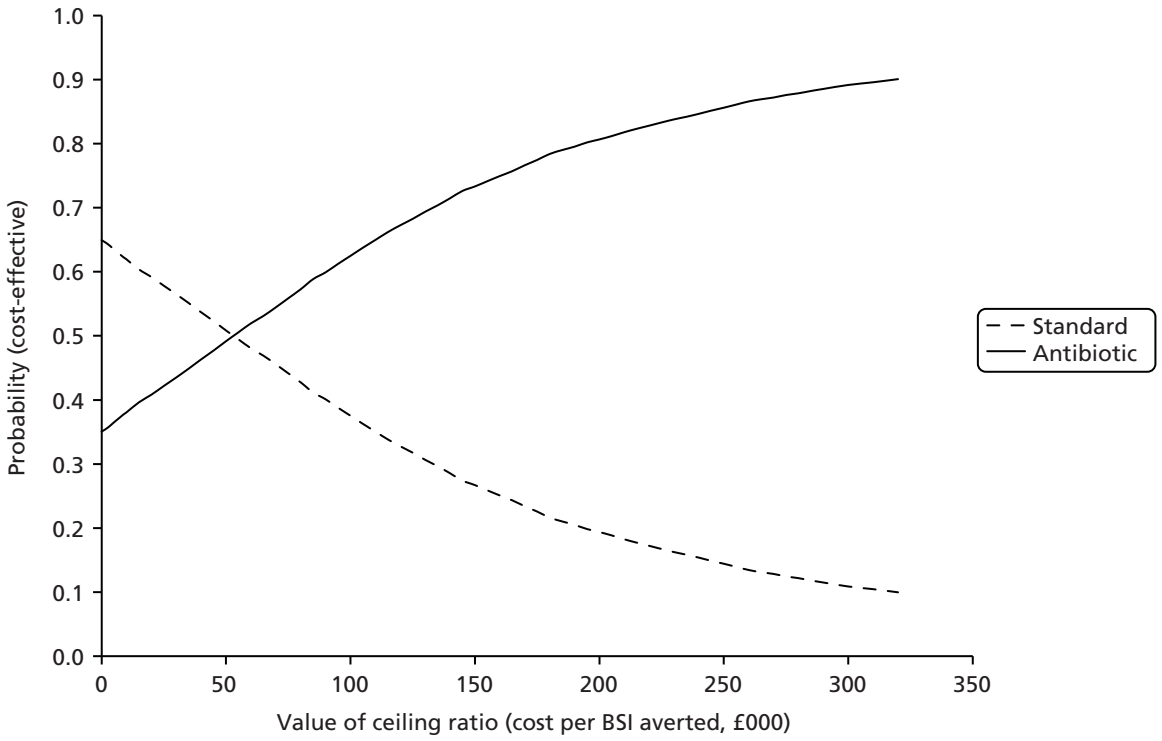

FIGURE 5 Cost-effectiveness acceptability curve based on a 6-month time horizon presenting the probabilities of antibiotic and standard CVCs being cost-effective for given values of ceiling ratio expressed as cost per BSI averted.

TABLE 20 Patient length of stay for hospitalisation episode from randomisation by intervention group

	Antibiotic		Heparin		Standard	
Unit	Mean	95% CI	Mean	95% CI	Mean	95% CI
Days on ICU	9.31	8.09 to 10.70	8.93	7.71 to 10.32	9.79	8.60 to 11.03
Days on HDU	1.70	1.25 to 2.25	1.39	1.09 to 1.76	1.51	1.24 to 1.80
Days on ward	11.13	9.19 to 13.18	10.32	8.59 to 12.18	10.79	9.03 to 12.70
Total days in hospital	22.14	19.48 to 24.89	20.65	18.27 to 23.16	22.09	19.76 to 24.51

Based only on the costs of the index stay, antibiotic CVCs dominated standard CVCs with a saving of £97,543 per BSI averted (see *Table 19*).

An analysis of the cumulative mean costs over the course of the 6 months (*Figure 6*) shows that costs in the heparin CVC group were lower overall, whereas costs in the antibiotic CVC group were variably cost incurring and cost saving in comparison to costs in the standard CVC group.

The resulting ICER for antibiotic compared with standard CVCs fluctuated considerably (*Figure 7*), ranging from £82,204 saved per BSI averted by day 50 post randomisation to being cost neutral by day 122 and to the base-case cost of £54,057 per BSI averted by 6 months.

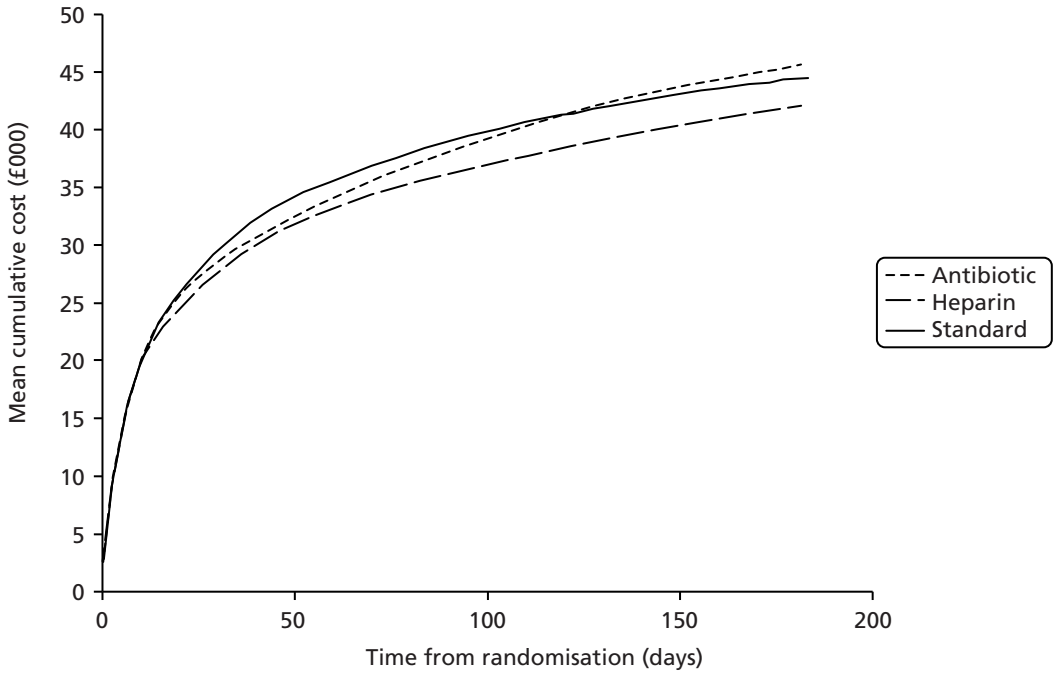

FIGURE 6 Relation between total costs (cumulative) and time since randomisation according to intervention group.

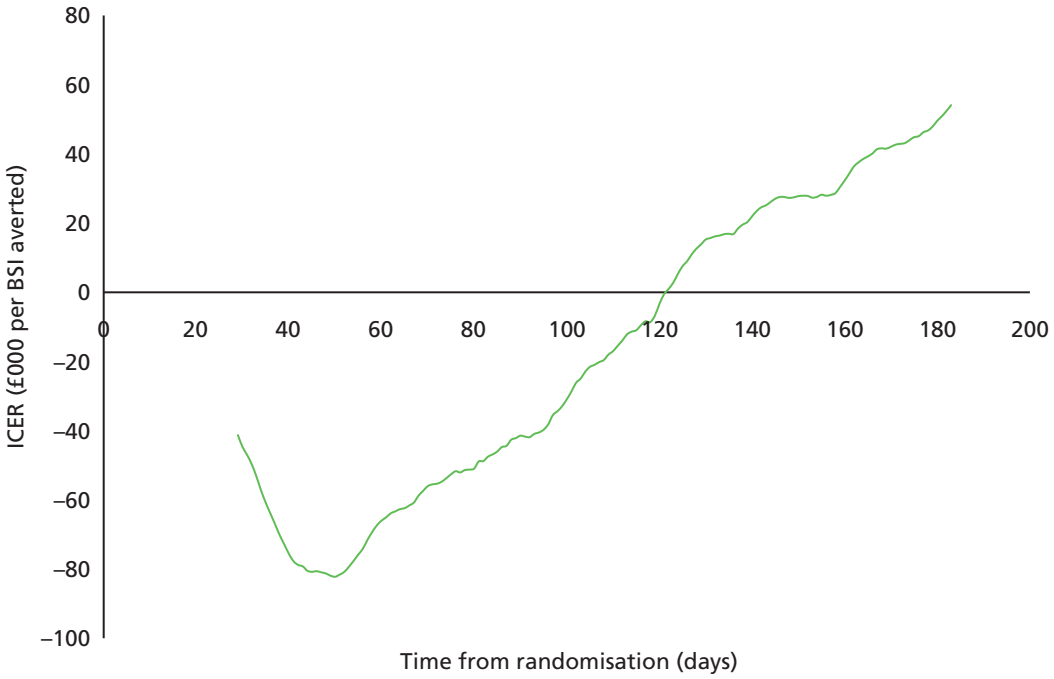

FIGURE 7 Relation between the ICER for antibiotic CVCs compared with standard CVCs and time since randomisation. Positive ICERs are cost incurring and negative ICERs represent incremental savings per BSI averted.

Chapter 5 Generalisability study

Introduction

The CATCH trial was the largest trial carried out in PICUs to date, recruiting 1485 children within 14 PICUs in 12 NHS trusts in England, corresponding to 5% of children admitted to all PICUs in England and Wales during the trial period (2010–12). However, if antibiotic-impregnated CVCs were to be adopted, it is likely that these CVCs would be bulk purchased and used for all children requiring CVCs in PICUs, not just children like those in the trial. Those making decisions on whether or not to purchase antibiotic-impregnated CVCs therefore need to take into account the generalisability of benefits to all children who need a CVC and the cost impact of purchasing the more expensive impregnated CVCs.

In terms of generalisability, trial populations may have different characteristics and outcomes from the characteristics and outcomes of those who receive the intervention in practice, for a variety of reasons.[76] In the CATCH trial there were two specific reasons why those recruited might differ from those likely to receive impregnated CVCs outside the trial setting. First, children recruited to the CATCH trial were expected to require a CVC for ≥ 3 days and would therefore have a higher risk of BSI than those staying for < 3 days. Second, the introduction of CVC care bundles and ongoing improvements in infection control in recent years have been associated with rapidly decreasing rates of BSI over the past decade, meaning that the background BSI rate may be lower now than it was at the start of the trial.[33,34]

In terms of budget impact, impregnated CVCs are approximately twice as expensive as standard CVCs. However, the additional costs might be outweighed by the number of BSIs averted through using the more effective CVCs and the associated reduction in the use of health-care resources.

We determined the generalisability of the CATCH trial findings by estimating risk-adjusted trends in the rate of BSIs for children expected to require CVCs in PICUs, based on a data linkage study including children not participating in the CATCH trial.[77] We determined the budget and cost impacts of adopting antibiotic-impregnated CVCs for all children requiring a CVC in the PICU by synthesising the following evidence: (1) the estimated risk of BSI using standard CVCs (derived from the data linkage study); (2) the number of BSIs potentially averted by using antibiotic-impregnated CVCs (based on the relative treatment effect in the trial); (3) the additional costs associated with purchasing impregnated CVCs for all children expected to require a CVC (numbers of CVCs based on PICU survey data); and (4) the value of the health-care resources associated with each BSI (from the CATCH cost-effectiveness analysis).

Methods

Rate of bloodstream infections using standard central venous catheters

Data sources

There is no single data set from which the rate of BSIs in PICUs across the NHS can be estimated for children requiring standard CVCs. Linkage between the national laboratory surveillance system co-ordinated by PHE (LabBase2)[78] and data from PICANet[57] has provided an enhanced data set from which to estimate the baseline rate of BSIs.

Details of the data linkage study have been published elsewhere.[77] Briefly, a combination of deterministic linkage and a method called prior-informed imputation was used to identify PICANet admission records that had a corresponding record of a BSI in LabBase2.[79,80] A set of deterministic rules based on agreement between NHS number, hospital number, first name, surname, date of birth and postcode was used to identify unequivocal links. For the remaining records, match probabilities were calculated based on date of birth, Soundex code for surname, sex and location (laboratory and hospital). Match probabilities were used to inform imputation of values for uncertain links using prior-informed imputation.[79,80] Five imputed data sets were produced and analysed separately, with results combined using Rubin's rules.[81]

The resulting linked data set captured approximately 71% of all children aged < 16 years admitted to 20 of the 25 PICUs in England and Wales between March 2003 and December 2012 and is broadly representative of the whole PICU population.[82] As some PICUs used impregnated CVCs for some patients, we restricted the linked data set to children expected to require a standard CVC in a PICU in England. Types of CVCs used for emergency and elective admissions at each PICU were derived from responses to a PICU practice survey sent to a designated consultant at each PICU in 2009.[32] When no response was obtained or the PICU was not included in the survey, we assumed that standard CVCs were used.

Identifying children with central venous catheters

Central venous catheter use is not routinely captured for all admissions in PICANet, so we identified admissions likely to have included use of a CVC using a statistical model. We estimated the probability of CVC use for all admissions based on a subset of individual-level audit data in which CVC used was recorded.[82] Presence of a CVC was recorded for 2488 admissions as part of two audits: London's Great Ormond Street Hospital (January 2006–December 2010) and Cambridge's Addenbrooke's Hospital (July 2009–December 2009). We used a multivariable logistic regression model to predict the probability of CVC use for all admissions, based on potentially predictive variables recorded in PICANet (e.g. use of vasoactive agents, length of stay and other clinical factors). The best-fitting predictive model was chosen based on the Bayesian information criterion (BIC).

The internal validity of the model was assessed using bootstrapping, accounting for any model overfitting from developing and testing the model in the same data set.[83–85] The external validity was assessed using aggregate data from a further two PICUs. We identified the subset of admissions most likely to have required a CVC using a probability cut-off based on the Youden Index.[86] Full details of the predictive model are provided in *Appendix 4*.

Estimated BSI rates were based on the subset of admissions identified by the predictive model as most likely to have received standard CVCs.

Case definition

We estimated CVC-days at risk of BSI by assuming that, for children expected to require a CVC, bed-days in the PICU were equivalent to CVC-days, that is, CVCs were inserted at admission and removed at discharge from the PICU. We defined an episode of BSI as any positive blood culture isolated from a blood sample taken from 2 days after admission to 2 days after discharge from the PICU. Repeated samples with positive cultures of the same organism within 14 days were treated as the same episode.

Statistical analysis

Rates of BSI per 1000 CVC-days were modelled using multilevel Poisson regression. We accounted for clustering of admissions within PICUs by including a random effect for PICU. The appropriateness of the Poisson model was verified using a goodness of fit test based on the deviance statistic. For comparisons between units and over time, rates were adjusted for risk factors identified as being significant ($p < 0.05$). Likelihood ratio tests were used to identify significant interactions between risk factors.

We compared BSI rates between CATCH participants using a standard CVC and non-participating admissions expected to require a standard CVC and non-participating admissions in the same PICUs but not expected to require a CVC. For non-participating PICUs, the trial period was defined as the period between December 2010 (when the first PICU began recruiting) and December 2012 (when the last PICU stopped recruiting).

Number of bloodstream infections averted using antibiotic central venous catheters

We estimated the difference in the number of BSIs if antibiotic CVCs were used in place of standard CVCs. We asked PICUs to provide the percentage of emergency and elective admissions receiving CVCs in a second PICU practice survey conducted in 2012 (not published but a repeat of the first survey[32]). The number of admissions requiring CVCs in all 23 PICUs in England was then estimated by applying these percentages to the number of emergency and elective admissions within each PICU. The total number of CVC-days was estimated by multiplying the number of CVCs required by the mean number of CVC-days for children expected to require a CVC in PICANet.

We estimated the BSI rate using antibiotic CVCs in place of standard CVCs by applying the relative treatment effect (rate ratio) from the trial to the BSI rate using standard CVCs.

We assumed that the relative treatment effect would be the same regardless of the baseline rate of BSIs, that is, the effect would be the same for children who would have been ineligible for the trial because they were expected to stay for < 3 days in the PICU. We reasoned that the biological mechanism through which impregnated CVCs work is the same for low- and high-risk patients (impregnated CVCs reduce the chance that bacteria track internally or externally along the CVC from the insertion site). RCTs of impregnated CVCs show similar results for long- and short-term CVCs, suggesting that the effect is not modified in groups with a different baseline risk or length of stay.[2] In reality, 72% of children recruited in the CATCH trial required a CVC for ≥ 3 days.

Budget impact: additional costs of antibiotic central venous catheters

Antibiotic CVCs are more expensive than standard CVCs: £73 compared with £42 for double-lumen CVCs and £79 compared with £43 for triple-lumen CVCs. The total additional costs of antibiotic CVCs were calculated by multiplying the number of CVCs required by the maximum additional cost per CVC, that is £36. We assumed, conservatively, that any change in PICU length of stay, nursing or other resources would not impact on hospital budgets. The budget impact was therefore based on the additional costs of antibiotic CVCs only.

Cost impact: value of resources associated with managing bloodstream infections

Assuming that any differences in costs between arms were the result of differences in the number of BSIs, the cost impact analysis utilised the estimated difference in the 6-month risk-adjusted costs between patients who had a BSI and those who did not (£10,975 per BSI, 95% CI –£2801 to £24,751) (cost-effectiveness analysis; see *Table 18*).

The total number of BSIs potentially averted was estimated by applying the BSI rate assuming that all children in 2012 had used either standard CVCs or antibiotic CVCs. The cost impact (total value of resources associated with managing BSIs with standard CVCs) was calculated by multiplying the costs per BSI by the estimated number of BSIs averted if antibiotic CVCs were used instead of standard CVCs.

Sensitivity analysis

We estimated the budget and cost impacts based on best- and worst-case scenarios for the total number of CVCs required and the excess number of BSIs for standard compared with antibiotic CVCs. We also performed probabilistic sensitivity analysis using Monte Carlo simulation to reflect uncertainty in both costs and number of BSIs. Values for each parameter were sampled from probability distributions based on observed data and 5000 iterations were performed to provide a 95% uncertainty interval for the cost impact.[87]

Results

Rate of bloodstream infections using standard central venous catheters

Of the 2488 admissions in the CVC audit data, 1431 (58%) required a CVC. The best-fitting prediction model included length of stay, vasoactive agent, admission from ward, renal support and invasive ventilation (see *Appendix 4*, *Table 37*). With a probability cut-off of 0.57, the sensitivity of the predictive model for capturing admissions requiring a CVC was 61%, specificity was 82%, the positive predictive value was 82% and the negative predictive value was 61%. The predictive model identified 80% of the CATCH admissions as requiring a CVC.

Survey responses for the types of CVCs used prior to the CATCH trial were obtained for 18 of the 23 PICUs in England (see *Appendix 4*, *Table 36*). Only two PICUs reported not using standard CVCs for any admissions (both used heparin CVCs). BSI rates were estimated based on linked data from the remaining 16 English PICUs.

Applying the predictive model to the 16 PICUs in the linked data set identified a subset of 21,381 admissions most likely to have received a standard CVC between 2003 and 2012. The characteristics of these admissions (based on PICANet data) are provided in *Appendix 4* (see *Table 38*). Risk-adjusted rates of BSI using standard CVCs decreased steadily between 2003 and 2012 and were greater for CATCH PICUs (5.27, 95% CI 5.06 to 5.49 per 1000 CVC-days in 2012) than for non-participating PICUs (2.09, 95% CI 1.60 to 2.58 per 1000 CVC-days in 2012) (*Figure 8*). Of the subset of admissions predicted to receive a CVC in 2012, 103 out of 3021 (3.4%) experienced a BSI, corresponding to an overall BSI rate using standard CVCs of 4.58 (95% CI 4.42 to 4.74) per 1000 CVC-days (*Table 21*). This was non-significantly lower than the rate observed during the trial (8.24, 95% CI 4.7 to 11.8 per 1000 CVC-days; see *Table 9*), partially because of the inclusion of all children with CVCs (not just those requiring CVCs for ≥ 3 days). Further explanations for this difference are the potentially incomplete reporting of BSIs to the national infection surveillance system, use of bed-days instead of CVC-days in the estimated rate and the increased frequency of sampling in trial PICUs during the CATCH trial.

Number of bloodstream infections averted using antibiotic central venous catheters

Survey responses indicated that, on average, 60% of emergency admissions and 50% of elective admissions require a CVC (see *Appendix 4*, *Table 36*). The estimated number of children using CVCs in 2012 was 8831, corresponding to a total of 85,971 CVC-days (see *Table 21*). The rate ratio for BSIs for antibiotic compared with standard CVCs was estimated as 0.40 (95% CI 0.17 to 0.97; see *Table 10*) in the trial. The point estimate of the number of BSIs averted by switching from standard to antibiotic CVCs for all children requiring CVCs in 2012 was therefore 232, with best- and worst-case scenarios of 332 and 11 respectively (*Table 22*).

Budget impact: additional costs of antibiotic central venous catheters

Based only on a CVC cost difference of £36, the additional cost of purchasing antibiotic CVCs for all children in 2012 was 8831 × £36 = £317,916.

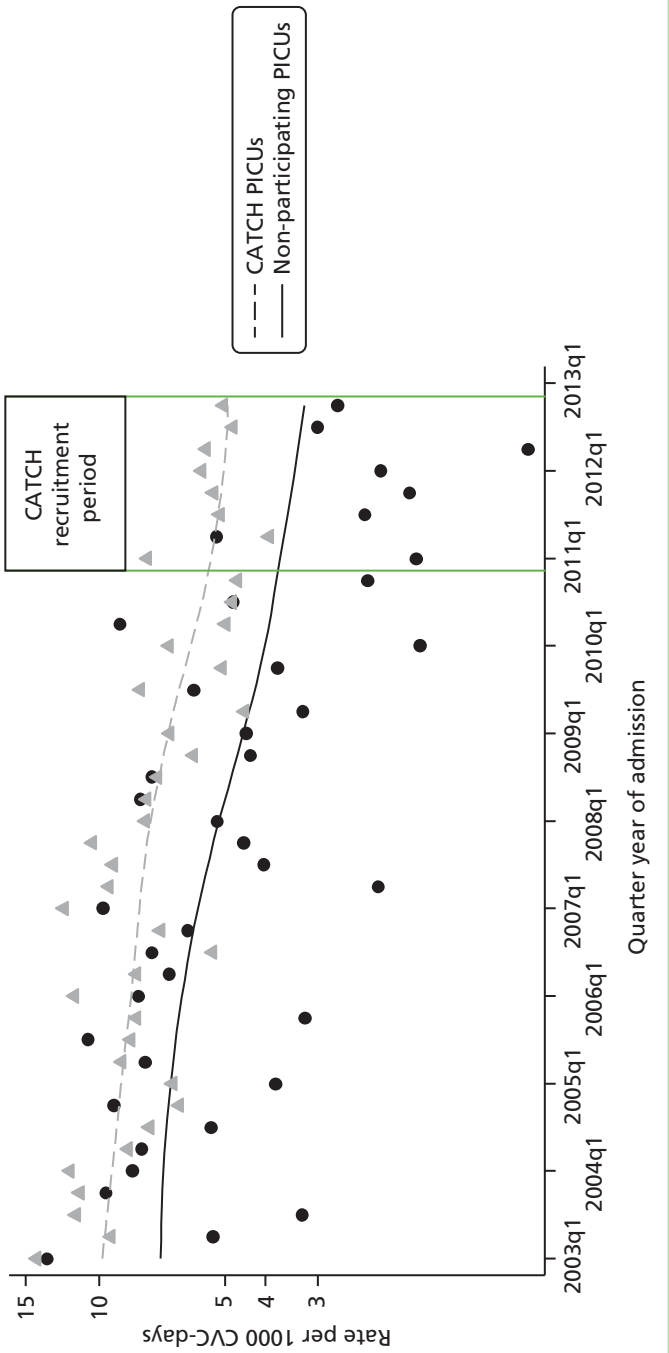

FIGURE 8 Risk-adjusted rates of BSIs for children expected to have a CVC based on linked PICANet–LabBase2 data for 16 PICUs in England. Symbols = observed rates; lines = smoothed adjusted rates (log scale).

TABLE 21 Parameter estimates for the cost impact and sensitivity analyses

Variable	Base case	Source	Sensitivity analysis
BSI rate using standard CVCs in 2012 per 1000 CVC-days	4.58 (95% CI 4.42 to 4.74)	3021 admissions in 15 PICUs – subset of admissions identified as most likely to have received a standard CVC by applying the predictive model to the linked data set. Admissions identified by survey responses as receiving non-standard (heparin or antibiotic) CVCs were excluded	Random sample taken with replacement from the linked data set for the number of admissions expected to require a CVC
Rate ratio	0.40 (95% CI 0.17 to 0.97)	Trial clinical effectiveness analyses (see *Table 10*)	Log-normal distribution with parameters (–0.913, 0.415)
Estimated BSI rate using antibiotic CVCs in 2012 per 1000 CVC-days	1.83; worst case 4.29, best case 0.81	Rate ratio from the CATCH trial applied to the estimated BSI rate using standard CVCs for PICUs in England	Derived from (i) the BSI rate using standard CVCs and (ii) the rate ratio
Number of admissions requiring CVCs in 2012	8831	Average survey estimates for the percentage of emergency (60%) and elective (50%) admissions requiring CVCs, applied to all admissions in PICANet in 2012 (15,739 admissions in 23 PICUs)	Beta distributions with stated parameters: emergency: beta (60,40); elective: beta (50,50)
Number of CVC-days in 2012	85,971	Average bed-days per admission in the subset of admissions identified as most likely to have received a standard CVC by applying the predictive model to the linked data set, multiplied by the number of admissions requiring a CVC in 2012	Random sample taken with replacement from the linked data set for admissions expected to require a CVC
Number of BSIs averted in 2012	232	BSI rate applied to CVC-days for admissions requiring a CVC in 2012	Derived from (i) the number of admissions requiring a CVC in 2012 and (ii) the estimated BSI rate using antibiotic CVCs
Additional cost of antibiotic CVCs	£36	Difference in costs between standard (£43) and antibiotic (£79) CVCs (conservative case assuming triple-lumen CVCs used for all children)	Fixed at £36
Costs associated with managing each BSI	£10,975 (95% CI –£2801 to £24,751)	CATCH trial cost-effectiveness analysis (see *Table 18*)	Normal distributions with parameters (£10,975, £7,023)

TABLE 22 Cost impact analysis of managing BSIs occurring with standard compared with antibiotic CVCs, with best- and worst-case scenarios for all PICUs in 2012[a] and hypothetical scenarios for a typical PICU with 350 admissions per year

Scenario	BSI rate using standard CVCs	Rate ratio	BSI rate using antibiotic CVCs	BSI with standard CVCs	BSI with antibiotic CVCs	BSI averted cost–impact		
						Cost per BSI: –£2801	Cost per BSI: £10,975	Cost per BSI: £24,751
Base case	4.58	0.40	1.83	385.9	154.4	231.6	231.6	231.6
						–648,606	**2,541,397**	5,731,401
Worst case	4.42	0.97	4.29	372.5	361.3	11.2	11.2	11.2
						–31,297	122,631	276,559
Best case	4.74	0.17	0.81	399.4	67.9	331.5	331.5	331.5
						–928,583	3,638,415	8,205,414
	1	0.40	0.40	3.4	1.3	2.0	2.0	2.0
						–5,645	22,119	49,884
	2	0.40	0.80	6.7	2.7	4.0	4.0	4.0
						–11,290	44,238	99,767
	3	0.40	1.20	10.1	4.0	6.0	6.0	6.0
						–16,936	66,358	149,651
	4	0.40	1.60	13.4	5.4	8.1	8.1	8.1
						–22,581	88,477	199,534
	5	0.40	2.00	16.8	6.7	10.1	10.1	10.1
						–28,226	110,596	249,418
	6	0.40	2.40	20.2	8.1	12.1	12.1	12.1
						–33,871	132,715	299,301
	7	0.40	2.80	23.5	9.4	14.1	14.1	14.1
						–39,516	154,834	349,185
	8	0.40	3.20	26.9	10.7	16.1	16.1	16.1
						–45,161	176,954	399,069

a Best- and worst-case scenarios assume a total of 8831 CVCs required in PICUs in England during 2012 (based on survey responses).
BSI rate is per 1000 CVC-days.
Bold indicates cost used in base-case analysis.

Cost impact: value of additional costs associated with managing BSI

Based on each BSI being associated with a mean cost of £10,975 (95% CI –£2801 to £24,751; see *Table 18*), over 6 months the value of resources made available in 2012 through averting BSIs associated with standard CVCs (i.e. the total costs of managing these BSIs) would have been 232 × £10,975 = £2,541,397, with best- and worst-case scenarios of –£648,606 and £5,731,401 based on CIs for both estimates. The probabilistic sensitivity analysis provided a 95% uncertainty interval of –£66,544 to £5,557,451 for the total resources made available through averting BSIs in 2012. There was a probability of 0.90 that the value of resources made available would be more than the additional costs of purchasing antibiotic CVCs (*Figure 9*).

The estimated cost impact for a typical PICU with 350 admissions per year is shown for a range of BSI rates in *Table 22*. *Figure 10* shows that the cost of purchasing antibiotic CVCs for all children who require them will be less than the cost of managing BSIs with standard CVCs for PICUs with BSI rates > 1.2 per 1000 bed-days. This break-even value is substantially lower than the BSI rate observed in the standard arm of the trial (8.24, 95% CI 4.7 to11.8 per 1000 bed-days) or in the linked data set for PICUs in England (4.58, 95% CI 4.42 to 4.74 per 1000 bed-days).

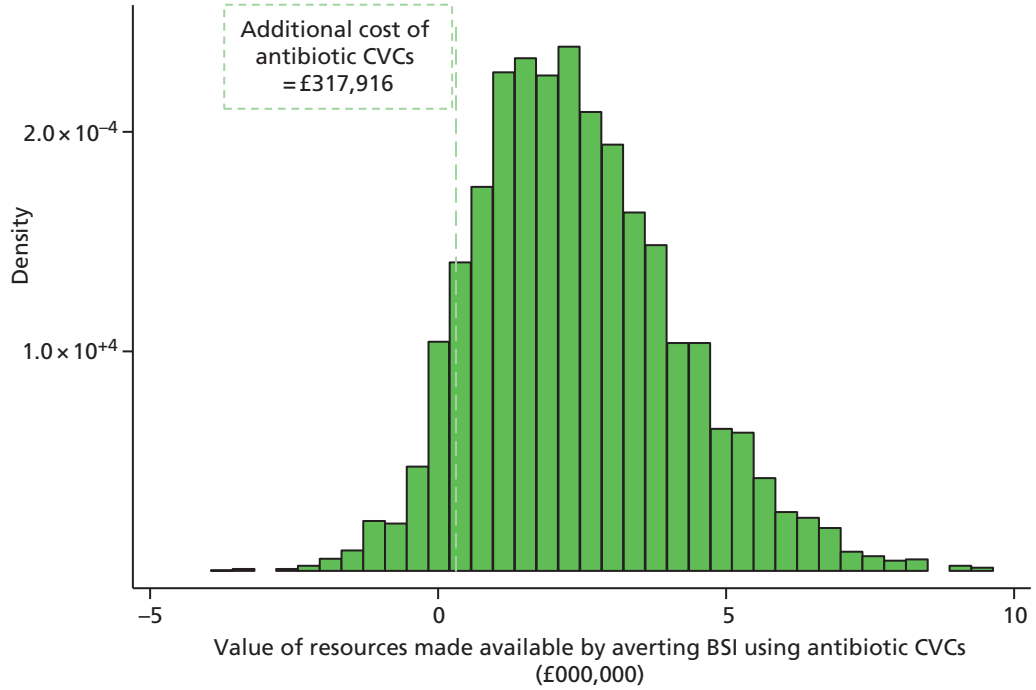

FIGURE 9 Probability distribution for the value of resources made available by averting BSIs using antibiotic CVC in all PICUs in England during 2012. In total, 90% of the distribution represented costs greater than the additional cost of purchasing antibiotic CVCs.

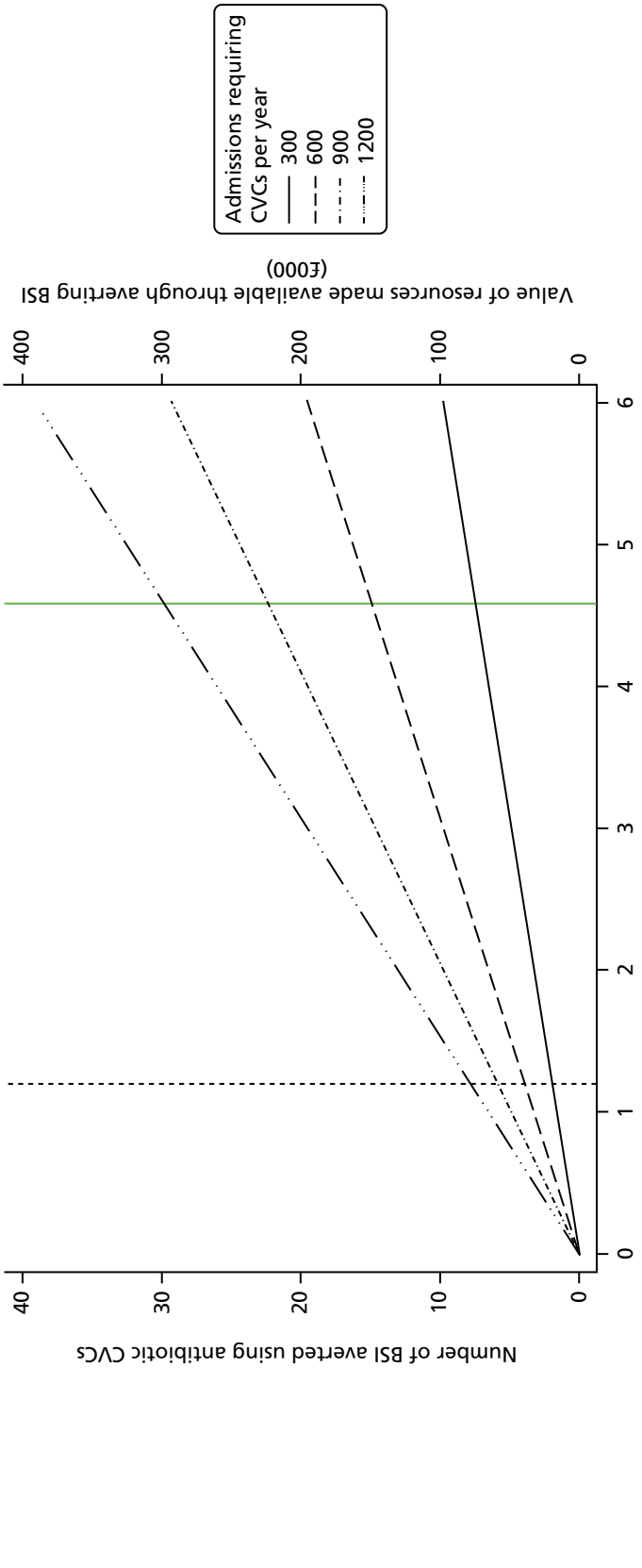

FIGURE 10 Cost impact: number of BSIs averted and value of resources made available using antibiotic in place of standard CVCs for a range of baseline BSI rates, assuming that each BSI is associated with a mean cost of £10,975.

Chapter 6 Discussion

Introduction

We aimed to inform NHS policy regarding impregnated CVCs for the intensive care of children. To address the question of whether or not impregnated CVCs should be adopted by PICUs in England and Wales, we undertook a large pragmatic RCT to determine the clinical effectiveness and cost-effectiveness of impregnated compared with standard CVCs. To determine the implications of adopting impregnated CVCs for all children who need them, we conducted a generalisability and cost impact study, using linked data from two national sources.

Clinical effectiveness

The primary analysis showed no evidence of a statistically significant difference in time to first BSI between any impregnated CVCs (antibiotic-impregnated and heparin-bonded CVCs combined) and standard CVCs. However, secondary analyses showed that antibiotic impregnation reduced the hazard of BSIs by 57% compared with standard CVCs and by 58% compared with heparin-bonded CVCs. Antibiotic-impregnated CVCs were associated with an absolute risk reduction of 2.15% compared with standard CVCs, meaning that 47 children would need to be treated with an antibiotic-impregnated CVC instead of a standard CVC to prevent one case of BSI.

Our choice of any BSI as a clinically important primary outcome and a recognised quality indicator is an important strength of our study, avoiding the biases inherent in measuring CR-BSI.[2,46,88,89] CR-BSI requires positive cultures from the blood and catheter tip and is highly susceptible to bias, as the tip can be easily contaminated during removal and residual antibiotic in the catheter tip may inhibit culture in the laboratory.[55,88]

A further strength of the study is the restriction to positive blood cultures that were clinically indicated. This increased the clinical relevance of the primary outcome, but diminished the sensitivity of the study to detect bacteraemia, as only 40% of children had a blood culture taken in the relevant time window. A third strength is the representativeness of the study population in terms of children admitted to the 14 largest PICUs (of 23) across England. We were able to enrol a similar proportion of emergency patients (two-thirds) as seen in practice, enabled by the inclusion of retrieved children and the use of deferred consent.[90]

A potential limitation of the study is that clinicians inserting the CVCs could not be blinded to allocation. However, we found no evidence of differential sampling by trial arm (see *Figure 1*). The number of children who received their allocated CVC was slightly higher for those in the standard arm, probably reflecting the fact that standard CVCs were the default CVC used in many units.[32] A second limitation is that, because of the lower than expected BSI rate in the standard arm of the trial, we had limited power to detect differences in the primary outcome comparing impregnated with standard CVCs. This choice of primary outcome was justified by the best available evidence to date – a systematic review and meta-analysis of direct and indirect comparisons of different types of impregnated and standard CVCs[28] – which showed that heparin-bonded and antibiotic-impregnated CVCs resulted in similar reductions in the risk of CR-BSI (70–80%). A third limitation is that resistance testing was not standardised across sites. This reflects local laboratory administration and processing, which centralised testing of all positive cultures could have mitigated. When reported, resistance occurred in all trial arms, predominantly in Gram-negative isolates, as expected. The low rates are consistent with the previous lack of evidence for the emergence of resistance.[1]

Few previous trials have reported the effectiveness of impregnated CVCs for any BSI.[45] However, the superiority of antibiotic-impregnated CVCs in children was consistent with the most recent systematic review reporting a pooled odds ratio for CR-BSI of 0.18 (95% CI 0.08 to 0.34).[28] Although our finding of a clinically important reduction in any BSI with antibiotic-impregnated CVCs (HR 0.25, 95% CI 0.07 to 0.09; $p = 0.04$) was based on a secondary comparison and should be viewed as exploratory, this result does add important evidence of the overall effectiveness of antibiotic-impregnated CVCs.

The finding that heparin CVCs were not effective for BSIs or CR-BSIs contradicts past evidence showing a pooled odds ratio for CR-BSI for heparin-bonded compared with standard CVCs of 0.20 (95% CI 0.06 to 0.44).[28] The difference in findings may reflect poor data quality in previous trials, highlighted by systematic reviews. Only one of the three trials comparing heparin with standard CVCs reported adequate concealment of randomisation, and this trial did not state whether or not clinicians were blinded to the intervention.[2] A further explanation for the discrepancy may be the low baseline event rate observed in the CATCH trial, which was conducted after implementation of CVC care bundles in PICUs to improve aseptic procedures during CVC insertion and maintenance.[32] It is conceivable that heparin CVCs are most effective in the context of high rates of surface colonisation, as they prevent thrombosis, which aids organism adherence to the CVC. Finally, the pairwise comparisons used to determine the most effective type of impregnation were not adequately powered to detect the anticipated small differences between antibiotic and heparin CVCs. However, our results suggest that antibiotic-impregnated CVCs can achieve further reductions in BSI rates, over and above that achieved by CVC care bundles.[33,34]

Cost-effectiveness

The ICER of antibiotic-impregnated CVCs compared with standard CVCs was £54,057 per BSI averted over the 6 months after randomisation. Assuming that the health impact of a BSI is no greater (on average) than a reduction of 1 year of full health (i.e. 1 QALY), then, at the cost-effectiveness threshold of £30,000 per QALY, antibiotic CVCs may not represent a cost-effective alternative to standard CVCs in a PICU setting. However, there is considerable uncertainty surrounding this estimate, which is driven mainly by the time horizon of analysis.

The sensitivity analysis in which costs were restricted to the index hospital stay resulted in antibiotic CVCs dominating standard CVCs, with £97,543 saved for each BSI averted. Antibiotic CVCs therefore appear highly cost-effective when considering events and costs accruing over comparable periods.

A secondary analysis of the CATCH trial indicated that heparin CVCs were not clinically effective, with a risk difference for a first BSI of –0.17 (95% CI –2.45 to 2.12) compared with standard CVCs. It follows, therefore, that heparin CVCs cannot be cost-effective by the same measure. Theoretically, a cost-minimisation analysis might apply, to assess whether or not heparin CVCs are less costly overall than standard CVCs. However, heparin CVCs are more expensive than standard CVCs (in terms of unit prices) and, as the only difference among CVCs can be in BSI rates, any difference in total cost (which was not statistically significant) was caused by random variation. A cost-minimisation analysis might therefore lead to an erroneous conclusion that heparin CVCs are more cost-effective than standard CVCs.

Our economic evaluation benefits from being conducted alongside a pragmatic clinical trial, which is representative of current practice in the UK PICU setting. The evaluation utilises data from a definitive and unbiased comparison of impregnated and standard CVCs and was conducted robustly according to accepted methods of trial-based economic evaluations.[74] We used patient-level HES data to reflect the reimbursement costs for hospitals and multiple data sources to measure hospital resource use to ensure that cost data were complete.

However, there are limitations that affect the strength of our findings. First, the CATCH trial was not powered to determine cost differences between each of the three CVCs. As a consequence, the results are susceptible to random variation in costs between trial arms. Although hypothesis testing may be considered less relevant to decision making in the context of net benefits, the non-statistically significant differences in costs between groups translated to uncertainty in the joint distribution of costs and benefits such that, in the base-case analysis, antibiotic CVCs had a probability of 0.35 of dominating standard CVCs.[91] Mean total costs associated with heparin CVCs were lower than those for both antibiotic and standard CVCs, despite their ineffectiveness in avoiding BSIs compared with standard CVCs. Being a rare event, BSI costs were diluted compared with the overall costs relating to the intensive care of patients.

Second, the economic evaluation did not consider QALYs, which is the standard metric for informing decisions on resource allocation. This was because the estimation of utilities in paediatric ICU populations is empirically and conceptually challenging[92,93] and because the main long-term consequence of BSIs, the impact on neurological outcomes, is poorly measured in children and was not measured in this trial. Short-term outcomes not considered in our economic analysis include mortality, antibiotic resistance and other adverse events. However, antibiotic resistance to minocycline or rifampicin did not differ by CVC allocation. There were no also no differences in 30-day mortality for antibiotic compared with standard CVCs (HR 0.96, 95% CI 0.61 to 1.51) or for heparin compared with standard CVCs (HR 0.65, 95% CI 0.40 to 1.07) and no differences in adverse events (see *Table 11*).

Assumptions regarding the time horizon of analysis represent a third limitation. The base-case, 6-month analysis was selected to include the costs of hospital readmissions in addition to the costs of the index hospitalisation and transfers that may have occurred subsequently. This was intended to capture the costs of managing any longer-term complications from BSIs, but, as the economic outcome was chosen to align with the primary clinical outcome, the health impacts of these complications were not included in the ICER. Consequently, as costs accrue over time with no corresponding change in the number of BSIs (these all occurred within 30 days), the ICER continued to increase over time.

Our findings are consistent with those of other studies in terms of the estimation of the costs associated with the management of BSIs. However, our ICER differs considerably and is inconclusive with regard to determining the cost-effectiveness of antibiotic CVCs. Published economic evaluations, including those that adopted a lifetime horizon of analysis, suggest dominance of antibiotic-impregnated CVCs over standard CVCs. One explanation for this discrepancy is in the methods of analysis. A decision-analytic model, based on a synthesis of data from various sources, is fundamentally different from a prospective RCT, in which differences between intervention groups are less evident, particularly in the context of rare events such as BSIs. In the evaluation by Hockenhull *et al.*,[29] for instance, the incremental cost saving of £138.20 per patient receiving an impregnated CVC was calculated as the additional cost of the antibiotic CVC less the expected cost per patient of managing excess BSIs. The equivalent calculation based on CATCH data for antibiotic CVCs results in a value of £200.08 saved for each antibiotic CVC used [(£78.28 – £42.91) – (£10,975 × 2.15%)]. Extending this further to calculate the ICER gives a value of £9326 saved per BSI averted (£200.08/2.15%), which differs appreciably from our base-case result [the differences between the ICER stated and the ICER calculated from the numbers in the text is due to rounding (difference in risk of BSI is 2.1453%)]. However, by analysing the data as a cohort study, separating the apparent costs of BSIs from the total costs relating to each intervention group, biases are likely to arise from assuming that the cost of managing BSIs is independent of CVC type.

In conclusion, the results of the cost-effectiveness analysis indicate that a policy of replacing standard CVCs with antibiotic-impregnated CVCs in paediatric ICUs would be more beneficial in terms of fewer patients developing BSIs. Given the low BSI rate, the variation in costs between arms and the sensitivity of analyses to the specified time horizon, there remains considerable uncertainty whether or not use of antibiotic CVCs represents a cost-effective use of NHS resources.

Generalisability and cost impact

We explored the generalisability of the CATCH trial results and the cost impact of changing practice in PICUs across England based on the trial results. In terms of generalisability, the observed rates of BSI using standard CVCs declined steadily over the past decade, including the period when children were enrolled into the CATCH trial.[34,94] In addition, children participating in the CATCH trial had a higher risk of BSI than all children receiving CVCs in practice, as they were expected to require a CVC for ≥ 3 days. This means that children currently receiving CVCs in PICUs are likely to have a lower BSI risk than those participating in the trial. This was reflected in the higher rate of BSIs observed in the standard arm of the trial (8.24 per 1000 bed-days) compared with linked administrative data from 16 PICUs in England for 2012 (4.58 per 1000 bed-days; see *Figure 8*).

In terms of budget impact, antibiotic CVCs are more expensive than standard CVCs. If adopted in PICUs, antibiotic CVCs would likely be bulk purchased for all children (including those with a lower risk of BSI than the risk for children participating in the trial). By estimating the number of BSIs potentially averted using antibiotic CVCs for all children (including those with a low risk of BSI), we showed that the additional cost of purchasing antibiotic CVCs is less than the value of resources associated with managing excess BSIs associated with using standard CVCs. A limitation of this study was that estimated BSI rates using standard CVCs relied on a predictive model for identifying children most likely to have required a CVC. Another limitation was the possible error in estimating CVC-days: we assumed that, for children in the linked data set likely to have required a CVC, the CVC would remain in place for the entire PICU stay. There is no clear direction of bias as we may have over- or underestimated CVC-days, but our assumptions are reasonable based on the subset of CATCH participants. Finally, we relied on survey responses to estimate the number of CVCs required in PICUs, but we addressed this and the uncertainty in other parameter estimates by performing sensitivity analyses.[95,96]

The generalisability of the RCT results can be assessed by accounting for differences in subgroup treatment effects, for example by reweighting treatment effects based on population distributions.[97,98] In the CATCH trial, the event rate was low and there was limited power to assess variation in the treatment effect according to the duration of CVC insertion. However, because of the nature of the intervention, we assumed that the treatment effect would be constant across groups and would be the same in children who were not enrolled into the trial, as there was no a priori reason for an interaction.

Our results suggest that the benefits of using impregnated CVCs apply even for PICUs with BSI rates as low as 1.2 per 1000 CVC-days. These finding are consistent with systematic review evidence on the cost-effectiveness of impregnated CVCs in adults, which indicates that implementation of impregnated CVCs would be cost-effective for a range of RRs and for a baseline incidence of CR-BSIs as low as 0.2%.[29] The CATCH trial is the first trial to assess the effectiveness of antibiotic-impregnated compared with standard CVCs in children, and our results adds to the strong evidence of effectiveness in adults. Furthermore, as our cost estimates consider only use of hospital resources, the true cost of BSIs and the benefits of antibiotic CVCs may be even greater when longer-term outcomes of BSIs are taken into account.

Other conclusions

Deferred consent

There is a growing recognition of the need for better evidence in paediatric settings, as evidence in adults cannot always be safely extrapolated to children.[99,100] However, achieving informed consent in emergency paediatric settings is complicated by the stressful situation and the need to avoid any delay in treatment.[56,101] As the CATCH trial was one of the first UK studies to use deferred consent in children, there was a lack of evidence on which to make decisions about the design and conduct of this aspect of the trial.[102,103] Our experience of deferred consent in the CATCH trial could help to inform future studies.

In the CATCH trial, deferred consent was obtained from 84% of families who were approached.[60] The use of deferred consent allowed us to recruit emergency admissions, reach the target sample size within the available funding and provide results that are convincing to clinicians working in the emergency setting. Participation in the CATCH trial after the intervention had taken place represented a minimal burden to children (use of data already collected and follow-up data collection only). However, a proportion of parents chose not to consent because of a perceived burden on the child. Ongoing in-depth research as part of the CONseNt methods in paediatric Emergency and urgent Care Trials (CONNECT) study[56,104] may help to explain further the experiences and choices of parents of children involved in the CATCH trial.

One of the main concerns relating to deferred consent in the CATCH trial was whether or not the decision to consent was related to the child's outcome. The ethics committee recommended not approaching families whose child had been discharged or transferred before the original approach for consent could be made. Inclusion rates were also lower in the group of children who died. Although there were no deaths related to the type of CVC in the CATCH trial, the low rate of consent for children who died could bias the validity of comparisons between treatment arm and outcomes, including adverse events. We propose that, in future, ethics committees allow use of linked administrative records without consent, when reasonable efforts to obtain consent have been made or are not feasible or are considered to be harmful.[60]

There is still uncertainty about the most appropriate ways to approach bereaved parents of children randomised in an emergency.[105] Our experience in the CATCH trial highlights that further in-depth research should be incorporated into the design of emergency trials involving populations with high mortality rates.[106,107]

Co-enrolment

Another challenge to improving evidence in paediatric settings is the limited population of children who can be recruited into trials. The CATCH trial was the largest RCT conducted in paediatric intensive care to date and overlapped with the second largest RCT [the Control of Hypoglycaemia in Paediatric Intensive Care (CHiP) trial],[108] which recruited 1369 children in 13 centres. Allowing co-enrolment into several trials at the same time can potentially enable efficient recruitment of children and has been successful in particular settings, for example in evaluating treatments for acquired immune deficiency syndrome.[88,90,109,110] Aside from statistical concerns, perceived burden to the child, ethics requirements and stress of recruiting into multiple trials are barriers to co-enrolment.[111–114]

Of five PICUs with the opportunity to recruit simultaneously to both the CATCH trial and the CHiP trial, only two units decided to allow co-enrolment. Of the remaining three units, one delayed recruitment of elective patients to the CATCH trial until the CHiP trial had closed, resulting in a loss of 6 recruiting weeks. Reasons provided for not allowing co-enrolment related to concerns about jeopardising recruitment targets for the earlier trial, asking too much of parents because of the overwhelming amounts of information involved for two trials and the stressful situation of intensive care.[112]

On the other hand, we found that parents were accepting of co-enrolment: recruitment rates at the same PICU were similar whether parents were approached for a single study (78% for CATCH, 51% for CHiP) or both studies (82% for CATCH, 51% for CHiP). Concerns of the PICUs were therefore not supported by evidence on parental decisions.[115,116]

Our experience with the CATCH trial highlighted that co-enrolment can be successful and acceptable, but that barriers to co-enrolment remain. Decisions on the appropriateness of co-enrolment need to take into account the potential impact on results, interaction between therapies, safety and internal and external validity. Strategies that allow increasing research capacity whilst minimising burden on patients and parents should continue to be developed.

Administrative/electronic health-care data to support randomised controlled trials

This study provides a convincing example of how administrative and electronic health-care data can be used to support and enhance RCTs.[117] It would not have been possible to provide such comprehensive information relating to the use of impregnated CVCs without the use of administrative data, which contributed to all three aspects of the study:

1. clinical effectiveness: trial participant data were linked with (i) mortality data from the ONS to allow evaluation of deaths within 30 days of randomisation and (ii) PICANet data to ascertain the primary diagnosis at admission and PIM2 score
2. cost-effectiveness: HES and PICANet data were used to estimate hospital, ICU and HDU costs up to 6 months after randomisation
3. generalisability and cost impact: PICANet data linked with national laboratory surveillance data were used to estimate rates of BSI outside of the trial setting.

There are other areas in which administrative and electronic health-care data could be used to enhance and support RCTs.[117] First, in terms of capturing outcomes, we used administrative data up to 6 months post randomisation. Ongoing linkage with administrative data could be useful to many RCTs for capturing further long-term outcomes and safety measures.[118]

Second, the sample size calculation in the CATCH trial was based on audit data from several PICUs prior to the trial. If PICANet and infection surveillance data had been linked prior to the study, even more accurate event rates, taking into account the context of decreasing BSI rates, could have been calculated. Using administrative data to identify variation in care across services and to aid site selection will lead to more well-designed trials that are likely to meet targets and provide evidence more quickly.

Third, we used administrative data collected during the trial period to assess the generalisability of trial participants and to identify the population for whom impregnated CVCs may be purchased. This could be extended post trial by monitoring the scaling up of effective interventions and for the continued study of the safety and efficacy of new medicines and devices.

Barriers to realising the full potential of integrating administrative data into RCTs include concerns about data quality, regulatory compliance and ethical issues relating to consent for data linkage. Decisions on the appropriateness of using administrative data should be made on a trial-by-trial basis. However, administrative data provide an opportunity to efficiently investigate short- and long-term effectiveness in real health-care settings, assess the broader impact of treatments across the NHS and provide evidence on interventions to help implement improved treatments quickly for those who would benefit most. The potential to improve quality and decrease the burden and cost of RCTs is particularly important in the paediatric setting.[99,119,120]

Implications for practice

Although our primary outcome showed no difference between the different types of CVC, secondary analyses demonstrated strong evidence of effectiveness of antibiotic-impregnated CVCs compared with standard and heparin-bonded CVCs in children. Based on these results, we consider that use of antibiotic-impregnated CVCs for children admitted to PICUs could result in clinically important reductions in BSI rates. We expect that the benefits of antibiotic-impregnated CVCs would be likely to apply even for PICUs with low BSI rates. At the cost-effectiveness threshold of £30,000 per QALY, antibiotic-impregnated CVCs may not represent a cost-effective alternative to standard CVCs in a PICU setting. However, there is considerable uncertainty surrounding this estimate, which is driven mainly by the time horizon of analysis. Careful monitoring of implementation would help to build up further evidence.

Recommendations for future research

Our research suggests that adoption of impregnated CVCs in PICUs should be considered. Implementation could be monitored through continued linkage of electronic health-care data and information on PICU practice. Such monitoring could allow routine feedback to PICUs and could be enhanced by routine capture of CVC insertion and removal dates in hospital records.

We do not recommend any further trials of antibiotic-impregnated or heparin-bonded CVCs compared with standard CVCs for children or adults in intensive care. However, further trials could be justified to determine whether or not antibiotic CVCs would be similarly effective in preterm neonates (for whom smaller line sizes are required, with potentially different mechanisms for BSI) or in those with long-term CVCs (to determine whether or not the effect of impregnation remains for longer periods). The NHS should work with industry to evaluate different types of impregnation for specific patient groups.

Use of linked administrative data should be considered for future trials to determine the generalisability of interventions in contexts in which outcomes are likely to change substantially over the lifetime of the trial and to monitor implementation of effective interventions.[117]

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Trial oversight committees

We would like to thank all of the members of the trial oversight committees for their support and work throughout the study and the recommendations in *Table 23*: Trial Steering Committee – Robert Tasker (Chair), Stephen Playfor (Chair), Andy Vail, Derek Roebuck, Jim Gray and Hazel Greig-Midlane; IDSMC – Paul Ewings (Chair), Mike Sharland, Neena Modi; and the Trial Management Group – Ruth Gilbert (Chair and Chief Investigator), Carroll Gamble, Kerry Dwan, Tracy Moitt, Rachel Breen, Colin Ridyard, Angie Wade, Dyfrig Hughes, Quen Mok, Liz Draper, Shane Tibby, Michael Millar, Oliver Bragshaw, Padmanabhan Ramnarayan, Julia Harris and Darren Hewett.

All members of the Trial Management Group, the Trial Steering Committee and the IDSMC were invited to comment on the final draft of the report.

Ethics

For PICANet, collection of personally identifiable data was approved by the National Information Governance Board for Health and Social Care (formerly the Patient Information Advisory Group) [see www.nigb.nhs.uk/s251/registerapp (accessed 25 November 2015)] and ethical approval was granted by the Trent Medical Research Ethics Committee (reference number 05/MRE04/17). PICANet also has specific permission from the National Research Ethics Service for linkage with PHE laboratory data on BSIs using personal identifiers and to share PICANet data with PHE. An exemption under Section 251 of the NHS Act 2006[121] (previously Section 60 of the Health and Social Care Act 2001[122]) allows PHE to receive patient-identifiable data from other organisations without patient consent to monitor infectious disease. Specific permission for the PICANet–PHE linkage has been granted by the National Information Governance Board for Health and Social Care.

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TABLE 23 Trial oversight committee meetings and recommendations

Oversight committee	Meeting dates	Recommendations
IDSMC	26 October 2009, 26 March 2010, 10 February 2012, 14 June 2012	Trial to be continued
Trial Steering Committee	26 October 2009, 26 March 2010, 12 March 2012, 2 August 2012	Support for continuing to recruit past the target number

Contributions of authors

Katie Harron (research fellow), **Dyfrig A Hughes** (Professor of Pharmacoeconomics) and **Ruth E Gilbert** (Professor of Clinical Epidemiology) prepared drafts of the report, which were reviewed and amended by coauthors [**Quen Mok** (Consultant in Paediatric Intensive Care), **Kerry Dwan** (Statistician), **Tracy Moitt** (senior trials manager), **Michael Millar** (Consultant in Infection), **Padmanabhan Ramnarayan** (Consultant in Paediatric Intensive Care and Retrieval), **Shane M Tibby** (Consultant in Paediatric Intensive Care), Berit Muller-Pebody (Consultant in Infection Control) and **Carrol Gamble** (Professor in Medical Statistics)].

Statistical analyses were conducted by **Kerry Dwan** (research associate) and **Carrol Gamble** (Professor of Medical Statistics).

Colin H Ridyard (research officer in Health Economics) performed the cost-effectiveness analyses.

Berit Muller-Pebody co-ordinated the linkage of PICANet data to laboratory surveillance data.

The end-point review for the primary outcome was carried out by **Quen Mok** (Consultant in Paediatric Intensive Care), **Michael Millar** and **Ruth E Gilbert** (Professor of Clinical Epidemiology).

All authors were invited to comment on the final draft of the report.

Publications

Research articles

Harron K, Ramachandra G, Mok Q, Gilbert R. Consistency between guidelines and reported practice for reducing the risk of catheter-related infection in British paediatric intensive care units. *Intensive Care Med* 2011;**37**:1641–7.

Goldstein H, Harron K, Wade A. The analysis of record-linked data using multiple imputation with data value priors. *Stat Med* 2012;**31**:3481–93.

Harron K, Lee T, Ball T, Mok Q, Gamble C, Macrae D, *et al.* Making co-enrolment feasible for randomised controlled trials in paediatric intensive care. *PLOS ONE* 2012;**7**:e41791.

Harron K, Goldstein H, Wade A, Muller-Pebody B, Parslow R, Gilbert R. Linkage, evaluation and analysis of national electronic healthcare data: application to providing enhanced blood-stream infection surveillance in paediatric intensive care. *PLOS ONE* 2013;**8**:e85278.

Harron K, Wade A, Muller-Pebody B, Goldstein H, Parslow R, Gray J, *et al.* Risk-adjusted monitoring of blood-stream infection in paediatric intensive care: a data linkage study. *Intensive Care Med* 2013;**39**:1080–7.

Woolfall K, Frith L, Gamble C, Young B. How experience makes a difference: practitioners' views on the use of deferred consent in paediatric and neonatal emergency care trials. *BMC Med Ethics* 2013;**14**:45.

Harron K, Mok Q, Parslow R, Muller-Pebody B, Gilbert R, Ramnarayan P. Risk of bloodstream infection in children admitted to paediatric intensive care units in England and Wales following emergency inter-hospital transfer. *Intensive Care Med* 2014;**40**:1916–23.

Harron K, Wade A, Gilbert R, Muller-Pebody B, Goldstein H. Evaluating bias due to data linkage error in electronic healthcare records. *BMC Med Res Methodol* 2014;**14**:36.

Harron K, Parslow R, Mok Q, Tibby S, Wade A, Muller-Pebody B, *et al.* Monitoring quality of care through linkage of administrative data: national trends in bloodstream infection in UK paediatric intensive care units 2003–2012. *Crit Care Med* 2015;**43**:1070–8.

Harron K, Woolfall K, Dwan K, Gamble C, Mok Q, Ramnarayan P, *et al.* Deferred consent for randomized controlled trials in emergency care settings. *Pediatrics* 2015;**136**:e1316–22.

Woolfall K, Frith L, Gamble C, Gilbert R, Mok Q, Young B, *et al.* How parents and practitioners experience research without prior consent (deferred consent) for emergency research involving children with life threatening conditions: a mixed method study. *BMJ Open* 2015;**5**:e008522.

Gilbert RE, Mok Q, Dwan K, Harron K, Moitt T, Millar M, *et al.* Impregnated central venous catheters for prevention of bloodstream infection in children (the CATCH trial): a randomised controlled trial [published online ahead of print March 3 2016]. *Lancet* 2016. http://dx.doi.org/10.1016/S0140-6736(16)00340-8

Harron K, Mok Q, Hughes D, Muller-Pebody B, Parslow R, Ramnarayan P, *et al.* Generalisability and cost-impact of antibiotic-impregnated central venous catheters for reducing the risk of bloodstream infection in paediatric intensive care units in England. *PLOS ONE* 2016; in press.

Letters and editorials

Mok Q, Gilbert R. Interventions to reduce central venous catheter-associated infections in children: which ones are beneficial? *Intensive Care Med* 2011;**37**:566–8.

Harron K, Wade A, Muller-Pebody B, Goldstein H, Gilbert R. Opening the black box of record linkage. *J Epidemiol Community Health* 2012;**66**:1198.

Gilbert R, Harron K, Mok Q, Gamble C. Impregnated central venous catheters should be readily used to reduce risk of bloodstream infection. *BMJ* 2013;**347**:f7169.

Harron K, Gilbert R. Research: increasing value, reducing waste. *Lancet* 2014;**383**:1124.

Harron K, Gamble C, Gilbert R. E-health data to support and enhance randomised controlled trials in the United Kingdom. *Clin Trials* 2015;**12**:180–2.

Data sharing statement

All available data can be obtained, subject to data sharing agreements, from the Medicines for Children Clinical Trials Unit.

References

1. Falagas ME, Fragoulis K, Bliziotis IA, Chatzinikolaou I. Rifampicin-impregnated central venous catheters: a meta-analysis of randomized controlled trials. *J Antimicrob Chemoth* 2007;**59**:359–69. http://dx.doi.org/10.1093/jac/dkl522
2. Gilbert R, Harden M. Effectiveness of impregnated central venous catheters for catheter related blood stream infection: a systematic review. *Curr Opin Infect Dis* 2008;**21**:235–45. http://dx.doi.org/10.1097/QCO.0b013e3282ffd6e0
3. O'Grady N, Alexander M, Dellinger E, Gerberding J, Heard S, Maki D, *et al.* Guidelines for the prevention of intravascular catheter-related infections. *Am Acad Pediatr Policy* 2002;**110**:e51–74. http://dx.doi.org/10.1067/mic.2002.129427
4. Pellowe C, Pratt R, Loveday H, Harper P, Robinson N, Jones S. The epic project. Updating the evidence-base for national evidence-based guidelines for preventing healthcare-associated infections in NHS hospitals in England: a report with recommendations. *J Hosp Infect* 2005;**5**:10. http://dx.doi.org/10.1016/j.jhin.2004.11.007
5. Raad I, Hanna H, Maki D. Intravascular catheter-related infections: advances in diagnosis, prevention, and management. *Lancet Infect Dis* 2007;**7**:645–57. http://dx.doi.org/10.1016/S1473-3099(07)70235-9
6. Costello J, Graham D, Morrow D, Potter-Bynoe G, Sandora T, Laussen P. Risk factors for central line-associated bloodstream infection in a pediatric cardiac intensive care unit. *Pediatr Crit Care Med* 2009;**10**:453–9. http://dx.doi.org/10.1097/PCC.0b013e318198b19a
7. Mello M, Albuquerque M, Lacerda H, Souza W, Correia J, Britto M. Risk factors for healthcare-associated infection in pediatric intensive care units: a systematic review. *Cad Saude Publica* 2009;**25**:373–91. http://dx.doi.org/10.1590/S0102-311X2009001500004
8. Milstone AM, Sengupta A. Do prolonged peripherally inserted central venous catheter dwell times increase the risk of bloodstream infection? *Infect Control Hosp Epidemiol* 2010;**31**:1184–7. http://dx.doi.org/10.1086/656589
9. Niedner MF, Huskins WC, Colantuoni E, Muschelli J, Harris JM II, Rice TB, *et al.* Epidemiology of central line-associated bloodstream infections in the pediatric intensive care unit. *Infect Control Hosp Epidemiol* 2011;**32**:1200. http://dx.doi.org/10.1086/662621
10. Wylie MC, Graham DA, Potter-Bynoe G, Kleinman ME, Randolph AG, Costello JM, *et al.* Risk factors for central line-associated bloodstream infection in pediatric intensive care units. *Infect Control Hosp Epidemiol* 2010;**31**:1049–56. http://dx.doi.org/10.1086/656246
11. Bhutta A, Gilliam C, Honeycutt M, Schexnayder S, Green J, Moss M, *et al.* Reduction of bloodstream infections associated with catheters in paediatric intensive care unit: stepwise approach. *BMJ* 2007;**334**:362–5. http://dx.doi.org/10.1136/bmj.39064.457025.DE
12. Miller MR, Griswold M, Harris JM II, Yenokyan G, Huskins WC, Moss M, *et al.* Decreasing PICU catheter-associated bloodstream infections: NACHRI's quality transformation efforts. *Pediatrics* 2010;**125**:206–13. http://dx.doi.org/10.1542/peds.2009-1382
13. Pronovost P, Goeschel C, Colantuoni E, Watson S, Lubomski L, Berenholtz S, *et al.* Sustaining reductions in catheter related bloodstream infections in Michigan intensive care units: observational study. *BMJ* 2010;**340**:c309. http://dx.doi.org/10.1136/bmj.c309

14. Bion J, Richardson A, Hibbert P, Beer J, Abrusci T, McCutcheon M, *et al.* 'Matching Michigan': a 2-year stepped interventional programme to minimise central venous catheter-blood stream infections in intensive care units in England. *BMJ Qual Saf* 2012;**22**:110–23. http://dx.doi.org/10.1136/bmjqs-2012-001325

15. Department of Health (DH). *Saving Lives: Reducing Infection, Delivering Clean and Safe Care*. London: DH; 2007.

16. Jeong IS, Park SM, Lee JM, Song JY, Lee SJ. Effect of central line bundle on central line-associated bloodstream infections in intensive care units. *Am J Infect Control* 2013;**41**:710–16. http://dx.doi.org/10.1016/j.ajic.2012.10.010

17. Pronovost P, Needham D, Berenholtz S, Sinopoli D, Chu H, Cosgrove S, *et al.* An intervention to decrease catheter-related bloodstream infections in the ICU. *New Engl J Med* 2006;**355**:2725–32. http://dx.doi.org/10.1056/NEJMoa061115

18. Reddy KK, Samuel A, Smiley KA, Weber S, Hon H. Reducing central line-associated bloodstream infections in three ICUs at a tertiary care hospital in the United Arab Emirates. *Jt Comm J Qual Patient Saf* 2014;**40**:559.

19. Zuschneid I, Schwab F, Geffers C, Rüden H, Gastmeier P. Reducing central venous catheter-associated primary bloodstream infections in intensive care units is possible: data from the German nosocomial infection surveillance system. *Infect Control Hosp Epidemiol* 2003;**24**:501–5. http://dx.doi.org/10.1086/502236

20. Abou Elella R, Najm H, Balkhy H, Bullard L, Kabbani M. Impact of bloodstream infection on the outcome of children undergoing cardiac surgery. *Pediatr Cardiol* 2010;**31**:483–9. http://dx.doi.org/10.1007/s00246-009-9624-x

21. Elward AM, Hollenbeak CS, Warren DK, Fraser VJ. Attributable cost of nosocomial primary bloodstream infection in pediatric intensive care unit patients. *Pediatrics* 2005;**115**:868–72. http://dx.doi.org/10.1542/peds.2004-0256

22. Lakshmi KS, Jayashree M, Singhi S, Ray P. Study of nosocomial primary bloodstream infections in a pediatric intensive care unit. *J Trop Pediatr* 2007;**53**:87–92. http://dx.doi.org/10.1093/tropej/fml073

23. Yogaraj JS, Elward AM, Fraser VJ. Rate, risk factors, and outcomes of nosocomial primary bloodstream infection in pediatric intensive care unit patients. *Pediatrics* 2002;**110**:481–5. http://dx.doi.org/10.1542/peds.110.3.481

24. Dominguez TE, Chalom R, Costarino ATJ. The impact of adverse patient occurrences on hospital costs in the pediatric intensive care unit. *Crit Care Med* 2001;**29**:169–74. http://dx.doi.org/10.1097/00003246-200101000-00033

25. Nowak JE, Brilli RJ, Lake MR, Sparling KW, Butcher J, Schulte M, *et al.* Reducing catheter-associated bloodstream infections in the pediatric intensive care unit: business case for quality improvement. *Pediatr Crit Care Med* 2010;**11**:579–87. http://dx.doi.org/10.1097/PCC.0b013e3181d90569

26. Slonim AD, Kurtines HC, Sprague BM, Singh N. The costs associated with nosocomial bloodstream infections in the pediatric intensive care unit. *Pediatr Crit Care Med* 2001;**2**:170–4. http://dx.doi.org/10.1097/00130478-200104000-00012

27. Health Protection Agency. *English National Point Prevalence Survey on Healthcare-Associated Infections and Antimicrobial Use: 2011*. URL: www.gov.uk/government/publications/healthcare-associated-infections-hcai-point-prevalence-survey-england (accessed 6 October 2014).

28. Wang H, Huang T, Jing J, Jin J, Wang P, Yang M, *et al.* Effectiveness of different central venous catheters for catheter-related infections: a network meta-analysis. *J Hosp Infect* 2010;**76**:1–11. http://dx.doi.org/10.1016/j.jhin.2010.04.025

29. Hockenhull J, Dwan K, Boland A, Smith G, Bagust A, Dündar Y, *et al.* The clinical effectiveness and cost-effectiveness of central venous catheters treated with anti-infective agents in preventing bloodstream infections: a systematic review and economic evaluation. *Health Technol Asses* 2008;**12**(12).

30. Lai NM, Chaiyakunapruk N, Lai NA, O'Riordan E, Pau WSC, Saint S. Catheter impregnation, coating or bonding for reducing central venous catheter-related infections in adults. *Cochrane Database Syst Rev* 2013;**6**:CD007878. http://dx.doi.org/10.1002/14651858.cd007878.pub2

31. Gilbert R, Harron K, Mok Q, Gamble C. Impregnated central venous catheters should be readily used to reduce risk of bloodstream infection. *BMJ* 2013;**347**:f7169. http://dx.doi.org/10.1136/bmj.f7169

32. Harron K, Ramachandra G, Mok Q, Gilbert R. Consistency between guidelines and reported practice for reducing the risk of catheter-related infection in British paediatric intensive care units. *Intensive Care Med* 2011;**37**:1641–7. http://dx.doi.org/10.1007/s00134-011-2343-9

33. Harron K, Wade A, Muller-Pebody B, Goldstein H, Parslow R, Gray J, *et al.* Risk-adjusted monitoring of blood-stream infection in paediatric intensive care: a data linkage study. *Intensive Care Med* 2013;**39**:1080–7. http://dx.doi.org/10.1007/s00134-013-2841-z

34. Harron K, Parslow R, Mok Q, Tibby S, Wade A, Muller-Pebody B, *et al.* Monitoring quality of care through linkage of administrative data: national trends in bloodstream infection in UK paediatric intensive care units 2003–2012. *Crit Care Med* 2015;**43**:1070–8. http://dx.doi.org/10.1097/CCM.0000000000000941

35. Chatzinikolaou I, Finkel K, Hanna H, Boktour M, Foringer J, Ho T, *et al.* Antibiotic-coated hemodialysis catheters for the prevention of vascular catheter–related infections: a prospective, randomized study. *Am J Med* 2003;**115**:352–7. http://dx.doi.org/10.1016/S0002-9343(03)00367-X

36. Cox EG, Knoderer CA, Jennings A, Brown JW, Rodefeld MD, Walker SG, *et al.* A randomized, controlled trial of catheter-related infectious event rates using antibiotic-impregnated catheters versus conventional catheters in pediatric cardiovascular surgery patients. *J Ped Infect Dis* 2013;**2**:67–70. http://dx.doi.org/10.1093/jpids/pis066

37. Darouiche RO, Berger DH, Khardori N, Robertson CS, Wall MJ Jr, Metzler MH, *et al.* Comparison of antimicrobial impregnation with tunneling of long-term central venous catheters: a randomized controlled trial. *Ann Surg* 2005;**242**:193. http://dx.doi.org/10.1097/01.sla.0000171874.29934.61

38. Hanna H, Benjamin R, Chatzinikolaou I, Alakech B, Richardson D, Mansfield P, *et al.* Long-term silicone central venous catheters impregnated with minocycline and rifampin decrease rates of catheter-related bloodstream infection in cancer patients: a prospective randomized clinical trial. *J Clin Oncol* 2004;**22**:3163–71. http://dx.doi.org/10.1200/JCO.2004.04.124

39. León C, Ruiz-Santana S, Rello J, Maria V, Vallés J, Álvarez-Lerma F, *et al.* Benefits of minocycline and rifampin-impregnated central venous catheters. *Intensive Care Med* 2004;**30**:1891–9. http://dx.doi.org/10.1007/s00134-004-2378-2

40. Marik PE, Abraham G, Careau P, Varon J, Fromm RE. The ex vivo antimicrobial activity and colonization rate of two antimicrobial-bonded central venous catheters. *Crit Care Med* 1999;**27**:1128–31. http://dx.doi.org/10.1097/00003246-199906000-00034

41. Raad I, Darouiche R, Dupuis J, Abi-Said D, Gabrielli A, Hachem R, *et al.* Central venous catheters coated with minocycline and rifampin for the prevention of catheter-related colonization and bloodstream infections: a randomized, double-blind trial. *Ann Intern Med* 1997;**127**:267–74. http://dx.doi.org/10.7326/0003-4819-127-4-199708150-00002

42. Yücel N, Lefering R, Maegele M, Max M, Rossaint R, Koch A, *et al.* Reduced colonization and infection with miconazole–rifampicin modified central venous catheters: a randomized controlled clinical trial. *J Antimicrob Chemoth* 2004;**54**:1109–15. http://dx.doi.org/10.1093/jac/dkh483

43. Abdelkefi A, Achour W, Ben Othman T, Ladeb S, Torjman L, Lakhal A, *et al.* Use of heparin-coated central venous lines to prevent catheter-related bloodstream infection. *J Support Oncol* 2007;**5**:273–8.

44. Appelgren P, Ransjo U, Bindslev L, Espersen F, Larm O. Surface heparinization of central venous catheters reduces microbial colonization in vitro and in vivo: results from a prospective, randomized trial. *Crit Care Med* 1996;**24**:1482–9. http://dx.doi.org/10.1097/00003246-199609000-00009

45. Pierce CM, Wade A, Mok Q. Heparin-bonded central venous lines reduce thrombotic and infective complications in critically ill children. *Intensive Care Med* 2000;**26**:967–72. http://dx.doi.org/10.1007/s001340051289

46. Geffers C, Zuschneid I, Eckmanns T, Rüden H, Gastmeier P. The relationship between methodological trial quality and the effects of impregnated central venous catheters. *Intensive Care Med* 2003;**29**:403–9.

47. Niel-Weise B, Stijnen T, Van den Broek P. Anti-infective-treated central venous catheters for total parenteral nutrition or chemotherapy: a systematic review. *J Hosp Infect* 2008;**69**:114–23. http://dx.doi.org/10.1016/j.jhin.2008.02.020

48. Mok Q, Gilbert R. Interventions to reduce central venous catheter-associated infections in children: which ones are beneficial? *Intensive Care Med* 2011;**37**:566–8. http://dx.doi.org/10.1007/s00134-011-2135-2

49. Mermel L. Prevention of intravascular catheter-related infections. *Ann Intern Med* 2000;**132**:391–402. http://dx.doi.org/10.7326/0003-4819-132-5-200003070-00009

50. Barnett AG, Batra R, Graves N, Edgeworth J, Robotham J, Cooper B. Using a longitudinal model to estimate the effect of methicillin-resistant *Staphylococcus aureus* infection on length of stay in an intensive care unit. *Am J Epidemiol* 2009;**170**:1186–94. http://dx.doi.org/10.1093/aje/kwp249

51. Graves N, Harbarth S, Beyersmann J, Barnett A, Halton K, Cooper B. Estimating the cost of health care-associated infections: mind your p's and q's. *Clin Infect Dis* 2010;**50**:1017–21. http://dx.doi.org/10.1086/651110

52. Halton K, Graves N. Economic evaluation and catheter-related bloodstream infections. *Emerging infectious diseases* 2007;**13**:815–23. http://dx.doi.org/10.3201/eid1306.070048

53. Gilbert RE, Mok Q, Dwan K, Harron K, Moitt T, Millar M, *et al.* Impregnated central venous catheters for prevention of bloodstream infection in children (the CATCH trial): a randomised controlled trial [published online ahead of print March 3 2016]. *Lancet* 2016. http://dx.doi.org/10.1016/S0140-6736(16)00340-8

54. Cook Incorporated. *Cook Spectrum® Central Venous Catheter Minocycline/Rifampin Antibiotic Impregnated Power Injectable*. Bjaeverskov, Denmark: William Cook Europe; 2013.

55. Mermel LA, Stolz SM, Maki DG. Surface antimicrobial activity of heparin-bonded and antiseptic-impregnated vascular catheters. *J Infect Dis* 1993;**167**:920–4. http://dx.doi.org/10.1093/infdis/167.4.920

56. Woolfall K, Frith L, Gamble C, Young B. How experience makes a difference: practitioners' views on the use of deferred consent in paediatric and neonatal emergency care trials. *BMC Med Ethics* 2013;**14**:45. http://dx.doi.org/10.1186/1472-6939-14-45

57. PICANet. *Paediatric Intensive Care Audit Network: A Decade of Data*. Leeds: University of Leeds; 2014.

58. Slater A, Shann F, Pearson G. PIM2: a revised version of the Paediatric Index of Mortality. *Intensive Care Med* 2003;**29**:278–85.

59. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat* 1988;**16**:1141–54. http://dx.doi.org/10.1214/aos/1176350951

60. Harron K, Woolfall K, Dwan K, Gamble C, Mok Q, Ramnarayan P, *et al.* Deferred consent for randomized controlled trials in emergency care settings. *Pediatrics* 2015;**136**:e1316–22. http://dx.doi.org/10.1542/peds.2015-0512

61. Halton KA, Cook DA, Whitby M, Paterson DL, Graves N. Cost effectiveness of antimicrobial catheters in the intensive care unit: addressing uncertainty in the decision. *Crit Care* 2009;**13**:R35. http://dx.doi.org/10.1186/cc7744

62. Frank U, Chojnacki T, Dettenkofer M, Daschner FD. Cost-effectiveness of an antiseptic-impregnated central venous catheter in the ICU. *Intensive Care Med* 2003;**29**:139.

63. Marciante KD, Veenstra DL, Lipsky BA, Saint S. Which antimicrobial impregnated central venous catheter should we use? Modeling the costs and outcomes of antimicrobial catheter use. *Am J Infect Control* 2003;**31**:1–8. http://dx.doi.org/10.1067/mic.2003.35

64. Shorr AF, Humphreys CW, Helman DL. New choices for central venous catheters: potential financial implications. *Chest* 2003;**124**:275–84. http://dx.doi.org/10.1016/S0012-3692(15)36021-9

65. Veenstra DL, Saint S, Sullivan SD. Cost-effectiveness of antiseptic-impregnated central venous catheters for the prevention of catheter-related bloodstream infection. *JAMA* 1999;**282**:554–60. http://dx.doi.org/10.1001/jama.282.6.554

66. Goudie A, Dynan L, Brady PW, Rettiganti M. Attributable cost and length of stay for central line-associated bloodstream infections. *Pediatrics* 2014;**133**:e1525–32. http://dx.doi.org/10.1542/peds.2013-3795

67. Wilson MZ, Rafferty C, Deeter D, Comito MA, Hollenbeak CS. Attributable costs of central line-associated bloodstream infections in a pediatric hematology/oncology population. *Am J Infect Control* 2014;**42**:1157–60. http://dx.doi.org/10.1016/j.ajic.2014.07.025

68. Health & Social Care Information Centre. *Data Linkage & Extract Service*. URL: www.hscic.gov.uk/dles (accessed 8 June 2014).

69. Department of Health. *National Schedule of Reference Costs 2012–13*. URL: www.gov.uk/government/publications/nhs-reference-costs-2012-to-2013 (accessed 8 June 2014).

70. Department of Health. *PbR Tariff Information Spreadsheet for 2012 to 2013*. URL: www.gov.uk/government/publications/confirmation-of-payment-by-results-pbr-arrangements-for-2012–13 (accessed 8 June 2014).

71. Department of Health. *A Simple Guide to Payment by Results*. November 2012. URL: www.gov.uk/government/uploads/system/uploads/attachment_data/file/213150/PbR-Simple-Guide-FINAL.pdf (accessed 11 December 2015).

72. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Econ* 2001;**10**:779–87. http://dx.doi.org/10.1002/hec.635

73. Mihaylova B, Briggs A, O'Hagan A, Thompson SG. Review of statistical methods for analysing healthcare resources and costs. *Health Econ* 2011;**20**:897–916. http://dx.doi.org/10.1002/hec.1653

74. Glick HA, Doshi JA, Sonnad SS, Polsky D. *Economic Evaluation in Clinical Trials*. Oxford: Oxford University Press; 2007.

75. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, *et al.* Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *BMJ* 2013;**346**:f1049. http://dx.doi.org/10.1136/bmj.f1049

76. Braunholtz DA, Edwards SJ, Lilford RJ. Are randomized clinical trials good for us (in the short term)? Evidence for a 'trial effect'. *J Clin Epidemiol* 2001;**54**:217–24. http://dx.doi.org/10.1016/S0895-4356(00)00305-X

77. Harron K, Goldstein H, Wade A, Muller-Pebody B, Parslow R, Gilbert R. Linkage, evaluation and analysis of national electronic healthcare data: application to providing enhanced blood-stream infection surveillance in paediatric intensive care. *PLOS ONE* 2013;**8**:e85278. http://dx.doi.org/10.1371/journal.pone.0085278

78. Wilson J, Elgohari S, Livermore DM, Cookson B, Johnson A, Lamagni T, *et al.* Trends among pathogens reported as causing bacteraemia in England, 2004–2008. *Clin Microbiol Infect* 2011;**17**:451–8. http://dx.doi.org/10.1111/j.1469-0691.2010.03262.x

79. Goldstein H, Harron K, Wade A. The analysis of record-linked data using multiple imputation with data value priors. *Stat Med* 2012;**31**:3481–93. http://dx.doi.org/10.1002/sim.5508

80. Harron K, Wade A, Gilbert R, Muller-Pebody B, Goldstein H. Evaluating bias due to data linkage error in electronic healthcare records. *BMC Med Res Methodol* 2014;**14**:36. http://dx.doi.org/10.1186/1471-2288-14-36

81. Rubin D. *Multiple Imputation for Nonresponse in Surveys*. New York, NY: Wiley; 1987. http://dx.doi.org/10.1002/9780470316696

82. Harron K. *Evaluating Data Linkage Techniques for the Analysis of Bloodstream Infection in Paediatric Intensive Care*. PhD thesis. London: University College London; 2014.

83. Steyerberg EW, Harrell FE Jr, Borsboom GJJM, Eijkemans MJC, Vergouwe Y, Habbema JDF. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. *J Clin Epidemiol* 2001;**54**:774–81. http://dx.doi.org/10.1016/S0895-4356(01)00341-9

84. Steyerberg EW, Eijkemans MJC, Harrell FE, Habbema JDF. Prognostic modeling with logistic regression analysis: in search of a sensible strategy in small data sets. *Med Decis Making* 2001;**21**:45–56. http://dx.doi.org/10.1177/0272989X0102100106

85. Harrell F, Lee KL, Mark DB. Tutorial in biostatistics multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996;**15**:361–87. http://dx.doi.org/10.1002/(SICI)1097-0258(19960229)15:4<361::AID-SIM168>3.0.CO;2-4

86. Fluss R, Faraggi D, Reiser B. Estimation of the Youden Index and its associated cutoff point. *Biom J* 2005;**47**:458–72. http://dx.doi.org/10.1002/bimj.200410135

87. O'Hagan A, McCabe C, Akehurst R, Brennan A, Briggs A, Claxton K, *et al.* Incorporation of uncertainty in health economic modelling studies. *Pharmacoeconomics* 2005;**23**:529–36. http://dx.doi.org/10.2165/00019053-200523060-00001

88. Angus DC, Mira JP, Vincent JL. Improving clinical trials in the critically ill. *Crit Care Med* 2010;**38**:527. http://dx.doi.org/10.1097/CCM.0b013e3181c0259d

89. Schierholz J, Fleck C, Beuth J, Pulverer G. The antimicrobial efficacy of a new central venous catheter with long-term broad-spectrum activity. *J Antimicrob Chemoth* 2000;**46**:45–50. http://dx.doi.org/10.1093/jac/46.1.45

90. Dondorp AM, Fanello CI, Hendriksen ICE, Gomes E, Seni A, Chhaganlal KD, *et al.* Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. *Lancet* 2010;**376**:1647–57. http://dx.doi.org/10.1016/S0140-6736(10)61924-1

91. Claxton K. The irrelevance of inference: a decision-making approach to the stochastic evaluation of health care technologies. *J Health Econ* 1999;**18**:341–64. http://dx.doi.org/10.1016/S0167-6296(98)00039-3

92. Kerren R, Pati S, Feudtner C. The generation gap; difference between children and adults pertinent to economic evaluations of health interventions. *Pharmacoeconomics* 2004;**22**:71–81.

93. Tarride JE, Burke N, Bischof M, Hopkins RB, Goeree L, Campbell K, *et al.* A review of health utilities across conditions common in paediatric and adult populations. *Health Qual Life Outcomes* 2010;**8**:12. http://dx.doi.org/10.1186/1477-7525-8-12

94. Harron K, Mok Q, Parslow R, Muller-Pebody B, Gilbert R, Ramnarayan P. Risk of bloodstream infection in children admitted to paediatric intensive care units in England and Wales following emergency inter-hospital transfer. *Intensive Care Med* 2014;**40**:1916–23. http://dx.doi.org/10.1007/s00134-014-3516-0

95. Briggs A. Probabilistic analysis of cost-effectiveness models: statistical representation of parameter uncertainty. *Value Health* 2005;**8**:1–2. http://dx.doi.org/10.1111/j.1524-4733.2005.08101.x

96. Claxton K, Sculpher M, McCabe C, Briggs A, Akehurst R, Buxton M, *et al.* Probabilistic sensitivity analysis for NICE technology assessment: not an optional extra. *Health Econ* 2005;**14**:339–47. http://dx.doi.org/10.1002/hec.985

97. Cole SR, Stuart EA. Generalizing evidence from randomized clinical trials to target populations: the ACTG 320 Trial. *Am J Epidemiol* 2010;**172**:107–15. http://dx.doi.org/10.1093/aje/kwq084

98. Stuart EA, Cole SR, Bradshaw CP, Leaf PJ. The use of propensity scores to assess the generalizability of results from randomized trials. *J R Stat Soc Ser A Stat Soc* 2011;**174**:369–86. http://dx.doi.org/10.1111/j.1467-985X.2010.00673.x

99. Junker A, Klassen T. Improving standards for paediatric clinical trials. *Paediatr Child Health* 2011;**16**:539–40.

100. Hartling L, Wittmeier KDM, Caldwell P, van der Lee H, Klassen TP, Craig JC, *et al.* StaR Child Health: developing evidence-based guidance for the design, conduct, and reporting of pediatric trials. *Pediatrics* 2012;**129**:S112–17. http://dx.doi.org/10.1542/peds.2012-0055C

101. Gamble C, Nadel S, Snape D, McKay A, Hickey H, Williamson P, *et al.* What parents of children who have received emergency care think about deferring consent in randomised trials of emergency treatments: postal survey. *PLOS ONE* 2012;**7**:e35982. http://dx.doi.org/10.1371/journal.pone.0035982

102. Molyneux S, Njue M, Boga M, Akello L, Olupot-Olupot P, Engoru C, *et al.* 'The words will pass with the blowing wind': Staff and parent views of the deferred consent process, with prior assent, used in an emergency fluids trial in two African hospitals. *PLOS ONE* 2013;**8**:e54894. http://dx.doi.org/10.1371/journal.pone.0054894

103. Brierley J, Larcher V. Emergency research in children: options for ethical recruitment. *J Med Ethics* 2011;**37**:429–32. http://dx.doi.org/10.1136/jme.2010.040667

104. Woolfall K, Young B, Frith L, Appleton R, Iyer A, Messahel S, *et al.* Doing challenging research studies in a patient-centred way: a qualitative study to inform a randomised controlled trial in the paediatric emergency care setting. *BMJ Open* 2014;**4**:e005045. http://dx.doi.org/10.1136/bmjopen-2014-005045

105. Jansen T, Kompanje EJ, Druml C, Menon D, Wiedermann C, Bakker J. Deferred consent in emergency intensive care research: what if the patient dies early? Use the data or not? *Intensive Care Med* 2007;**33**:894–900. http://dx.doi.org/10.1007/s00134-007-0580-8

106. Davies H, Shakur H, Padkin A, Roberts I, Slowther A-M, Perkins GD. Guide to the design and review of emergency research when it is proposed that consent and consultation be waived. *Emerg Med J* 2014;**31**:794–5. http://dx.doi.org/10.1136/emermed-2014-203675

107. Maitland K, Molyneux S, Boga M, Kiguli S, Lang T. Use of deferred consent for severely ill children in a multi-centre Phase III trial. *Trials* 2011;**12**:90. http://dx.doi.org/10.1186/1745-6215-12-90

108. Macrae D, Grieve R, Allen E, Sadique Z, Morris K, Pappachan J, *et al.* A randomized trial of hyperglycemic control in pediatric intensive care. *New Engl J Med* 2014;**370**:107–18. http://dx.doi.org/10.1056/NEJMoa1302564

109. Ellenberg SS, Finkelstein DM, Schoenfeld DA. Statistical issues arising in AIDS clinical trials. *JAMA* 1992;**87**:562–9.

110. Maitland K, Kiguli S, Opoka RO, Engoru C, Olupot-Olupot P, Akech SO, *et al.* Mortality after fluid bolus in African children with severe infection. *New Engl J Med* 2011;**364**:2483–95. http://dx.doi.org/10.1056/NEJMoa1101549

111. Cook DJ, Blythe D, Rischbieth A, Hebert PC, Zytaruk N, Menon K, *et al.* Enrollment of intensive care unit patients into clinical studies: A trinational survey of researchers' experiences, beliefs, and practices. *Crit Care Med* 2008;**36**:2100–5. http://dx.doi.org/10.1097/CCM.0b013e31817c00b0

112. Harron K, Lee T, Ball T, Mok Q, Gamble C, Macrae D, *et al.* Making co-enrolment feasible for randomised controlled trials in paediatric intensive care. *PLOS ONE* 2012;**7**:e41791. http://dx.doi.org/10.1371/journal.pone.0041791

113. Myles PS, Williamson E, Oakley J, Forbes A. Ethical and scientific considerations for patient enrollment into concurrent clinical trials. *Trials* 2014;**15**:470. http://dx.doi.org/10.1186/1745-6215-15-470

114. Shilling V, Williamson PR, Hickey H, Sowden E, Beresford MW, Smyth RL, *et al.* Communication about children's clinical trials as observed and experienced: qualitative study of parents and practitioners. *PLOS ONE* 2011;**6**:e21604. http://dx.doi.org/10.1371/journal.pone.0021604

115. Burgess E, Singhal N, Amin H, McMillan D, Devrome H, Fenton A. Consent for clinical research in the neonatal intensive care unit: a retrospective survey and a prospective study. *Arch Dis Child Fetal Neonatal Ed* 2003;**88**:F280. http://dx.doi.org/10.1136/fn.88.4.F280

116. Morley C, Lau R, Davis P, Morse C. What do parents think about enrolling their premature babies in several research studies? *Arch Dis Child Fetal Neonatal Ed* 2005;**90**:F225. http://dx.doi.org/10.1136/adc.2004.061986

117. Harron K, Gamble C, Gilbert R. E-health data to support and enhance randomised controlled trials in the UK. *Clinical Trials* 2015;**12**:180–2. http://dx.doi.org/10.1177/1740774514562030

118. Ford I, Murray H, Packard CJ, Shepherd J, Macfarlane PW, Cobbe SM. Long-term follow-up of the West of Scotland Coronary Prevention Study. *New Engl J Med* 2007;**357**:1477–86. http://dx.doi.org/10.1056/NEJMoa065994

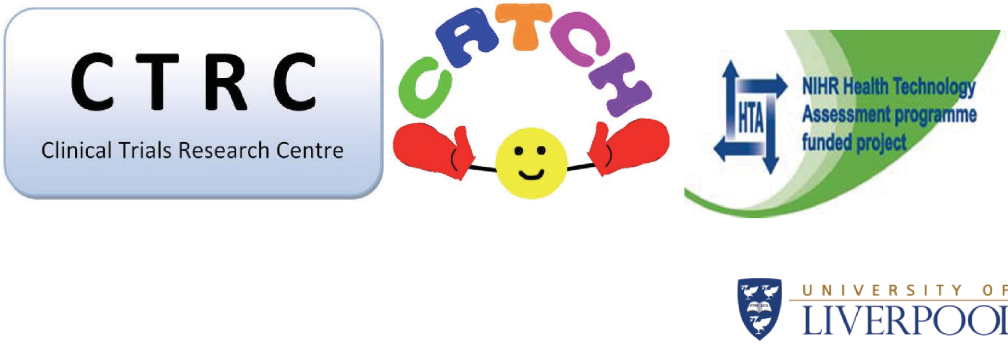
119. Rawlins M. *A New Pathway for the Regulation and Governance of Health Research*. The Academy of Medical Sciences; 30 January 2011. URL: www.acmedsci.ac.uk/p47prid88.html (accessed 15 June 2012).

120. Stephenson T. The medicines for children agenda in the UK. *Br J Clin Pharmacol* 2006;**61**:716–19. http://dx.doi.org/10.1111/j.1365-2125.2006.02676.x

121. Great Britain. *NHS Act 2006*. London: The Stationery Office; 2006.

122. Great Britain. *Health and Social Care Act 2001*. London: The Stationery Office; 2001.

Appendix 1 Statistical analysis plan



CATCH

CATheter Infections in CHildren

Statistical Analysis Plan

	ORIGINATED BY
Name	Kerry Dwan
Title	Trial Statistician
Date	12/08/2014
Protocol Version and Date	5.0 01/10/2012

Form prepared: 06/12/2013 v1.1 for CATCH Study

Change Control

Updated SAP version no.	Section number changed	Description of change	Date changed	Initials
1.1	13 and 14	Comments from Paul Ewings addressed	06/12/2013	KD
1.2	Appendix D	Organisms added to the appendix	21/02/2014	KD
1.3	Section 5.2 Section 5.2 Section 7.1, 13 Section 11 Section 12 Section 14.10 Section	Data for 'primary reason for admission based on ICD 10 code, categorised as Infection, Renal, Cancer, Respiratory, Neurological, Circulatory, Other' will now be obtained from PICANET data. PIMS2 score has been added using PICANET data. Clarification on timepoint for primary outcome. Date of randomisation and date of insertion are used interchangeably. Version 1 of the SAP does state that the time to event analysis will be calculated from date of randomisation. This has been clarified in the SAP in all relevant sections. Per protocol analyses have been removed as this was never stated in the protocol. Clarification has been made on the definition of elective and emergency patients. Protocol deviations will not be signed off as a per protocol analysis is not being undertaken Adverse events will be grouped into fewer groups. Clarification has been made to reporting of the two outcomes thrombosis and unexplained thrombocytopenia: 'to avoid double counting of unexplained thrombocytopenia will be presented as an adverse event and thrombosis will be presented as a secondary outcome as the outcome is time to event. Clarification has been added to the secondary outcome 'length of time in PICU' that this is for the first stay in PICU only as stated in appendix E. Also, CICU and NICU will be treated as PICU For the secondary outcome 'Time to a composite	15/05/2014	KD

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	14.3 Appendix E	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', antibiotics need to be grouped as they are included on CRFs as free text so often misspelt. This grouping has been added to the appendix. Clarification has been added to the appendix for the time between the two events of flushing or difficulty drawing back blood, this should be up to 5 days.		
1.4	Section 13 Section 14.2 Appendix F	Clarification has been added regarding the process when times are not available and details on censoring. Clarification has been added regarding the process when times are not available and details on censoring. Antibiotics were grouped by a clinical member of the TMG	12/08/2014	KD

Form prepared: 06/12/2013 v1.1 for CATCH Study

1 Table of Contents

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2 Introduction

This Statistical Analysis Plan (SAP) provides a detailed and comprehensive description of the pre-planned final full analysis for the study “CATCH”.

This study is carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996) amendments and will be conducted in compliance with the protocol, Clinical Trials Research Centre (CTRC) Clinical Trials Unit (CTU) Standard Operating Procedures (SOPs) and EU Directive 2001/20/EC, transposed into UK law as the UK Statutory Instrument 2004 No 1031: Medicines for Human Use (Clinical Trials) Regulations 2004.

These analyses will be performed by the trial statistician. The analysis results will be described in a statistical analysis report, to be used as the basis of the primary research publications according to the study publication plan specified within the study protocol.

All analyses will be performed with standard statistical software (SAS version 9 or later). The finalised analysis datasets, programs and outputs will be archived following Good Clinical Practice guidelines and SOP IS006 Study Closedown and Archiving. The testing and validation of the statistical analysis programs will be performed following SOP ST001: Statistical Analysis and Reporting - v.2.0.

3 Study design and objectives

This study is designed as a prospective, parallel, controlled, multicentre, randomised clinical trial comparing the effectiveness of heparin bonded or antibiotic impregnated CVCs with standard CVCs for preventing hospital acquired blood stream infection in children (aged less than 16 years) admitted to PICU, who require insertion of a CVC for at least 3 days.
The primary objective of this trial is to determine the effectiveness of heparin bonded or antibiotic impregnated CVCs (combined) compared with standard CVCs for preventing hospital acquired blood stream infection

Secondary objectives are:

a. To determine the cost effectiveness of heparin bonded or antibiotic impregnated CVCs compared with standard CVCs, based on the primary outcome and costs of acute care from the perspective of the NHS.
b. To determine the effectiveness of type of CVC in 3-way comparisons of heparin bonded versus antibiotic impregnated versus standard CVCs for preventing hospital acquired blood stream infection, based on culture, quantitative bacterial DNA, and clinical measures of infection.
c. To determine the effect of type of CVC on clinical measures of care (duration of CVC insertion, duration of antibiotic use, and duration of stay).

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d. To determine the effect of type of CVC on mortality at 30 days.
e. To identify adverse effects of CVC type on pathogen selection, antibiotic resistance, clinical evidence of CVC thrombosis and thrombocytopenia.

The null hypothesis is that there is no difference in time to first blood stream infection between the standard and impregnated (antibiotic and heparin combined) groups. The alternative hypothesis is that there is a difference between the two groups.

Randomisation

Randomisation lists were generated in STATA using simple block randomisation with random variable block length and a 1:1:1 ratio of treatment allocation.
Randomisation was stratified by elective and emergency participants and centre with further stratification within centre to permit multiple cvc allocation/storage sites.

The randomisation numbers are 9 digits long.

Digits 1 to 4 indicate the UK CRN number;
Digit 5 indicates whether a participant is elective (0) or emergency (1);
Digit 6 indicates the place where the cvc is stored and
Digits 7 to 9 are sequential numbers within place and site.
Treatment allocation could not be blinded to the clinician responsible for randomising a patient and inserting the CVC but was concealed from patients, their parents and PICU personnel responsible for their care.

There was an interim analysis of the primary outcome mid-way (650 patients randomised and consented and entered onto the database) through the trial, using Peto-Haybittle stopping rules.

3.1 Sample size calculations

Sample size calculations were undertaken using NQuery Advisor software.
At a sample size of 1200, we would have 80% power to detect a relative risk of 0.5 at a 5% level of significance given a baseline risk of 10%, using a Fisher’ s exact test. At the lower expected baseline event rate of 5%, there would be 80% power to detect a relative risk of 0.32 (absolute risk difference 3.4%) whereas at a baseline event rate of 15% there would be 80% power to detect a relative risk of 0.6 (absolute risk difference of 6%). The power to detect these effects would be similar for survival analyses. Explicit power calculations have not been given for the survival analysis to avoid making potentially erroneous assumptions about the distribution of infection times in the standard arm based on the limited information available at present.

3.2 Interim analysis

The interim analysis of the primary outcome was completed mid-way (approximately half of the patients randomised and consented and entered onto the database), through the trial, using Peto-Haybittle stopping rules. This was completed under version 2.0 of the SOP as version 3.0 of the SOP was released later (30/06/2012). Details can be found in the IDSMC report dated 22/05/2012.

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4 Inclusion / Exclusion Criteria

4.1 Inclusion Criteria

Patients with the following characteristics will be eligible for inclusion in the trial:
a. Less than 16 years of age;
b. Admitted to or being prepared for admission to an intensive care unit participating in the trial;
c. Require insertion of a CVC as part of good clinical management;
d. Require one of the CVC sizes available to the trial;
e. Expected to require a CVC for at least 3 days;
f. Appropriate consent obtained (prospective consent for elective surgical patients, deferred consent for emergency admission patients).

4.2 Exclusion Criteria

Patients with the following characteristics will be excluded from the trial:
a. Patients previously enrolled in the CATCH trial;
b. Patients with a known allergy or hypersensitivity to tetracyclines (including minocycline), rifampicin or heparin;
c. Patients known to be pregnant;
d. Patients with a history of heparin induced thrombocytopenia;
e. Patients are in a randomised controlled trial that excludes participation in CATCH

5 Description of study population

5.1 Representativeness of study sample and patient throughput

Details will be presented on:

- the number of patients, both elective and emergency who were randomised,
- those emergency patients who were randomised but did not provide deferred consent,
- those who received the randomised allocation,
- those who did not receive the randomised allocation,
- those randomised but where CVC insertion was not attempted,
- those where CVC insertion was attempted but the CVC was not inserted,
- those who withdrew from the study after randomisation and
- those who were lost to follow-up

will be summarised in a CONSORT flow diagram (Appendix A) (1). Due to the nature of the trial, information could not be collected regarding eligible emergency participants who were not randomised. Therefore, this information is not presented for elective patients.

5.2 Baseline comparability of randomised groups

Baseline characteristics will be descriptively summarised (numbers and percentages). Table columns will be: Standard; impregnated (heparin or antibiotic); antibiotic; heparin; and total. This table will be produced across all sites and by site. Variable to be included in the table are:

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Descriptor	Form
Baseline characteristics	
Number of patients randomised	1, 2 and 3
Elective/ emergency	1 and 3
Age, categorised as <3 months, 3 months-<1 year, 1-10 years and 11+ years. A median and interquartile range will also be calculated.	
Gender (male/female)	4
Weight, categorised as <3kgs, 3-10kgs, >10kgs. A median and interquartile range will also be calculated.	4
Electives - Type of surgery, categorised as cardiac/other.	4
Source of admission to PICU, categorised as: Elective, same hospital or Emergency, Same hospital or Other hospital – retrieved by: Specialist retrieval team, Other	4
Disease characteristics	
Pre-existing CVC at time of randomisation or within 72 hours prior to time of randomisation (Yes/ No)	1 or 3 and 4
Health status BEFORE the acute problem precipitated PICU admission: (Healthy/ Not Healthy).	4
Anticoagulant medication within 72 prior to randomisation: (yes/no).	4
Antibiotics 72 hours prior to randomisation: (yes/no).	4
Primary reason for admission based on ICD 10 code, categorised as Infection, Renal, Cancer, Respiratory, Neurological, Circulatory, Other.	PICANET data
PIMS2 score (<1%, 1-5%, 5-15%, 15-30%, 30%+)	PICANET data
Positive blood culture within 72 hours prior to time of randomisation (yes/no).	4
Suspected infection at time of randomisation (yes/no).	4
Immune compromised (yes/no).	4
Description of interventions	
Where the CVC was inserted, stratified by elective and emergency and then same hospital and other hospital and then: ICU (PICU/NICU/CICU); other ward (HDU or other ward); theatre; other /A&E	1 or 3
Size of line: (4, 5 or 7)	1 or 3
Number of lumens (triple or double lumen)	1 or 3
Site: (femoral or other)	1 or 3
Sterile procedures used split by elective and emergency: yes/no	1 or 3

Descriptor	Form
48 hours post randomisation	
Other devices in situ in addition to CVC: Less than 4 Greater than or equal to 4	4

5.3 Loss to follow-up

The number lost to follow up within each treatment group will be reported and the reasons where known will be provided.

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Reasons for loss to follow up are: transferred to a site not participating in CATCH; deferred consent not obtained. For deaths – see follow up assessments (section 6).

6 Follow up assessments

Where CVC insertion was successful, patients will be followed up to 48 hours after CVC removal. For those where insertion was attempted but not successful, patients will be followed up to 48 hours after attempted insertion.

6.1 Blood culture samples

Blood culture samples may be taken from CVC lumens, peripheral veins, or if necessary, from the arterial line (although this is discouraged). To differentiate potential contaminants or line infection from blood stream infection the best approach to sampling is in the following diminishing order of preference

a. take both a peripheral blood sample and a CVC culture at the same time
b. Take a peripheral blood culture;
c. Take a CVC culture – from all available lumens of the randomised CVC;
d. Take a CVC culture – from all available lumens of any other CVC;
e. Take an arterial line culture (high risk of contamination).

A minimum of 0.5ml of blood should be taken for any blood culture. For CVC cultures, a minimum of 0.5ml of blood will be taken from each lumen and inoculated into separate culture bottles (note total volume is 1ml for neonates in whom double lumen CVCs are used). Sampling from multiple lumens will be used because sampling from one lumen reduces sensitivity for catheter related bloodstream infection.

Blood culture contributes to definitions of:

- Time to first blood stream infection (7.1)
- Rate of blood stream infection during CVC insertion per 1000 CVC days (7.2.1)
- Time to a composite measure of clinically indicated blood stream infection (7.2.3)
- A CVC related blood stream infection (7.2.4)
- Type of bacteria and fungi isolated from positive blood cultures (7.2.6)
- Resistance to minocycline or rifampicin of blood culture or CVC tip isolates (7.2.7)

6.2 Clinically indicated

Clinically indicated means blood cultures taken because infection is suspected by the clinician either due to a change in the patient's condition (e.g. pyrexia, change in oxygen or inotrope requirements, hypotension, poor perfusion), or removal of the CVC line due to suspected infection, or a high likelihood of infection due to their risk status. Guidelines will be developed to improve standardisation of practice, but not to dictate what must ultimately be a clinical judgement of signs of infection. Blood cultures will be taken routinely at CVC removal, to allow comparison of isolate with the CVC tip culture. This culture will be counted as 'clinically indicated' if the line was removed for suspected infection or if there were signs of infection at the CVC exit site .

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Clinically indicated contributes to definitions of:

- Time to first blood stream infection (7.1)
- Rate of blood stream infection during CVC insertion per 1000 CVC days (7.3.2)
- Time to a composite measure of clinically indicated blood stream infection (7.2.3)

6.3 Positive blood culture

Positive blood culture will be defined as:

a. one or more positive blood cultures with a non-skin organism from a sample taken from any vascular site; or

b. the same skin organism isolated from 2 or more positive blood cultures (from any vascular site) within 48 hours of each other. One or more of the samples must be taken 48 hrs after CVC insertion or within 48 hours after removal. A review committee will independently classify multiple cultures according to same or different organisms based on species and antibiogram as to whether it is the same BSI or not.

Positive blood culture contributes to definitions of:

- Time to first blood stream infection (7.1)
- Rate of blood stream infection during CVC insertion per 1000 CVC days (7.2.1)
- Time to a composite measure of clinically indicated blood stream infection (7.2.3)
- A CVC related blood stream infection (7.2.4)
- Resistance to minocycline or rifampicin of blood culture or CVC tip isolates (7.2.7)

6.4 High bacterial DNA load indicative of blood stream infection

High bacterial DNA load indicative of blood stream infection will be defined as more than 0.25 pg of bacterial DNA per microlitre of whole blood detected from one or more sites taken more than 48 hours after CVC insertion and before 48 hours after CVC removal. High bacterial DNA load indicative of CVC related blood stream infection will be defined by differential results for high bacterial load from multiple lumens (i.e. not all above or below 0.25 pg/microlitre. Note that this may be influenced in advances in methodology since the protocol was approved). Analysis of bacterial DNA load will be based on a minimum sample of 0.2ml from each lumen taken at the same time as the blood culture, placed in separate EDTA bottles for each lumen, and frozen at -20ºC till batching within 1 month of sampling. The rationale for using quantitative PCR measures of bacterial DNA is because most children in PICU will be on antibiotic treatment, which reduces the sensitivity of blood culture. PCR appears to be more sensitive than culture for detecting blood stream infection.

High bacterial DNA load indicative of blood stream infection contributes to the definition of:

- Time to a composite measure of clinically indicated blood stream infection (7.2.3)

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6.5 Culture negative infection

Culture negative infection will be defined by a change in antibiotic treatment on the same or subsequent day after a blood culture sample more than 48 hours after CVC insertion or up until 48 hr after CVC removal in the presence of negative blood cultures, and 1 or more clinical signs of infection and at least one other sign (clinical or laboratory). The signs of infection include the following: clinical signs – temperature >38oC or temperature instability, haemodynamic instability (hypotension, mottled, poor perfusion, capillary refill>3s); or laboratory signs - C-reactive protein rising above normal range; white blood cell count (falling below 2 x 10^9/l or above 10 x 10^9/l or showing a rising trend).

Culture negative infection contributes to definitions of:

- Time to a composite measure of clinically indicated blood stream infection (7.2.3)

6.6 Antibiotic resistance

Antibiotic resistance will be recorded as an **adverse event** if resistance is detected to minocycline or rifampicin using standard E tests on isolates from blood or the CVC tip. All microbiology laboratories supporting PICUs involved in the trial will be asked to use E strips to test for minocycline or rifampicin resistance in any isolates from blood cultures or CVC tips.

Antibiotic resistance contributes to the definition of:

- Resistance to minocycline or rifampicin of blood culture or CVC tip isolates (07.2.7)

6.7 Positive CVC tip culture

Positive CVC tip culture will be based on any sized tip of the catheter, removed using a sterile procedure, and cultured according to standard methods. A positive culture will be considered a secondary outcome only if the blood culture is positive for the same isolate and positive blood culture sample was taken within 7 days prior to the CVC removal. This is because CVCs are easily contaminated during removal.

Positive CVC tip culture contributes to definitions of:

- A CVC related blood stream infection (7.2.4)
- Resistance to minocycline or rifampicin of blood culture or CVC tip isolates (7.2.7)

6.8 Exit site infection

Exit site infection will be defined by erythema extending 0.5cm or more for infants, 1cm for older children and 2cm for adolescents from the exit site of the CVC, or pus at the exit site.

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Exit site infection is listed within the Adverse Events (Section 12.1) and also contributes to the definition of:

- Time to first blood stream infection (7.1)
- A CVC related blood stream infection (7.2.4)

7 Study Outcomes

7.1 Primary Outcome

The primary outcome will be time to first blood stream infection defined by a positive blood culture from a sample that was clinically indicated and taken more than 48 hours after randomisation and up to 48 hours after CVC removal.

7.2 Secondary Outcomes

7.2.1 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.
Second episode of blood stream infection (defined as per primary outcome) will be defined by a positive blood culture (see definition above) 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.

7.2.2 Time to CVC thrombosis - defined clinically by (any one or more of the following):

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

7.2.3 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 (Section 6.2) 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

7.2.4 A CVC related blood stream infection will be 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;

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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

7.2.5 Mortality by 30 days

7.2.6 Type of bacteria and fungi isolated from positive blood cultures

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

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

7.2.9 Time to randomised CVC removal

7.2.10 Length of stay requiring PICU

7.2.11 Total length of hospital stay for current episode (for up to 6 month postrandomisation)

7.2.12 Cost effectiveness of heparin bonded vs. antibiotic-impregnated vs. standard CVC

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8 Description of compliance with treatment

The number of patients where CVC insertion was attempted but was not successful, where insertion was not attempted after randomisation and for those that received a CVC other than the randomised CVC will be reported in the CONSORT flow diagram (Appendix A).

9 Trial monitoring

There have been two IDSMC meetings, one in February 2012 to investigate the control group event rate and the other in June 2012 for the interim analysis of the primary outcome for 650 patients randomised, consented and entered onto the database. The recommendation from both of these meetings was to continue recruitment.

10 Unblinding of randomised treatments

The number of patients who were unblinded prior to database lock will be reported for each treatment group along with the reasons as to why they were unblinded.

Checks were made on the order of patients being randomised and records were kept of any unblinding requests that were made by sites.

11 Patient groups for analysis

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.

The membership of the analysis set for each outcome will be determined and documented. Reasons for participant exclusion will be given prior to blinding being broken and the randomisation lists being requested. Reasons may include missing data or loss to follow up.

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).

Patients to be excluded from populations will be defined in template ST001TEM04 (Protocol deviations and population exclusions template) and will be agreed and approved prior to any release of randomisation codes.

Patients will be classified as elective/emergency based on consent given i.e. deferred/prospective.

12 Protocol deviations

Any protocol deviations will be tabulated and the frequency of these deviations presented by site and in total, and by treatment group.

Protocol deviations have been defined in the draft monitoring plan (Appendix B). The monitoring plan also defines whether each deviation is considered major or minor.

Description of safety outcomes

12.1 Adverse reactions/events

All related adverse events (AEs) or adverse reactions (ARs) and serious adverse events (SAEs) reported by the clinical investigator (as in Section 10.4 of the protocol) will be presented, identified by treatment group. The number (and percentage) of patients experiencing each AE/SAE will be presented for each treatment arm categorised by severity. For each patient, only the maximum severity experienced of each type of AE will be displayed. The number (and percentage) of occurrences of each AE/SAE will also be presented for each treatment arm. No formal statistical testing will be undertaken.

Any adverse events entered in free text will be assessed by a team of clinical professionals and summarised as below.

- Thrombosis
- Exit site infection
- Antibiotic resistance
- Low platelets/hypersensitivity
- Line displacement (falling out/tip displaced)
- Trauma from line insertion
- Line breakage/mechanical problem
- Mortality

To avoid double counting of unexplained thrombocytopenia will be presented as an adverse event and thrombosis will be presented as a secondary outcome as the outcome is time to event.

13 Analysis of primary efficacy outcome

The primary efficacy outcome is time to first blood stream infection defined by a positive blood culture from a sample that was clinically indicated and taken more than 48 hours after CVC insertion and up to 48 hours after CVC removal (see section 7.1 and Appendix C, D, E).

- If an organism is cultured it is identified on the microbiology form. Organisms cultured will be discussed with the microbiologist to identify whether they are skin or non skin organisms (Appendix D). If a non skin organism is identified

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then this is automatically a positive blood stream infection. If a skin organism is identified then the microbiology form will be checked to identify whether the same skin organism has occurred again from any site within 48 hours (only one sample has to be within the correct timeframe for the primary outcome). This will be checked with the microbiologist and clinician endpoint review committee (Appendix G) to ensure the skin organisms are in fact the same. If this is confirmed then this will be a positive blood stream infection. Date and time of the samples are included on the microbiology form.

- Timings will then be checked to ensure the sample was taken 48 hours post randomisation (insertion also used in a sensitivity analysis) and up to 48 hours after removal of the CVC. These timings are included on form 1 section B (date and time of randomisation and date and time of successful insertion) and form 5 (date and time of CVC removal). The sample times are indicated on forms 9 and 10 (date and time sample taken). If no CVC removal date was recorded, date of transfer was used. For those with no time for removal but when the date is the same as randomisation, the time was set to 23.59.
- Clinically indicated: defined in section 6.2. The sampling form will then be checked to determine whether there were one or more clinical indices within 48 hours of the sample being taken. Clinical indication of infection is recorded on form 9 (sampling form: section A question 4 and section B question 1), 6 (progress log) and on form 5 (CVC insertion follow up form: section A question 1 and section B question 3. Note that there may be two reasons for removal) if the reason for removal is 'CVC associated infection suspected'. Raised CRP and white blood cell counts alone will not be regarded as clinical indicators of infection.

The number of positive blood stream infections taken more than 48 hours after randomisation and up to 48 hours after CVC removal will be presented split by treatment, the site of the sample (i.e. lumen, arterial, peripheral) and whether the organisms cultured were skin or non-skin.

Kaplan-Meier survival curves stratified by CVC will be presented. A survival analysis will be performed using the Log rank test and Cox proportional hazard regression models if appropriate for heparin bonded or antibiotic impregnated CVCs (combined) compared with standard CVCs and adjusted for one the variables used for stratifying randomisation (elective and emergency participants). In the design, the stratification of CATCH between emergency and elective was due to prognostic importance but centre and storage site were logistical. ICH E9 states that "In some trials there may be no reason to expect the centres to have any influence on the primary or secondary variables because they are unlikely to represent influences of clinical importance. In other trials the limited number of subjects per centre will make it impracticable to include centre effects in the statistical model" (3). Heterogeneity of treatment effects by centre will be considered in a graphical display.

Since the hazard of infection may not be constant post CVC insertion, non-proportional hazards survival models will also be investigated. Results will be presented using Hazard Ratios and 95% confidence intervals. Survival times will be measured from the date and time of randomisation to the date and time of positive

blood stream infection as identified above. For those not experiencing the primary outcome, they will be censored at death, 48 hours after CVC removal or for those with no CVC inserted, 48 hours after randomisation/attempted insertion.

Differences between date and time of randomisation and date and time of insertion will be summarised using medians and IQR.

A secondary analysis will compare each impregnated CVC against standard CVC i.e. i) heparin bonded versus standard and ii) antibiotic impregnated versus standard.

Regression models will be used to further investigate the outcomes between the groups, including: type of admission (emergency clean, emergency dirty or elective); Immune compromised (yes/no); infection at admission (yes/no) and other devices in situ (4 or more in addition to CVC), age (as categorised within the baseline table), site (femoral vs other). An interaction of elective and emergency will also be considered.

A p-value of 0.05 or less will be used to declare statistical significance for all analyses.

The number needed to treat (NNT) and 95% confidence intervals will be calculated (4).

13.1 Analyses of missing data

As much information as possible will be collected about the reasons for missing outcome data and this will be used to inform sensitivity analyses.

If there are clinical indicators of infection but no microbiology report of blood cultures then no blood stream infection will be assumed, a sensitivity analysis will assess whether the conclusion differs if we assume there is an infection. Clinical indicators of infection will not be included where the clinical indicator that was on the sampling form was only for raised CRP or white blood cell counts or both. The ICD-10 code reason for admission will also be considered.

If the patients without microbiology reports are included in the denominator of the primary outcome then this assumes that there was no clinically indicated blood stream infection. The following classifications (Table 1) make use of all data available for each case and present reasonable assumptions on their primary outcome classification. Where there is uncertainty these cases are highlighted for sensitivity analysis.

TABLE 1: ASSUMPTIONS FOR SENSITIVITY ANALYSIS

Clinically indicated and samples taken	Include in numerator for sensitivity analysis
Clinically indicated but no samples taken (taking into account ICD-10 code)	Include in numerator for sensitivity analysis
Not clinically indicated and no samples at removal	Included in denominator only

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Inserted for less than 48 hours/ attempted after 12 hours after randomisation/not successfully inserted	Included in denominator only
'None' was not ticked for organisms and there were no other organisms noted.	Included in denominator only

13.2 Sampling frequency

Samples will be descriptively summarised (numbers and percentages) for samples taken 48 hours after insertion and within 48 hours after removal that are clinically indicated. Table columns will be: Standard; impregnated (heparin or antibiotic); antibiotic; heparin; and total. These tables will be produced across all sites and by site.

a) Type of sample – arterial, peripheral or CVC

b) Number with multiple samples from same cvc and different lumens

c) Site (femoral, other)

d) CVC tip sampled and paired CVC tip and blood culture within 48 hours

e) PCR sampled

14 Analysis of secondary efficacy outcomes

The null hypothesis for each secondary outcome (in which statistical tests are being performed) will be that there is no difference in outcome between the standard and impregnated (antibiotic and heparin) groups. The alternative hypothesis is that there is a difference between the two groups. The stratification variable elective/emergency participants will be included as a covariate. The outcomes will also be analysed with the groups separately. (Appendix C, D, E, F)

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

Data obtained as per the primary outcome although the CVC must be in situ. For a second infection the isolate needs to be a different strain (review conducted blind to allocation by a team of clinical professionals) and not within 48 hours to that identified in the primary outcome otherwise considered same infection.

The analysis will involve the number of infections and the number of days the CVC is in situ. This will be standardised to 1000 CVC days and the rate ratio and 95% confidence intervals will be presented based on poisson regression.

14.2 Time to CVC thrombosis

Data will be obtained from form 1 or 3 (Section B question 2: date and time of randomisation), 11 (difficulty withdrawing blood, episodes of flushing, swollen limb, ultrasound done – positive results obtained from sites), form 9 (section A, question 2: date and time sample taken and question 3: difficulty withdrawing blood), form 6

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(thrombosis indicated, not bleeding back as a reason for no sample taken – to confirm unclear text with clinical team), form 5 (Section B, question 1: date and time of CVC removal and question 3: reason for removal 'CVC blocked').

This will also be checked against the related adverse events form (form 12) to ensure all thrombosis events have been recorded on the thrombosis form and reviewed by a team of clinical professionals. There was no time on the progress log (form 6) or thrombosis form (form 11) therefore the time was set at 23.59. Patients with no event were censored at 48 hours after removal.

The survival analysis will use the method of the Log rank test and Cox proportional hazard regression models if appropriate. Results will be presented using Hazard Ratios and 95% confidence intervals. Kaplan-Meier curves stratified by CVC will be presented. Survival times will be measured from the date and time of randomisation to the date and time of CVC thrombosis.

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

Data used will include forms 1, 3 (date and time of randomisation), 5 (removal due to CVC infection), 6 (as per primary outcome), 7 (change in antibiotics), 9 (clinical signs of infection),10 and downloads (microbiology – culture negative and high DNA load, Appendix D). A blood culture must have been taken.

The date/ time of randomisation (form 1 and 3) and the date/time of first indication of a composite measure of clinically indicated blood stream infection will be used to calculate the time to a composite measure of clinically indicated blood stream infection.

Antibiotics will be grouped by a clinical professional (Appendix F). Data will be reviewed by a team of clinical professionals (Appendix G).

The survival analysis will use the method of the Log rank test and Cox proportional hazard regression models if appropriate. Results will be presented using Hazard Ratios and 95% confidence intervals. Kaplan-Meier curves stratified by CVC will be presented. Survival times will be measured from the date and time of randomisation to the date and time of the blood stream infection.

14.4 A CVC related blood stream infection

Data will be obtained as per the primary outcome although CVC tip is included and exit site infection (forms 5 and 12). Differential positivity will be reviewed by a team of clinical professionals (Appendix G).

The analysis will use the method of Fishers exact test to compare proportions in the standard group compared to the impregnated groups and relative risks will be presented with 95% confidence intervals.

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14.5 Mortality by 30 days

At the time of clinical analysis death will be taken as that recorded prior to discharge (form 16). ONS data will be obtained and reconciled with that held on form 16 and final analysis completed upon the reconciled data set.

The analysis will use the method of Fishers exact test to compare proportions in the standard group compared to the impregnated groups and relative risks will be presented with 95% confidence intervals.

14.6 Type of bacteria and fungi isolated from positive blood cultures

The data will be taken from the microbiology form (form 10) and also obtained from a microbiology download from each site. Line listings will be given to the microbiologist to specify the groupings (Appendix D and F).

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

The data will be obtained from a microbiology download from each site from positive blood cultures for the primary outcome and repeat bloodstream infections identified in Outcome 14.1 and CVC tip**Error! Reference source not found.** and provided to the microbiologist to determine resistance (Appendix G).

The analysis will use the method of Fishers exact test to compare proportions in the standard group compared to the impregnated groups and relative risks will be presented with 95% confidence intervals.

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

The data will be obtained from the adverse event form (form 12 number 2 and 13). This will be measured from randomisation up to 48 hours after removal.

The analysis will use the method of Fishers exact test to compare proportions in the standard group compared to the impregnated groups and relative risks will be presented with 95% confidence intervals.

14.9 Time to randomised CVC removal

The date and time of randomisation will be taken from form 1 and 3, section B, question 2. The date and time of CVC removal will be taken from form 5, section B, question 1. Note this does not have to be the randomised CVC, but rather the CVC inserted following randomisation.

The survival analysis will use the method of the Log rank test and Cox proportional hazard regression models if appropriate. Survival times will be measured from the date and time of randomisation to the date and time of CVC removal. Results will be

presented using Hazard Ratios and 95% confidence intervals. Kaplan-Meier curves stratified by CVC will be presented.

14.10 Length of stay requiring PICU

The length of stay will be measured from the date of randomisation to the date of transfer/discharge from PICU for the first stay in PICU (NICU and CICU will also be treated as PICU). Date of randomisation (form 1 and 3 section B) or, date admitted to PICU (form 4) will be used as the start date and details of the ward will be used (form 1 and 3 section B question 7). Date and time of transfer/discharge from PICU is included on form 14 section A. A small number will need data from HES (those randomised at end of recruitment period)

The analysis will use the method of the two sample t test or Mann Whitney U test depending on the distribution of the data. Means will be presented with 95% confidence intervals or medians and interquartile range as appropriate.

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

The date/time of randomisation (form 1 and 3) and the date/time of transfer/ discharge (form 14) will be used. A small number will need data from HES (those randomised at end of recruitment period).

The analysis will use the method of the two sample t test or Mann Whitney U test depending on the distribution of the data. Means will be presented with 95% confidence intervals or medians and interquartile range as appropriate.

14.12 Cost effectiveness of heparin bonded vs. antibiotic-impregnated vs. standard CVCs

The analysis will be undertaken by health economics using data downloaded from HES. Please see health economics analysis plan.

15 Setting results in context of previous research

Once the trial has been completed the results of the trial will be set in context of the existing evidence base**.** This will compare the results of the trial with those reported within relevant systematic reviews.

Generalisability of results

Once the trial has been completed the results will be used in analyses that take into account trends in blood stream infection across all PICUs in the UK, in order to estimate the absolute risk difference associated with purchasing impregnated vs standard CVCs. The analysis will be undertaken by the team at UCL-ICH. Please see the generalizability study analysis plan.

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16 References

1. Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. Ann Int Med 2010;152. Epub 24 March.
2. ICH E3 chapter 12.
3. ICH E9 chapter 3.
4. Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. *BMJ* 1999;319:1492–5.

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Approval and agreement

Two versions of the SAP should be approved.

1. SAP version 1.0 should be created after it has been reviewed and signed-off to ensure all are in agreement with the planned analysis and no further changes are foreseen.

2. The final SAP version should be converted to PDF and signed following the blinded review for protocol deviations and immediately prior to database lock as evidence of the analysis planned prior to unblinding of the study.

SAP Version Number being approved: _____

Trial Statistician

Name _____

Signed _____ Date _____

Senior Statistician or Head of Statistics

Name _____

Signed _____ Date _____

Chief Investigator

Name _____

Signed _____ Date _____

OR Electronic approval attached ☐

Chair of Trial Steering Committee

Name _____

Signed _____ Date _____

OR Electronic approval attached ☐

OR TSC not reviewing SAP (ensure agreement is documented) ☐

Chair of Data Monitoring Committee

Name _____

Signed _____ Date _____

OR Electronic approval attached ☐

OR IDSMC not reviewing SAP (ensure agreement is documented) ☐

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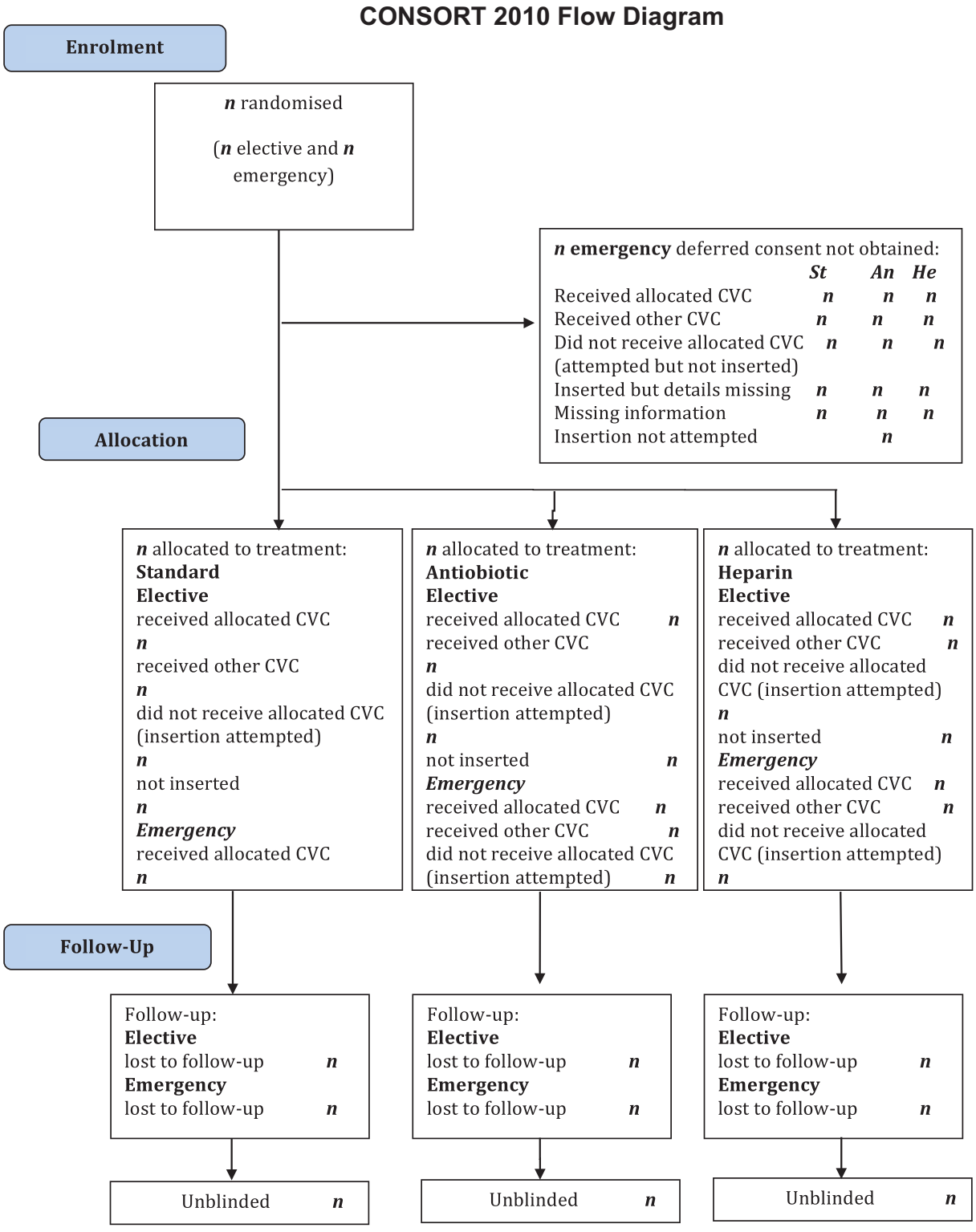
SAP APPENDIX A: CONSORT DIAGRAM



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SAP APPENDIX B: PROTOCOL DEVIATIONS

Eligibility	**Major/minor**
Child over 16	Minor
Randomised multiple times	Major
Trial Procedures	
Patient not followed up for full trial duration from randomisation to 48 hours after follow up	Major
CVC was not needed for 48 hours and removed	Major
CVC inserted more than 12 hours after randomisation	Major
Samples not taken within 48 hours of clinical indication	Major
Line not required following randomisation (post 12hrs) randomisation pack returned to CTU	Minor
Randomisation and sequence	
Incorrect randomisation envelope used - elective randomising envelope for an emergency line insertion or emergency randomising envelope for an elective line insertion	Minor

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SAP APPENDIX C: OUTCOME DEFINITION TABLE

End Point	Clinically indicated (one or more) *	Timing of sample with reference to CVC			Positive blood culture		CVC tip		Site	Notes
		Up to 48 hours after insertion	48 hours after insertion to removal	Up to 48 hours after removal	Non-Skin	Skin	Non Skin	Skin	A=arterial P=peripheral C=CVC MC=multiple lumens of the CVC T=CVC tip E=exit site	
Primary Endpoint										
Time to first blood stream infection defined by a positive blood culture from a sample that was clinically indicated and taken more than 48 hours after CVC insertion and up to 48 hours after CVC removal	Y	N	Y	Y	Y One sample taken from cvc lumen, arterial, peripheral	Y But need at least 2 positive blood culture samples with matching isolate taken within 48 hrs of each other. Only one sample needs to be in time window.	N	N	A P C	Arterial, peripheral and CVC apply. a 'skin' BSI *always* requires at least two blood samples with an indistinguishable (by ID and antibiotic suseptibility) strain within defined period. **Assessed by team of clinical professionals**
Secondary Endpoint										
Rate of blood stream infection during CVC insertion per 1000 CVC days	Y As per primary outcome (PO)	Y	Y	N	PO	PO	PO	PO	A P C	Arterial, peripheral and CVC apply **Assessed by team of clinical professionals**
					For a second infection the isolate needs to be different strain and AB resistance profile to that identified in the PO and taken from a second sample more than 48 hours after first positive BSI otherwise considered same infection.					

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End Point	Clinically indicated (one or more) *	Timing of sample with reference to CVC			Positive blood culture		CVC tip		Site	Notes
		Up to 48 hours after insertion	48 hours after insertion to removal	Up to 48 hours after removal	Non-Skin	Skin	Non Skin	Skin	A=arterial P=peripheral C=CVC MC=multiple lumens of the CVC T=CVC tip E=exit site	
Time to CVC thrombosis - defined clinically • 2 records of difficulty drawing back blood from one or more lumen; • 2 or more episodes of flushing; • an episode of swollen limb; • positive ultrasound (up to 5 days after removal); • removal of CVC because of clinical evidence of a blocked CVC	NA.	Y	Y	Y	NA	NA	NA	NA	NA	**Assessed by team of clinical professionals**
Time to a composite measure of a clinically indicated blood stream infection (any one of below) • primary outcome	Y	N	Y	Y	Y One sample taken from cvc lumen, arterial, peripheral	Y But need at least 2 blood samples with matching isolate taken within 48 hrs of each other. Only one sample needs to be in time window.	N	N	A P C	

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End Point	Clinically indicated (one or more) *	Timing of sample with reference to CVC			Positive blood culture		CVC tip		Site	Notes
		Up to 48 hours after insertion	48 hours after insertion to removal	Up to 48 hours after removal	Non-Skin	Skin	Non Skin	Skin	A=arterial P=peripheral C=CVC MC=multiple lumens of the CVC T=CVC tip E=exit site	
• high bacterial DNA load	Y	N	Y	Y	NA	NA	NA	NA	NA	
• culture negative bloodstream infection based on clinical criteria defined by: • a change in antibiotic treatment on the same or subsequent day after a blood culture sample more than 48 hours after CVC insertion **and** • 1 or more clinical signs of infection. clinical signs - temperature >38°C or temperature instability, - haemodynamic instability (hypotension, mottled, poor perfusion, capillary refill>3s); - OR CVC removed for infection	Y	N	Y	Y	NA	NA	NA	NA	NA	Laboratory signs only counted if one other clinical sign present – excluding crp or wcc Blood culture sample had to have been taken And no other sources of infection except clinical signs **Culture negative infections assessed by team of clinical professionals**
CVC related blood stream infection a) the same isolate (species and antibiogram) from the CVC tip and from a blood culture	N	N – blood Y-tip	Y	Y	Y	Y	Y If positive BSI in time window	Y If positive BSI (one skin)	A P C T	Positive BSI AND same organism and antibiogram for tip. If positive BSI>48

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End Point	Clinically indicated (one or more) *	Timing of sample with reference to CVC			Positive blood culture		CVC tip		Site	Notes
		Up to 48 hours after insertion	48 hours after insertion to removal	Up to 48 hours after removal	Non-Skin	Skin	Non Skin	Skin	A=arterial P=peripheral C=CVC MC=multiple lumens of the CVC T=CVC tip E=exit site	
										hours, tip can be anytime.
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).	N	N	Y	Y	Y	Y	N	N	MC	when the primary outcome definition for a BSI has been fulfilled, and where there are multiple CVC lumens, and blood cultures have been collected from multiple lumens at the same sampling time, but not all give a positive result.
c) OR positive BSI AND CVC removed for infection	N	N	Y	Y	Y One sample taken from cvc lumen, arterial, peripheral	Y any positive BSI, two BSI needed	N	N	A P C	
d) OR positive BSI AND CVC exit site infection	N	N	Y	Y	Y One sample taken from cvc lumen, arterial, peripheral	Y any positive BSI one BSI only needed	N	N	A P C E	

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End Point	Clinically indicated (one or more) *	Timing of sample with reference to CVC			Positive blood culture		CVC tip		Site	Notes
		Up to 48 hours after insertion	48 hours after insertion to removal	Up to 48 hours after removal	Non-Skin	Skin	Non Skin	Skin	A=arterial P=peripheral C=CVC MC=multiple lumens of the CVC T=CVC tip E=exit site	
Mortality by 30 days	NA	NA	NA	NA	NA	NA	NA	NA	NA	
Type of bacteria and fungi isolated from positive blood cultures	List of all isolates to be sent to a team of clinical professionals to classify									
Resistance to minocycline or rifampicin of blood culture or CVC tip isolates >15 isolates e-test will be performed	NA	Y	Y	Y	Y	Y	Y	Y	A P C	Data from download from individual sites. Report separately for BSI and tip **Assessed by team of clinical professionals**
Unexplained thrombocytopenia after insertion of CVC- detected by routine laboratory monitoring	NA	NA	NA	NA	NA	NA	NA	NA	NA	

* Note: Raised WBC and/or CRP are not sufficient criteria alone for clinically indicated blood stream infection. Other additional criteria are required. Must be clinically indicated within 48 hours of the sample taken.

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SAP APPENDIX D: SKIN AND NONSKIN ORGANISMS

The contents of this table have been developed over the data monitoring committee reports by the statisticians and microbiologist. These organisms will be reconciled with the microbiology downloads. This table is based on the line listings as entered into the clinical trials database. No correction has been made to spelling mistakes or abbreviations, so each has been classified as it appears on the database. For production of a table summarizing the different types of organisms self evident corrections agreed by the clinical team will be utilized.

Organism as stated in the CRF	Corrected organism name	Skin/nonskin	Minocycline/ Rifampicin active/inactive
Coagulase-negative staphylococcus	Many possible names – *Staphylococcus epidermidis, Staphylococcus spp.*, Anything with *Staphylococcus* which does not include *aureus*.	skin	Active
Staph.aureus	*Staphylococcus aureus*	Non skin	M and R Active
Klebsiella spp.	*Klebsiella spp.* (or a species name – *oxytoca, pneumonia* etc.)	Non skin	Inactive
Enterobacter spp.	*Enterobacter spp*. (or a species name – for example *cloacae*)	Non skin	Inactive
E.coli	*Escherichia coli*	Non skin	Inactive
Enterococcus spp.	*Enterococcus spp*. (or a species name such as *faecalis*)	Non skin	MR and R variable
Candida spp.	*Candida spp*. (or a species name such as *albicans*)	Non skin	Inactive
Acinetobacter spp.	*Acinetobacter spp.* (or a species name such as *baumanii*)	Non skin	Inactive
Haemophilus influenzae	Haemophilus influenza	Non skin	A
gram negative coccus	Gram negative coccus	Non skin	A
viridans streptococcus	Streptococcus spp.	Non skin	A
Yeast or yeasts	Yeast	Non skin	I
germ tube negative	Yeast	Non skin	I
gram Positive cocci	*Staphylococcus spp.*	Skin	A
Gram +ve cocci query staph	*Staphylococcus spp.*	Skin	A
Escherichia coli or Escherichia Coli or escherichia coli	Escherichia coli	Non skin	I
E.coli	Escherichia coli	Non skin	I
staphylococcus epidermis	Staphylococcus epidermis	Skin	A
Coliform Strain 1 coliform strain 2	Enterobacteriaceae	Non skin	I
Staph.aureus	Staphylococcus aureus	Non skin	A
Serratia Marcescens or SERRATIA MARCESCENS	Serratia marcescens	Non skin	I
Pseudomonas aeruginosa or Pseudomonas Aeruginosa or pseudomonas aeruginosa or PSEUDOMONAS AERUGINOSA or Pseudomonas Aeruginose or Pseudomonas	Pseudomonas aeruginosa	Non skin	I

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aeruignosa or Pseudomonas Aerginosa or Pseudomonas Aerugonsa or pseudomonas aeruguosa or			
Pseudomonas or pseudomonas	Pseudomonas spp.	Non skin	I
Viridans Streptococcus	Streptococcus spp.	Non skin	A
Enterococcus spp.	Enterococcus spp.	Non skin	A
Serraha soecies coliform	Serratia species	Non skin	I
Candida spp.	Candida spp.	Non skin	I
MRSA	Meticillin-resistant Staphylococcus aureus	Non skin	A
Staph.aureus	Staphylococcus aureus	Non skin	A
Coliform or Coliforms	Enterobacteriaceae	Non skin	I
Enterobacter spp.	Enterobacter spp.	Non skin	I
Mixed growth including viridans streptococcus	Streptococcus spp.	Non skin	A
Enterococcus spp	Enterococcus spp	Non skin	A
Klebsiella pneumoniae	Klebsiella pneumoniae	Non skin	I
Klebsiella spp.	Klebsiella spp.	Non skin	I
Cellulomas	Cellulomas spp.	Non skin	I
Acinetobacter spp.,	Acinetobacter spp.,	Skin	I
Micrococcus luteus	Micrococcus luteus	Skin	A
88 >15 colonies staphylococcus epidermus (STAEP)	Staphylococcus epidermus	Skin	A
Gram negative bacilli	Gram negative bacillus	Non skin	I
Gram negative Bacilli	Gram negative bacillus	Non skin	I
Scanty Growth	Scanty growth	Non skin	NA
+ PCR Influenza A	Virus	Non skin	NA (exclude from analysis as viral)
99 Aerobic spore bearing bacillus	Bacillus spp.	Non skin	A
Viridans Streptococcus	Streptococcus spp.	Non skin	A
Streptococcus	Streptococcus spp.	Non skin	A
Uepidermidis	Staphylococcus epidermidis	Skin	A
Staphylococcus or staphylococcus	Staphylococcus spp.	Skin	A
Staphyloccus epidermidis or Staphyloccus epidemidis or STAPHYLOCOCCUS EPIDERMIDIS	Staphylococcus epidermidis	Skin	A
staphylococcus epidermidis	Staphylococcus epidermidis	Skin	A
Staca Staep Eccf	Staphylococococcus capitis, Staphylococcus epidermidis (skin) Enterococcus faecalis (non-skin)	Skin Non –skin	A
Menigococcal -ve pneumococcal -ve	Negative result	Non skin	NA (exclude from analysis as negative result)
Serraha soecies coliform	*Serratia spp.*	Non skin	I
Rothia Sp	Rothia spp.	Skin	A
Neisseria Meningitidis or Neisseria meningitides or n meningitidis	Neisseria meningitidis	Non skin	A
Meningoccocus or Meningococcus	Neisseria meningitidis	Non skin	A
N:Meningitis Group B (PCR)	Neisseria meningitidis	Non skin	A
Micrococcus SP	Micrococcus spp.	Skin	A

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Beta haem streptococcus group B	Streptococcus agalactiae	Non skin	A
Diphtheroid Species or Diphtheroid species	Corynebacterium spp.	Skin	A
Group B Streptococcus or group b streptococcus	Streptococcus agalactiae	Non skin	A
Coliform and coliform strain 2	Coliform	Non-Skin (NS)	I
Serratia Macsecens	Serratia marcescens	NS	I
scanty mixed flora	(Mixture)	?	?
Scanty Respiratory flora	(Mixture)	?	?
streptococcus pneumoniae	Streptococcus pneumonia	NS	A
raoultella planticola	Raoultella panticola	NS	I
Rothia Mucilginosis	Rothia mucilaginosis	Skin (S)	A
s.capitis	Staphylococcus capitis	S	A
s epidermidis or S Epidermidis	Staphylococcus epidemidis	S	A
streptococcus mitis	Streptococcus mitis	NS	A
s.oralis	Streptococcus oralis	NS	A
Staoh Hacomolyticus	Staphylococcus haemolyticus	S	A
S Hominis	Staphylococcus hominis	S	A
S EPI	Staphylococcus epidermidis	S	A
s. parasanguis, s salivarius	Streptococcus parasanguis & Streptococcus salivarius	NS	A
s. warneri	Staphylococcus warnerii	S	A
staph scuiri	Staphylococcus scuiri	S	A
Fungi	Fungi	NS	I
lactococcus lacis	Lactococcus lactis	NS	A
group b strep	Streptococcus agalactiae	NS	A
less than colonies staca	Staphylococcus capitis	S	A
gramulicatella adiacens	Gramulicatella adjacens	NS	A
<15 colonies staphylococcus epidermidis	Staphylococcus epidermidis	S	A
Staphylococcus Uepidermidis	Staphylococcus epidermidis	S	A
Micrococcus luteus	Micrococcus luteus	S	A
staphylococcus warnen STAWA) and staphlococcus hominis (STAHO)	Staphylococcus warneri & Staphylococcus hominis	S	A
ENTEROCOCCUS FAECIUM or enterococcus faecium	Enterococcus faecium	NS	I
STAEP	Staphylococcus epidermidis	S	A
Staphyloccus SP (STA)	Staphylococcus spp.	S	A
<15 rothia	Rothia spp.	S	A
Micrococcus SP	Micrococcus spp.	S	A
Beta heam streptococcus group B	Streptococcus agalactiae	NS	A
Staphyloccus epidermis	Staphylococcus epidermidis	S	A
Escherichia Col staphylococcus epidermidis yeast	Escherichia coli Staphylococcus epidermidis& yeast	NS & S	I & A
Gram Negative bacilli	Gram negative bacilli	NS	I
Staca Staep Eccf	Staphylococcus capitis & Staphylococcus epidermidis & Enterococcus faecalis	S & NS	I & A
Staep	Staphylococcus epidermidis	S	A
Staca less than 15 colonies	Staphylococcus capitis	S	A

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> 15 colonies staphylococcus hominis	Staphylococcus hominis	S	A
Mixed	(Mixture)	?	?
Small amount of mixed organisms	(Mixture)	?	?
mixed organisms	(Mixture)	?	?
candida albicans	Candida albicans	NS	I
coliform bacilli or Coliform baolli	Coliform	NS	I
strep mitis	Streptococcus mitis	NS	A
aspergillis niger	Aspergillus niger	NS	I
>100 colonies of candida aubicans	Candida albicans	NS	I
gram +ve stapylococci	Staphylococcus spp.	S	A
propionibacterium	Propionibacterium spp.	S	A
gram positive staph	Staphylococcus spp.	S	A
Group B Strep	Streptococcus agalactiae	NS	A
mixed skin flora	(Mixture)	S	A
coagulase negative staphyloccus #2 or coagulase-negative staphylococcus #2	Staphylococcus spp.	S	A
micrococcus	Micrococcus spp.	S	A
streptococcus porincus	Streptococcus porcinus	NS	A
k pneumoniae ssp pneumoniae	Klebsiella pneumoniae	NS	I
alpha haemolytic streptococcus streptococcus mitis	Streptococcus mitis	NS	A
serratia liquifaciens & lactococcus lactis	Serratia liquifaciens & Lactococcus lactis	NS	I & A
lactococcus lactis	Lactococcus lactis	NS	A
serratia liquifaciens & lactococcus lactis	Lactococcus lactis & Serratia liqifaciens	NS	A & I
k pneumoniae	Klebsiella pneumoniae	NS	I
methicillin resistant staph aureus	Methicillin resistant Staphylococcus aureus (MRSA)	NS	A
neisseria meningitidis	Neisseria menigitidis	NS	A
N.Meningitiois	Neisseria menigitidis	NS	A
88 Group B Streptococus	Streptococcus agalactiae	NS	A
candida albicans	Candida albicans	NS	I
Positive Cocci	Gram positive cocci	?S	?A
Micrococcus species Enterococcus faecium	Micrococcus spp.& Enterococcus faecium	S & NS	A & I
esbl e.coli	Escherichia coli (ESBL)	NS	I
escherichia coli	Escherichia coli	NS	I
Gram positive cpcco	Gram positive cocci	?S	?A
Pseudomonas (High resistance strain)	Pseudomonas spp.	NS	I
Scant growth of stpaph epidermin	Staphylococcus epidermidis	S	A
heavy Growtyh Staphyloccous epidermis	Staphylococcus epidermidis	S	A
88 scanty growth capitis	Staphylococcus capitis	S	A
Scanty Growth Staph Epidermin	Staphylococcus epidermidis	S	A
Neisseria Meningitis	Neisseria meningitidis	NS	A
Betahaemolytic Streptococcus	Streptococcus spp.	NS	A
Scanty Growth Staphepidermis and capitis	Staphylococcus epidermidis & capitis	S	A

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Nesseira meningitiolis	Neisseria meningitidis	NS	A
staph epidermis	Staphylococcus epidermidis	S	A
Staphyloccous hominis	Staphylococcus hominis	S	A
Staph Heminis	Staphylococcus hominis	S	A
Staphylococus Heminis	Staphylococcus hominis	S	A
Entrococcus Faecalis	Enterococcus faecalis	NS	I
gram positive bacilli	Gram positive bacilli	NS	A
Meningococcal Type B	Neisseria meningitidis group B	NS	A
group b streplococcus	Streptococcus agalactiae	NS	A
adenovirus & parainfluenza 3	Virus	Not relevant	Not relevant
neisseria meningitidis type b	Neisseria meningitidis group B	NS	A
scanty bacillus	Bacillus spp.	NS	A
(at local) group A strep	Streptococcus pyogenes	NS	A
Gram + Cocci	Gram positive cocci	S	A
enterococcus faecalis	Enterococcus faecalis	NS	I
strepsobinue	Streptococcus spp.	NS	A

The A indicates that minocycline and rifampicin would be expected to be Active against the bug. The I indicates that the micocycline and rifampicin are less likely to be active. NA indicates that this is not applicable.

Neisseria meningitidis and Group B streptococci are very unlikely to be CVC associated infections.

staphylococcus epidermis Staphylococococcus capitis, Staphylococcus epidermidis (skin)
Staphylococcus spp. Gram +ve coccus = *Staphylococcus spp*. (coagulase –ve)

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SAP APPENDIX E: STEPS TAKEN TO OBTAIN OUTCOME DATA

Primary outcome: Time to first blood stream infection defined by a positive blood culture from a sample that was clinically indicated and taken more than 48 hours after CVC insertion and up to 48 hours after CVC removal.

Step 1

Identify those with microbiology blood sample taken (CVC tip is excluded)

a. Results with no organisms cultured are classed as negative
b. Those with organisms (bacteria or fungi) are categorised as either skin/non-skin by microbiologist and a new variable created to indicate skin/non-skin classification.
    i. Non skin= positive blood culture
    ii. Skin
        1. If a skin organism is identified, check whether any other skin organisms have been identified
        2. If so, check whether they are within 48 hours of each other.
        3. If so, check to see if this is the same organism based on clinician endpoint review
        4. If 1-3 = yes then this results in a positive blood culture all others are negative

Note that this assumes those with missing microbiology are negative cultures. However, the microbiology downloads will be checked if there is no microbiology CRF for a participant or if one skin organism within the time frame has been detected.

Step 2

Timepoints.

For those with a positive blood culture identified from step 1 we check whether the sample was taken 48 hours after randomisation and within 48 hours after removal (This is done at this point as there are implications for skin organisms). For positive blood culture based on skin organisms at least one of the samples has to be within the above timeframe but not both. If timeframe is not that specified here then the result is coded as a negative blood culture.

Positive blood cultures outside of the timeframe will be tabulated along with the time of occurrence.

Step 3

For each remaining positive blood culture need to determine whether this was clinically indicated based on one of the criteria a to c below:

a. check whether the CVC was removed because a CVC associated infection was suspected (form 5 section B question 3, note that some participants have two reasons for removal) or whether there were signs of exit site infection (form 5, section A, question 1)
b. check progress log (form 6) to see whether clinically indicated was marked as 'yes'

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c. check sampling form (form 9 section A question 4) to see whether one or more of the clinical indicators were present (WBC and/or CRP are not sufficient to clinically indicate infection) or whether there were signs of CVC infection prior to sampling (form 9 section B question 1)
d. check that a clinical indicator (from step a-c) is present within 48 hours either side of the positive blood culture. For positive cultures from a skin organism, the clinical indication has to be within 48 hours of the sample taken in the time window in step 2.
e. If the positive blood culture is clinically indicated, this results in a positive blood stream infection.

The time of randomisation and the time the sample of the positive blood culture was taken is used to calculate the time to first blood stream infection. For positive blood cultures from two skin organisms, the first skin organism to occur in the specified time frame will be the organism used for first positive blood culture.

Secondary outcomes:

1. **Rate of blood stream infection during CVC insertion per 1000 CVC days.**

Second episode of blood stream infection (defined as per primary outcome) will be defined by a positive blood culture of a different isolate (in terms of species) 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.

- Same as PO but not after removal
- Data to be presented to the clinician endpoint review: first infection, second infection and the time between these who will decide how many separate blood stream infection each participant had.

2. **Time to CVC thrombosis - defined clinically by:**
   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.

- To check thrombosis form (form 11) and AE form (form 12), sampling form (form 9) and progress log (form 6), follow up form (form 5)
  1. Create an indicator if there are 2 or more occasions of difficulty drawing back blood (form 9 and 11)
  2. Create an indicator if there are 2 or more occasions of an episode of flushing to unblock (form 11)
  3. Create an indicator if there was a swollen limb (form 11, form 12)
  4. Create an indicator if there was a positive ultrasound (form 11 and separate data received from sites)
  5. Note if removal of CVC was because of clinical evidence of a blocked CVC (form 5, note that there may be two reasons for removal)
- If any of these (i to v) then a thrombosis has occurred.

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- Check whether thrombosis was indicated on the progress log (form 6)

The date/ time of randomisation (form 1 and 3) and the date/time of first indication of thrombosis will be used to calculate the time to CVC thrombosis.

Extra information to check for thrombosis

1) If indicated on the progress log that they have the corresponding entry on the thrombosis form (And vice versa);
2) If indicated as text on the progress log i.e. not bleeding back , not sampling back – that there is a relevant entry on the progress log and thrombosis form (possibly form 9
depending on the interpretation);
3) On form 5 (not sampling back/ Not bleeding back) thrombosis event recorded on the progress log, thrombosis form and possibly form 9 depending on the interpretation;
4) CVC blocked/ not sampling back as reason for removal – corresponding thrombosis event on progress log, Thrombosis form and Sampling Form (form 9 depending on the interpretation)
5) Any lumens on Form 9 not bleeding back – check entry on Thrombosis Form, Progress log and Sampling form ;
6) Thrombosis events are on the AE form and ensuring the corresponding events are on the thrombosis form – therefore the AE's can be ignored;
7) Progress log - the same event can continue during the trial however only one row of data would be indicated on the thrombosis form – check that each day with an event has a corresponding row of data.

3. 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 (negative) 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

- As primary outcome
- High bacterial DNA load from a PCR positive or negative result initially taken from microbiology downloads. A positive will fulfil the high bacterial load criterion.
- change in antibiotics (form 7 and Appendix F)
- check form 5 as to whether removal of CVC was for infection (note that there may be two reasons for removal).

The date/ time of randomisation (form 1 and 3) and the date/time of first indication of a composite measure of clinically indicated blood stream infection will be used to calculate the time to a composite measure of clinically indicated blood stream infection.

4. A CVC related blood stream infection will be defined by:

a. the same isolate (species) from the CVC tip and from a blood culture sample (one skin or one non skin) taken from any site more than 48 hours after CVC insertion and within 48 hours following CVC removal;

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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).
    i. Non-skin and both negative =No
    ii. Non-skin and both positive =No
    iii. Non-skin and one negative and one positive =Yes
    iv. Skin and one negative and one positive on two occasions (otherwise, as primary outcome criteria) =Yes
c. OR positive BSI AND CVC removed for infection (and two skin organisms)
d. OR positive BSI AND CVC exit site infection (and two skin organisms)

- Organisms cultured sent to clinical review team to decide if they are the same isolate.
- Note positivity of isolates
- Positive BSI as noted for primary outcome and reason for removal is infection (form 5)
- Positive BSI and reason for removal is exit site infection (form 5)
- If a-d is yes then CVC related BSI

5. Mortality by 30 days

- Check death form (form 16)
- Date/time of death (form 16)
- Date/time of randomisation (form 1 and 3)
- Data will also come from HES

6. Type of bacteria and fungi isolated from positive blood cultures

- Line listings will be given to the microbiologist to specify what the groupings for each are. (CRF 10 and downloads)

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

- Microbiologist to classify based on organisms listed (CRF 10) for positive blood cultures only (see primary outcome (main analysis) and secondary outcome 1) between 48 hours after insertion and within 48 hours after removal.

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

- AE form (12 number 2 and 13)
- From randomisation up to 48 hours after removal.

9. Time to randomised CVC removal

- Date/ time of randomisation (form 1 and 3)
- Date/ time of removal (form 5)
- Note this does not have to be the randomised CVC, but rather the CVC inserted following randomisation.

10. Length of stay requiring PICU (for first episode)

- Date/time admitted to PICU (form 1, 3 and 4)
- Date/ time discharged from PICU/ transferred (form 14)

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- A small number will need data from HES (those randomised at end of recruitment period)

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

- Date/ time admitted (form 1 and 3)
- Date/ time discharged (form 14)
- Data will come from HES

12. Cost effectiveness of heparin bonded vs. antibiotic-impregnated vs. standard CVC

- see health economics plan

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SAP APPENDIX F: ANTIBIOTIC GROUPING

Antibiotic name	Group
1% chloramphenical ointment	0
1% clotrimazole	0
Aciclofvir	0
aciclovi	0
Aciclovir	0
ACICLOVIR	0
aciclovir	0
Aciclovir 3% ointment	0
aclclovir	0
Acliclovir	0
Aclovir	0
Acyclovir	0
ACYCLOVIR	0
acyclovir	0
Acylivir	0
ACYLOVIR	0
Acylovir	0
Amakacin	1
Ambisome	3
ambisome	3
Ambisone	3
ambisone	3
amicacin	1
Amikacin	1
Amikacin	1
AMikacin	1
AMIKACIN	1
amikacin	1
Amikazin	1
Amixicillin	2
Amkacin	1
Amoxacillin	2
amoxacillin	2
amoxcicillin	2
Amoxcycillin	2
Amoxicilin	2
amoxicillan	2
Amoxicillin	2
AMOXICILLIN	2
amoxicillin	2
Amoxiclin	2
amoxiclin	2
Amoxtcillin	2
Amoxycillin	2
amoxycillin	2
Amoxyclillin	2
Ampcillin	2
Amperotericin	3
amphiotericin	3
Amphoitericin	3
Amphoteracin	3
AMPHOTERACIN	3
amphotercin	3
Amphotericin	3
AMphotericin	3
amphotericin	3
AMPHOTERICIN	3
amphotericin B	3
amphotericin b	3
Amphotericin Liposomal	3
amphotericin liposomal	3
Amphotericin Liposome	3
Amphotericin Liposoml	3
Amphotericin Lipsomal (Ambisone)	3
Amphotericin/Liposome	3
amphoteritinlipsoml	3
ampiccillin	2
ampicilin	2
Ampicilin	2
Ampicillin	2
AMPICILLIN	2
ampicillin	2
Ampicilllin	2
Ampiclillin	2
Ampiicillin	2
anoxycillin	2
Augmentin	2
augmentin	2

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augmentin duo	2
Ayciclovir	0
Azithromicin	4
azithromicin	4
Azithromycin	4
AZITHROMYCIN	4
azithromycin	4
Azithromycin1	4
Azithromycn	4
Aztreonam	5
aztreonam	5
Baclofen	0
Bacroban	0
bactoban	0
bactrobam	0
Bactroban	0
bactroban	0
BACTROBAN 2%	0
Bactron	0
Basiliximab	0
Benpencillin	6
benpenicillin	6
Benzlpenecillin	6
benzlpenicillin	6
Benzlypenicillin	6
benzy penicillin	6
benzyl pencillin	6
Benzyl pencillin	6
Benzyl Penicillin	6
benzyl penicillin	6
Benzylepenicillin	6
Benzylpencillin	6
Benzyl-pencillin	6
benzylpencillin	6
benzylpenecillin	6
Benzylpenecillin	6
benzylpenicilin	6
Benzylpenicilin	6
Benzylpenicillin	6
benzyl-penicillin	6
BENZYLPENICILLIN	6
benzylpenicillin	6
Benzyl-Penicillin	6
Benzyl-penicillin	6
Benzylpenicllin	6
BENZYLPENILLIN	6
Benzylpenillin	6
benzypenicillin	6
Benzypenicillin	6
biopatch	0
BIOPATCH	0
Biopatch	0
Cafotaxime	7
Caftazidime	7
Canesten 1%	0
casfungin	9
Casofungin	9
Caspofungin	9
caspofungin	9
Cefalexin	7
cefataxime	7
Ceferiaxone	7
cefhazidine	7
Ceflacor	7
Ceflazidime	7
ceflazidime	7
Ceflazidine	7
ceflazidine	7
Cefofaxime	7
Cefofaxime	7
Cefofaxime	7
Cefofaxime	7
Cefofaxime	7
Cefofaxime	7
Cefofaxime	7
Cefofaxime	7
Cefofaxime	7
Cefofaxime	7
Cefofaxime	7
Cefofaxime	7
Cefofaxime	7
Cefohaxime	7

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Cefolaxime	7
cefolaxime	7
Ceforoxime	7
Cefotamime	7
Cefotamine	7
Cefotaxim	7
CEFOTAXIME	7
Cefotaxime	7
cefotaxime	7
Cefotaximine	7
cefotaxine	7
Cefotaxinme	7
Cefotaxiome	7
Cefotaxome	7
Cefotriaxone	7
Cefriaxone	7
Cefroxime	7
Cefrtiaxone	7
Cefruxime	7
Ceftaidime	7
Ceftaoxime	7
ceftaxidime	7
Ceftaxime	7
ceftazidime	7
Ceftazidime	7
ceftazidine	7
Ceftdazadime	7
Ceftiaxone	7
Ceftlazidime	7
Ceftoaxime	7
Ceftqazidime	7
Ceftraxone	7
Ceftriaxone	7
CEFTRIAXONE	7
ceftriaxone	7
Ceftriazone	7
Ceftrioxone	7
Ceftrixone	7
Ceftruaxone	7
Cefuoxime	7
Cefuroime	7
Cefuromxime	7
cefuroxim	7
Cefuroxime	7
CEFUROXIME	7
cefuroxime	7
Cefuroxime2	7
Cefuroxine	7
Cefurozime	7
Cefurxime	7
Cephalexin	7
cephalexin	7
ceptriaxone	7
cetotaxime	7
Cetotaxime	7
Chloramphenical	0
Chloramphenical eye drops	0
chloramphenicol	0
Chloramphenicol	0
Chloramphenicol 0.5%	0
Chloramphenicol 1%	0
chloramphenicol 1% eye ointment	0
Chloramphenicol 1% ointment	0
Chloramphenicol 1.1%	0
chloraphenical eye drop 1%	0
chloraphenicol	0
Chloraphenicol	0
chlorhexidine	0
chlorhexidine biopatch	0
chlorhexidine mouth gel	0
Chrolamphenicol	0
Ciclosporin	0
Cidofavir	0
cidofivir	0
Cidofovir	0
Ciproflaxacin	13
Ciproflaxin	13
Ciprofloxacillin	13
ciprofloxacillin	13
Ciprofloxacin	13
CIPROFLOXACIN	13
ciprofloxacin	13

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ciprofloxacine	13
ciprofloxcain	13
ciprofloxican	13
Ciproflxacillin	13
Ciproflxacin	13
ciproloxacin	13
Ciprolxacin	13
Clariithromycin	4
Clarithomicin	4
Clarithomycin	4
Clarithromycin	4
clarithromycin	4
Clarithromyin	4
clarithromyrin	4
Clarithroycin	4
Clarithroymcin	4
Clarithroymicin	4
clarithyromycin	4
Clarithyromycin	4
clarothromycin	4
clarythromycin	4
Clindamycin	15
CLINDAMYCIN	15
CLindamycin	15
clindamycin	15
CLINDOMYCIN	15
CLOTIMAZOLE CREAM 1%	0
CLOTRAMAZOLE	0
Clotrimazole	0
clotrimazole	0
clotrimazole 1%	0
clotrimazole 1% cream	0
Clotrimazole Cream	0
CLOTRIMAZOLE CREAM 1%	0
clotrimazole cream 1%	0
Co Amoxiclav	2
co- amoxiclav	2
co amoxiclav	2
Co amoxiclav 125/31	2
co amoxiclav 250/62	2
Co Amoxiclav Suspension	2
Coamixoclav	2
Co-Amixoclav	2
co-amixoclav	2
Co-amixoclav	2
Co-Amoixiclav	2
co-amoxacillin	2
Co-amoxcillin	2
Co-Amoxicillin	2
Co-amoxiclan	2
coamoxiclav	2
Co-amoxiclav	2
CoAmoxiclav	2
CO-AMOXICLAV	2
Co-Amoxiclav	2
co-amoxiclav	2
Coamoxiclav	2
Co-Amoxiclav (125 mg + 31mg/5mls)	2
co-amoxiclav (250/62)	2
Co-amoxiclav (Augmentin)	2
co-amoxiclav 125/31	2
Co-amoxiclav 125/31	2
co-amoxiclav 250/62.5	2
Co-Amoxiclav 250mg + 31 mg/5ml suspension	2
co-amoxiclav 400/51	2
co-amoxiclav 400/57	2
Coamoxyclav	2
co-amoxyclav	2
Co-amoxyclav	2
Co-Aoxiclav	2
Co-aoxiclav	2
colistimethate	0
Colistimethate	0
colistin	17
COLISTIN	0
Colistin	17
colistin cream	0
Coliston	0
colomycin	17
Colomycin	17
Contrimaxazole	16
Corsodyl Gel	0

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cotriamoxazole	16
cotrimaxazole	16
Co-Trimaxazole	16
Co-trimaxazole	16
Cotrimaxole	16
Co-trimaxozole	16
Co-trimazole	16
Cotrimazole 1% Cream	0
Co-trimexazole	16
Cotrimoxaole	16
Cotrimoxazole	16
Co-Trimoxazole	16
co-trimoxazole	16
cotrimoxazole	16
Co-trimoxazole	16
Co-Trimoxazole 1%	0
co-trimoxozole	16
Co-Trimozaole	16
Cotrimozazole	16
Co-trinoxazole	16
co-trinoxazole	16
Cufuroxime	7
daktarin cream	0
dermol	0
doxycycline	17
erithromycin	4
Erthomycin	4
Erthromicin	4
Erthromycin	4
erthyromycin (prokinetic dose)	0
Erythomycin	4
Erythormycin	4
erythromicin	4
Erythromicin	4
Erythromycin	4
ERYTHROMYCIN	4
erythromycin	4
Erythromycin (for prokinetic)	0
Erythromycin (Gastric motility)	0
erythromyln	4
Erytromycin	4

Ethambutol	20
ethambutol	20
Eyrthromycin	4
Flagyl	27
flagyl	27
Flocloxacillin	21
Flocoxacillin	21
Flucanazole	22
fluccoxacilin	21
fluccoxicillin	21
Flucloaxacillin	21
fluclonazole	22
Flucloxacill,in	21
Flucloxacillin	21
FLUCLOXACILLIN	21
FLucloxacillin	21
flucloxacillin	21
Flucloxacilllin	21
Flucloxaillin	21
FLUCLOXAXILLIN	21
Flucloxaxillin	21
Flucloxazillin	21
flucloxicillin	21
Flucloxicillin	21
flucloxzcillin	21
Fluconazole	22
FLUCONAZOLE	22
fluconazole	22
FLuconazole	22
Fluconzale	22
Fluconzaole	22
Fluconzole	22
Flucoxacilin	21
Flucoxacillin	21
flucoxacillin	21
Fluonazole	22
Foscarnet	0
g.levofloxacin	21
Ganciclovir	0
GANCICLOVIR	0
ganciclovir	0

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ganciclovire	0
Gantamicin	1
GCSF Leuograstin	0
Gentamicin	1
GENTAMICIN	1
gentamicin	1
Gentamin	1
gentamin	1
gentamiycin	1
Gentammicin	1
Gentamycin	1
gentamycin	1
gentaycin	1
gentaycinn	1
gentomicin	1
Gentomycin	1
gentomycin	1
Getamicin	1
Getamycin	1
Grentamicin	1
Heparin	0
Isoniazid	24
isoniazid	24
Itraconazole	25
itraconazole	25
Linezolid	26
LINEZOLID	26
linezolid	26
liposomal amphotercin	3
liposomal amphotericin	3
Liposomal aphotericin	3
lymecycline	17
maxitrol ointment	0
Melonidazole	27
Menepenem	27
Menopanem	27
Menopenem	27
Merepenum	27
Meroopenan	27
Meropenam	27
meropenam	27
Meropene	27
Meropenem	27
MEROPENEM	27
meropenem	27
Meropenen	27
Meropenim	27
Meropenom	27
Meropenum	27
MEROPENUM	27
meropenum	27
Meroperem	27
meroprenem	27
Metopenem	27
metrinidazole	27
Metrondazole	27
Metrondiazole	27
Metronidazole	27
METRONIDAZOLE	27
metronidazole	27
metronidzole	27
metronirazole	27
metronizadole	27
metroridazole	27
Micafongin	29
MICAFUNGIN	29
Micafungin	29
micafungin	29
miconazole	0
Miconazole	0
Miconazole gel	0
miconozole	0
MNetronidazole	27
mupirocin	0
naseptin	0
neomycin	0
NEOMYCIN	0
Neomycin	0
nitrofurantoin	30
Nstatin	0
Nsystatin	0
Nysatin	0

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Nystain	0
Nystatin	0
nystatin	0
NYSTATIN	0
Nystatin Cream	0
nystatin suspension	0
nystol	0
Octenilin Wound Gel 0.05%	0
octenisan	0
OCTENISAN 0.3%	0
ofloxacin	0
Omeprazole	0
omeprazole	0
Oselhamivir	0
Oseltamavir	0
Oseltamir	0
oseltamirir	0
Oseltamive	0
Oseltamivir	0
oseltamivir	0
OSELTAMIVIR	0
osomal amphotericin	3
Osteltamive	0
Osteltamivir	0
PENCILLIN V	0
Penicillin	0
penicillin	0
Penicillin V	0
PENICILLIN V	0
penicillin v	0
phenoxymethyl penicillin	0
Phenoxy-methyl penicillin	0
PHENOXYMETHYL/PENICILLIN	0
phenoxymethylpenicillin	0
Phenoxymethyl-penicillin	0
Pifampicin	31
pip tazobactam	32
pip/tazobactam	32
pipazobactam	32
Pipazobactam	32
Pipeicillin/Tazobactam	32
Piperacilin/Tazobactam	32
Piperacillin	32
piperacillin	32
PIPERACILLIN & TAZOBACTAM	32
Piperacillin & Tazobactam	32
piperacillin & tazobactam	32
piperacillin & tazobactum	32
Piperacillin / Tazoabactam	32
Piperacillin / Tazobactam	32
Piperacillin / Tazobactan	32
Piperacillin + Tazobactam	32
Piperacillin + tazobactam	32
piperacillin + tazobactam	32
Piperacillin 2g/Tazobactam 250 mg	32
Piperacillin 2g/tazobactam 250mg	32
Piperacillin 4g/Tazobactam 500g	32
Piperacillin 4g/Tazobactam 500mg	32
Piperacillin and Tazobactam	32
piperacillin and tazobactam	32
Piperacillin and tazobactam	32
Piperacillin and Tazobactem	32
piperacillin tazobachim	32
Piperacillin Tazobactam	32
piperacillin tazobactam	32
Piperacillin tazobactam	32
piperacillin tazobactan	32
Piperacillin Tazobactum	32
piperacillin tazobactum	32
Piperacillin w/Tazobactam	32
Piperacillin W/Tazobactam	32
Piperacillin with tazobactam	32
Piperacillin with Tazobactam	32
piperacillin with tazobactam	32
PIPERACILLIN/ TAZOBACTAM/TAZOCIN	32
PIPERACILLIN/TAZOBACTAM	32
Piperacillin/Tazobactam	32
Piperacillin/tazobactam	32
piperacillin/tazobactam	32
Piperacillin/Tazobactan	32
piperacillin/tazobactum	32
Piperacillin/Tazobactum	32

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Piperacillin/Tazobatam	32
piperacillin-tazobactam	32
pipercillin + tazobactam	32
Pipercillin and Tazobactam	32
Pipercillin Tazobactam	32
Pipercillin/Tazobacran	32
Pipercillin/Tazobactam	32
Pipercillin/tazobactam	32
pipercillin/tazobactom	32
PIPERCILLIN/TAZOBACTUM	32
Pipertazobactam	32
Piptazbactam	32
PIPTAZOBACAM	32
Piptazobactam	32
piptazobactam	32
Piptazobactern	32
piptazobactum	32
piptazocin	32
Pitazobactam	32
Pyrazinamide	33
Pyridoxine	0
rasburicase	0
Ribavirin	0
rifabutin	31
rifampacin	31
Rifampicin	31
rifampicin	31
SDD gel	0
SDD GEL	0
SDD Gel	0
sdd gel	0
sdd gell	0
SDD paste	0
SDD Paster	0
Septin	16
septrin	16
Septrin	16
Tabromycin Base	0
tarocin	34
taurolock	0
tazobactam/piperacillin	32
Tazocin	32
TAZOCIN	32
tazocin	32
Tazocin (Pipercillin and Tazobactam)	32
tazocin/piperacillin tazobactam	32
tazolin	32
teicloplanin	35
Teicloplanin	35
Teicopanin	35
Teicoplanim	35
Teicoplanin	35
teicoplanin	35
TEICOPLANIN	35
Teicoplaning	35
Teicopleinin	35
teicopleinin	35
Teicoplnanin	35
Teicplanin	35
Telcoplanin	35
Tiecoplanin	35
Tobramycin	34
TOBRAMYCIN	34
tobramycin	34
Tobramycin base	0
TOBRAMYCIN BASE	0
Tobramycin Base	0
tobramycin base	0
Tobtamycin	34
Tqazocin	32
Trimethoprim	36
TRIMETHOPRIM	36
trimethoprim	36
trimethroprim	36
trimetroprim	36
Trimpethoprim	36
Vacomycin	37
valganciclovir	0
Vancomycin	37
VANCOMYCIN	37
vancomycin	37
Vancomyin	37

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Vancoycin	37
vanomycin	37
Vanomycin	37
Vaoncymycin	37
Variconazole	37
Vencomycin	37
Voncomycin	37
Voriconazole	37
voriconazole	37
Warfarin	0
Zanamavir	0
Zanamivir	0

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SAP APPENDIX G: CLINICAL ENDPOINT REVIEW

TABLE 2: PATIENT IDENTIFIER

Randomisation number	Date of birth	Age (years)	Initials	Date/time of randomisation	Date/time of removal	Time from randomisation to removal (hours)

TABLE 3: SKIN ORGANISMS IN THE TIME FRAME FOR THE PRIMARY OUTCOME

Date/time of sample	Time from randomisation (hours)	Time from removal (hours)	Blood/ CVC tip	Isolate (skin)	ICD-10 code for primary reason for admission*	Committee decision (same isolate/not the same isolate)

*This has been inserted to determine the status of those with no microbiology for the sensitivity analyses

TABLE 4: NUMBER OF SEPARATE BLOODSTREAM INFECTIONS (RATE OF BLOOD STREAM INFECTION DURING CVC INSERTION PER 1000 CVC DAYS)

Date/time of sample	Time from randomisation (hours)	Blood/ CVC tip	Isolate	Skin/ non-skin	Committee decision: number of separate bloodstream infections

Note microbiology profile comes from patient uploads: sensitive/ resistant/ intermediate

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TABLE 5: COMMITTEE DECISION: CVC RELATED BLOOD STREAM INFECTION

Date/time of sample	Time from randomisation (hours)	Time from removal (hours)	Blood/ CVC tip	Isolate	Positivity of isolates	Positive BSI (as in primary outcome)	CVC removed for infection	CVC exit site infection	Committee decision: CVC related blood stream infection (Yes/No)

TABLE 6: A COMPOSITE MEASURE OF CLINICALLY INDICATED BLOOD STREAM INFECTION

Date/time of sample	Time between randomisation and sample (hours)	Time between removal and sample (hours)	Date/time of antibiotic change	Time between blood culture and antibiotic change (hours)	Blood/ CVC tip	PCR result (positive/negative)	Primary Outcome Positive BSI (Yes/No)	CVC removed for infection	CVC exit site infection	Committee decision: Composite measure of clinically indicated blood stream infection (Yes/No)

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TABLE 7: THROMBOSIS

Date/time	Difficulty drawing back blood	Flushing	Swollen limb	Positive ultrasound	Comment from ultrasound (if available)	Removal of CVC because of clinical evidence of a blocked CVC	Committee decision: thrombosis (yes/no: if yes give date and time of thrombosis)

TABLE 8: RESISTANCE TO MINOCYCLINE OR RIFAMPICIN OF BLOOD CULTURE OR CVC TIP ISOLATES

Date/time of sample	isolate	Blood sample/ CVC tip	e-test result	Committee decision: (Resistant/ Not resistant)

NOTE THAT THERE MAY BE A PROBLEM MATCHING E-TEST RESULTS WITH SAMPLES AS THERE IS NO TIME AVAILABLE FOR E-TEST RESULTS

Type of bacteria and fungi isolated from positive blood cultures: CRF

a. Line listings presented to microbiologist (separately for i-iii)
    i. For primary outcome
    ii. For rate of blood stream infection (those not in primary outcome and between 0 and 48 hours)
    iii. For CVC related bloodstream infection (those not in primary outcome and skin organisms only)

This will be presented as in Appendix D of the SAP

Form prepared: 06/12/2013 v1.1 for CATCH Study

Appendix 2 Clinical effectiveness study additional data

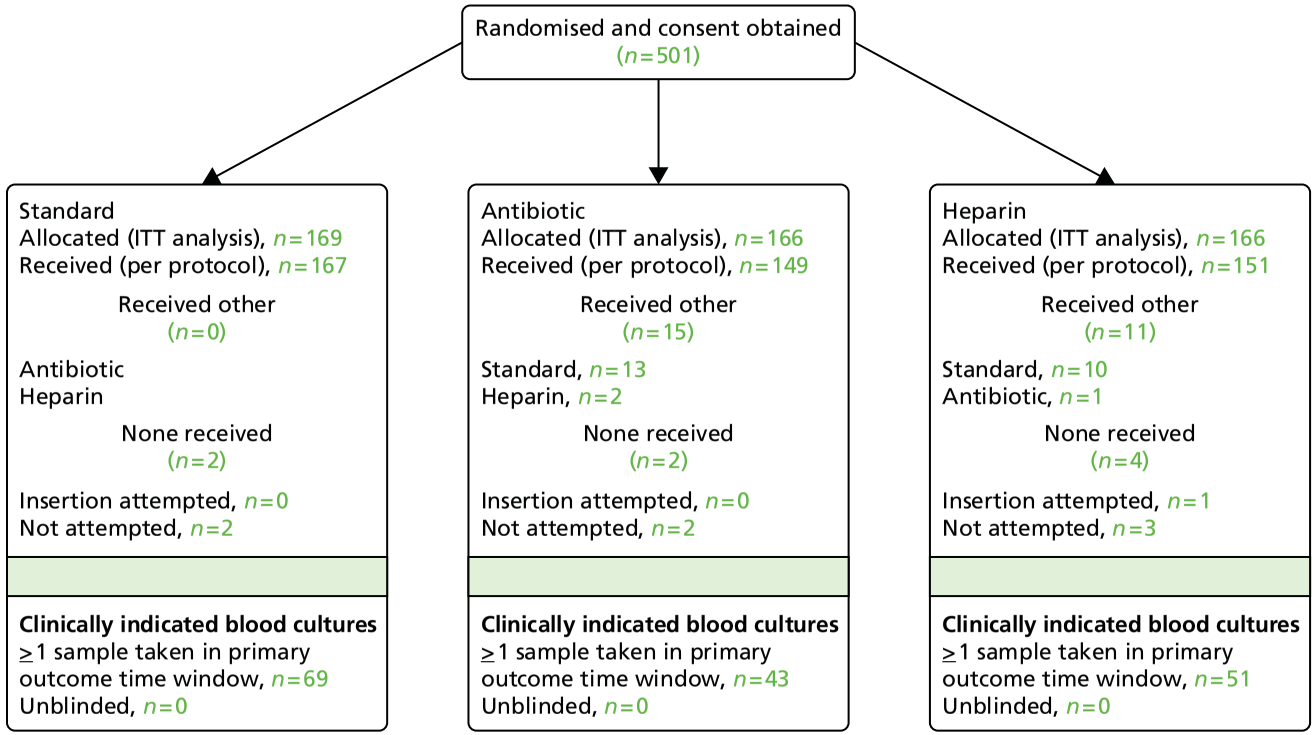


FIGURE 11 Consolidated Standards of Reporting Trials (CONSORT) flow diagram for prospective consent.
ITT, intention to treat.

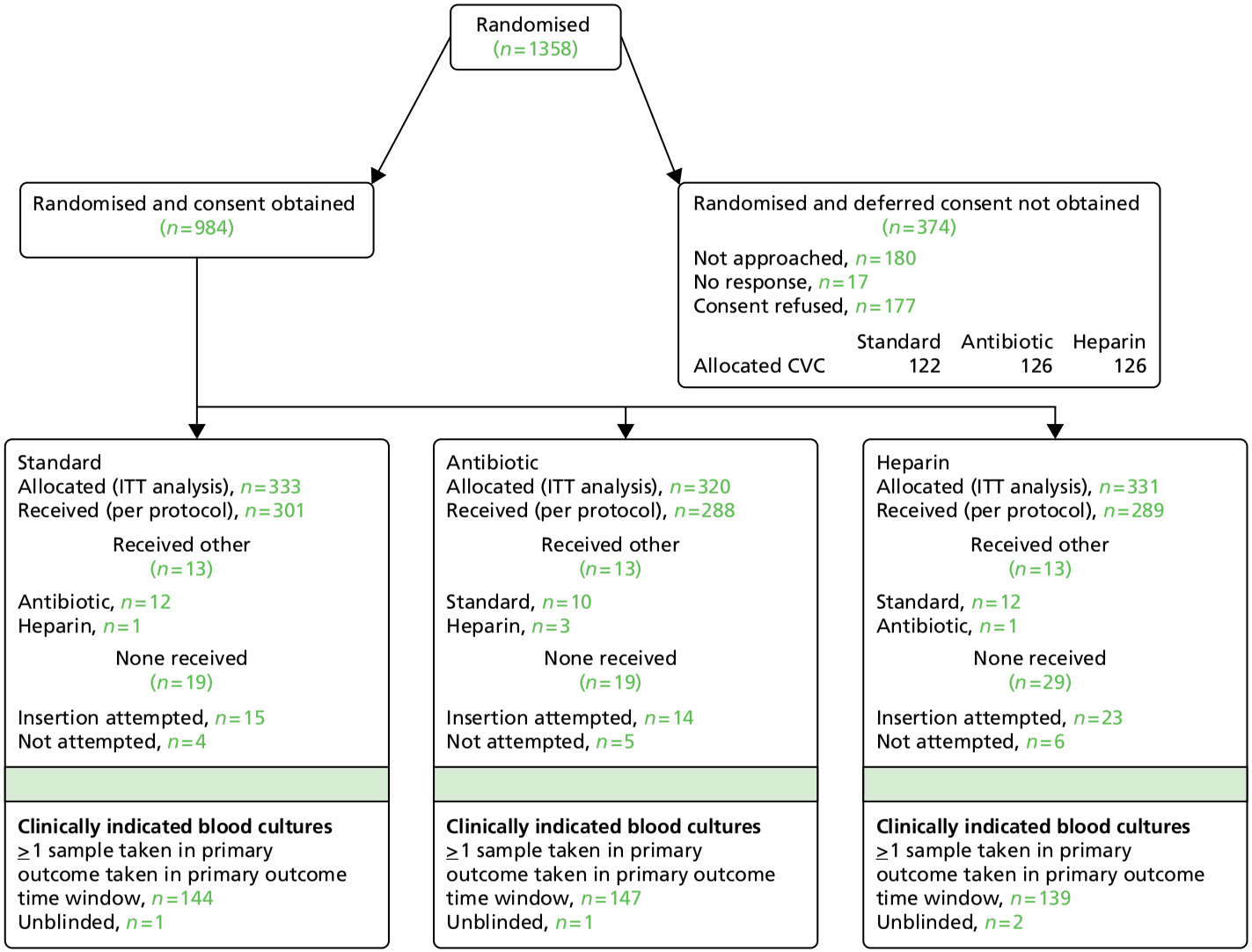
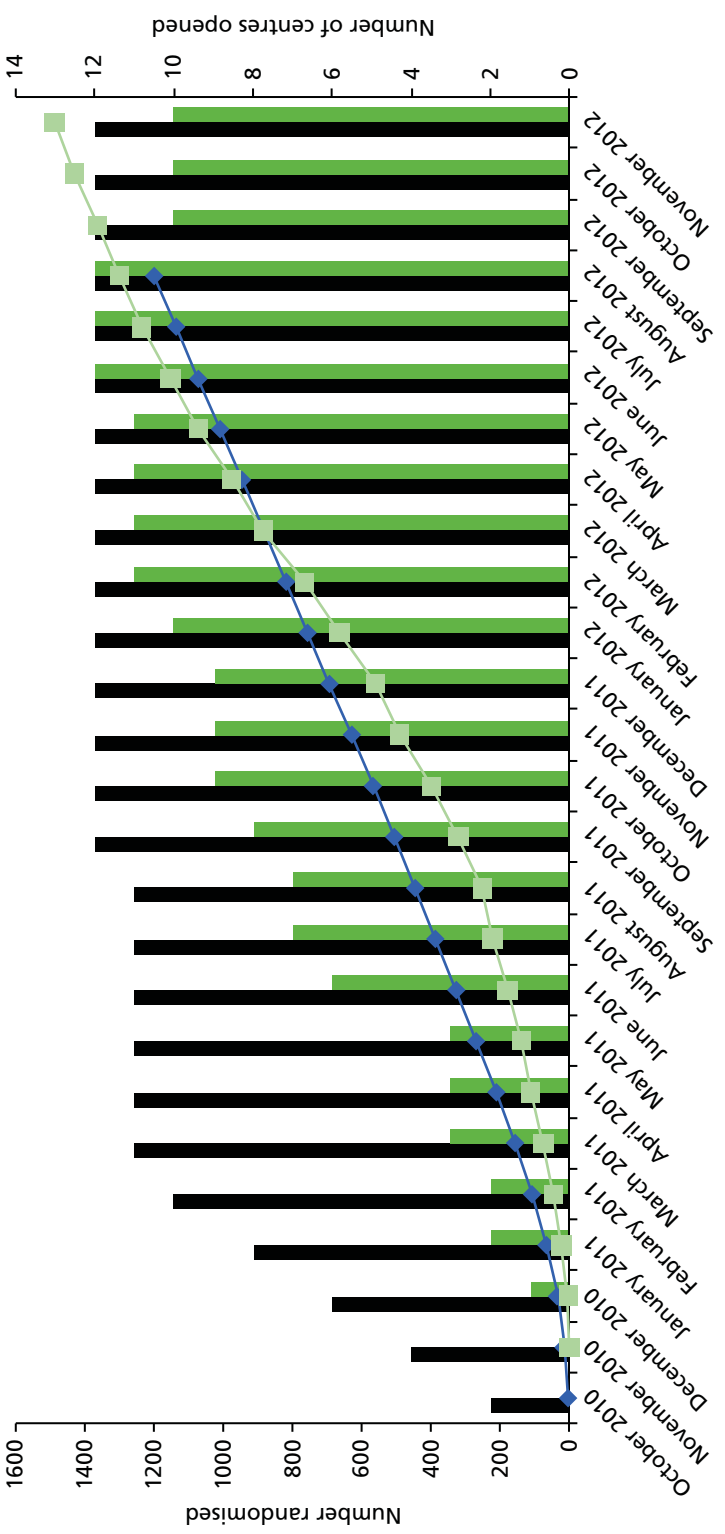


FIGURE 12 Consolidated Standards of Reporting Trials (CONSORT) flow diagram for deferred consent. ITT, intention to treat.

TABLE 24 Recruitment by site

Centre	Date site initiated	Date of first randomisation	Target recruitment	Number randomised and consented	Prospective consent	Deferred consent
Great Ormond Street Hospital PICU/CICU	10/02/2011	15/04/2011	200	362	27	335
Evelina London Children's Hospital (Guy's and St Thomas')	25/11/2010	06/01/2011	100	161	43	118
Royal Brompton Hospital	17/06/2011	24/08/2011	100	49	29	20
St Mary's Hospital, London	01/02/2012	07/02/2012	100	26	0	26
Southampton General Hospital	27/06/2011	11/07/2011	100	200	140	60
Bristol Royal Hospital for Children	20/06/2011	24/06/2011	100	109	61	48
Alder Hey Children's Hospital	05/07/2011	11/07/2011	100	113	69	44
Birmingham Children's Hospital	22/08/2011	01/09/2011	100	150	34	116
Glenfield Hospital	13/10/2011	22/10/2012	100	65	48	17
Leicester Royal Infirmary	13/10/2011	11/01/2012		15	3	12
Royal Victoria Infirmary	25/01/2012	03/02/2012	50	41	0	41
Freeman Hospital	26/01/2012	10/02/2012		18	13	5
Leeds General Infirmary	14/12/2010	22/12/2010	100	149	32	117
Queen's Medical Centre	11/05/2012	16/05/2012	50	27	2	25
Total			1200	1485	501	984

CICU, cardiac intensive care unit.



	Centres expected	Centres opened	Expected	Actual
October 2010	2	0	4	
November 2010	4	0	17	0
December 2010	6	1	36	4
January 2011	8	2	66	22
February 2011	10	2	108	47
March 2011	11	3	157	77
April 2011	11	3	211	111
May 2011	11	3	269	140
June 2011	11	6	327	178
July 2011	11	7	386	221
August 2011	11	7	445	252
September 2011	12	8	505	320
October 2011	12	9	567	399
November 2011	12	9	629	489
December 2011	12	9	692	561
January 2012	12	10	756	665
February 2012	12	11	819	764
March 2012	12	11	882	884
April 2012	12	11	946	975
May 2012	12	11	1009	1071
June 2012	12	12	1073	1151
July 2012	12	12	1136	1235
August 2012	12	12	1200	1300
September 2012	12	10		1363
October 2012	12	10		1430
November 2012	12	10		1485

FIGURE 13 Recruitment by month.

TABLE 25 Samples taken by trial arm and site

Centre	Standard ($n = 502$)			Antibiotic ($n = 486$)			Heparin ($n = 497$)			Total ($n = 1485$)		
	Total randomised and consented	Patients sampled (no. of samples)	%	Total randomised and consented	Patients sampled (no. of samples)	%	Total randomised and consented	Patients sampled (no. of samples)	%	Total randomised and consented	Patients sampled (no. of samples)	%
Great Ormond Street Hospital PICU/CICU	128	106 (273)	82.8	117	90 (260)	76.9	117	96 (304)	82.1	362	292 (837)	80.7
Evelina London Children's Hospital (Guy's and St Thomas)	54	49 (163)	90.7	50	40 (110)	80.0	57	50 (123)	87.7	161	139 (396)	86.3
Royal Brompton Hospital	15	11 (29)	73.3	17	11 (29)	64.7	17	13 (46)	76.5	49	35 (104)	71.4
St Mary's Hospital, London	7	5 (10)	71.4	10	9 (21)	90.0	9	9 (31)	100.0	26	23 (62)	88.5
Southampton General Hospital	65	53 (162)	81.5	66	63 (143)	95.5	69	63 (162)	91.3	200	179 (467)	89.5
Bristol Royal Hospital for Children	35	29 (71)	82.9	39	34 (91)	87.2	35	33 (88)	94.3	109	96 (250)	88.1
Alder Hey Children's Hospital	41	33 (94)	80.5	36	29 (62)	80.6	36	28 (87)	77.8	113	90 (243)	79.6
Birmingham Children's Hospital	50	41 (128)	82.0	48	32 (124)	66.7	52	34 (123)	65.4	150	107 (375)	71.3
Glenfield Hospital	21	15 (42)	71.4	22	14 (27)	63.6	22	13 (31)	59.1	65	42 (100)	64.6
Leicester Royal Infirmary	6	4 (8)	66.7	4	3 (5)	75.0	5	5 (16)	100.0	15	12 (29)	80.0
Royal Victoria Infirmary	13	13 (44)	100.0	14	13 (45)	92.9	14	13 (44)	92.9	41	39 (133)	95.1
Freeman Hospital	7	5 (14)	71.4	5	3 (9)	60.0	6	4 (10)	66.7	18	12 (33)	66.7
Leeds General Infirmary	50	44 (151)	88.0	48	41 (156)	85.4	51	46 (187)	90.2	149	131 (494)	87.9
Queen's Medical Centre	10	7 (26)	70.0	10	7 (21)	70.0	7	5 (13)	71.4	27	19 (60)	70.4
Total	502	415 (1215)	82.7	486	389 (1103)	80.0	497	412 (1265)	82.9	1485	1216 (3583)	81.9

CICU, cardiac intensive care unit.

TABLE 26 Threats to validity

Threats to validity	Standard ($n = 502$)		Antibiotic ($n = 486$)		Heparin ($n = 497$)		Total ($n = 1485$)	
	n	%	*n*	%	*n*	%	*n*	%
CVC inserted	481	95.8	465	95.7	464	93.4	1410	94.9
Internal validity								
Randomised multiple times	15	3.0	12	2.5	11	2.2	38	2.6
Clinical indication 48 hours after randomisation, no sample taken in primary outcome time window[a]	183	38.0	196	42.2	196	42.2	575	40.8
External validity								
Child aged > 16 years	2	0.4	4	0.8	0	0.0	6	0.4
CVC inserted but removed before 48 hours[a,b]	94	19.5	96	20.6	96	20.7	286	20.3
CVC inserted > 12 hours after randomisation[a]	1	0.2	1	0.2	4	0.9	6	0.4
Line not required following randomisation (post 12 hours); randomisation pack returned to the CTU								
CVC attempted but not inserted	15	3.0	14	2.9	24	4.8	53	3.6
CVC insertion not attempted	6	1.2	7	1.4	9	1.8	22	1.5
Incorrect randomisation envelope used	4	0.8	8	1.6	9	1.8	21	1.4

CTU, Medicines for Children Clinical Trials Unit.

a Based on any clinical indicator, including abnormal C-reactive protein or white cell count, which were not considered sufficient clinical indication on their own.

b Of whom five were transferred before the CVC had been inserted ($n = 2$ standard, $n = 2$ heparin and $n = 1$ antibiotic); follow-up data were missing for one participant.

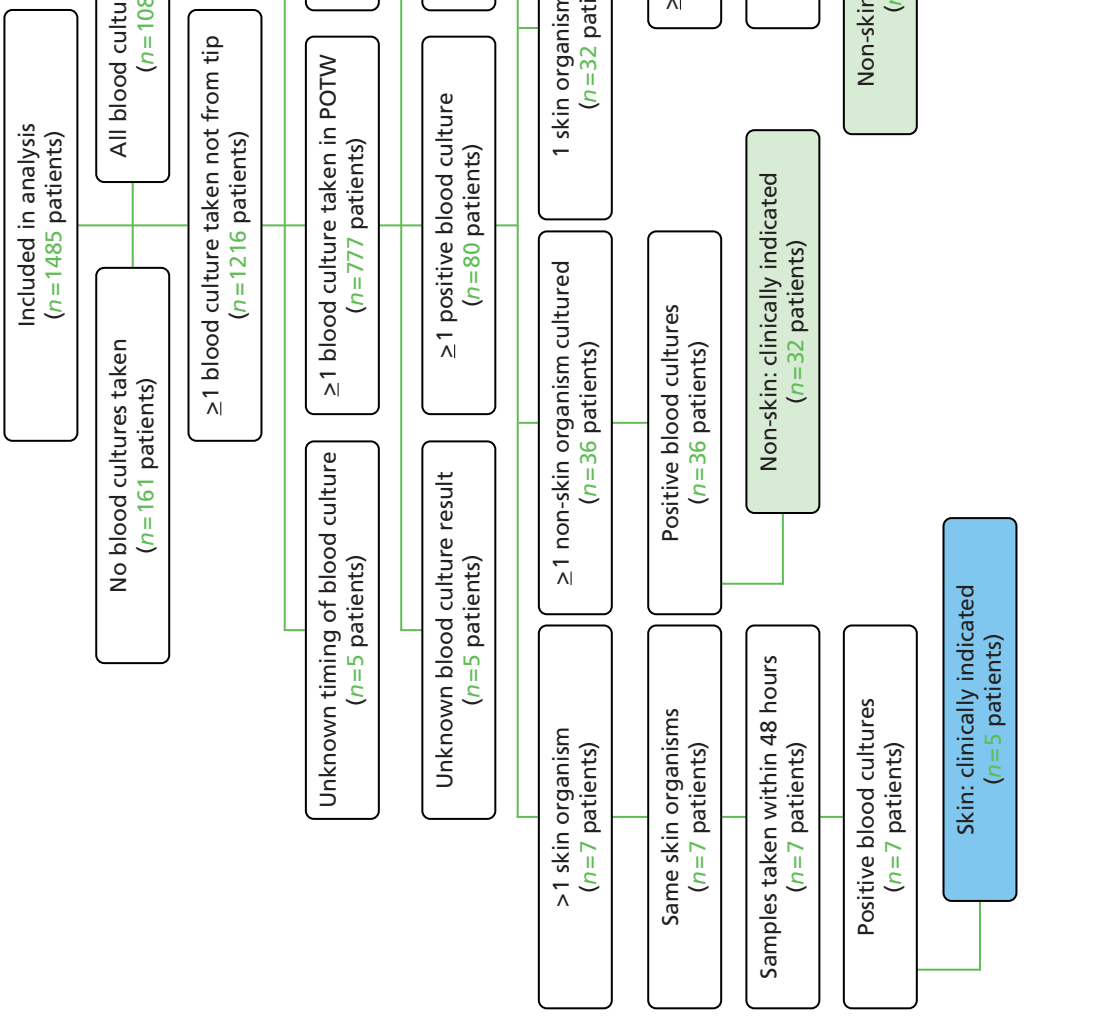


FIGURE 14 Samples contributing to the primary outcome. a, The non-skin organism was from a sample taken at 47 hours and 55 minutes after randomisation. Shading indicates whether samples contributing to the primary outcome included skin organisms (dark), non-skin organisms (light) or both skin and non-skin organisms (medium). POTW, primary outcome time window.

TABLE 27 Primary outcome: sensitivity analysis assuming the presence of a BSI in patients with clinical indicators for infection who had no blood culture sample taken in the primary outcome time window

Group	Total randomised	Primary outcome		Clinical indication but no sample taken in time window		Total included in sensitivity analysis		HR vs. standard[a] (95% CI)	*p*-value
		n	%	*n*	%	*n*	%		
Standard	502	18	3.6	8	1.6	26	5.2		
Any impregnated	983	24	2.4	9	0.9	33	3.4	0.67 (0.39 to 1.15)	0.15
Antibiotic	486	7	1.4	6	1.2	13	2.6	0.54 (0.29 to 1.02)	0.06
Heparin	497	17	3.4	3	0.6	20	4.1	0.83 (0.47 to 1.49)	0.54
Total	1485	42	2.8	17	1.1	59	4.0		

a HR for antibiotic vs. heparin = 0.64 (95% CI 0.32 to 1.27; $p = 0.20$).

TABLE 28 Indicators of the composite outcome of BSI

Indicator	Standard (*n* = 502)		Antibiotic (*n* = 486)		Heparin (*n* = 497)		Total (*n* = 1485)	
	n	%	*n*	%	*n*	%	*n*	%
Primary outcome only	2	0.4	0	0.0	4	0.8	6	0.4
Clinical indication, blood culture, plus								
Bacterial DNA detected by PCR only	2	0.4	1	0.2	1	0.2	4	0.3
Change in antibiotic on the same day or next day only	79	15.7	71	14.6	64	12.9	214	14.4
CVC removal for infection only	6	1.2	12	2.5	7	1.4	25	1.7
Primary outcome and CVC removal for infection	1	0.2	0	0.0	0	0.0	1	0.1
Primary outcome and antibiotic change	8	1.6	6	1.2	6	1.2	20	1.3
CVC removal for infection and antibiotic change	7	1.4	11	2.3	13	2.6	31	2.1
PCR positive and antibiotic change	1	0.2	1	0.2	0	0.0	2	0.1
Primary outcome, CVC removal for infection and antibiotic change	6	1.2	1	0.2	6	1.2	13	0.9
CVC removal for infection, PCR positive and antibiotic change	0	0.0	0	0.0	0	0.0	0	0.0
Primary outcome, bacterial DNA detected by PCR, CVC removal for infection and antibiotic change	1	0.2	0	0.0	1	0.2	2	0.1
Total[a]	113	22.5	103	21.2	102	20.5	318	21.4

a Overall number of indicators in an exclusive descending hierarchy: BSI = 42; PCR positive = 5; CVC removed for infection = 56; change or start of antibiotics same or next day = 214.

TABLE 29 Type of bacteria and fungi isolated from positive blood cultures

Organism group	Organism	Standard	Antibiotic	Heparin	Total
Gram positive	*Staphylococcus aureus*	1	1	3	5
	Streptococcus spp.	1	0	0	1
	Methicillin-resistant *S. aureus*	1	0	0	1
	Enterococcus spp.	2	0	4	6
	Streptococcus mitis	1	0	1	2
	Streptococcus parasanguis and *Streptococcus salivarius*	0	1	0	1
Gram negative	*Serratia marcescens*	1	1	0	2
	Pseudomonas aeruginosa	2	1	1	4
	Gram-negative bacillus	1	0	1	2
	Escherichia coli	0	1	0	1
	E. coli and coliform	0	1	0	1
	Coliform	1	0	0	1
	Klebsiella spp.	0	0	1	1
	Cellulomas spp.	0	0	1	1
	Raoultella panticola and Enterobacter spp.	1	0	0	1
Gram positive and Gram negative	Enterococcus spp. and *Klebsiella pneumoniae*	0	0	1	1
Fungi	Candida spp.	2	0	2	4
	Candida albicans	0	0	1	1
Skin bacteria and Gram positive	Coagulase-negative staphylococcus and enterococcus spp.	1	0	0	1
Skin bacteria	Coagulase-negative staphylococcus spp.	3	1	1	5
Total		18	7	17	42

TABLE 30 Causes of death recorded on CRFs as adverse events[a]

		Standard ($n = 533$)		Antibiotic ($n = 451$)		Heparin ($n = 479$)		Total ($n = 1463$)	
Related/unrelated	Cause of death	*n*	%	*n*	%	*n*	%	*n*	%
Unrelated	Related to comorbidities at admission	58	10.9	37	8.2	35	7.3	130	8.9
	Cerebral haemorrhage	0	0.0	0	0.0	1	0.2	1	0.1
	Multiorgan failure as a result of calcification of the arteries	1	0.2	0	0.0	0	0.0	1	0.1
	Pneumonitis and multiorgan failure	1	0.2	0	0.0	1	0.2	2	0.1
	Pseudomonas septicaemia second to peritonitis	0	0.0	1	0.2	0	0.0	1	0.1
	Severe birth asphyxia	1	0.2	0	0.0	0	0.0	1	0.1
	Complication of treatment	1	0.2	0	0.0	0	0.0	1	0.1
	Cerebral bleeding by ventricular assist device	1	0.2	0	0.0	0	0.0	1	0.1
	Group B streptococcus infection/sepsis	1	0.2	0	0.0	0	0.0	1	0.1
	Multiorgan failure and systemic inflammatory response syndrome	0	0.0	0	0.0	1	0.2	1	0.1
	Multiorgan failure	0	0.0	1	0.2	0	0.0	1	0.1
	Exact cause not known	0	0.0	1	0.2	0	0.0	1	0.1
	Pulmonary haemorrhage	1	0.2	0	0.0	0	0.0	1	0.1
Unlikely to be related	Related to comorbidities at admission	0	0.0	2	0.4	0	0.0	2	0.1
Missing		1	0.2	2	0.4	0	0.0	3	0.2
Total		66	12.4	44	9.8	38	7.9	148	10.1

a *n* = participants by CVC received or attempted to be inserted, i.e. safety analysis.

TABLE 31 Antibiotic resistance to minocycline or rifampicin by CVC allocation

		Etest result	
CVC allocation	Organism	Minocycline	Rifampicin
Standard	Coliform bacilli	Resistant	Resistant
	Enterococcus faecalis	Resistant	Resistant
	Serratia marcescens	Resistant	Resistant
	Staphylococcus aureus	Sensitive	Sensitive
	Methicillin-resistant *S. aureus*	Sensitive	Sensitive
Antibiotic	*Escherichia coli*	Resistant	Resistant
	Staphylococcus spp.	Resistant	Resistant
Heparin	*Klebsiella pneumoniae*	Resistant	Resistant
	K. pneumoniae	Resistant	Resistant
	S. aureus	Sensitive	Sensitive
	Coagulase-negative staphylococcus spp.	Sensitive	Sensitive
	Enterococcus hirae and coagulase-negative staphylococcus spp.	Resistant, sensitive	Sensitive, resistant

TABLE 32 Positive PCR detection of bacterial DNA

CVC allocation	Primary outcome	PCR value (pg of DNA/µl)
Antibiotic	No	0.011
	No	0.023
	No	0.05
Heparin	No	0.006[a]
	No	0.008[a]
	No	0.05
	Yes	0.16375
Standard	No	0.013
	No	0.02
	No	0.02
	No	0.024
	Yes	0.36

a Samples from the same child.

Appendix 3 Cost-effectiveness study additional data

TABLE 33 A list of all bundled HRGs, costed for inpatient stays using the national tariff guidance[a]

HRG	HRG name (inpatient)	Elective spell tariff (£)	Elective long-stay trim point (days)	Non-elective spell tariff (£)	Non-elective long-stay trim point (days)	Per-day long-stay payment (for days exceeding trim point) (£)
LB08Z[b]	Ureter Major Endoscopic Procedure	1379.00	5	2468.00	12	301.00
PA03Z[b]	Febrile Convulsions	928.00	1	661.00	3	304.00
PA14A[b]	Lower Respiratory Tract Disorders without Acute Bronchiolitis with CC	3215.00	13	2473.00	14	222.00
CZ06N[b]	Minor Throat Procedures with CC	1431.00	3	3222.00	24	281.00
FZ03B[c]	Diagnostic and Intermediate Procedures on the Upper GI Tract ≤ 18 Years	852.00	5	1267.00	5	223.00
GB04A[c]	Endoscopic/Radiology Category 1 with Major CC	1879.00	8	6347.00	54	228.00
AA16Z	Intracranial Procedures except Trauma with Non-Transient Stroke or Cerebrovascular Accident, Nervous System Infections or Encephalopathy – Category 1 or 2	4255.00	24	7371.00	66	210.00
EA24Z	Complex Congenital Surgery	9631.00	21	14,934.00	46	205.00
EA25Z	Intermediate Congenital Surgery	9571.00	19	13,009.00	58	205.00
PA14C	Lower Respiratory Tract Disorders without Acute Bronchiolitis with Length of Stay ≥ 1 Day with CC	3602.00	22	2301.00	15	291.00
DZ07B	Fibreoptic Bronchoscopy ≤ 18 Years	1146.00	5	1394.00	5	190.00
VA11D	Multiple Trauma Diagnoses Score ≥ 51 with Interventions Score 1–8	5246.00	94	5246.00	94	232.00
PA16A	Major Infections with CC	1719.00	8	2856.00	22	291.00
QZ15B	Therapeutic Endovascular Procedures with Intermediate CC	1523.00	5	5389.00	49	227.00

continued

TABLE 33 A list of all bundled HRGs, costed for inpatient stays using the national tariff guidance[a] (*continued*)

HRG	HRG name (inpatient)	Elective spell tariff (£)	Elective long-stay trim point (days)	Non-elective spell tariff (£)	Non-elective long-stay trim point (days)	Per-day long-stay payment (for days exceeding trim point) (£)
DZ37B	Non-Invasive Ventilation Support Assessment ≤ 18 Years	927.00	5	927.00	5	190.00
PA23B	Cardiac Conditions without CC	1420.00	5	1427.00	5	291.00
PA15B	Acute Bronchiolitis without CC	1066.00	8	910.00	8	291.00
PA23A	Cardiac Conditions with CC	1956.00	5	3638.00	16	291.00
EA23Z	Major Complex Congenital Surgery	12,638.00	36	19,436.00	66	205.00
PA14E	Lower Respiratory Tract Disorders without Acute Bronchiolitis with Length of Stay 0 Days	561.00	5	434.00	5	291.00
FZ11A	Large Intestine – Major Procedures with Major CC	5441.00	33	8053.00	68	228.00
PA63B	Head, Neck and Ear Disorders with Length of Stay ≥ 1 Day with CC	2514.00	9	972.00	6	291.00
PA48A	Blood Cell Disorders with CC	1474.00	8	2335.00	10	291.00
PB02Z	Minor Neonatal Diagnoses	1041.00	14	1041.00	14	291.00
FZ07A	Major Small Intestine Procedures with CC	4569.00	19	8028.00	62	228.00
VA15D	Multiple Trauma Diagnoses Score ≥ 51 with Interventions Score ≥ 45	20,844.00	143	20,844.00	143	232.00
HC12Z	Intradural Spine Minor 1	571.00	5	739.00	5	231.00
PA12Z	Asthma or Wheezing	563.00	5	622.00	5	291.00
FZ06A	Very Major Small Intestine Procedures with CC	7781.00	40	8308.00	63	228.00
PA25B	Major Gastrointestinal or Metabolic Disorders without CC	949.00	5	1177.00	8	291.00
AA21Z	Intracranial Procedures except Trauma with Other Diagnoses – Category 1 or 2	1096.00	5	5346.00	42	210.00
HB99Z	Other Procedures for Non Trauma	331.00	5	331.00	5	231.00
GA05B	Hepatobiliary Procedures Category 5 without CC	5598.00	17	5980.00	35	221.00

TABLE 33 A list of all bundled HRGs, costed for inpatient stays using the national tariff guidance[a] (*continued*)

HRG	HRG name (inpatient)	Elective spell tariff (£)	Elective long-stay trim point (days)	Non-elective spell tariff (£)	Non-elective long-stay trim point (days)	Per-day long-stay payment (for days exceeding trim point) (£)
PA47Z	Sickle-Cell Anaemia with Crisis	494.00	8	1587.00	9	291.00
QZ15A	Therapeutic Endovascular Procedures with Major CC	9835.00	86	10,258.00	107	227.00
AA02Z	Intracranial Procedures for Trauma with Intermediate Diagnosis	6738.00	40	6738.00	40	210.00
EA26Z	Standard Congenital Surgery	5615.00	15	5615.00	15	205.00
QZ14A	Vascular Access except for Renal Replacement Therapy with CC	548.00	5	1353.00	8	227.00
PA02A	Epilepsy Syndrome with CC	1043.00	5	942.00	5	291.00
PA15A	Acute Bronchiolitis with CC	2254.00	15	1962.00	14	291.00
PA25A	Major Gastrointestinal or Metabolic Disorders with CC	1715.00	5	2583.00	14	291.00
QZ13A	Vascular Access for Renal Replacement Therapy with CC	1287.00	5	1571.00	8	227.00
VA14D	Multiple Trauma Diagnoses Score ≥ 51 with Interventions Score 30–44	11,259.00	129	11,259.00	129	232.00
DZ06Z	Minor Thoracic Procedures	729.00	5	1063.00	5	190.00
DZ03A	Major Thoracic Procedures with CC	3371.00	14	6985.00	39	190.00
AA20Z	Intracranial Procedures except Trauma with Muscular, Balance, Cranial or Peripheral Nerve Disorders or Epilepsy – Category 1 or 2	1957.00	10	3883.00	32	210.00
CZ07O	Exteriorisation of Trachea with Major CC	8640.00	98	7363.00	95	250.00
PB01Z	Major Neonatal Diagnoses	1511.00	16	1511.00	16	291.00
HB16B	Minor Hip Procedures for Non Trauma Category 1 with CC	1267.00	33	1267.00	33	231.00
FZ05A	Major Stomach or Duodenum Procedures ≥ 2 Years with CC	3591.00	16	6539.00	57	228.00

continued

TABLE 33 A list of all bundled HRGs, costed for inpatient stays using the national tariff guidance[a] (*continued*)

HRG	HRG name (inpatient)	Elective spell tariff (£)	Elective long-stay trim point (days)	Non-elective spell tariff (£)	Non-elective long-stay trim point (days)	Per-day long-stay payment (for days exceeding trim point) (£)
FZ05C	Major Stomach or Duodenum Procedures ≤ 1 Year	5402.00	16	4582.00	11	228.00
PA44Z	Neoplasm Diagnoses with Length of Stay 0 Days	541.00	5	527.00	5	291.00
FZ12A	General Abdominal – Very Major or Major Procedures with Major CC	5070.00	29	6963.00	54	228.00
PA18A	Minor Infections with CC	843.00	5	1204.00	8	291.00
AA09Z	Intracranial Procedures except Trauma with Other Diagnoses – Category 4	2396.00	5	8293.00	49	210.00
HB63Z	Minor Shoulder and Upper Arm Procedures for Non Trauma	1401.00	5	1401.00	5	231.00
EA20Z	Other Complex Cardiac Surgery and Re-do's	10,511.00	26	12,806.00	57	205.00
EA14Z	Coronary Artery Bypass Graft (First Time)	7358.00	16	9055.00	39	205.00
EA12Z	Implantation of Cardioverter – Defibrillator Only	5556.00	5	7248.00	34	205.00
DZ02A	Complex Thoracic Procedures with Major CC	8271.00	31	9426.00	54	190.00
VA11B	Multiple Trauma Diagnoses Score 24–32 with Interventions Score 1–8	3864.00	24	3864.00	24	232.00
PA26A	Other Gastrointestinal or Metabolic Disorders with CC	1603.00	5	1076.00	5	291.00
PA59C	Major Congenital Conditions under 1 Year with CC	2444.00	8	3609.00	31	291.00
PA59E	Major Congenital Conditions ≥ 1 Year with CC	1148.00	5	3142.00	13	291.00
PA08B	Intermediate Injury without Intracranial Injury without CC	790.00	5	757.00	5	291.00
PA28A	Feeding Difficulties and Vomiting with CC	2136.00	10	1012.00	5	291.00
HB23B	Intermediate Knee Procedures for Non Trauma with CC	2342.00	29	2342.00	29	231.00

TABLE 33 A list of all bundled HRGs, costed for inpatient stays using the national tariff guidance[a] (*continued*)

HRG	HRG name (inpatient)	Elective spell tariff (£)	Elective long-stay trim point (days)	Non-elective spell tariff (£)	Non-elective long-stay trim point (days)	Per-day long-stay payment (for days exceeding trim point) (£)
PA19B	Viral Infections with Length of Stay ≥ 2 Days	1255.00	5	1255.00	5	291.00
PA06Z	Head Injury with Intracranial Injury	1689.00	9	1689.00	9	291.00
PA67Z	Diabetes Mellitus with Ketoacidosis or Coma	954.00	6	954.00	6	291.00
PA45Z	Febrile Neutropenia with Malignancy	8858.00	51	3894.00	13	291.00
LB10Z	Bladder Major Open Procedures/ Reconstruction	5348.00	24	7019.00	52	215.00
PA17A	Intermediate Infections with CC	1067.00	5	1274.00	9	291.00
PA03B	Febrile Convulsions ≥ 1 Year	705.00	5	595.00	5	291.00
QZ05A	Miscellaneous Vascular Procedures with CC	1687.00	5	3733.00	30	227.00
VA13D	Multiple Trauma Diagnoses Score ≥ 51 with Interventions Score 19–29	8858.00	117	8858.00	117	232.00
AA10Z	Intracranial Procedures except Trauma with Non-Transient Stroke or Cerebrovascular Accident, Nervous System Infections or Encephalopathy – Category 3	7598.00	74	11,733.00	74	210.00
JC01A	Major Multiple Skin Procedures with Major CC	9610.00	62	9608.00	79	223.00
GA05A	Hepatobiliary Procedures Category 5 with CC	6767.00	26	7488.00	57	221.00
EA52Z	Repair or Replacement of More Than One Heart Valve	12,196.00	31	15,633.00	84	205.00
DZ03B	Major Thoracic Procedures without CC	2429.00	9	3884.00	20	190.00
QZ04Z	Extracranial or Upper Limb Arterial Surgery	3567.00	7	5606.00	34	227.00
EA39Z	Pacemaker Procedure without Generator Implant (Includes Resiting and Removal of Cardiac Pacemaker System)	2748.00	5	5302.00	33	205.00
PA38D	Renal Disease with Renal Failure with Length of Stay ≥ 1 Day	3800.00	9	3184.00	15	291.00

continued

TABLE 33 A list of all bundled HRGs, costed for inpatient stays using the national tariff guidance[a] (*continued*)

HRG	HRG name (inpatient)	Elective spell tariff (£)	Elective long-stay trim point (days)	Non-elective spell tariff (£)	Non-elective long-stay trim point (days)	Per-day long-stay payment (for days exceeding trim point) (£)
PA07B	Head Injury without Intracranial Injury without CC	539.00	5	506.00	5	291.00
VA10D	Multiple Trauma Diagnoses Score ≥ 51 with No Interventions	3712.00	93	3712.00	93	232.00
PA21A	Infectious and Non-Infectious Gastroenteritis with CC	1855.00	8	810.00	5	291.00
PA16B	Major Infections without CC	696.00	5	1659.00	11	291.00
FZ01C	Complex Oesophageal Procedures ≤ 18 Years	14,175.00	63	14,175.00	63	228.00
QZ01A	Aortic or Abdominal Surgery with CC	6487.00	27	7307.00	53	227.00
HB13Z	Intermediate Hip Procedures for Non Trauma Category 2	5194.00	26	5194.00	26	231.00
HC08Z	Intradural Spine Major 1	4992.00	31	4992.00	31	231.00
AA11Z	Intracranial Procedures except Trauma with Haemorrhagic Cerebrovascular Disorders – Category 3	6166.00	50	8917.00	50	210.00
PA01A	Nervous System Disorders with CC	1146.00	5	2368.00	15	291.00
PA34A	Musculoskeletal or Connective Tissue Disorders with CC	1112.00	5	1246.00	8	291.00
LB02D	Kidney Major Open Procedure ≤ 18 Years	4289.00	7	8972.00	36	215.00
HB16C	Minor Hip Procedures for Non Trauma Category 1 without CC	969.00	5	969.00	5	231.00
VA12D	Multiple Trauma Diagnoses Score ≥ 51 with Interventions Score 9–18	7012.00	102	7012.00	102	232.00
CZ01S	Minor Mouth or Throat Procedures ≤ 18 Years with CC	1551.00	5	3137.00	8	250.00
HB14B	Intermediate Hip Procedures for Non Trauma Category 1 with CC	3509.00	61	3509.00	61	231.00
PA63A	Head, Neck and Ear Disorders with Length of Stay 0 Days	540.00	5	383.00	5	291.00

TABLE 33 A list of all bundled HRGs, costed for inpatient stays using the national tariff guidance[a] (*continued*)

HRG	HRG name (inpatient)	Elective spell tariff (£)	Elective long-stay trim point (days)	Non-elective spell tariff (£)	Non-elective long-stay trim point (days)	Per-day long-stay payment (for days exceeding trim point) (£)
PA60C	Other Congenital Conditions under 1 Year with CC	945.00	5	1336.00	9	291.00
VA10C	Multiple Trauma Diagnoses Score 33–50 with No Interventions	3453.00	47	3453.00	47	232.00
HB15F	Minor Hip Procedures for Non Trauma Category 2 ≤ 18 Years with CC	1725.00	23	1725.00	23	231.00
FZ20C	Appendicectomy Procedures ≤ 18 Years	2367.00	5	2292.00	7	228.00
FZ27D	Endoscopic or Intermediate General Abdominal Procedures ≤ 18 Years	1216.00	5	1729.00	8	228.00
LA05Z	Renal Replacement Peritoneal Dialysis Associated Procedures	1138.00	5	1195.00	5	215.00
LB05D	Kidney Intermediate, Endoscopic and Percutaneous Interventions ≤ 18 Years	2372.00	5	4973.00	25	215.00
AA04Z	Intracranial Procedures except Trauma with Non-Transient Stroke or Cerebrovascular Accident, Nervous System Infections or Encephalopathy – Category 4	7936.00	74	11,733.00	74	210.00
PA19A	Viral Infections with Length of Stay ≤ 1 Day	446.00	5	444.00	5	291.00
PA21B	Infectious and Non-Infectious Gastroenteritis without CC	705.00	5	520.00	5	291.00
EA11Z	Percutaneous Congenital Interventions: Other Including Septostomy, Embolisations, Non-Coronary Stents and Energy Moderated Perforation	1934.00	5	4417.00	33	205.00
FZ25B	Therapeutic Endoscopic or Intermediate Stomach or Duodenum Procedures ≤ 18 Years	996.00	5	996.00	5	228.00
FZ04A	Very Major Stomach or Duodenum Procedures with Major CC	8135.00	44	11,299.00	84	228.00
AB04Z	Major Pain Procedures	570.00	5	2624.00	24	210.00

continued

TABLE 33 A list of all bundled HRGs, costed for inpatient stays using the national tariff guidance[a] (*continued*)

HRG	HRG name (inpatient)	Elective spell tariff (£)	Elective long-stay trim point (days)	Non-elective spell tariff (£)	Non-elective long-stay trim point (days)	Per-day long-stay payment (for days exceeding trim point) (£)
LB11B	Urinary Diversion without Cystectomy without Malignancy	5913.00	30	9562.00	71	215.00
VA12C	Multiple Trauma Diagnoses Score 33–50 with Interventions, Score 9–18	6487.00	61	6487.00	61	232.00
VA11A	Multiple Trauma Diagnoses Score ≤ 23 with Interventions, Score 1–8	1965.00	10	1965.00	10	232.00
SA14Z	Plasma Exchanges 2–9	2385.00	13	7293.00	55	237.00
AA19Z	Intracranial Procedures except Trauma with Cerebral Degenerations or Miscellaneous Disorders of Nervous System – Category 1 or 2	1843.00	8	5014.00	25	210.00
VA11C	Multiple Trauma Diagnoses Score 33–50 with Interventions Score 1–8	4513.00	45	4513.00	45	232.00
PB03Z	Healthy Baby	0.00	5	0.00	5	0.00
PA49Z	Coagulation Disorders	666.00	5	691.00	5	291.00
PA35A	Skin Disorders with CC	1103.00	5	1187.00	8	291.00
PA42Z	Brain Tumours with Length of Stay ≥ 1 Day	2660.00	9	2830.00	9	291.00
GB03A	Endoscopic/Radiology Category 2 with CC	1020.00	5	6235.00	53	221.00
GB01Z	Endoscopic/Radiology Category 4	2366.00	9	4813.00	58	221.00
PA68Z	Diabetes Mellitus without Ketoacidosis or Coma	941.00	5	941.00	5	291.00
QZ15C	Therapeutic Endovascular Procedures without CC	1178.00	5	3091.00	26	227.00
SA15Z	Plasma Exchanges 10–19	4892.00	13	7293.00	55	237.00
PA51Z	Child Safeguarding (Welfare and Protection)	854.00	5	854.00	5	291.00
GA03A	Hepatobiliary Procedures Category 7 with CC	10,784.00	49	14,235.00	71	221.00
DZ02B	Complex Thoracic Procedures with CC	6356.00	18	6729.00	26	190.00
PA14D	Lower Respiratory Tract Disorders without Acute Bronchiolitis with Length of Stay ≥ 1 Day without CC	2286.00	16	1035.00	6	291.00

TABLE 33 A list of all bundled HRGs, costed for inpatient stays using the national tariff guidance[a] (*continued*)

HRG	HRG name (inpatient)	Elective spell tariff (£)	Elective long-stay trim point (days)	Non-elective spell tariff (£)	Non-elective long-stay trim point (days)	Per-day long-stay payment (for days exceeding trim point) (£)
CZ04Q	Complex Major Mouth or Throat Procedures without CC	7565.00	39	7565.00	39	250.00
AA17Z	Intracranial Procedures except Trauma with Haemorrhagic Cerebrovascular Disorders – Category 1 or 2	2794.00	12	6852.00	64	210.00
QZ11B	Amputations without Major CC	8011.00	53	10,771.00	95	227.00
HC11Z	Intradural Spine Minor 2	3138.00	18	3138.00	18	231.00
EA10Z	Percutaneous Congenital Interventions: Balloon Valve Intermediate Interventions and Arterial Duct Closure	4111.00	6	8275.00	48	205.00
FZ02Z	Very Major Oesophageal Procedures	3802.00	11	6158.00	39	228.00
FZ11B	Large Intestine – Major Procedures without Major CC	2643.00	14	4640.00	32	228.00
AA15Z	Intracranial Procedures except Trauma with Other Diagnoses – Category 3	2396.00	5	8293.00	49	210.00
QZ05B	Miscellaneous Vascular Procedures without CC	1035.00	5	2402.00	14	227.00
EA43Z	Implantation of Prosthetic Heart or Ventricular Assist Device	42,583.00	90	42,583.00	90	205.00
FZ07B	Major Small Intestine Procedures without CC	3134.00	15	4551.00	28	228.00

CC, comorbidity; GI, gastrointestinal.
a 2012–13 tariff unless stated otherwise.
b 2010–11 tariff.
c 2011–12 tariff.

TABLE 34 A list of all bundled HRGs, costed for outpatient attendances using the national tariff guidance

Treatment function	Treatment function name (outpatient)	WF01B First Attendance – Single Professional (£)	WF02B First Attendance – Multi Professional (£)	WF01A Follow Up Attendance – Single Professional (£)	WF02A Follow Up Attendance – Multi Professional (£)
100	General Surgery	191.00	207.00	101.00	101.00
101	Urology	177.00	196.00	96.00	99.00
103	Breast Surgery	154.00	154.00	84.00	85.00
104	Colorectal Surgery	131.00	157.00	72.00	105.00
105	Hepatobiliary and Pancreatic Surgery	166.00	166.00	102.00	102.00
106	Upper Gastrointestinal Surgery	140.00	140.00	82.00	82.00
107	Vascular Surgery	234.00	234.00	116.00	116.00
110	Trauma and Orthopaedics	137.00	137.00	83.00	83.00
120	Ear, Nose and Throat	114.00	141.00	63.00	73.00
130	Ophthalmology	115.00	138.00	67.00	75.00
140	Oral Surgery	130.00	185.00	80.00	126.00
143	Orthodontics	186.00	285.00	83.00	129.00
144	Maxillo-Facial Surgery	115.00	190.00	70.00	99.00
160	Plastic Surgery	117.00	131.00	67.00	85.00
170	Cardiothoracic Surgery	227.00	227.00	142.00	162.00
171	Paediatric Surgery	191.00	241.00	109.00	163.00
172	Cardiac Surgery	293.00	293.00	171.00	171.00
173	Thoracic Surgery	260.00	260.00	159.00	159.00
190	Anaesthetics	98.00	98.00	95.00	95.00
191	Pain Management	181.00	195.00	91.00	119.00
211	Paediatric Urology	182.00	196.00	111.00	111.00
214	Paediatric Trauma and Orthopaedics	154.00	163.00	100.00	113.00
215	Paediatric Ear Nose and Throat	116.00	141.00	74.00	74.00
216	Paediatric Ophthalmology	156.00	172.00	89.00	125.00
217	Paediatric Maxillo-Facial Surgery	154.00	190.00	116.00	116.00
219	Paediatric Plastic Surgery	182.00	182.00	98.00	98.00
251	Paediatric Gastroenterology	279.00	279.00	158.00	158.00
252	Paediatric Endocrinology	305.00	352.00	172.00	185.00

TABLE 34 A list of all bundled HRGs, costed for outpatient attendances using the national tariff guidance (*continued*)

Treatment function	Treatment function name (outpatient)	WF01B First Attendance – Single Professional (£)	WF02B First Attendance – Multi Professional (£)	WF01A Follow Up Attendance – Single Professional (£)	WF02A Follow Up Attendance – Multi Professional (£)
253	Paediatric Clinical Haematology	414.00	464.00	218.00	247.00
257	Paediatric Dermatology	49.00	168.00	107.00	108.00
258	Paediatric Respiratory Medicine	315.00	315.00	172.00	172.00
263	Paediatric Diabetic Medicine	353.00	353.00	119.00	119.00
300	General Medicine	210.00	251.00	105.00	121.00
301	Gastroenterology	265.00	265.00	83.00	116.00
302	Endocrinology	230.00	230.00	106.00	116.00
303	Clinical Haematology	268.00	288.00	106.00	106.00
306	Hepatology	224.00	290.00	139.00	151.00
307	Diabetic Medicine	242.00	321.00	99.00	147.00
320	Cardiology	210.00	251.00	105.00	121.00
321	Paediatric Cardiology	289.00	289.00	170.00	170.00
329	Transient Ischaemic Attack	477.00	477.00	–	–
330	Dermatology	112.00	168.00	69.00	108.00
340	Respiratory Medicine	223.00	244.00	105.00	128.00
341	Respiratory Physiology	189.00	189.00	122.00	122.00
350	Infectious Diseases	255.00	255.00	195.00	195.00
360	Genitourinary Medicine	133.00	148.00	82.00	82.00
361	Nephrology	299.00	454.00	124.00	219.00
370	Medical Oncology	228.00	290.00	98.00	115.00
410	Rheumatology	246.00	246.00	102.00	102.00
420	Paediatrics	231.00	288.00	129.00	159.00
430	Geriatric Medicine	303.00	303.00	139.00	139.00
501	Obstetrics	119.00	154.00	60.00	60.00
502	Gynaecology	138.00	142.00	81.00	99.00
503	Gynaecological Oncology	154.00	271.00	90.00	132.00
560	Midwife Episode	119.00	154.00	60.00	60.00
800	Clinical Oncology	228.00	290.00	98.00	115.00
812	Diagnostic Imaging	0.00	0.00	0.00	0.00

TABLE 35 A list of all bundled HRGs, costed for A&E attendances using the national tariff guidance

HRG code	HRG name (A&E)	Band	24-hour A&E units tariff (£)	Non-24-hour A&E units and minor injury units tariff (£)
VB01Z	Any Investigation with Category 5 Treatment	1	235.00	54.00
VB02Z	Category 3 Investigation with Category 4 Treatment	1	235.00	54.00
VB03Z	Category 3 Investigation with Category 1–3 Treatment	2	151.00	54.00
VB04Z	Category 2 Investigation with Category 4 Treatment	2	151.00	54.00
VB05Z	Category 2 Investigation with Category 3 Treatment	2	151.00	54.00
VB06Z	Category 1 Investigation with Category 3–4 Treatment	3	81.00	54.00
VB07Z	Category 2 Investigation with Category 2 Treatment	4	112.00	54.00
VB08Z	Category 2 Investigation with Category 1 Treatment	4	112.00	54.00
VB09Z	Category 1 Investigation with Category 1–2 Treatment	3	81.00	54.00
VB10Z	Dental Care	5	54.00	54.00
VB11Z	No Investigation with No Significant Treatment	5	54.00	54.00

Appendix 4 Generalisability study additional data

Predictive model identifying children most likely to require a central venous catheter in the paediatric intensive care unit

The PICANet database does not record insertion or removal of CVCs. However, through the use of CVC audit data from two PICUs, it was possible to create a predictive model to identify admissions in the PICANet data set most likely to have required a CVC.

Methods

Central venous catheter audit data

Central venous catheter audit data were obtained from four PICUs. Data from PICUs 1 and 2 consisted of individual-level information and data from PICUs 3 and 4 consisted of aggregate data. At PICU 1, the insertion and duration of insertion of CVCs were recorded for 6 months between July and December 2009. At PICU 2, the number of CVCs present for each patient was recorded on a daily basis between December 2005 and March 2012. At PICU 3, the total number of patients admitted and the number of patients with one or more CVCs was recorded by month between January 2011 and February 2012. At PICU 4, the total number of patients admitted, the number of patients with one or more CVC and the total number of CVCs in place were recorded each day between December 2009 and June 2012.

A predictive model for central venous catheter use

Central venous catheter use was identified within the PICANet data set using the PICANet ID and hospital number from the audit data. Multivariable logistic regression was then used to model the probability of CVC use dependent on a set of predictors:

$$\log \frac{\pi_i}{1-\pi_i} = \alpha + \beta_1 x_{i1} + \beta_2 x_{i2} + \cdots \beta_j x_{ij} = \beta x_i, \quad (3)$$

where π_i is the probability of CVC use for patient i, a is the constant term and $\beta_1 \ldots \beta_j$ are the set of predictors. To identify the best-fitting set of predictors, all possible regression models were tested, ranging from the model including only the intercept to the model including all possible predictor variables. Models were compared using the BIC.

Evaluating the performance of the predictive model

To quantify the performance of a predictive model, two measures are typically used:[83]

- discrimination (the ability of predicted probabilities to correctly classify children by CVC use)
- calibration (agreement between observed CVC use and predicted probability of CVC use)

To measure the discrimination of the predictive model, the c-index [equivalent to the area under the receiver operating characteristic (ROC) curve] was calculated. The c-index corresponds to the chance that the predicted probability of CVC use in someone who did require a CVC is greater than the predicted probability of CVC use in someone who did not require a CVC. The greater the c-index, the more discriminative the model.

To measure the calibration of the predictive model, observed CVC use and predicted probabilities were compared using the calibration slope (or linear predictor), as described in Steyerberg *et al.*[83] The calibration slope is the regression coefficient β in the logistic regression of observed CVC use (binary variable) with predicted CVC use (probability) as the only predictor. Predicted CVC use is calculated as the linear

combination of regression coefficients as estimated from the predictive model. In a perfectly calibrated model, the regression coefficient β in the following model would be equal to 1:

$$\text{Observed CVC use} = \alpha + \beta\,(\text{predicted CVC use}). \quad (4)$$

By definition, when the model is developed and tested in the same sample, the calibration slope will be equal to 1. However, when predictive models are tested with new data, the calibration slope is often < 1 as most models provide predictions that are too extreme. The closer the β coefficient to 1, the better the calibration of the model.

Internal validation

When predictive models are derived and tested within the same sample of data, measures of predictive ability (e.g. calibration/discrimination) are likely to be overoptimistic. This is because of model overfitting, in which the 'apparent' performance in the model derivation data set is likely to be better than the performance in a new set of data. Bootstrapping is an approach that addresses this problem and makes use of all available data, producing more stable results.[83,84] The method involves repeatedly sampling from the original data, a process that simulates sampling from the underlying population from which the original data were drawn. An estimate of the 'optimism' in the predictive ability of the model is made by comparing model performance in bootstrap samples with 'apparent' performance in the derivation sample.

Bootstrapping was used to estimate the optimism in the predictive ability of the model as measured in the derivation sample of data (i.e. the 'apparent' performance in the CVC audit data). The optimism reflects the difference between model performance in the derivation data set and model performance in a separate but similar data set drawn from the same underlying population. Optimism was estimated as the difference between the apparent performance of a model derived in a bootstrap sample and 'test' performance when the same model was applied to the derivation sample (CVC audit data).

Finally, apparent model performance (as measured in the derivation sample) was adjusted for optimism/overfitting by subtracting the estimate of optimism from the measure of predictive ability (calibration slope or c-index). The resulting measure of performance is said to be 'internally validated'.[85]

Choosing a probability cut-off

A probability cut-off is required to classify children as either requiring a CVC or not requiring a CVC. Higher probability cut-offs result in greater specificity; lower probability cut-offs results in greater sensitivity. A visualisation of the trade-off between sensitivity and specificity was provided by the ROC curve. Two main criteria are used for finding the optimal cut-off based on maximising the area under the ROC curve, and probability cut-offs according to both of these criteria were calculated:[86,119]

1. the minimum distance criterion assumes that the optimal cut-off minimises the distance between the point (0,1) and the ROC curve, that is, the minimal value of $(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2$
2. the Youden Index criterion assumes that the optimal cut-off maximises the vertical distance between the ROC curve and the line of equality where sensitivity = 1 – specificity, that is, the maximum value of sensitivity + specificity – 1.

External validation

Aggregate CVC audit data from PICUs 3 and 4 were not used for development of the predictive model (individual-level data were not available) but could provide estimates of the average proportion of children requiring a CVC in the PICU. To externally validate the predictive model, the actual numbers of admissions and bed-days with CVCs in the audit data from PICUs 3 and 4 were compared with the results of the predictive model (with shrinkage factor applied).

Results

A predictive model for central venous catheter use

The best-fitting model included length of stay, vasoactive agent, admission from ward, renal support and invasive ventilation. No significant first-order interactions were found. The predicted probability of CVC use for each admission (π_i) was derived from the logistic model:

$$\pi_i = \frac{e^{\beta x_i}}{1+e^{\beta x_i}}, \quad (5)$$

where βx_i was the linear predictor of the BIC model. Model coefficients are provided in *Table 37*.

Evaluating the performance of the predictive model

Discrimination

The c-index of the predictive model in the original sample was estimated as 0.778. The average c-index in 100 bootstrap samples was 0.778 and, on average, the c-index as measured in the derivation sample was 0.004 higher than when measured in the test sample. Subtracting this estimate of optimism from the apparent performance in the derivation sample produced an internally validated c-index of $0.778 - 0.004 = 0.774$. This indicated that the model performed reasonably well at classifying children as requiring a CVC.

Calibration

By definition, the calibration slope (β coefficient) for the regression of observed CVC use and predicted CVC use in the original sample was 1, as the model was developed and tested in the same sample:

$$\text{Observed CVC use} = (2.02 \times 10^{-9}) + 1(\text{predicted CVC use}). \quad (6)$$

The average calibration slope in 100 bootstrap samples was 0.967 and, on average, the calibration slope in the derivation data set was 0.033 higher than when measured in the test data set. Subtracting this estimate of optimism from the apparent performance in the derivation sample produced an internally validated calibration slope of $1 - 0.033 = 0.967$. This indicated close agreement between observed CVC use and CVC use as predicted in the model.

The coefficients in the original model were multiplied by the shrinkage factor of 0.967 to provide a final model, adjusted for overfitting.[85]

Choosing a probability cut-off

The Youden Index indicated that the optimal probability cut-off was 0.57. With this cut-off, the sensitivity of the predictive model for capturing admissions requiring a CVC was 61%, the specificity was 82%, the positive predictive value was 82% and the negative predictive value was 61%.

External validation

Compared with the aggregate CVC data, the model predicted that 54.6% and 63.5% of admissions in the Newcastle PICU and Birmingham PICU, respectively, required a CVC, compared with true values of 49.4% and 54.6% respectively. The predictive model identified 80% of the CATCH admissions as having a CVC.

TABLE 36 Survey results on type of CVC used prior to the CATCH trial and percentage of admissions requiring a CVC

	Type of CVC used prior to the CATCH 2009 survey		Admissions requiring a CVC, 2012 survey	
PICU trust	Emergency admissions	Elective admissions	Emergency admissions (%)	Elective admissions (%)
1	Not surveyed	Not surveyed	75	25
2	Standard/heparin	Standard/heparin	57	93
3	Not surveyed	Not surveyed	< 5	< 5
4	Standard/heparin	Standard	80	90
5	Standard	Standard	85	50
6	Standard	Standard	No response	No response
7	Standard/antibiotic	Standard	60–100	60–90
8[a]	Standard	Standard	80	80
9[a]	Heparin	Heparin	60	30
10	Standard	Standard	30	50
11	Standard	Standard	50	50
12	Standard	Standard	No response	No response
13	Standard	Standard	No response	No response
14	Standard	Standard	75	No response
15	Heparin	Heparin	87	18
16	Standard	Standard	60	20
17	Standard	Standard	70	80
18	Standard	Standard	No response	No response
19	No response	No response	No response	No response
20	Standard	Antibiotic	50	50
21	Heparin	Standard/heparin	50	30
22[a]	Not surveyed	Not surveyed	No response	No response
23[a]	Not surveyed	Not surveyed	60	50
Average			60	50

a No data in linked data set.
Shaded boxes correspond to the 12 NHS trusts participating in the CATCH trial (14 PICUs).

TABLE 37 Independent predictors of CVC use in CVC audit data (basis for the predictive model)

Predictor	Odds ratio (95% CI)	*p*-value
Length of stay (hours)	1.003 (1.000 to 1.004)	< 0.0001
Vasoactive agent	4.443 (3.600 to 5.513)	< 0.0001
Admission from ward	1.428 (1.200 to 1.738)	< 0.0001
Renal support	3.952 (2.000 to 7.822)	< 0.0001
No ventilation or non-invasive ventilation only	1	
Invasive ventilation	2.547 (1.900 to 3.350)	< 0.0001
Invasive and non-invasive ventilation	2.278 (1.500 to 3.395)	< 0.0001

TABLE 38 Characteristics of admissions during the 23-month trial period (December 2010–November 2012) in all PICUs in England

Characteristic	CATCH participants[a] (*n* = 1398)		Admissions expected to require a CVC (*n* = 20,199)		All admissions during the trial period (*n* = 53,897)	
	n	%	*n*	%	*n*	%
Length of stay (hours)						
1 to < 4	3	0.2	186	0.9	1482	2.7
4 to < 12	18	1.3	438	2.2	3764	7.0
12 to < 24	101	7.2	1699	8.4	9647	17.9
24 to < 48	175	12.5	2959	14.6	10,919	20.3
48+	1101	78.8	14,917	73.9	28,085	52.1
Age (years)						
< 1	815	58.3	11,775	58.3	27,323	50.7
1–4	327	23.4	4473	22.1	13,405	24.9
5–10	144	10.3	2023	10.0	6837	12.7
11–15	112	8.0	1926	9.5	6328	11.7
Unknown		0.0	2	0.0	4	0.0
Vasoactive agents	1054	75.4	17,081	84.6	18,792	34.9
Renal support	148	10.6	1469	7.3	1684	3.1
PIM2						
< 1%	150	10.7	1857	9.2	13,855	25.7
1 to < 5%	744	53.2	10,332	51.2	25,840	47.9
5 to < 15%	354	25.3	5472	27.1	10,520	19.5
15 to < 30%	103	7.4	1486	7.4	2290	4.2
30%+	47	3.4	1052	5.2	1392	2.6
Ventilation status						
Neither	33	2.4	442	2.2	12,652	23.5
Non-invasive only	10	0.7	159	0.8	2620	4.9
Invasive only	1017	72.7	16,170	80.1	32,882	61.0
Both	337	24.1	3424	17.0	5625	10.4
Unknown	1	0.1	4	0.0	118	0.2
Type of admission						
Planned	572	40.9	9015	44.6	21,844	40.5
Unplanned	826	59.1	11,180	55.3	31,992	59.4
Unknown		0.0	4	0.0	61	0.1
Source of admission						
Same hospital	729	52.1	11,713	58.0	32,966	61.2
Other hospital	667	47.7	8374	41.5	20,210	37.5
Unknown	2	0.1	112	0.6	721	1.3

continued

TABLE 38 Characteristics of admissions during the 23-month trial period (December 2010–November 2012) in all PICUs in England (*continued*)

Characteristic	CATCH participants[a] (*n* = 1398)		Admissions expected to require a CVC (*n* = 20,199)		All admissions during the trial period (*n* = 53,897)	
	n	%	*n*	%	*n*	%
Primary diagnosis at admission						
Cardiac	707	50.6	10,687	52.9	16,818	31.2
Respiratory	273	19.5	3751	18.6	14,295	26.5
Infection	100	7.2	1078	5.3	2333	4.3
Other	318	22.7	4683	23.2	20,451	37.9
Care area of admission						
A&E	242	17.3	2379	11.8	9422	17.5
HDU	72	5.2	878	4.3	2410	4.5
ICU/PICU/NICU	222	15.9	3802	18.8	8112	15.1
Other intermediate care area	8	0.6	466	2.3	1315	2.4
Recovery only	3	0.2	39	0.2	155	0.3
Theatre and recovery	565	40.4	8422	41.7	20,566	38.2
Unknown	9	0.6	165	0.8	919	1.7
Ward	273	19.5	3889	19.3	10,417	19.3
Radiography/ endoscopy/CT	4	0.3	159	0.8	581	1.1
Retrieval, yes	596	42.6	7464	37.0	18,230	33.8
Retrieval team						
Non-specialist team	19	1.4	721	3.6	2031	3.8
Other specialist team	306	21.9	4358	21.6	9681	18.0
Own team	263	18.8	2339	11.6	6388	11.9
Unknown	8	0.6	46	0.2	130	0.2
Sex						
Male	811	58.0	11,363	56.3	30,428	56.5
Female	587	42.0	8830	43.7	23,449	43.5
Unknown		0.0	6	0.0	20	0.0
PICU type						
General	59	4.2	2831	14.0	15,828	29.4
Mixed	1286	92.0	16,997	84.1	37,386	69.4
Cardiac	53	3.8	371	1.8	683	1.3
PICU size (admissions per year)						
< 650	59	4.2	2373	11.7	14,255	26.4
650–1000	620	44.3	3227	16.0	8731	16.2
> 1000	719	51.4	14,599	72.3	30,911	57.4

CT, computerised tomography.
a Consenting to linkage with the PICANet data set.

Appendix 5 Statistical analysis report

CATCH

CATheter Infections in CHildren

SAP Report Shell

	ORIGINATED BY
Name	Kerry Dwan
Title	Trial Statistician
Date	16/08/2013
Protocol Version and Date	5.0 01/10/2012

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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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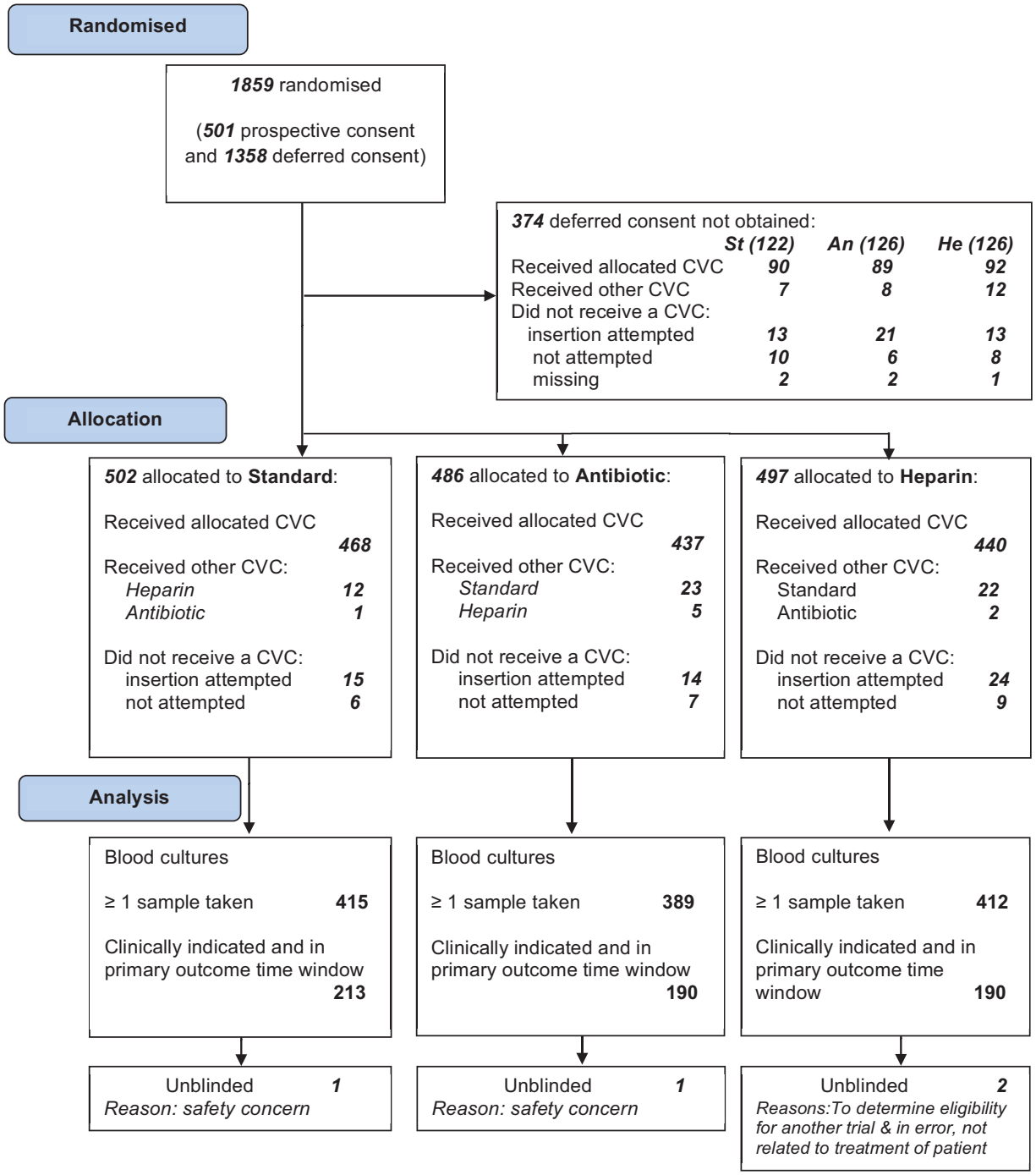
Figure 1: CONSORT 2010 Flow Diagram - Overall



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

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Figure 2: CONSORT 2010 Flow Diagram – Prospective consent

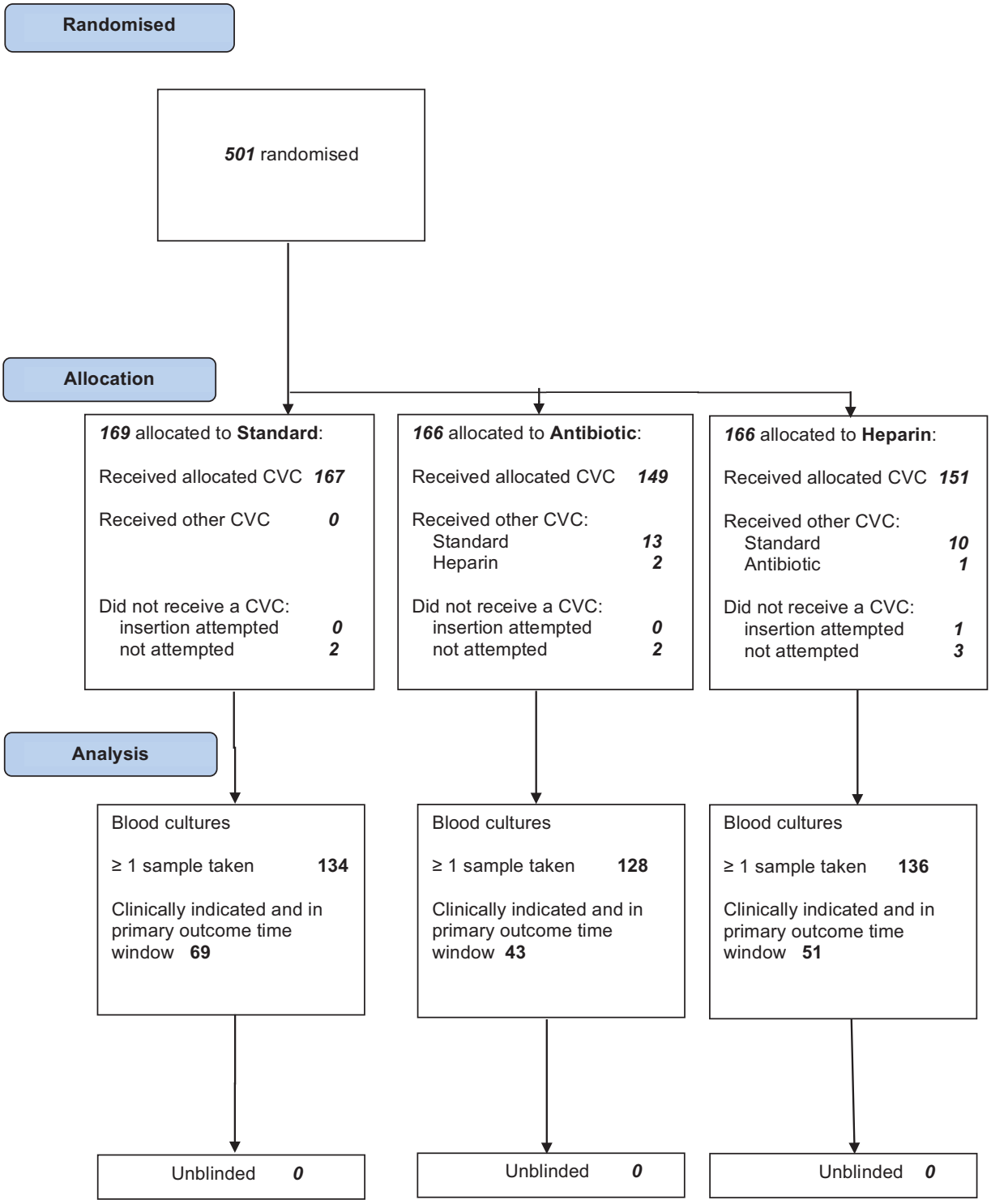

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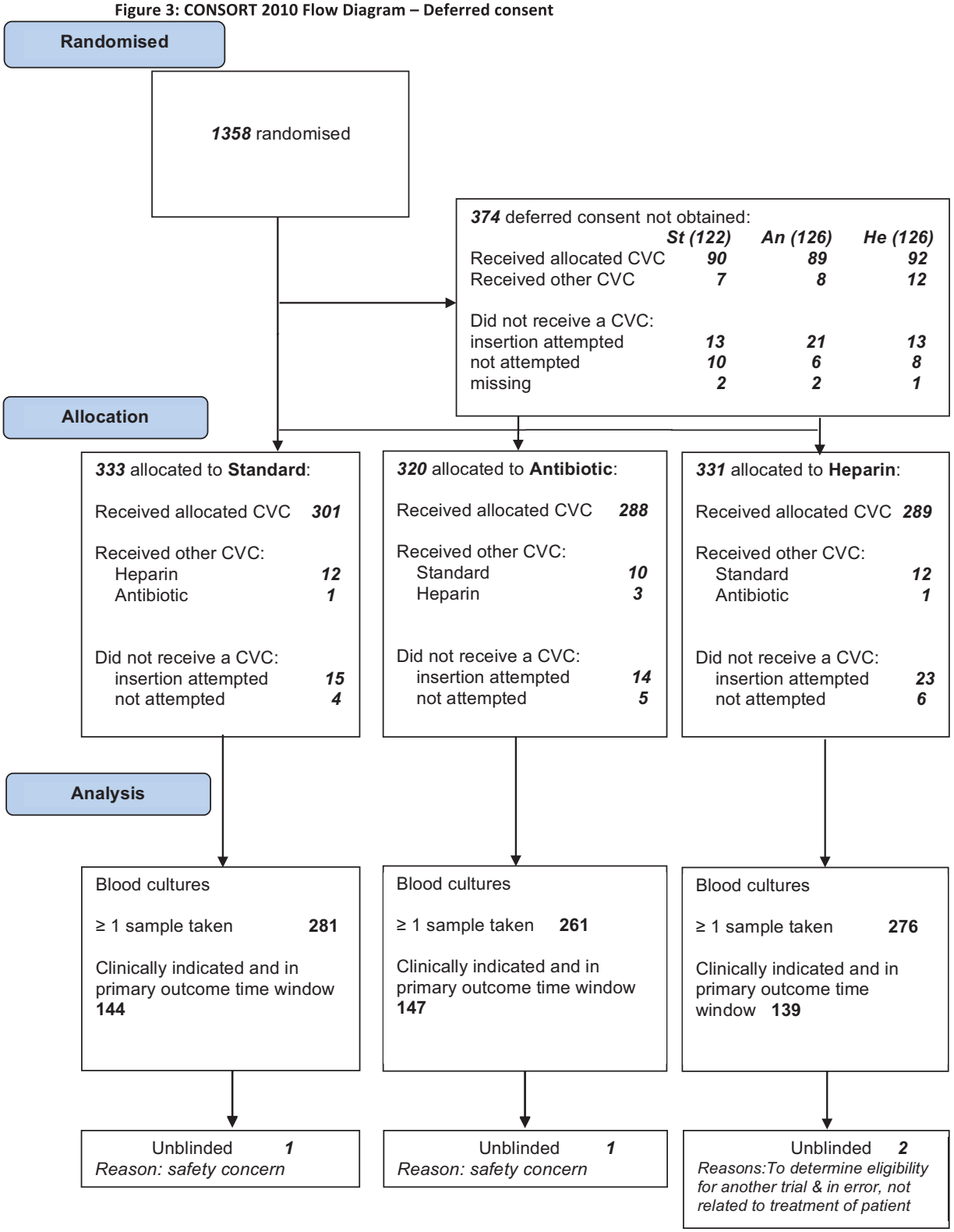
Figure 3: CONSORT 2010 Flow Diagram – Deferred consent



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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

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	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

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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.

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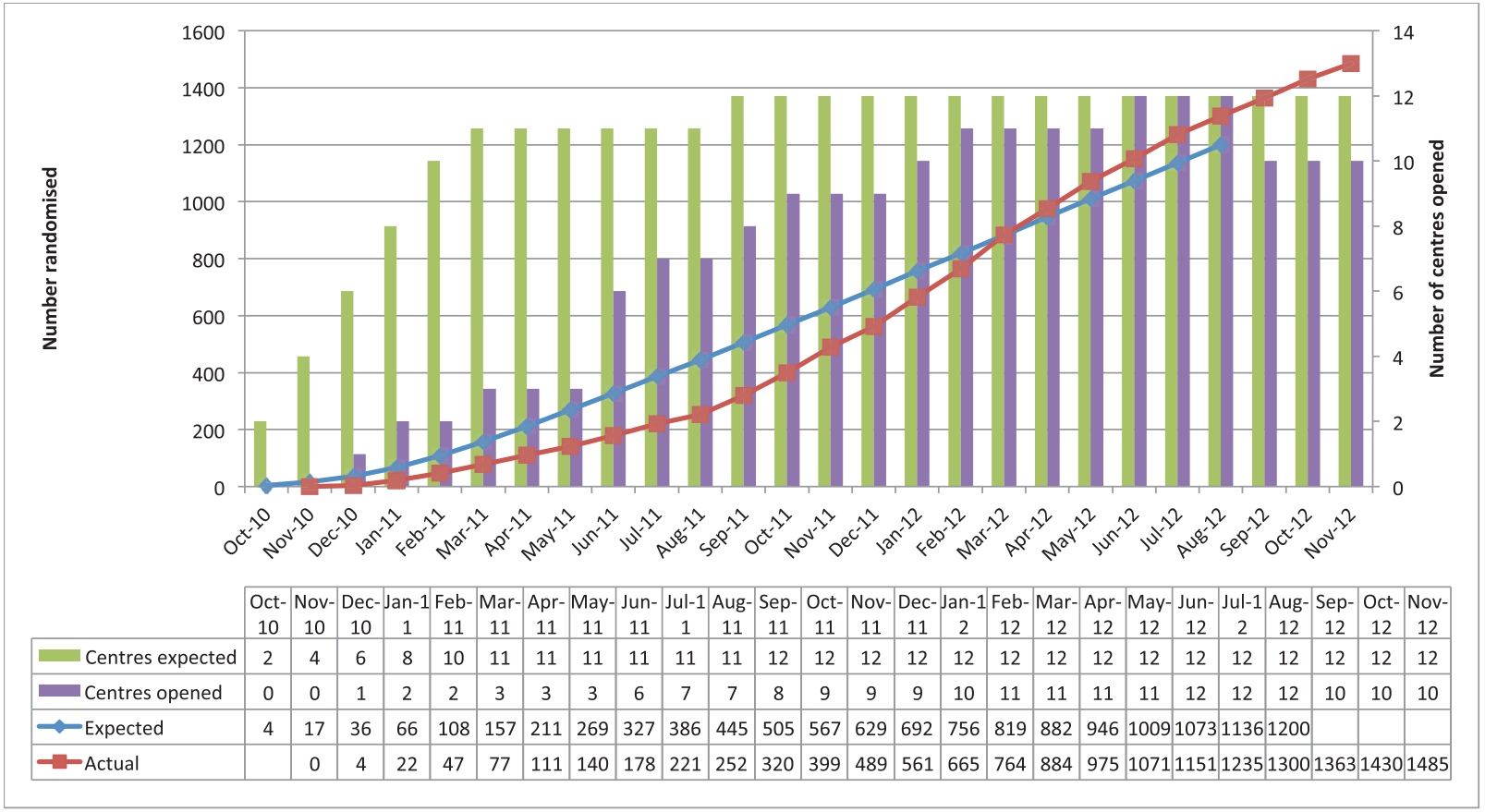
Figure 4: Overall recruitment graph



	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

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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)

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	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:					

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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)

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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

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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).

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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.

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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.

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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

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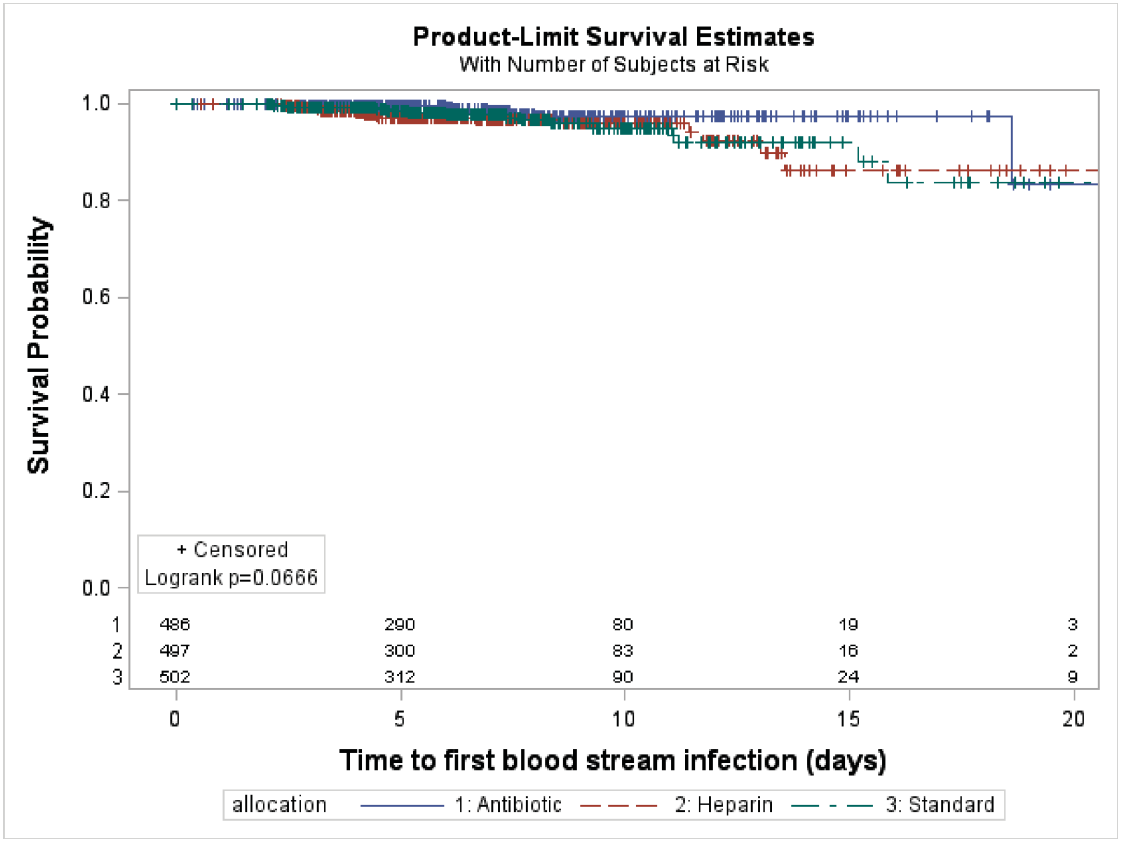
Figure 5: Time to first blood stream infection



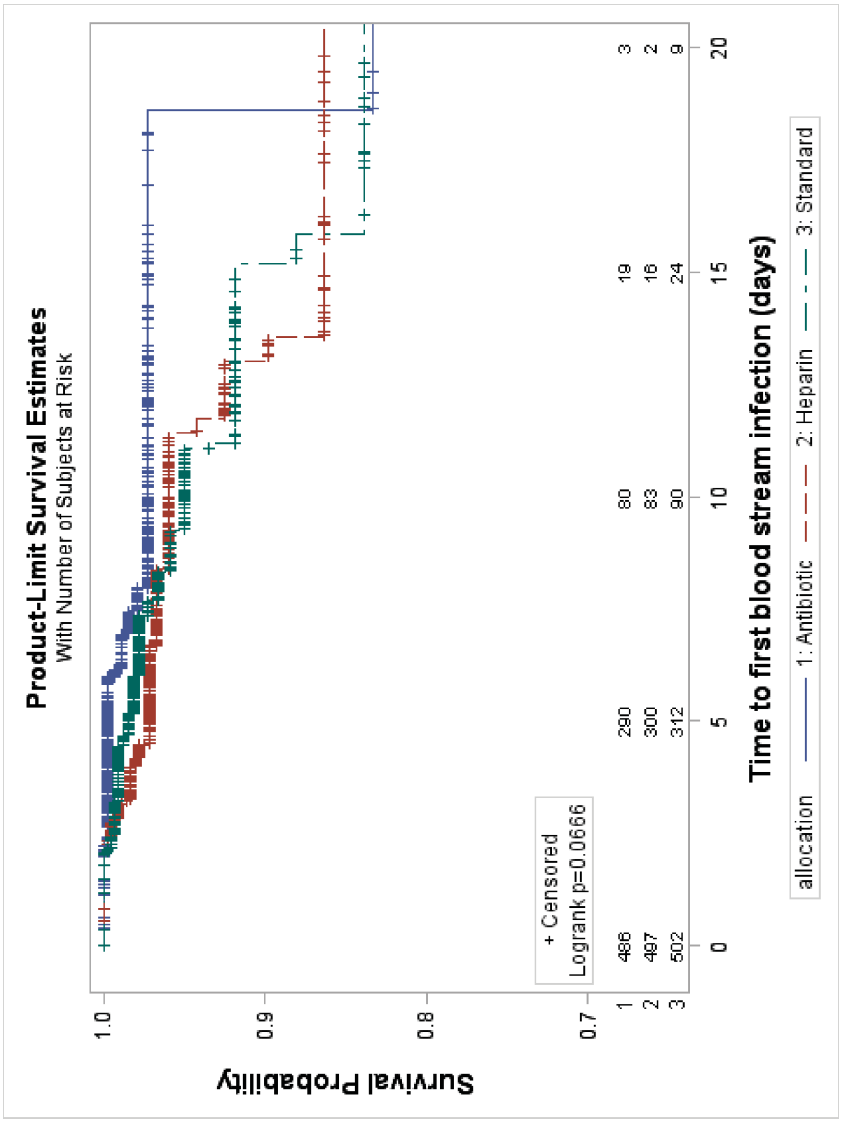


Figure 6: Time to first blood stream infection (y axis cut)

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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

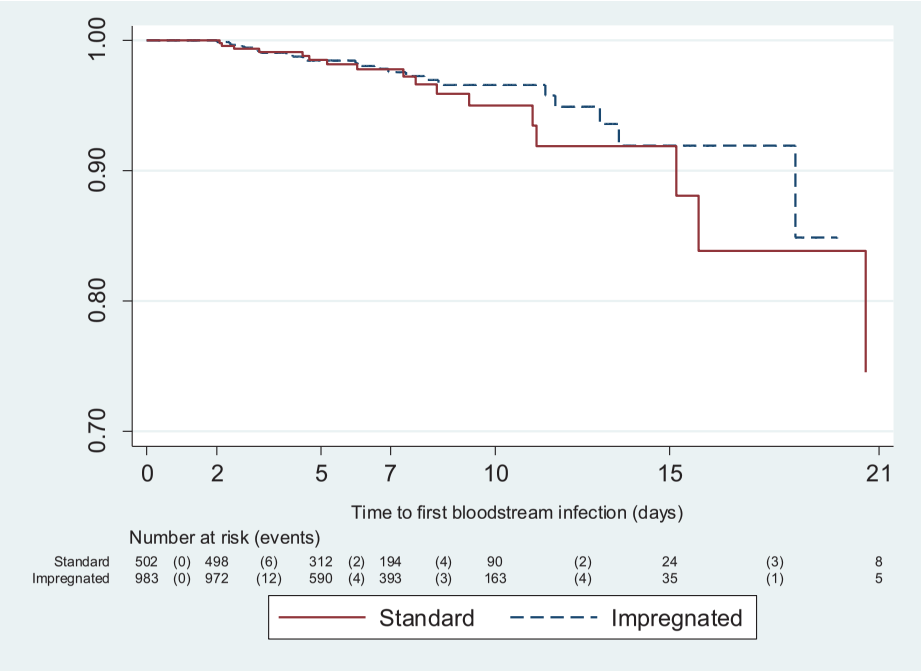

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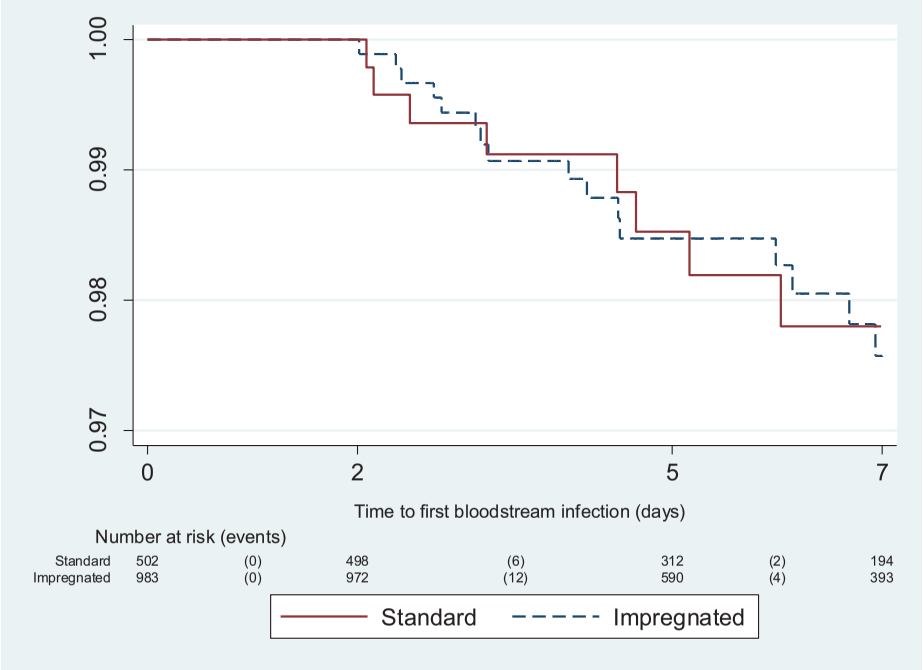
Figure 8: Time to first blood stream infection: standard versus impregnated, days 0-7



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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.

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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.

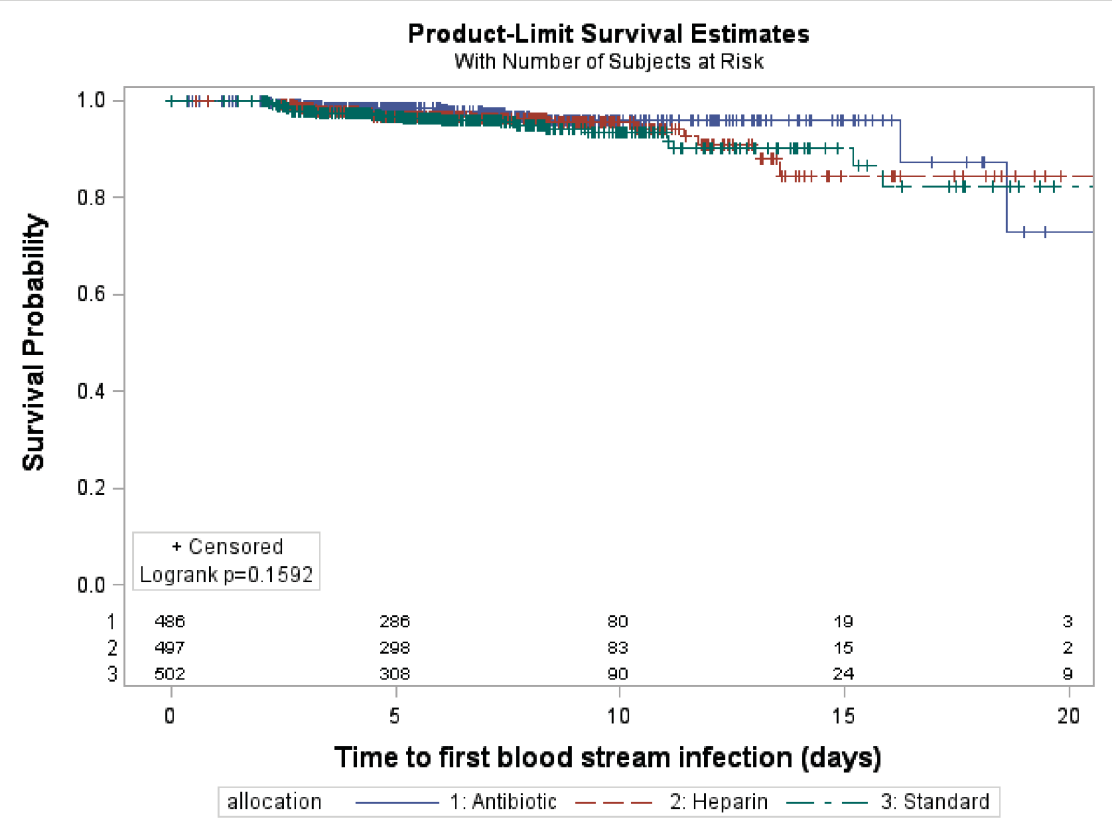
Table 23: Time to first blood stream infection: sensitivity analysis (post-hoc)

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



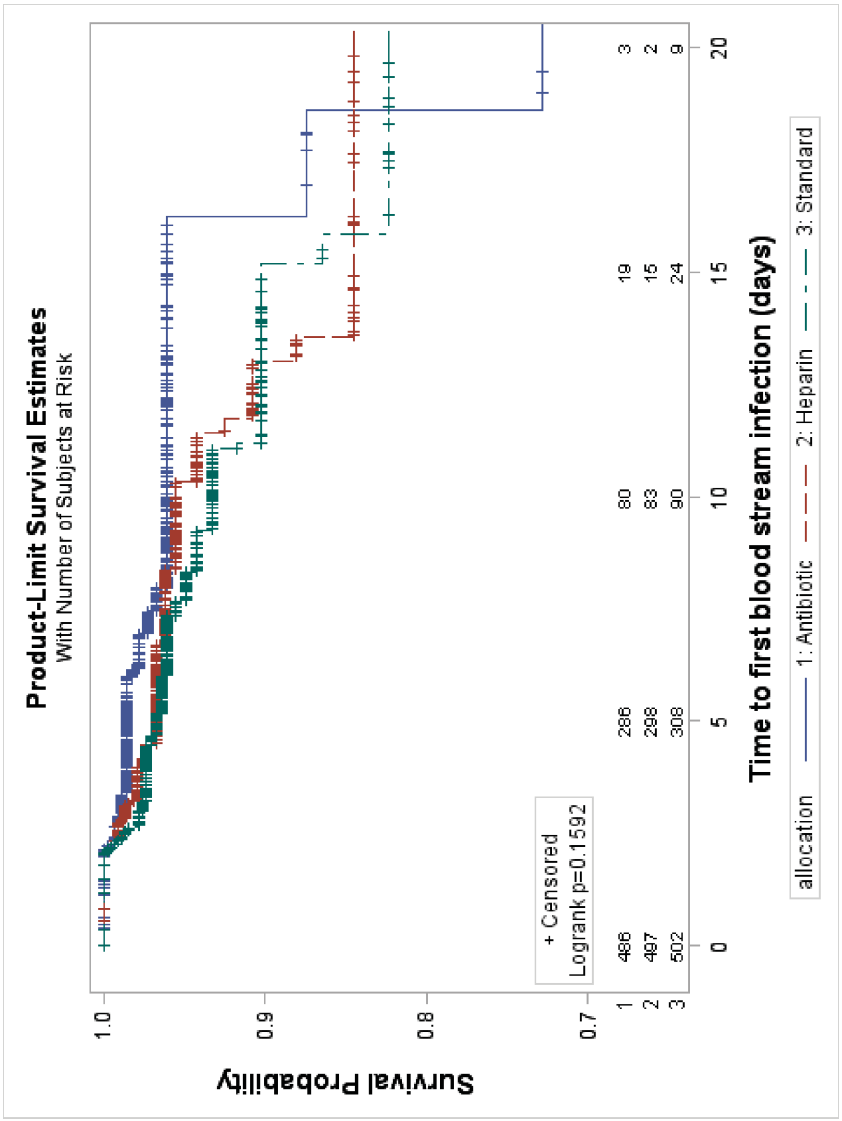


Figure 10: Sensitivity analysis (y axis cut)

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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)

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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

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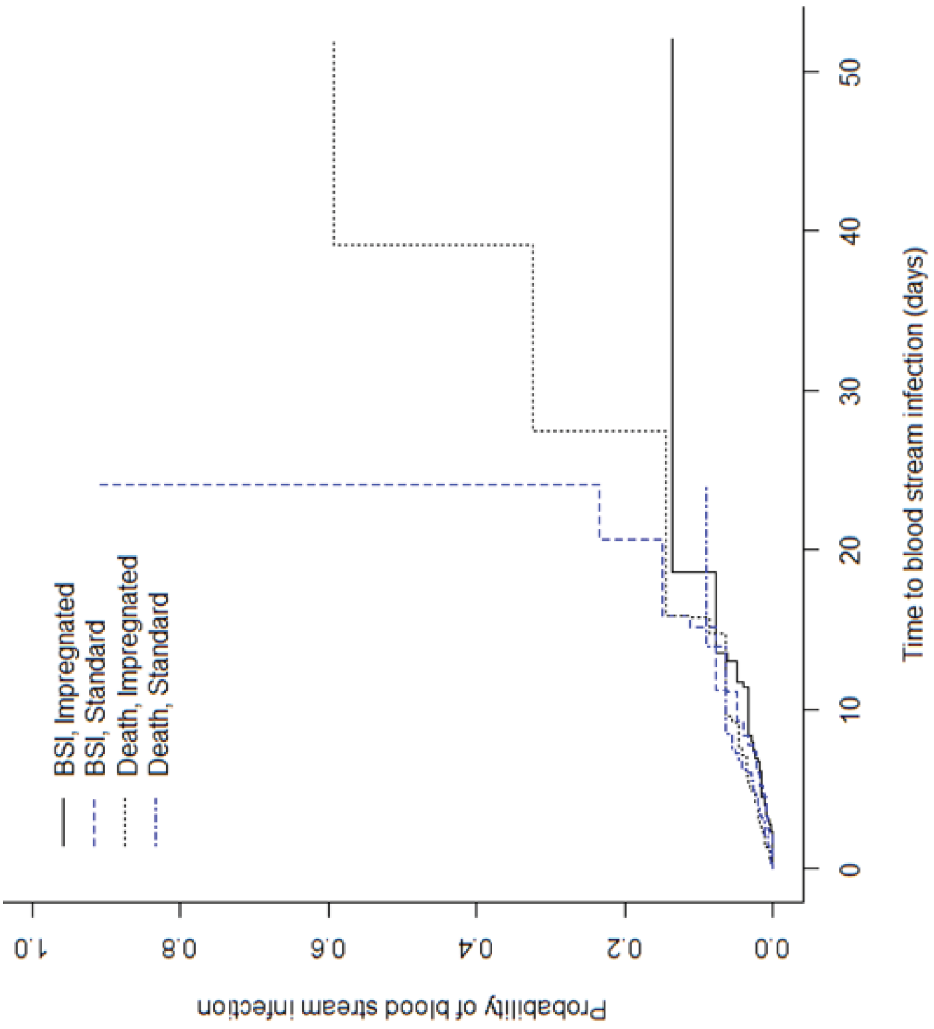
Figure 11: Time to first blood stream infection – cumulative incidence plot



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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)

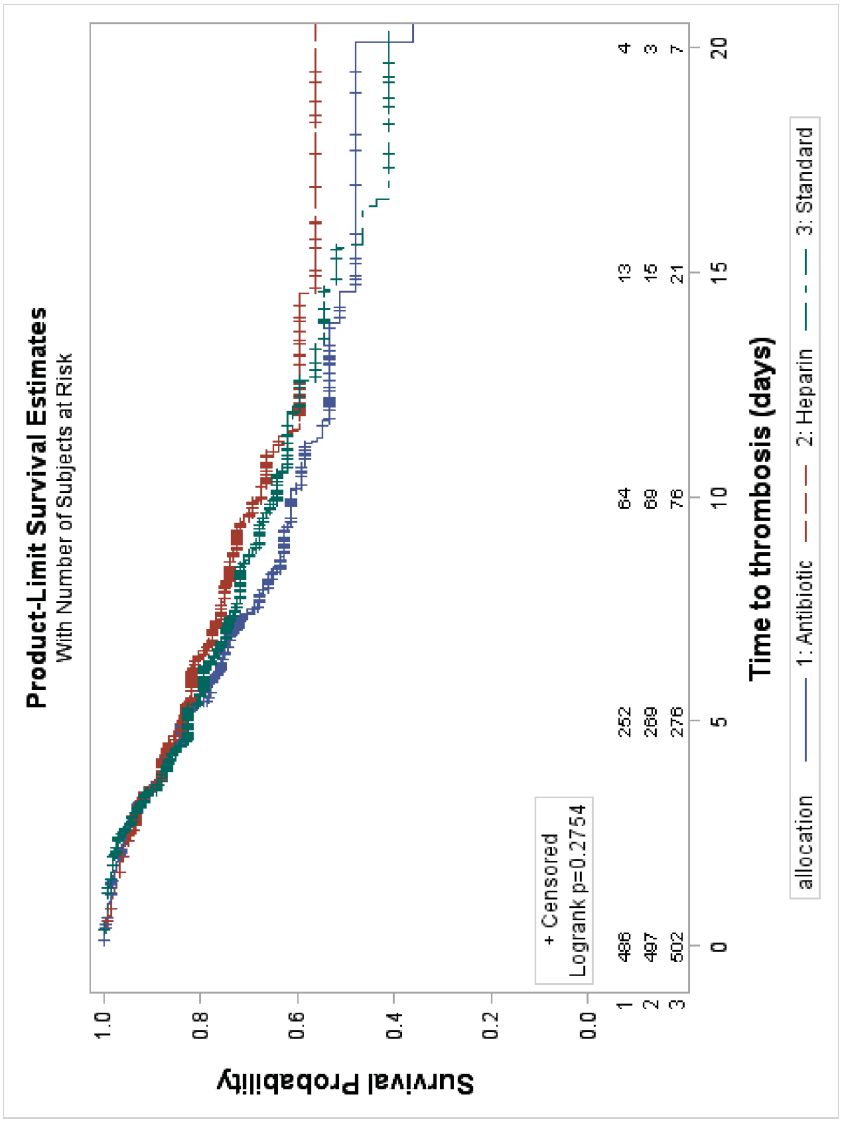

Figure 12: Time to thrombosis

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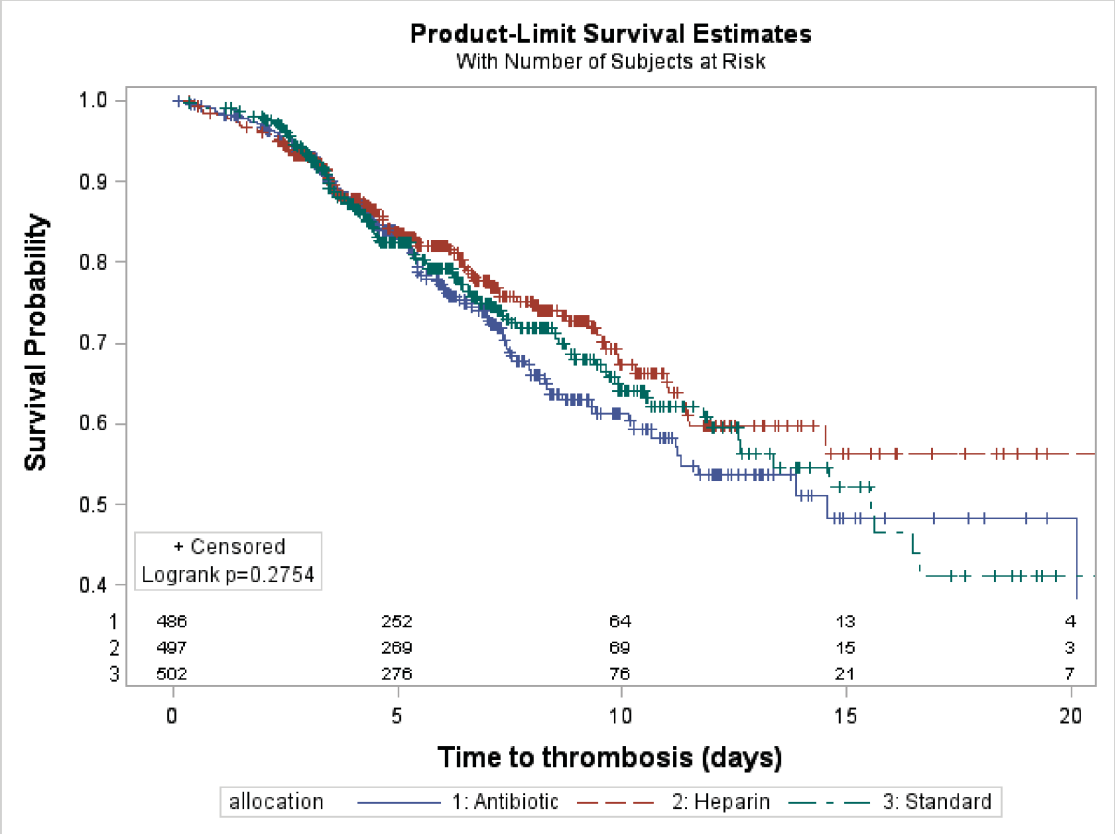
Figure 13: Time to thrombosis (y axis cut)



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

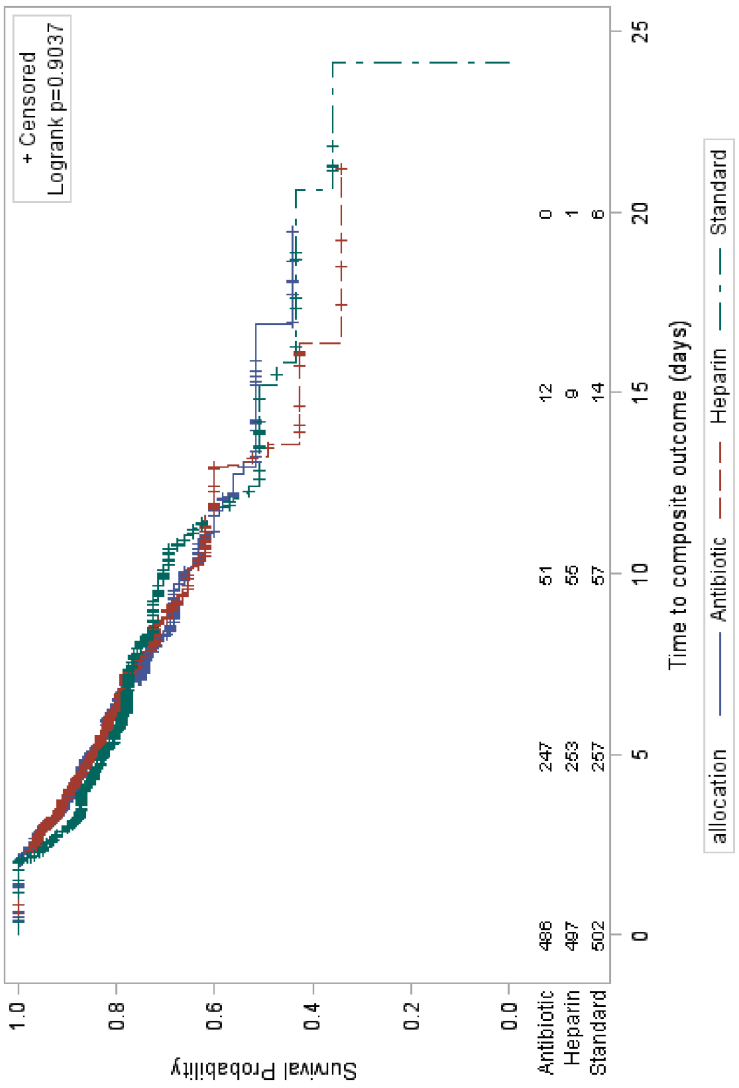


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Table 35: Composite measure of clinically indicated blood stream infection

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)

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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

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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

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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)

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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

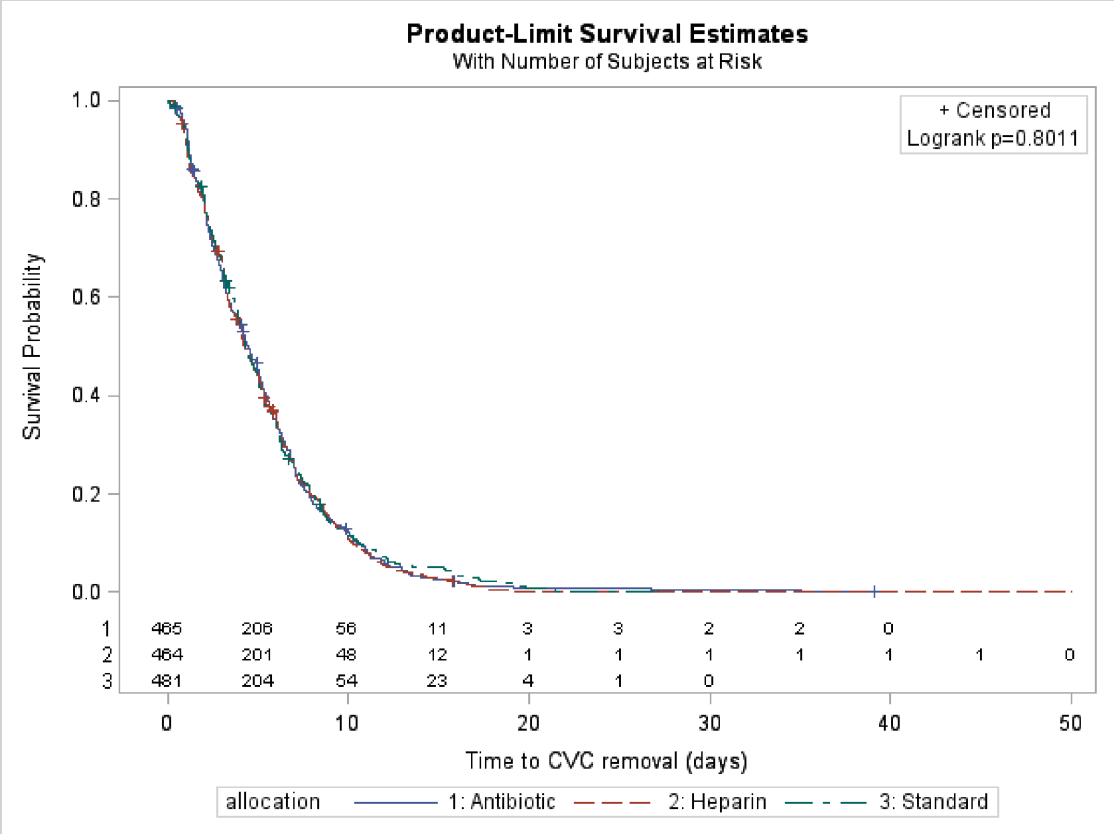
Analysis	Treatment	Number randomised	Number of participants with a successful CVC insertion	Hazard ratio (95% confidence interval)	p-value
Baseline comparator: standard					
-	Standard	502	481	-	-
Primary	Antibiotic or Heparin	983	929	1.04 (0.93, 1.16)	0.53
Secondary	Antibiotic	486	465	1.02 (0.90, 1.17)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



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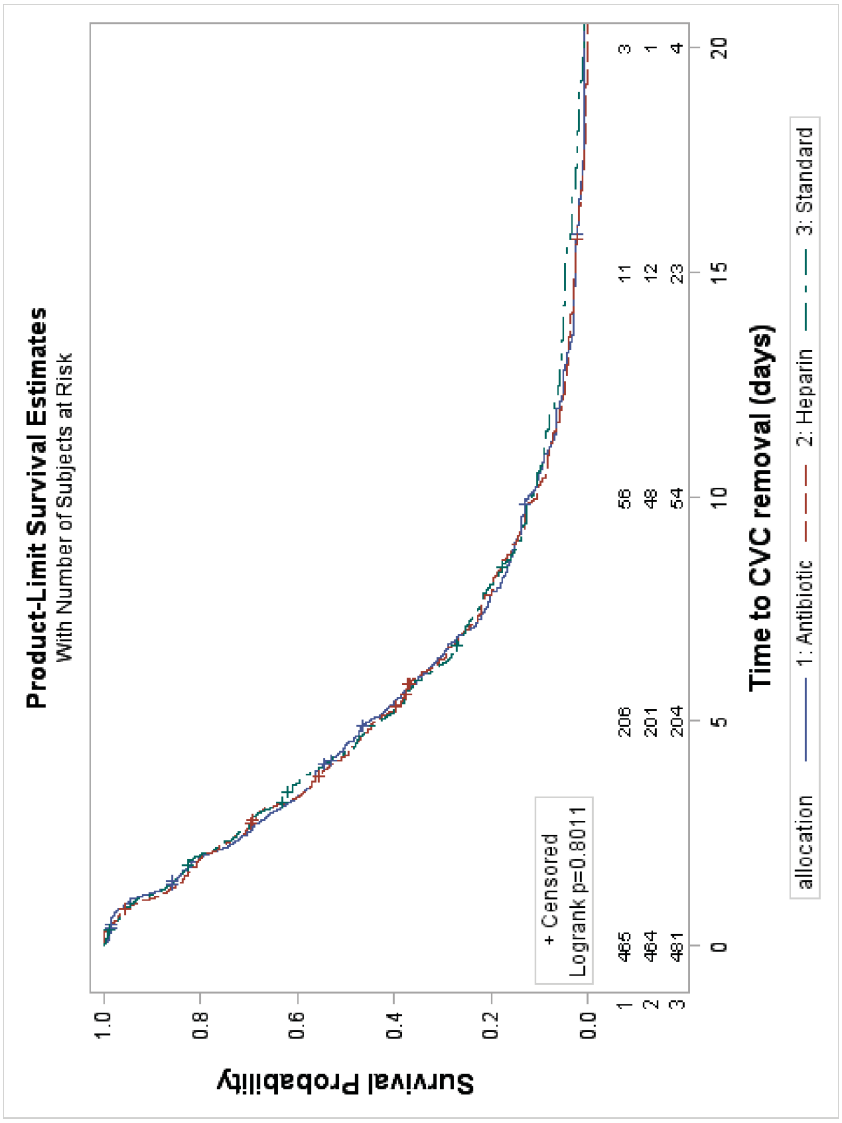

Figure 16: Time to CVC removal (x axis cut)

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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.

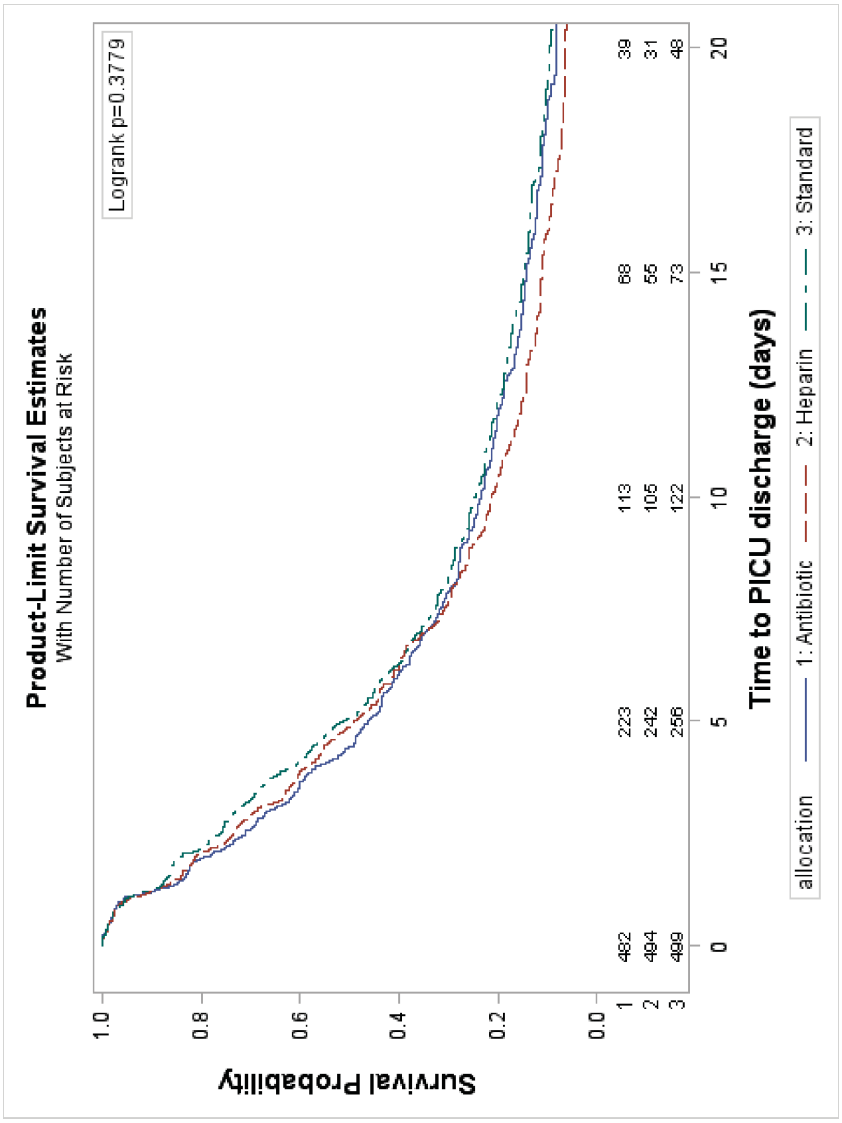

Figure 17: Time to PICU discharge (post hoc analysis)

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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

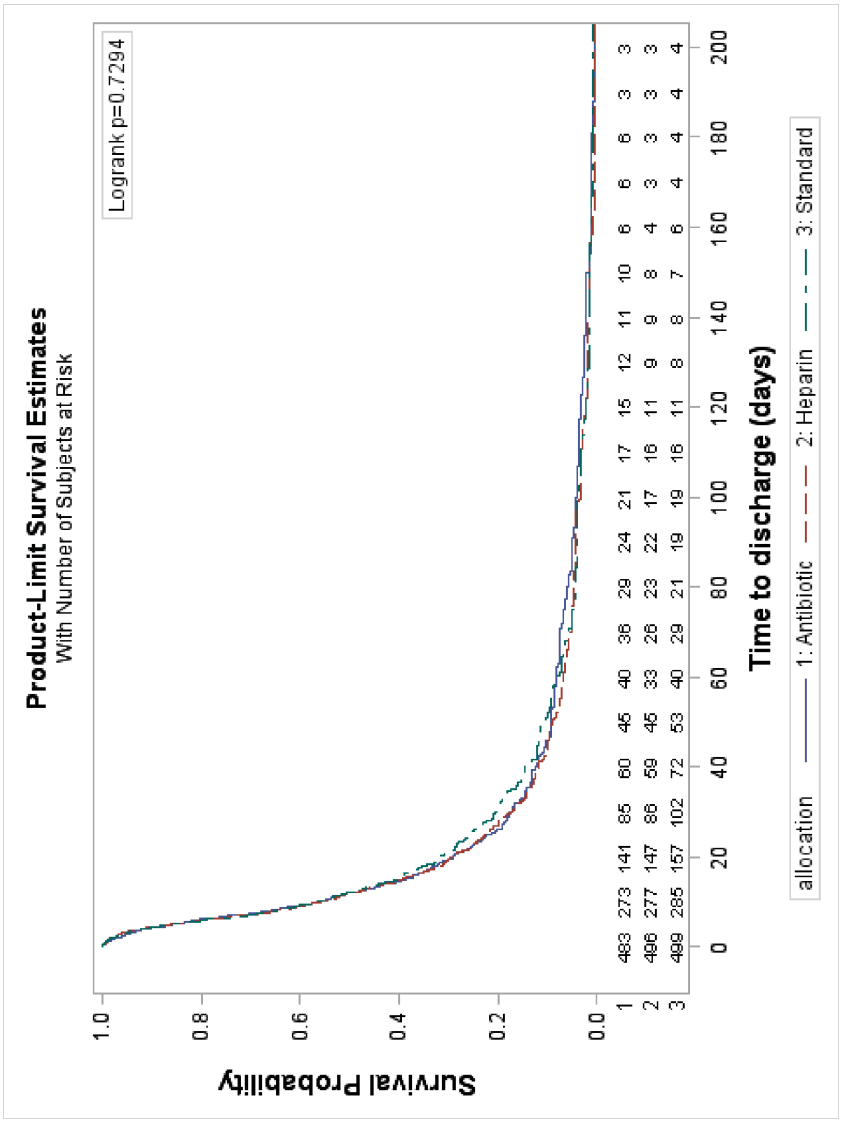

Figure 18: Time to discharge (post hoc analysis)

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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	-	-	-

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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 ☐

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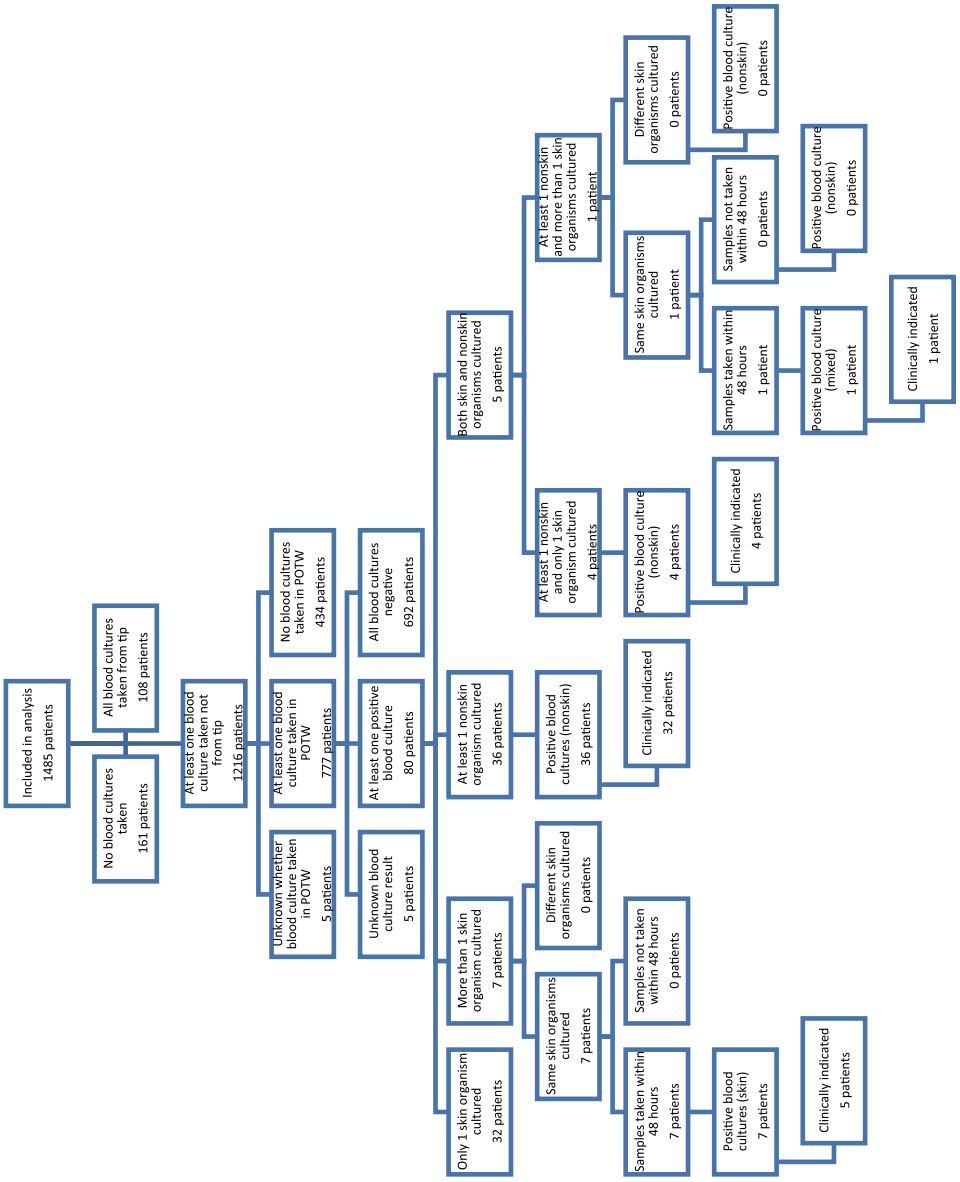

Figure 19: Flow of patients for the primary outcome

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