**The CATCH trial**

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

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**CONTENTS**

LIST OF FIGURES 5

LIST OF ABBREVIATIONS 7

ABSTRACT 8

SCIENTIFIC SUMMARY 11

Background 11

Objectives 11

1) RANDOMISED CONTROLLED TRIAL: CLINICAL EFFECTIVENESS 12

Methods 12

Results 14

2) COST-EFFECTIVENESS 16

Methods 16

Results 17

3) GENERALISABILITY AND COST-IMPACT 18

Methods 18

Results 18

Conclusions 19

PLAIN ENGLISH SUMMARY 20

CHAPTER 1 INTRODUCTION 21

Use in practice 21

Rationale 21

Risks and benefits 23

Overview of aims and research questions 24

CHAPTER 2 CLINICAL EFFECTIVENESS: METHODS 26

Trial design 26

Setting and participants 26

Interventions 26

Randomisation and consent 26

Blinding 27

Comparisons and outcomes 27

Sample size 29

Statistical methods 29

Study oversight and role of funders 30

CHAPTER 3 CLINICAL EFFECTIVENESS: RESULTS 31

Study population 31

Comparison of interventions 31

CHAPTER 4 COST-EFFECTIVENESS ANALYSIS 46

Introduction 46

Methods 48

Results 52

CHAPTER 5 GENERALISABILITY STUDY 67

Introduction 67

Methods 68

Results 71

CHAPTER 6 DISCUSSION 78

Introduction 78

Clinical effectiveness 78

Cost-effectiveness 80

Generalisability and cost-impact 82

Other conclusions 83

Implications for practice 86

Recommendations for future research 86

REFERENCES 88

# LIST OF FIGURES

Figure 1: CONSORT flow diagram for all trial participants 24

Figure 2 Number of children included in the primary outcome, the rate of BSI and catheter related BSI according to time since randomisation 25

Figure 3: Kaplan-Meier curve for time to first BSI by CVC allocation 26

Figure 4: Flow diagram of the methods employed for the economic evaluation. 56

Figure 5: Ranking of total, 6-month costs by intervention group, indicating patients who experienced a bloodstream infection. 57

Figure 6: Cost-effectiveness acceptability curve based on a 6 month time horizon presenting the probability of antibiotic and standard CVCs being cost-effective for given values of ceiling ratio expressed as cost per bloodstream infection (BSI) averted 58

Figure 7: Relation between total costs (cumulative) and time since randomisation, according to intervention group 58

Figure 8: Relation between the ICER for antibiotic CVC versus standard CVC, and time since randomisation. Positive ICERs are cost-incurring, negative values represent incremental savings per BSI averted 59

Figure 9: Risk-adjusted rates in bloodstream infection for children expected to have central venous catheters based on linked PICANet-Labbase2 data for 16 PICUs in England; symbols=observed rates; lines=smoothed adjusted rates (log-scale) 68

Figure 10: Probability distribution for the value of resources made available by averting BSI using antibiotic CVC in all PICUs in England during 2012, 90% of the distribution represented costs greater than the additional cost of purchasing antibiotic CVCs 69

Figure 11: Cost-impact: Number of BSI averted and value of resources made available using antibiotic in place of standard CVCs for a range of baseline rates, assuming each BSI is associated with a mean cost of £10,975 70

LIST OF TABLES

Table 1: Baseline characteristics and clinical condition before randomisation (n=number of participants by randomised CVC) 28

Table 2: Details of the intervention and characteristics at 48 hours post randomisation (n=number of participants with CVC inserted) 29

Table 3: Samples taken in primary outcome time window (n=number of participants by randomised CVC) 30

Table 4: Primary outcome (absolute measures) and type of organism isolated, according to CVC allocation (values are n by randomised CVC (%) unless otherwise stated)) 31

Table 5: Risk difference for first BSI and hazard ratio for time to first BSI according to CVC allocation (hazard ratios p<0.05 are in bold) 31

Table 6: Regression results for primary outcome 32

Table 7: Competing risk analysis for primary outcome of time to first BSI 32

Table 8: Secondary outcomes (absolute measures) by CVC allocation (n is number of participants by randomised CVC who experienced the outcome) 33

Table 9: Risk difference and/or hazard ratios for secondary outcomes according to CVC allocation (hazard ratios p<0.05 are in bold) 34

Table 10: Safety analyses of CVC-related adverse events and mortality (n is number by type of received or if not inserted, type attempted to be inserted) 35

Table 11: PCR results for bacteria in blood samples taken during the primary outcome time window by CVC type (N is number by randomised CVC) 36

Table 12: Unit cost for intensive care and high dependency care, based on HRGs from the National Schedule tariff (2012-13) 47

Table 13: Hospital ward bed-day rates as provided by hospital finance departments and adjusted for inflation (£ sterling, 2013) 48

Table 14: Patients' lengths 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 by intervention group 49

Table 15: Disaggregated and total costs (£) by intervention group from randomisation to end of the six-month timeframe 50

Table 16: Adjusted, total (6-month) costs: results of Ordinary Least Squares regression of total costs based on significant baseline variables 52

Table 17: Value of healthcare resource associated with managing a BSI: results of Ordinary Least Squares regression for estimating the cost of BSI, with total costs as the dependent variable and univariately significant baseline explanatory variables 53

Table 18: Incremental Analysis of unadjusted costs (6 month timeframe and index hospitalisation) 54

Table 19: Patients' length of stay for hospitalisation episode from randomisation by intervention group 54

Table 20: Parameter estimates for cost-impact analysis and sensitivity analysis 66

Table 21: Cost impacted analysis of managing BSIs occurring with standard versus antibiotic CVCs with best and worst case scenarios\* and hypothetical scenarios for a typical PICU with 350 admissions per year 67

# LIST OF ABBREVIATIONS

|  |  |  |  |
| --- | --- | --- | --- |
| AE | Adverse Event | IDSMC | Independent Data and Safety and Monitoring Committee |
|  |  |  |  |
| AI | Adverse Incident | Ln | Natural logarithm |
|  |  |  |  |
| AIC | Adverse Incident Centre | MHRA | Medicines and Healthcare products Regulatory Agency |
|  |  |  |  |
| BSI | Blood Stream Infection | MRSA | Methicillin-resistant Staphylococcus aureus |
|  |  |  |  |
| Bundled HRG | HRG referring to patient pathway of care such as ward stay | NHS | National Health Service |
|  |  |  |  |
| CATS | Children’s Acute Transport Service | NRES | National Research Ethics Service |
|  |  |  |  |
| CEAC | Cost Effectiveness Acceptability Curve | ONS | Office for National Statistics |
|  |  |  |  |
| CFU | Colony Forming Units | PAS | Patient Admission System |
|  |  |  |  |
| CI | Chief Investigator | PCR | Polymerase Chain Reaction |
|  |  |  |  |
| CPA | Clinical Pathology Accreditations | PI | Principal Investigator |
|  |  |  |  |
| CRF | Case Report Form | PICANet | Paediatric Intensive Care Audit Network |
|  |  |  |  |
| CTRC | Clinical Trials Research Centre | PICU | Paediatric Intensive Care Unit |
|  |  |  |  |
| CTU | Clinical Trials Unit | QALY | Quality Adjusted Life Year |
|  |  |  |  |
| CVC | Central Venous Catheter | RCT | Randomised Controlled Trial |
|  |  |  |  |
| GP | General Practitioner | REC | Research Ethics Committee |
|  |  |  |  |
| HDU | High Dependency Unit | RN | Research Nurse |
|  |  |  |  |
| HES | Hospital Episodes Statistics | RR | Relative Risk |
|  |  |  |  |
| HRGs | Healthcare Resource Groups | SAE | Serious Adverse Event |
|  |  |  |  |
| HSCIC | Health and Social Care Information Centre | SOP | Standard Operating Procedure |
|  |  |  |  |
| HTA | Health Technology Assessment | TMG | Trial Management Group |
|  |  |  |  |
| MCRNCTU | Medicines for Children Research Network Clinical Trials Unit | TSC | Trial Steering Committee |
|  |  |  |  |
| ICER | Incremental Cost Effectiveness Ratio | unbundled HRGs | High cost or specialist service HRG in addition to patient pathway of care |
|  |  |  |  |
| ICU | Intensive Care Unit |  |  |

# ABSTRACT

### Background:

Impregnated central venous catheters (CVCs) are recommended for adults to reduce bloodstream infection (BSI) but not for children due to a lack of evidence for their effectiveness.

### Objective:

To determine the effectiveness of impregnated versus standard CVCs for reducing BSI in children admitted to intensive care.

### Design:

1. Multicentre randomised controlled trial
2. Cost-effectiveness analysis from an NHS perspective
3. Generalisability analysis and cost-impact analysis

### Setting:

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

### Participants:

Children <16 years, weighing >=3kg admitted to PICU and expected to require a CVC for >=3 days.

### Interventions:

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

### Main outcome measure:

Time to first BSI sampled between 48 hours after randomisation and 48 hours after CVC removal.

### Data:

Trial case report forms; hospital administrative data for 6 months pre- and post-randomisation; national linked PICU audit and laboratory data.

### Results:

#### Clinical effectiveness:

BSI occurred in 3.59% (18/502) children randomised to standard, 1.44% (7/486) to antibiotic and 3.42% (17/497) to heparin CVCs. Primary analyses comparing impregnated (antibiotic and heparin CVCs) with standard CVCs showed no effect (hazard ratio 0.71; 95% CI 0.37, 1.34). Secondary analyses showed antibiotic CVCs were superior to standard (HR 0.43; 0.20, 0.96) but heparin CVCs were not (HR 1.04; 0.53-2.03). Time to thrombosis, mortality by 30 days, and minocycline or rifampicin resistance did not differ by CVC.

#### **Cost-effectiveness:**

Heparin CVCs were not clinically effective and therefore not cost-effective. The incremental cost of antibiotic CVCs over a 6-month time horizon was £1,160 (-£4,743, £6,962) compared with standard CVCs, 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 healthcare resources associated with each BSI was £10,975 (£-2,801, £24,751).

#### **Generalisability and cost-impact:**

The baseline risk of BSI in 2012 for PICUs in England was 4.58 (95% CI 4.42, 4.74) per 1000 bed-days. An estimated 232 BSI 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 BSI in PICUs with standard BSI rates >1.2 per 1000 CVC-days.

### Conclusions:

The primary outcome, time to BSI, 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 as to whether they represent value for money to the NHS.

### Future work:

Implementation strategies to promote adoption of impregnated CVCs in PICU should be developed and could be monitored through linkage of electronic-healthcare data and clinical data on CVC use.

### Study registration:

ClinicalTrials.gov:NCT01029717

### Funding:

National Institute for Health Research Health Technology Assessment (NIHR HTA) programme (project number 08/13/47).

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randomised controlled trial, bloodstream, infection, central venous catheter, paediatric intensive care, antibiotic, heparin, impregnated, CVC

# SCIENTIFIC SUMMARY

## Background

Bloodstream infection (BSI) is an important cause of adverse clinical outcome and cost to the National Health Service (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) demonstrate substantial benefits of impregnated 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, with similar reductions in risk of CR-BSI (70-80%).1 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 an NHS perspective
3. To inform purchasing by assessing the generalisability and the cost-impact of adopting impregnated CVCs for all children who need them

## 1) 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.

#### Design, study population and intervention

Children admitted to 14 PICUs in England between December 2010 and November 2012 were randomised to heparin-bonded, antibiotic or standard CVCs manufactured by Cook Medical Incorporated (IN 47404 USA).

Children <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 or more days. For children admitted to PICU following elective surgery, we sought prospective parental consent during pre-operative 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 bedside or in theatre immediately prior to 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.

CVC allocation was not blinded to the clinician responsible for inserting the CVC (due to different colour strips for impregnated CVCs) but since 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 for the trial compared antibiotic or heparin CVCs with standard CVCs. Secondary analyses comprised three-way comparisons of 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 due to 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:

(1) CR-BSI: the same organisms cultured from blood and 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 infection.

(2) Rate of BSI per 1000 CVC-days: number of BSI between randomisation and CVC removal.

(3) Time to a composite measure of BSI comprising the primary outcome or a negative blood culture combined with a positive 16S PCR result for bacterial DNA, 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

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 D. 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.

## Results

#### Study population

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

#### Baseline characteristics

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

#### Endpoints

*Primary outcome*

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

*Secondary outcomes*

For CR-BSI, there was no significant difference between any impregnated and standard CVCs (p=0.13), but risk of CR-BSI was significantly lower for antibiotic versus standard CVC (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 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 12/42 children with the primary outcome BSI 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).

## 2) COST-EFFECTIVENESS

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

1. Trial case report forms (CRFs) recording admission and transfer/discharge dates for PICUs, high dependency units (HDUs) and paediatric wards within participating hospitals.
2. Hospital Episode Statistics (HES)containing health resource groups (HRGs) for admissions to NHS hospitals in England.
3. PICANet, containing length of stay and HRGs for HDU and PICU admissions.
4. Hospital Patient Administration Systems (PAS) of participating hospitals, capturing length of stay and HRGs in PICUs and wards.

The primary cost analysis was based on CRF and PAS, 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: i) ranking type of CVC according to decreasing effectiveness; ii) eliminating ineffective or dominated interventions (those which are less effective, but more costly than others). The incremental cost-effectiveness ratio (ICER) for remaining CVCs was calculated as the difference in adjusted total costs divided by the difference in BSI.

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

#### Value of healthcare resources associated with BSI

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

All analyses were performed using STATA Version 10.

## Results

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

Mean 6-month unadjusted costs per patient were £44,503 (95% CI £40,554, £48,776) for standard CVCs, £45,663 (95% CI £41,600, £49,994) for antibiotic and £42,065 (95% CI £38,220, £46,246) for heparin, and were not significantly different by CVC type (p=0.46). Six-month incremental costs were positive (£1,160; 95% CI -£4,743, £6,962) for antibiotic and negative (-£2,439; 95% CI, -£8,164, £3,359) for heparin compared with standard CVCs.

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

Costs were very sensitive to 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 break-even point for the costs of antibiotic and standard CVCs was 122 days post randomisation.

The value of healthcare resources associated with managing each BSI, estimated from the regression analysis, was £10,975 (95% CI -£-2801, £24,751).

## 3) GENERALISABILITY AND COST-IMPACT

The generalisability and cost-impact analysis aimed to inform 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 CVCs in PICU were estimated from a data linkage study using detailed information from PICANet and national laboratory surveillance data coordinated by Public Health England. Rates of BSI per 1000 bed-days were modelled using multi-level Poisson regression, adjusting for significant patient risk-factors (p<0.05).

#### Cost-impact analysis

The baseline risk was defined as the number of BSI 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 BSI 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: i) the estimated risk of BSI using standard CVCs (derived from the data linkage study); ii) the number of BSI potentially averted by using antibiotic-impregnated CVCs (based on the relative treatment effect in the trial); iii) 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 iv) the value of the healthcare resources associated with each averted BSI (from the trial economic analysis).

## Results

The additional costs 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, management of BSI in PICUs costs £2.5 million annually (95% uncertainty interval: -£66,544 to £5,557,451). The BSI rate using standard CVCs was 4.58 (95% CI 4.42, 4.74) per 1000 estimated CVC-days in 2012. Applying the rate-ratio gave an estimated 232 BSI averted using antibiotic CVCs. The additional costs of antibiotic CVCs would be less than the value of resources associated with managing BSI in PICUs with standard BSI rates >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 as to whether they are cost-effective for the NHS.

#### Recommendations for research

* Implementation strategies to promote adoption of antibiotic-impregnated CVCs should be developed and could be monitored through continued linkage of infection surveillance and electronic healthcare data. Such monitoring could allow feedback to PICUs and could be enhanced by routine capture of CVC insertion and removal dates.
* 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 of interventions where the event rate is likely to change substantially over the lifetime of the trial, and to monitor implementation of effective interventions.

# 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 these impregnated CVCs work the same way in the much narrower CVCs used for children. The only way to find out which type of CVC (standard non-coated, antibiotic, or heparin) 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.

BSI 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 healthcare costs for the 6-months after trial participation. Although doubt remains as to whether antibiotic CVCs would results 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.

# 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 due to organisms tracking along the CVC from the skin or from the external parts of the CVC to colonise the CVC tubing and tip.2-6

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.7-11 Risk of BSI is reduced by strict adherence to aseptic procedures during CVC insertion and whenever the CVC is breached.12-14 To help ensure staff follow aseptic procedures, audited check lists (called CVC bundles) have been introduced in several countries.15-20

In this report, we focus on children who need a CVC as part of their intensive care treatment. PICUs have one of the highest reported rates of hospital-acquired BSI of any clinical specialty,21-24 and BSI is an important cause of adverse clinical outcome and healthcare costs in critically ill children.22, 25-27 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.28 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

CVC impregnation with anti-infective substances has been used for over 25 years.1 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). 1, 3, 6, 29, 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.1 Heparin-bonded or antibiotic-impregnated CVCs were found to be the most effective options, being associated with similar reductions (70% to 80%) in the risk of CVC related BSI. Heparin-bonding acts by reducing thrombus formation and bacterial adherence to thrombus, 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 randomised controlled trials 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.4, 16, 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 i) gaps in the evidence relating to children; ii) concerns about the quality of previous trials; and iii) 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, heparin-bonded and antibiotic-impregnated CVCs are the most effective options, with similar effects compared with standard CVCs.1 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.1 In the UK, the additional costs of heparin-bonded or antibiotic-impregnated CVCs are similar, 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 with standard CVCs (n=2073 patients) included children and was terminated early due to 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 versus standard CVCs may differ in children and adults. Evidence is stronger for benefits of heparin-bonded CVCs, as two of the three RCTs comparing heparin-bonded with standard CVCs (n= 472) included children.43-45

Several systematic reviews raise concerns that the poor quality of previous studies means that the benefits of impregnated CVCs may have been overestimated.6, 29, 46, 47 Firstly, few trials reported good concealment of treatment allocation or blinding of clinicians to the intervention and many failed to account for losses or withdrawals, all factors that could lead to overestimation of the effect.6, 29 Secondly, all previous trials relied on catheter-related BSI (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 BSI after CVC insertion, not just on CR-BSI, 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 BSI in PICU, in the context of ongoing reductions in BSI rates associated with the introduction of CVC care bundles.12, 14, 15, 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 the relatively large reductions in relative risk 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 a question as to whether 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.21, 22, 25-27, 49 For children in intensive care, catheter-associated BSI have been associated with an additional 9-21 days stay in hospital (6.5-15 days in PICU).25-27 In adults, the additional acute healthcare costs attributable to a BSI are an estimated £9148 per patient, and could range between £2500 and £71,000.29 The few studies of cost of BSI in PICU patients have found a difference of $33,039 to $39,219 in PICU direct costs for infected and uninfected patients.22, 26 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 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 a 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.2

## Overview of aims and research questions

From a policy perspective, there could potentially be significant gains for children’s health and healthcare 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 randomised controlled trial to determine 1) clinical effectiveness; 2) cost-effectiveness of impregnated versus 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 versus standard CVCs for reducing BSI in children admitted to intensive care
* To determine which type of CVC is most effective, based on 3-way comparisons of measures of BSI, mortality, and adverse events

Data source: Clinical outcomes captured on case report forms in the RCT.

#### 2) Cost-effectiveness:

* To determine the cost-effectiveness of impregnated versus standard CVCs for reducing BSI, based on incremental acute healthcare costs per BSI avoided

Data source: Clinical outcomes captured on case report forms in the RCT and records of healthcare 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 source: National data on PICU admissions (PICANet) linked with infection surveillance data collated by Public Health England and costs from the economic evaluation.

The specific objectives, methods and results for each of the three phases of the study are reported in separate sections. We discuss the implications of our findings for policy and recommendations for future research in the final chapter.

# CHAPTER 2 CLINICAL EFFECTIVENESS: METHODS

## Trial design

We conducted a parallel, three-arm RCT. 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 <16 years were eligible if they were admitted to a participating PICU or being prepared for PICU admission by an emergency retrieval team and were expected to require a CVC for 3 or more days. Children who had already participated in the trial were ineligible.

## Interventions

We used polyurethane CVCs manufactured by Cook Medical Incorporated (IN 47404 USA). Sizes used were French gauge 4 (double lumen), 5 or 7 (triple lumen). Both types of impregnation involve internal and external surfaces. Cook reports a concentration of 503 µg/cm minocycline and 480 µg/cm rifampicin for their antibiotic-impregnated CVC, which reduces biofilm formation.53 Heparin-bonding reduces thrombus and thereby biofilm formation and uses benzalkonium chloride as an anti-infective bonding agent.6, 54

## Randomisation and consent

For children admitted to PICU following elective surgery, we sought prospective parental consent during pre-operative 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, and 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 PICU or at another hospital where they were randomised by the PICU retrieval team prior to transfer to PICU. Further details are given in the protocol (http://www.nets.nihr.ac.uk/projects/hta/081347).

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 PICU).

Parents consented to the use of their child’s data for the trial, to follow-up using routinely recorded clinical data, and to 0.5ml of blood being collected whenever a blood culture was clinically required.55 The sample was sent for PCR testing for 16S rRNA of bacterial ribosome protein to detect bacterial infection.

We also sought consent to link data from the national Paediatric Intensive Care Audit Network (PICANet)56 to the child’s study data to categorise the primary reason for admission and the Paediatric Index of Mortality score on admission (PIM2) and to link to administrative hospital data for the economic analyses and death registration data to determine mortality after discharge from PICU.57

## Blinding

CVC allocation was not blinded to the clinician responsible for inserting the CVC (due to different colour strips for antibiotic and heparin CVCs) but since 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). This time interval was intended to capture BSI related to the type of CVC. All blood culture samples were clinically indicated, defined by removal of the CVC due to 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.

Secondary BSI outcomes were:

* CR-BSI: based on same organisms cultured from blood and 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 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: comprising the primary outcome or a negative blood culture, combined with: i) a positive 16S PCR result for bacterial DNA; ii) removal of the CVC because of suspected infection; or iii) 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 five days of each other of difficulty flushing the CVC or drawing back blood from the CVC, one episode of swollen limb, CVC removal due to 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 BSI included in the primary outcome

CVC-related outcomes evaluated in the safety analyses were:

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

Antibiotic resistance outcomes were based on etest strips applied to organisms isolated from BSI included in the primary outcome (www.biomerieux-diagnostics.com/etest). 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 relative risk (RR). We assumed detection of a RR of 0.5 in patients with a baseline risk of 10% would change policy. We assumed the RR would remain relatively constant across baseline risks while the absolute risk difference would be more variable. 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 Monitoring Committee recommended continuation of the study after: reviewing the first 209 children; an interim analysis of 650 children using the Peto-Haybittle stopping rule for the primary outcome; recruitment had reached the original target of 1200 pre-schedule in June 2012, before exhausting available funding (see Trial Oversight Committee and Table 22 at end of report).

## 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 type of CVC randomised, regardless of whether 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 4. A 5% level of statistical significance and 95% confidence intervals 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 BSI (defined as the total number of BSI per 1000 CVC-days occurring between randomisation and CVC removal). All analyses were conducted using SAS software.58

Post hoc analyses evaluated competing risks from death or time to first bloodstream infection, using cumulative incidence curves. We applied Gray’s test to detect whether there was a difference between impregnated and standard CVCs for the primary outcome.59 This analysis was conducted using R statistical software.60

## 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 of Health Research) had any role in the design of the study, collection or interpretation of data or reporting of results. The CATCH trial is registered with ClinicalTrials.gov (Identifier**:** NCT01029717). The protocol is available at http://www.nets.nihr.ac.uk/projects/hta/081347 and the statistical analysis plan is provided in Appendix 4. .

CHAPTER 3 CLINICAL EFFECTIVENESS: RESULTS

## Study population

1859 children were randomised, of whom 501 children were randomised prospectively. 1358 were randomised as an emergency and 984 of these subsequently provided deferred consent for inclusion in analyses (Figure 1; see Appendix 1.1 and 1.2 for numbers by emergency/elective randomisation). Reasons for non-consent in the deferred consent group included: not approached (n=180; 48%, mainly due to transfer to a non-participating unit or early discharge from PICU), no response (n=17; 4.5%), or consent refused (n=177; 47%). Detailed reasons for non-consent are reported elsewhere.61Numbers enrolled by site and by month are provided in Appendix 1.3 and 1.4.

## Comparison of interventions

The intention to treat sample comprised 1485 children; 1345 children received the allocated CVC. Threats to validity due to protocol deviations are provided in Appendix 1.5. Very few children had a clinical indication but no blood culture taken in the primary outcome time window (Figure 1). Timings of samples for positive BSI included in the primary and secondary outcomes are provided in Figure 2.

#### Baseline characteristics

Table 1 shows that baseline characteristics were similar according to randomised CVC. Over half (58%) of children were aged under 12 months at admission, with one-third aged less than 3 months. One third of children had surgery prior to admission to PICU and half of all children randomised had cardiovascular problems as their primary diagnosis at admission.

#### During follow up

Table 2 provides details of the CVC insertion and characteristics at 48 hours post randomisation. CVC insertion took place in the operating room for 437/493 (89%) in the prospective consent (elective) group, but in only 34/917 (4%) of the deferred consent (emergency) group.

Table 3 shows the number of arterial, peripheral and CVC samples taken by trial arm. Overall, 3583 blood samples were taken, and 1216/1485 (81.9%) of children had a sample taken. Sampling was similar by trial arm and site (see Appendix 1.6).

#### Primary outcome

The number of blood samples contributing to the primary outcome is shown in Appendix 1.7. Blood cultures were taken between 48 hours of randomisation and CVC removal for 40% of those randomised (593/1485; Figure 1). BSI was recorded for 42 children: standard 18/502 (3.59%); antibiotic 7/486 (1.44%); heparin 17/497 (3.42%). Gram-positive organisms accounted for the majority of BSI (Table 4).

Figure 3 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 (antibiotic and heparin) with standard CVCs (Table 5). However, risk of BSI was significantly lower for antibiotic versus standard CVCs (hazard ratio 0.43; 95% CI 0.20, 0.96) and for antibiotic versus heparin CVCs (HR 0.42; 95% CI 0.19, 0.93). The direction of these results was robust to the sensitivity analysis (see Appendix 1.8). Regression analysis showed no significant effect of pre-specified variables (type of consent and suspected infection at randomisation) and the effect of type of CVC was similar after adjusting for these variables (Table 6).

Competing risk analyses using Gray’s test indicated no difference between the treatments for either competing risks (p-values of p=0.29 for bloodstream infection and p=0.89 for death, Table 7).

#### Secondary outcomes

No children had more than one BSI whilst the trial CVC was in situ. The relationship between BSI outcomes by time since randomisation is shown in Figure 2.

Overall, 25 (1.7%) children experienced CR-BSI. There was no significant difference between any impregnated and standard CVCs (p=0.13, Table 8), but risk of CR-BSI was significantly lower for antibiotic versus standard CVC (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 (Table 8). However, the rate of BSI was significantly lower for antibiotic compared with standard (p=0.04) and heparin CVCs (p=0.03; Table 9). There was no significant difference in rate of BSI between heparin and standard CVCs (p=0.85).

A change in antibiotics on the same day or the next day as a negative blood culture made the largest contribution to the composite measure of BSI (see Appendix 1.9). Overall, 317 (21%) children experienced the composite measure of BSI, and this outcome did not differ by CVC type (Table 9).

There was no difference in any other secondary outcomes by CVC allocation (Table 9). The types of bacteria and fungi isolated from positive blood cultures are provided in Appendix 1.10.

#### Safety analyses

The cohort for safety analyses comprised more children in the standard group (n=533) than the antibiotic (n=451) or heparin groups (n=479). As standard CVCs were the default option in the majority of PICUs, more children received the allocated CVC in the standard arm (93%) compared with 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 were reported for 31 children (21 mild, 8 moderate and 2 severe (i.e. unable to perform routine activity; see Table 10). 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 PICU after-randomisation (Table 10). The majority of deaths were due to reasons related to co-morbidities at admission (see Appendix 1.11).

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; 8/12 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 Appendix 1.12.

#### Post-hoc analyses

A total of 1573 valid PCR samples were taken from 715 (48%) of children. Of these children, 11 (1.5%) had positive PCR results (12 samples). Positive PCR results were observed for 2 (8%) children with the primary outcome compared with 9 (1.3%) children without the primary outcome (Table 10). Values of the positive PCR results are provided in Appendix 1.13.

Figure 1: CONSORT flow diagram for all trial participants

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  | **Randomised** 1859 | | |  | | |  | | |  |  | | |  |  | |  |
|  |  |  |  |  | |  | | |  | | |  |  | | |  |  | |  |
| **Randomised and consent obtained:** | | 1485 |  |  | | **Randomised and deferred consent not obtained:** | | | | | | | | | | |  | | **374** |
|  | Prospective consent | 501 |  |  | |  | | | Not approached | | | | | | |  |  | | 180 |
|  | Deferred consent | 984 |  |  | |  | | | No response | | | | |  | |  |  | | 17 |
|  |  |  |  |  | |  | | | Consent refused | | | | | | |  |  | | 177 |
|  |  |  |  |  | |  | | |  |  |  | | | | | **Standard** | **Antibiotic** | | **Heparin** |
|  |  |  |  |  | | Trial arm | | | |  |  | | | | | 122 | 126 | | 126 |
|  |  |  |  |  | |  |  | | |  |  | | | | | |  | | |
|  |  |  |  |  | |  |  | | |  |  | | | | | |  | | |
| **Standard** |  |  |  | **Antibiotic** | | |  | | |  | **Heparin** | | | | | |  |  | |
| Allocated (ITT analysis) | | 502 |  | Allocated (ITT analysis) | | | 486 | | |  | Allocated (ITT analysis) | | | | | | 497 |  | |
| Received (per protocol) | | 468 |  | Received (per protocol) | | | 437 | | |  | Received (per protocol) | | | | | | 440 |  | |
|  |  |  |  |  | |  |  | | |  |  | | | | |  |  |  | |
| Received other: | | 13 |  | Received other: | | | 28 | | |  | Received other: | | | | | | 24 |  | |
|  | Antibiotic | 1 |  |  | Standard | | 23 | | |  |  | | | | Standard | | 22 |  | |
|  | Heparin | 12 |  |  | Heparin | | 5 | | |  |  | | | | Antibiotic | | 2 |  | |
|  |  |  |  |  |  | |  | | |  |  | | | |  | |  |  | |
| None received: | | 21 |  | None received: | | | 21 | | |  | None received: | | | | | | 33 |  | |
|  | Insertion attempted | 15 |  |  | Insertion attempted | | 14 | | |  |  | | | | Insertion attempted | | 24 |  | |
|  | Not attempted | 6 |  |  | Not attempted | | 7 | | |  |  | | | | Not attempted | | 9 |  | |
|  |  |  |  |  |  | |  | | |  |  | | | |  | |  |  | |
| Unblinded |  | 1 |  | Unblinded |  | | 1 | | |  | Unblinded | | | |  | | 2 |  | |
| Primary outcome\* | |  |  | Primary outcome\* | | |  | | |  | Primary outcome\* | | | | | |  |  | |
| **Clinical indicators recorded and :-** | | |  | **Clinical indicators recorded and :-** | | | | | |  | **Clinical indicators recorded and :-** | | | | | | |  | |
| ≥ 1 blood culture sample taken: | | 213 |  | ≥ 1 sample taken: | | | | 190 | |  | ≥ 1 sample taken: | | | | | | 190 |  | |
| No blood culture sample taken\*\* | | 8 |  | No blood culture sample taken\*\* | | | | 6 | |  | No blood culture sample taken\*\* | | | | | | 3 |  | |

**\*based on clinically indicated blood culture sample taken >=48 hours after randomisation and <48 hours after CVC removal; \*\* used in sensitivity analysis**

Figure 2 Number of children included in the primary outcome, the rate of BSI and catheter related BSI according to time since randomisation

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Randomisation | 48 hours after randomisation | CVC removal |  | 48 h after CVC removal |
|  | |  |  |  |
|  |  | Primary outcome of BSI | | |
|  |  | n=40 | n=2 | |
| Rate of BSI per 1000 CVC-days | | |  |  |
| n=10 | | n=40 |  |  |
|  |  | Catheter-related BSI (CR-BSI) | | |
|  |  | n=24 | n=1 | |

Figure 3: Kaplan-Meier curve for time to first BSI by CVC allocation

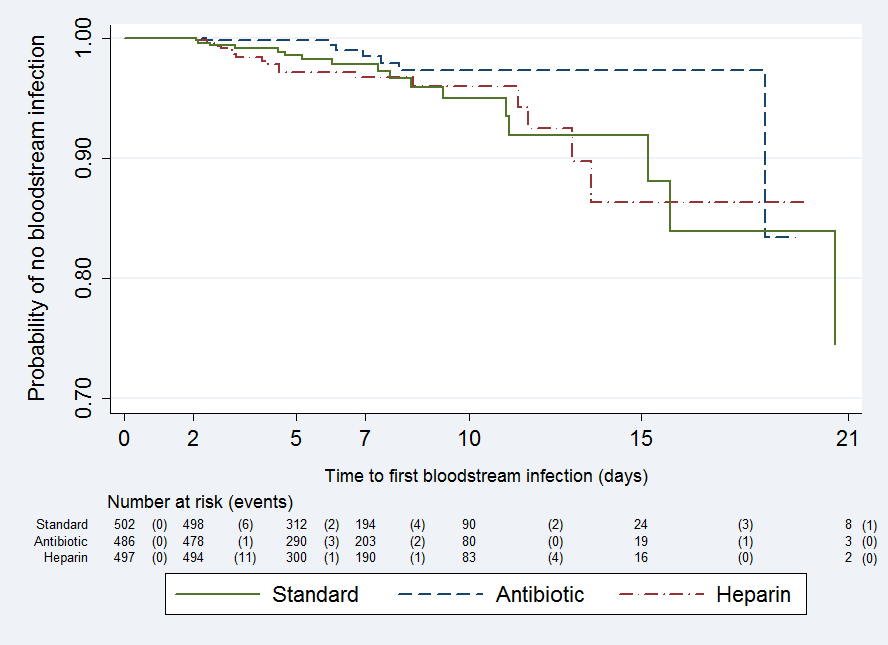


Table 1: Baseline characteristics and clinical condition before randomisation (n=number of participants by randomised CVC)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Standard** | | **Antibiotic** | | **Heparin** | |
|  |  | **n** | **%** | **n** | **%** | **n** | **%** |
| **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 | < 3kg | 41 | 8.2 | 38 | 7.8 | 56 | 11.3 |
| 3-10kg | 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 |
| Paediatric Index of Mortality (PIM2) | <1% | 54 | 11.3 | 48 | 10.5 | 48 | 10.1 |
| 1-5% | 264 | 55.1 | 236 | 51.8 | 247 | 52.2 |
| 5-<15% | 116 | 24.2 | 123 | 27.0 | 119 | 25.2 |
| 15-<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 |
| < 72h before randomised | 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 |
| Immune compromised | 44 | 8.8 | 31 | 6.4 | 29 | 5.8 |

Table 2: Details of the intervention and characteristics at 48 hours post randomisation (n=number of participants with CVC inserted)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Standard** | | **Antibiotic** | | **Heparin** | |
|  |  | **n** | **%** | **n** | **%** | **n** | **%** |
| **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\* | 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 |
| 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 | 5.0 | 18 | 3.9 |
| Missing | 11 | 2.3 | 13 | 2.8 | 16 | 3.5 |
| 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\*\* | 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 | 1.03 | 1 | 0.2 |

\*CVCs were inserted by the retrieval team prior to transfer to PICU

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

Table 3: Samples taken in primary outcome time window (n=number of participants by randomised CVC)

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

Table 4: Primary outcome (absolute measures) and type of organism isolated, according to CVC allocation (values are n by randomised CVC (%) unless otherwise stated))

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Standard** | | **Antibiotic** | | **Heparin** | |
| *Intention to treat analyses* | | *N=502* | % | *N=486* | % | *N=497* | % |
| Bloodstream infection | | 18 | 3.59 | 7 | 1.44 | 17 | 3.42 |
| 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$ | 2.99 | 6 | 1.23 | 16 | 3.22 |
| Skin | 3 | 0.60 | 1 | 0.21 | 1 | 0.20 |
| Organism group\* | Gram-positive$$ | 10 | 0.02 | 3 | 0.01 | 10 | 0.02 |
| Gram-negative | 6 | 0.01 | 4 | 0.01 | 5 | 0.01 |
| Candida | 2 | 0.00 | 0 | 0.00 | 3 | 0.01 |

\* = groups add to more than total due to multiple types of organisms isolated on same occasion in some patients

$ = includes 1 mixed BSI pathogen and skin organism

$$ = includes skin bacteria

Table 5: Risk difference for first BSI and hazard ratio for time to first BSI according to CVC allocation (hazard ratios p<0.05 are in bold)

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

Table 6: Regression results for primary outcome

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

Hazard ratios p<0.05 are in bold; \* participants with prospective consent were admitted electively and participants with deferred consent were admitted as an emergency.

Table 7: Competing risk analysis for primary outcome of time to first BSI

|  |  |  |
| --- | --- | --- |
| **Outcome** | **Hazard ratio (95% CI)** | **Gray’s test *p*-value** |
| Time to first BSI (hours) | 0.71 (0.39, 1.31) | 0.29 |
| Time to death (hours) | 1.08 (0.63, 1.85) | 0.89 |

Table 8: Secondary outcomes (absolute measures) by CVC allocation (n is number of participants by randomised CVC who experienced the outcome)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Standard (n=502)** | | **Antibiotic (n=486)** | | **Heparin (n=497)** | |
| *Primary analyses* | *n* | % | *n* | % | *n* | % |
| Catheter-related BSI (CR-BSI) | 12 | 2.4 | 3 | 0.6 | 10 | 2.0 |
| Rate of BSI per 1000 CVC days (95% CI)  BSI/1000 days | 8.24  21/2.547 | (4.7, 11.8) | 3.30  8/2.418 | (1.0, 5.6) | 8.78  21/2.391 | (5.0, 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) |

Table 9: Risk difference and/or hazard ratios for secondary outcomes according to CVC allocation (hazard ratios p<0.05 are in bold)

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

Primary analyses compared time to event for all secondary outcomes, except CR-BSI (^=risk ratio) and rate of BSI (\*=rate ratio)

Table 10: Safety analyses of CVC-related adverse events and mortality (n is number by type of received or if not inserted, type attempted to be inserted)

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Standard (n=533)** | | **Antibiotic (n=451)** | | **Heparin (n=479)** | | **Total**  **(n=1463)** | |
|  | n | % | n | % | n | % | n | % |
| **CVC-related adverse events** |  |  |  |  |  |  |  |  |
| 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\* | 0.9 |
| Line breakage / mechanical problem / manufacture complication | 2 | 0.4 | 3 | 0.7 | 2 | 0.4 | 7\* | 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 \*\* | *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)* |  |  |

\*One event reported as severe; \*\* measured on case report forms as an adverse event before discharge

Table 11: PCR results for bacteria in blood samples taken during the primary outcome time window by CVC type (N is number by randomised CVC)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  | **N**  **randomised** | **N (%)**  **with PCR\*** | | **N (%)**  **with PCR positive** | |
| **Standard** | Primary outcome = | No | 484 | 239 | (49.4) | 4 | (1.7) |
| Yes | 18 | 12 | (66.7) | 1 | (8.3) |
| **Antibiotic** | Primary outcome = | No | 479 | 221 | (46.1) | 3 | (1.4) |
| Yes | 7 | 5 | (71.4) | 0 | (0.0) |
| **Heparin** | Primary outcome = | No | 480 | 231 | (48.1) | 2 | (0.9) |
| Yes | 17 | 7 | (41.2) | 1 | (14.3) |
| **Total** | Primary outcome = | 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 (CVC) infections are a substantial and preventable cause of iatrogenic morbidity, mortality, excess length of stay and healthcare costs. In the setting of the paediatric intensive care unit (PICU), bloodstream infections (BSI) related to CVCs have been reported to occur in 3% to 8% of all CVC insertions. As approximately two-thirds of the 16,000 admissions to English PICUs each year 56 require CVCs, the overall impact represents a major burden to patients and the NHS. 21, 22

Impregnated CVCs are nearly twice as expensive as standard, 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 healthcare systems (Australia,62 Germany 63 and the USA 64-66). While 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 by comparison with standard CVCs in adult patients. The cost of managing CR-BSIs, estimated as £9,148, 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-BSI from 3% to 1.4%. The ICER of £8,530 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-BSI, divided by the absolute risk reduction. While intuitively simple, the model did not consider mortality effects or discriminate between different types of impregnated CVCs, and the authors recommended decision-makers to interpret the results with caution.

Halton et al. 62 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 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 32 ICU bed days and 95 general ward bed days would be released, with cost savings of AUD $130,289 per 1,000 CVCs.

Frank et al. 63 performed a case-control analysis of resource use and costs among 30 adults who developed CR-BSIs and 108 controls, 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 was unclear.

Marciante et al. 64-66 developed a series of decision models with patient-level clinical trial data to determine whether minocycline and rifampin impregnated CVCs are cost-effective in adults. Cost-effectiveness was indeterminable for CVCs inserted for a week or less, 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. 64-66 presented another decision analytic model based on a hypothetical cohort of 1,000 adult patients requiring a CVC. Incidence of CR-BSI, excess lengths of ICU and ward stays and associated costs were selected from published studies. Compared to standard CVCs, minocycline and rifampin impregnated CVCs were estimated to reduce the incidence of CR-BSI from 3.3% to 1.4%, resulting in a saving of US $9,605 for each CR-BSI averted.

Veenstra et al. 64-66 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 catheter-related infections. Modelling the use of chlorhexidine-silver sulfadiazine-impregnated compared with standard CVCs and resulted in a 2.2% decrease in the incidence of CR-BSI, 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 BSI 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 BSI. The only UK-based economic evaluation considered an adult population and assumed that a patient with a catheter-related BSI spends 6 additional days in ICU and 5 additional days in a general medical ward.29 A recent study of 1,339 cases of catheter-related BSI sampled from a US paediatric population and matched to controls by propensity-score, revealed a higher mean attributable length of stay of 19 days.67 While this is comparable with the 21 excess length of stay estimated for paediatric haematology/oncology patients 68, 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 randomised controlled trial. 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 warrants an economic evaluation to inform decisions on resource allocation. This is especially relevant if one type of CVC were to reduce total costs, be associated with shorter periods in PICU or reductions in the length of ward stays.

## Methods

Although cost-utility analyses, based on the quality-adjusted life-year (QALY) are more appropriate for informing decisions concerning allocative efficiency, there are practical and methodological challenges in estimating utility values in children, especially for very young children in the PICU setting. These include difficulty in responding to or understanding questions on health-related quality of life – whether for reasons of age, illness or consciousness; limitations of using proxy utilities, low event rate in the primary endpoint 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 BSI). The study methods were consistent with other economic evaluations of CVCs.63

#### 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 costs of the CVCs. The time horizon of the base-case analysis was selected to include the costs associated with managing bloodstream infections 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 were obtained from the following (see also Figure 4):

(i) The trial case report forms (CRFs). Research nurses completed the relevant sections of the CRF to record the dates during which patients were in neonatal or paediatric intensive care units, high dependency units and paediatric wards within the hospitals participating in the CATCH trial. Data recorded in CRFs were used for the dates of hospital discharge, transfer to another hospital and date of CVC removal.

(ii) Hospital Episode Statistics (HES) data from the Health and Social Care Information Centre (HSCIC).69 HES data contain details of all admissions to NHS hospitals in England and provide Healthcare Resource Groups (HRGs) on 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.

(iii) The Paediatric Intensive Care Audit Network (PICANet) dataset 56 records 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 different hospital ICUs. PICANet was used for the National Schedule Reference Cost HRGs for HDU and ICU stays 70, and for checking hospital admission, transfer and discharge dates.70

(iv) Hospital Patient Administration Systems (PAS) of CATCH-participating hospitals were accessed for patients’ lengths of stay in ICUs and wards, and for relevant HRGs. These were used to supplement data that were missing from other sources.

#### Unit costs

HRGs 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.71 These are bundled care packages, that is, they are reimbursed at a national level according to the NHS Payment by Results Scheme (see Appendix 2.1). The 2012-13 National Schedule of Reference Costs were applied to PICU, Neonatal Intensive Care Unit (NICU) and HDU codes.70 These are unbundled care packages as they are locally-reimbursed services (Table 12). Obsolete National Tariff and Schedule codes and hospital bed day rates used between 2010-2012 were inflated using the Consumer Price Index (4.3% for 2010-11 and 2.7% for 2011-12). The preferred Hospital Price Index was only available for 2010-11, but is similar to the Consumer Price Index, at 4.1%. The list prices of CVC devices were obtained from the supplier (Cook Medical, Bloomington, IN, USA).

#### Cost analysis

Bundled National Tariff costs were based on the hospital spell and incorporated excess ward days, market forces factor, and whether the case was elective or emergency. Tariff codes were obtained primarily from HES data (see Appendix 2) but where unavailable, PAS data. If bundled HRGs were missing from both of these sources, ward costs were assigned from the ward bed-day rate supplied by hospital finance departments (Table 13). Similarly, bed-day rates were applied to days of stay with unassignable National Tariff HRG codes (such as UZ01C and WA14Z) appearing in the HES and PAS data. These bed-day rates were needed in <1% of admissions.

Unbundled, locally reimbursed costs were calculated from the National Schedule ‘per day’ codes taken from PICANet (Table 12) or assigned as XA01C in the cases where Neonatal Critical Care was indicated in CRF data. In the 10% of cases where unbundled codes were missing, CRF data were consulted to determine whether the patient stay was in PICU or HDU. In addition, PICANet database entries (such as patient note summaries) were examined for any evidence for 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.70

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 relate to episodes of care which 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:

Total cost = (N/n+N) x (ward cost + PICU cost + HDU cost)

+ (outpatient costs + A&E costs + CVC costs)

Patients’ use of healthcare 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 bloodstream 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. The likelihood of a bloodstream infection 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: i) ranking CVCs according to decreasing effectiveness, ii) eliminating dominated interventions (those which are less effective or ineffective) or any extendedly dominated interventions. The incremental cost-effectiveness ratio (ICER) for remaining CVCs was consequently calculated according to:

Incremental cost-effectiveness ratio (ICER) = ΔCosts / ΔBSI

Where, ΔCosts is the difference in the means of total costs between interventions; and ΔBSI is the difference in proportion of bloodstream infections between interventions.

#### Uncertainty analysis

Nonparametric bootstrapping (10,000 replicates) was used to calculate bias-adjusted 95% central ranges for differences in costs and BSI, 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 on overall variability.73

The following pre-defined 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, immune compromised, 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 no positive blood culture (n=5). Missing data for weight (n=2) were imputed with the mean (11.95 kg). Missing reason 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 cost data, generalised linear models (GLMs) were specified using a range of families and links. Assessment of goodness of fit using Akaike Information Criterion (AIC) and the Modified Park’s test was inconclusive; but the best fitting link function, determined from the Pearson Correlation, Pregibon Link and the Modified Hosmer and Lemeshow tests, was the identity link. While 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 OLS regression was considered appropriate 73.

Bias-corrected confidence intervals for costs and BSI were estimated from bootstrapped data generated using the recycled predictions method.74

**Sensitivity analysis**

The pre-specified time horizon for the base-case analysis, of 6 months, was selected to capture longer term costs resulting from potential complications of BSI 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 (that is, excluding any subsequent re-admissions that may have occurred during the 6-months), and by analysing their relationship with time, from 1 month (when all BSI had occurred) to 6 months.

#### Value of healthcare resources associated with BSI

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

All analyses were performed using STATA Version 10, and the economic evaluation 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 total costs (length of stay) of ICU/HDU admission were £6,026 (3.19 days) for the standard CVC group, £5,188 (2.76 days) for the antibiotic CVC group and £6,616 (3.47 days) for the heparin CVC group. . Mean, total costs were £15,588, £16,933 and £16,722, respectively, and did not differ with respect to ICU/HDU (p=0.46) or total cost (p=0.71).

Patients randomised to antibiotic-impregnated CVC spent 10.8 days (95% CI, 9.3, 12.4) in PICU in the 6 months following randomisation, compared with 9.9 days (95% CI 8.6, 11.4) for those in the heparin-bonded CVC group and 10.5 days (95% CI 9.2, 11.9) for standard CVC (Table 14). There were no significant differences in lengths of stay between groups, either in PICU (p=0.70), HDU (p=0.43), or ward (p=0.52). The total days of hospital stay in the 6 months after randomisation were 34.8 days (95% CI 31.2, 38.5) for antibiotic CVC, 31.4 days (95%CI 28.2, 34.7) for heparin-bonded CVC and 31.7 (95% CI 28.8, 34.8) for the standard CVCs group. The 6 most significant HRGs (of 349 in total) accounted for 50% of ward costs. These related to congenital or other cardiac surgery and lower respiratory tract disorders.

Total and disaggregated costs are presented in Table 15. The mean 6-month costs were £44,503 (median £28,952; range £1,786, £360,983; 95% CI £40,619, £48,666) for standard CVCs, £45,663 (median £29,793; range £2,189, £442,365; 95% CI £41,647, £50,009) for antibiotic-impregnated CVCs and £42,065 (median £27,621; range £2,638, £382,431; 95% CI £38,322, £46,110) for heparin CVCs (Figure 5). These costs were not statistically significantly different among intervention groups (p=0.46); or when disaggregated according to bundled costs (p=0.43) and unbundled costs (p=0.73).

***Incremental costs***

Mean, unadjusted costs over the 6-month timeframe were not significantly different by CVC, but tended to be higher (by £1,160; 95% CI -£4,743, £6,962) for antibiotic compared with standard CVCs, and tended to be lower (-£2,439; 95% CI -£8,164, £3,359) for heparin 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), natural logarithm of 6-month pre-randomisation costs, health status before PICU admission, reason for admission, whether immune compromised, and admission type (elective or emergency; Table 16). The adjusted incremental costs associated with the antibiotic and heparin CVC groups, in relation to standard CVCs, were £1,220 (95% CI -£4,332, £6,773) and -£2,399 (95% CI -£7,914, £3,120), respectively, resulting in small improvements in precision.

#### Value of healthcare resources associated with BSI

Over 6 months, patients who had experienced a BSI (n=42) experienced 6.5 more days (95% CI 1.4 to 11.6) in PICU than those with no BSI (n=1,443), and 15.1 additional total days (95% CI 4.0 to 26.2) of hospitalisation. Unadjusted mean 6-month cost for patients with a BSI was £60,481 (n=42, 95% CI £47,873, £73,809) and without was £43,578 (n=1,443, 95% CI £41,185, £45,970), a difference of £17,263 (95% CI -£3,076, £31,450). The regression-derived adjusted difference in cost, representing the value of the resources used to manage BSI, was £10,975 (95% CI -£2,801, £24,751) (Table 17).

***Outcomes***

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

***Incremental and uncertainty analysis***

As heparin CVCs were shown not to be clinically effective when compared to standard CVCs there is no case for an incremental analysis: a clinically ineffective intervention cannot be cost-effective by the same measure of BSI. The calculation of the incremental cost-effectiveness ratio was therefore limited to the comparison of antibiotic and standard CVCs which resulted in an ICER of £54,057 per BSI averted (Table 18).

The cost-effectiveness acceptability curve yielded the probabilities of antibiotic CVCs being cost-effective at (arbitrary) thresholds of £10,000, £50,000 and £100,000 per BSI averted, as 0.38, 0.49 and 0.62, respectively (Figure 6). 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 during the 6 months from randomisation (e.g. 34.8 days for antibiotic CVCs; see Tables 19 and 14). Considering only the index hospitalisation, total costs tended to be lower in the antibiotic CVC group (£33,073; 95% CI £30,047, £36,337) and in the heparin CVC group (£32,245; 95% CI £29,013, £35,823) compared with the standard CVC group (£35,165; 95% CI £31,864, £38,670). The unadjusted incremental cost saving for antibiotic versus standard CVCs was -£2,093 (95% CI -£6,919, £2,583); and between heparin and standard CVCs -£2,920 (95% CI -£7,833, £2,180).

Based only on the costs of the index stay, antibiotic CVCs dominated standard CVCs with a saving of £97,543 per BSI averted (Table 18).

An analysis of the cumulative mean costs over the course of the 6 month (Figure 7), shows that costs in the heparin CVC group were lower overall, while costs in the antibiotic CVC group were variably cost-incurring and cost-saving in comparison to the standard CVC group.

The resulting ICER for antibiotic compared with standard CVCs fluctuated considerably (Figure 8), ranging from a minimum of £82,204 saved per BSI averted by day 50 post-randomisation, being cost-neutral by day 122 and to the base-case cost of £54,057 per BSI averted by 6 months.

Table 12: Unit cost for intensive care and high dependency care, based on HRGs from the National Schedule tariff (2012-13)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **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 extra-corporeal membrane oxygenation (ECMO) | ECMO, VAD and other highly complex procedures | £4,391 |
| XB02Z | Paediatric Critical Care, Intensive Care, Advanced Enhanced | Unstable multi-system failure with other complications | £2,409 |
| XB03Z | Paediatric Critical Care, Intensive Care, Advanced | Intensive nursing supervision at all times, undergoing complex monitoring and/or therapeutic procedures, including advanced respiratory support | Invasive ventilation with multi-system failure | £2,017 |
| XB04Z | Paediatric Critical Care, Intensive Care, Basic Enhanced | Intensive ventilation with more than one system failure | £2,110 |
| 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 | £1,743 |
| XB06Z | Paediatric Critical Care, High Dependency, Advanced | Require 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 IV drugs) | £1,335 |
| XB07Z | Paediatric Critical Care, High Dependency | Close monitoring, oxygen by mask, no invasive ventilation | £886 |
| XB08Z | Paediatric Critical Care, Transportation | Since 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 | | £2,799 |
| 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. | £1,118 |

Table 13: Hospital ward bed-day rates as provided by hospital finance departments and adjusted for inflation (£ sterling, 2013)

|  |  |  |  |
| --- | --- | --- | --- |
| **Hospital** | **HES hospital ID** | **Market Forces Factora** | **Ward Rateb** |
| Birmingham Children's Hospital | RQ3 | 1.05 | £290 |
| Bristol Hospital for Sick Children | RA7 | 1.08 | £366 |
| Evelina Children's Hospital | RJ1 | 1.28 | £595c |
| Freeman Hospital | RTD | 1.04 | £595c |
| Alder Hey | RBS | 1.04 | £364d |
| Glenfield Hospital | RWE | 1.04 | £751 |
| Great Ormond Street Hospital | RP4 | 1.29 | £2,157 |
| Leeds General Infirmary | RR8 | 1.05 | £542 |
| Leicester Royal Infirmary | RWE | 1.04 | £751 |
| Queens 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 | RYJ | 1.24 | £394 |

aused with HRGs only; b ward rate excludes ICU or HDU costs; c mean of series of wards provided by all hospitals except Alder Heyd mean of series wards provided by hospital

Table 14: Patients' lengths 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 by 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, 12.48 | 9.91 (5.00) | 8.57, 11.44 | 10.50 (5.00) | 9.17, 11.93 |
| Paediatric Critical Care, Intensive Care, ECMO/ECLS (XB01Z) | 0.31 (0.00) | 0.07, 0.72 | 0.39 (0.00) | 0.09, 0.80 | 0.41 (0.00) | 0.17, 0.72 |
| Paediatric Critical Care, Intensive Care, Advanced Enhanced (XB02Z) | 0.16 (0.00) | 0.09, 0.26 | 0.12 (0.00) | 0.09, 0.15 | 0.16 (0.00) | 0.10, 0.26 |
| Paediatric Critical Care, Intensive Care, Advanced (XB03Z) | 0.77 (0.00) | 0.51, 1.05 | 0.62 (0.00) | 0.43, 0.83 | 0.65 (0.00) | 0.46, 0.87 |
| Paediatric Critical Care, Intensive Care, Basic Enhanced (XB04Z) | 2.30 (0.49) | 1.92, 2.72 | 2.69 (0.78) | 2.09, 3.44 | 2.76 (0.00) | 2.14, 3.54 |
| Paediatric Critical Care, Intensive Care, Basic (XB05Z) | 6.96 (2.00) | 5.65, 8.45 | 5.63 (2.00) | 4.75, 6.59 | 6.40 (2.95) | 5.42, 7.47 |
| Neonatal Critical Care, Intensive Care (XA01C) | 0.29 (0.00) | 0.10, 0.55 | 0.46 (0.00) | 0.13. 1.03 | 0.11 (0.00) | 0.04, 0.20 |
| Days on HDU | 2.00 (0.59) | 1.48, 2.62 | 1.60 (0.59) | 1.28, 1.99 | 1.73 (0.00) | 1.44, 2.05 |
| Paediatric Critical Care, High Dependency, Advanced (XB06Z) | 1.28 (0.00) | 0.94, 1.70 | 1.09 (0.00) | 0.80, 1.45 | 1.22 (0.00) | 0.98, 1.49 |
| Paediatric Critical Care, High Dependency (XB07Z) | 0.72 (0.00) | 0.42, 1.16 | 0.51 (0.00) | 0.40, 0.64 | 0.51 (0.00) | 0.40, 0.64 |
| Days on ward | 22.01 (9.13) | 19.26, 24.80 | 19.85 (9.00) | 17.40, 22.40 | 19.48 (8.57) | 17.12, 21.94 |
| Total days in hospital | 34.80 (20.00) | 31.21, 38.48 | 31.36 (17.00) | 28.18, 34.65 | 31.72 (17.97) | 28.75, 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 |  |

Table 15: Disaggregated and total costs (£) by intervention group from randomisation to end of the six-month timeframe

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Antibiotic CVC** | | **Heparin CVC** | | **Standard CVC** | |
| **Unit** | **Mean (median)** | **95% CI** | **Mean (median)** | **95% CI** | **Mean (median)** | **95% CI** |
| Paediatric Critical Care, Intensive Care | | | | | | |
| ECMO/ECLS (XB01Z) | 1358 (0) | 310, 3159 | 1703 (0) | 386, 3509 | 1796 (0) | 723, 3156 |
| Advanced Enhanced (XB02Z) | 388 (0) | 207, 636 | 289 (0) | 216, 371 | 395 (0) | 228, 620 |
| Advanced (XB03Z) | 1545 (0) | 1031, 2124 | 1250 (0) | 872, 1674 | 1318 (0) | 933, 1752 |
| Basic Enhanced (XB04Z) | 4861 (1023) | 4060, 5738 | 5675 (1646) | 4418, 7260 | 5822 (0) | 4512, 7460 |
| Basic (XB05Z) | 12,137 (3486) | 9855, 14,730 | 9822 (3486) | 8274, 11,489 | 11,159 (5133) | 9440, 13,025 |
| Neonatal Critical Care, Intensive Care (XA01C) | 325 (0) | 113, 613 | 517 (0) | 142, 1150 | 125 (0) | 42, 225 |
| Paediatric Critical Care, HDU | | | | | | |
| High Dependency, Advanced (XB06Z) | 1709 (0) | 1254, 2271 | 1450 (0) | 1972, 1940 | 1629 (0) | 1301, 1992 |
| High Dependency (XB07Z) | 635 (0) | 372, 1025 | 454 (0) | 354, 567 | 456 (0) | 356, 566 |
| Transportation (XB08Z) | 1158 (0) | 1022, 1293 | 1258 (0) | 1109, 1413 | 1208 (0) | 1068, 1353 |
| Sub-total (PICU/HDU/NICU)a | 24,115 (12,201) | 20,824, 27,764 | 22,417 (11,903) | 19,429, 25,771 | 23,907 (12,495) | 20,989, 27,049 |
| Inpatient stayb | | | | | | |
| Complex Congenital Surgery (EA24Z) | 3011 (0) | 2445, 3593 | 2908 (0) | 2363, 3481 | 3144 (0) | 2565, 3753 |
| Intermediate Congenital Surgery (EA25Z) | 2166 (0) | 1670, 2699 | 1934 (0) | 1470, 2440 | 2044 (0) | 1583, 2545 |
| Major Complex Congenital Surgery (EA23Z) | 1865 (0) | 1315, 2481 | 1915 (0) | 1310, 2603 | 1466 (0) | 1013, 1960 |
| Cardiac Conditions with complication and comorbidity (PA23A) | 1277 (0) | 818, 1845 | 1173 (0) | 831, 1558 | 739 (0) | 495, 1025 |
| Lower Respiratory Tract Disorders without acute bronchiolitis with length of stay ≥1 day with complication and comorbidity (PA14C) | 858 (0) | 593, 1157 | 668 (0) | 454, 913 | 943 (0) | 657, 1268 |
| Implantation of Prosthetic Heart or Ventricular Assist Device (EA43Z) | 273 (0) | 0, 684 | 298 (0) | 0, 762 | 548 (0) | 103, 1155 |
| Other inpatient HRG costs | 10,316 (4017) | 8616, 12,231 | 8803 (3058) | 7524, 10,106 | 9930 (3259) | 7860, 12,409 |
| Sub-total (inpatient) | 19,766 (14122) | 17,934, 21,755 | 17,700 (13,716) | 16,308, 19,182 | 18,814 (13,748) | 16,649, 21,327 |
| Other | | | | | | |
| A&E costc | 89 (0) | 76, 104 | 85 (0) | 73, 99 | 91 (0) | 78, 104 |
| Outpatient costc | 1615 (883) | 1412, 1838 | 1784 (837) | 1496, 2109 | 1648 (881) | 1453, 1871 |
| CVC costd | 78.28 | 78, 78 | 78.25 | 78, 78 | 42.91 | 43, 43 |
| Total cost (full 6 months) | 45,663 (29793) | 41,647, 50,009 | 42,065 (27,621) | 38,322, 46,110 | 44,503 (28,952) | 40,619, 48,666 |

a National Schedule of Reference Costs 2012-2013; bTop 6 (of 349) HRGs ranked by cost, together contributing 50% of overall inpatient cost, c2012-2013 National Tariff HRGs <1% taken from bed day rates; dCosts supplied by CVC provider (Cook Medical).

Table 16: Adjusted, total (6-month) costs: results of Ordinary Least Squares regression of total costs based on significant baseline variables

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

AIC = 24.25; BIC = 2.89x1012; R2 = 0.092

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

R2 = 0.092

Table 18: Incremental Analysis of unadjusted costs (mean values with 95% central range)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Antibiotic** | **Heparin** | **Standard** |
| **Base-case analysis**  **(6-month time horizon)** |  |  |  |
| Total costs | £45,663  (£41,647, £50,009) | £42,064  (£38,322, £46,110) | £44,503  (£40,619, £48,666) |
| Incremental cost (versus standard) | £1,160  (-£4,743, £6,692) | -£2,438  (-£8,164, £3,359) | - |
| BSI | 1.44%  (0.4, 2.5) | 3.42%  (1.8, 5.0) | 3.59%  (2.0, 5.2) |
| Incremental BSI (versus standard) | -2.15%  (-4.1, -0.2) | -0.17%  (-2.5, 2.1) | - |
| ICER (versus standard) | £54,057  per BSI averted | -a | - |
| **Sensitivity analysis**  **(index hospitalisation)** |  |  |  |
| Total costs | £33,073  (£30,047, £36,337) | £32,245  (£29,013, £35,823) | £35,165  (£31,864, £38,670) |
| Incremental cost (versus standard) | -£2,093  (-£6,919, £2,583) | -£2,920  (-£7,833, £2,180) | - |
| BSI | 1.44%  (0.4, 2.5) | 3.42%  (1.8, 5.0) | 3.59%  (2.0, 5.2) |
| Incremental BSI (versus standard) | -2.15%  (-4.1, -0.2) | -0.17%  (-2.5, 2.1) | - |
| ICER (versus standard) | -£95,473  per BSI averted b | -a | - |

**aAs heparin CVC was not deemed to be clinically effective in reducing BSI rates, it cannot be cost-effective by the same outcome measure**

**b Cost-saving**

Table 19: Patients' 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, 10.70 | 8.93 | 7.71, 10.32 | 9.79 | 8.60, 11.03 |
| Days on HDU | 1.70 | 1.25, 2.25 | 1.39 | 1.09, 1.76 | 1.51 | 1.24, 1.80 |
| Days on ward | 11.13 | 9.19, 13.18 | 10.32 | 8.59, 12.18 | 10.79 | 9.03, 12.70 |
| Total days in hospital | 22.14 | 19.48, 24.89 | 20.65 | 18.27, 23.16 | 22.09 | 19.76, 24.51 |

Figure 4: Flow diagram of the methods employed for the economic evaluation.

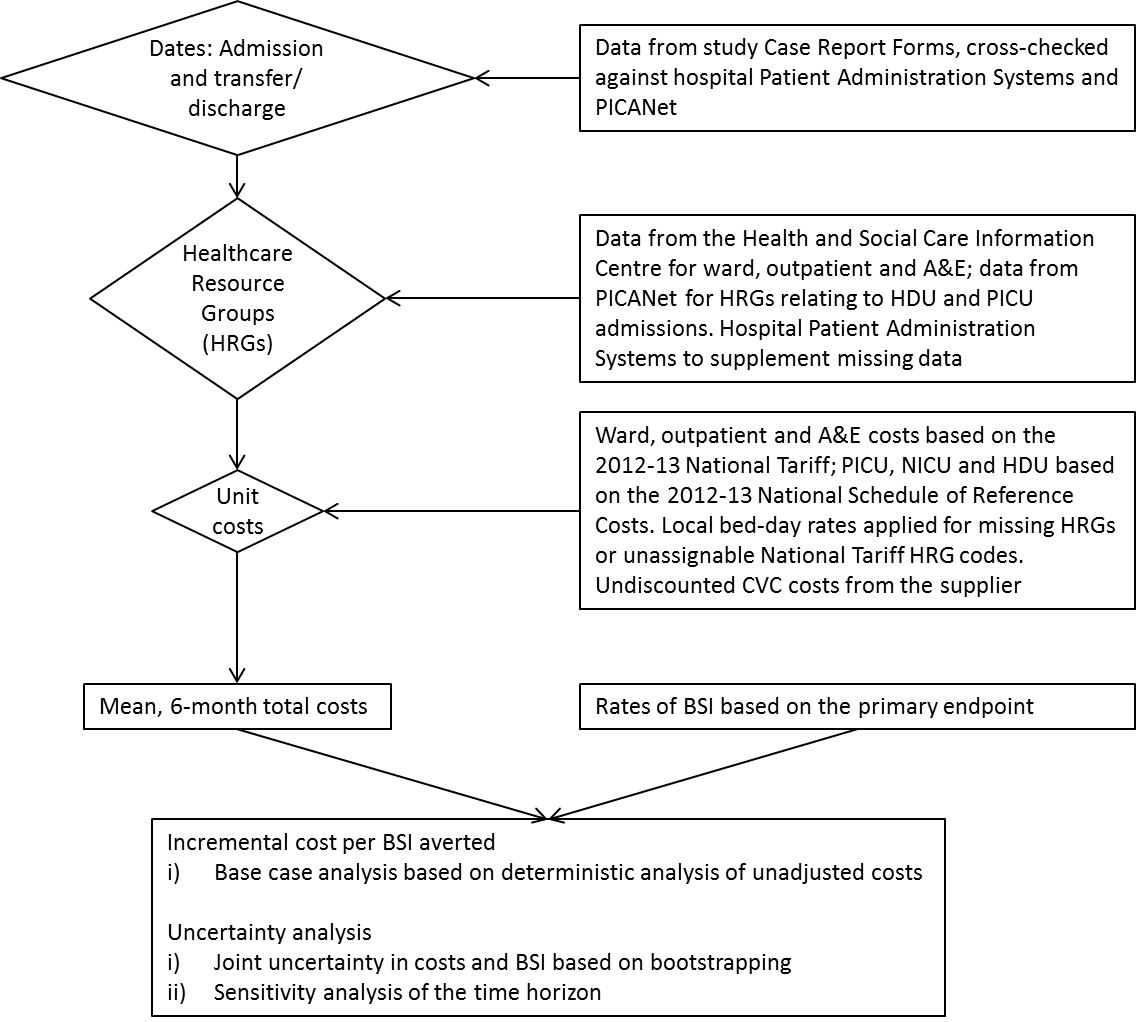


Figure 5: Ranking of total, 6-month costs by intervention group, indicating patients who experienced a bloodstream infection.

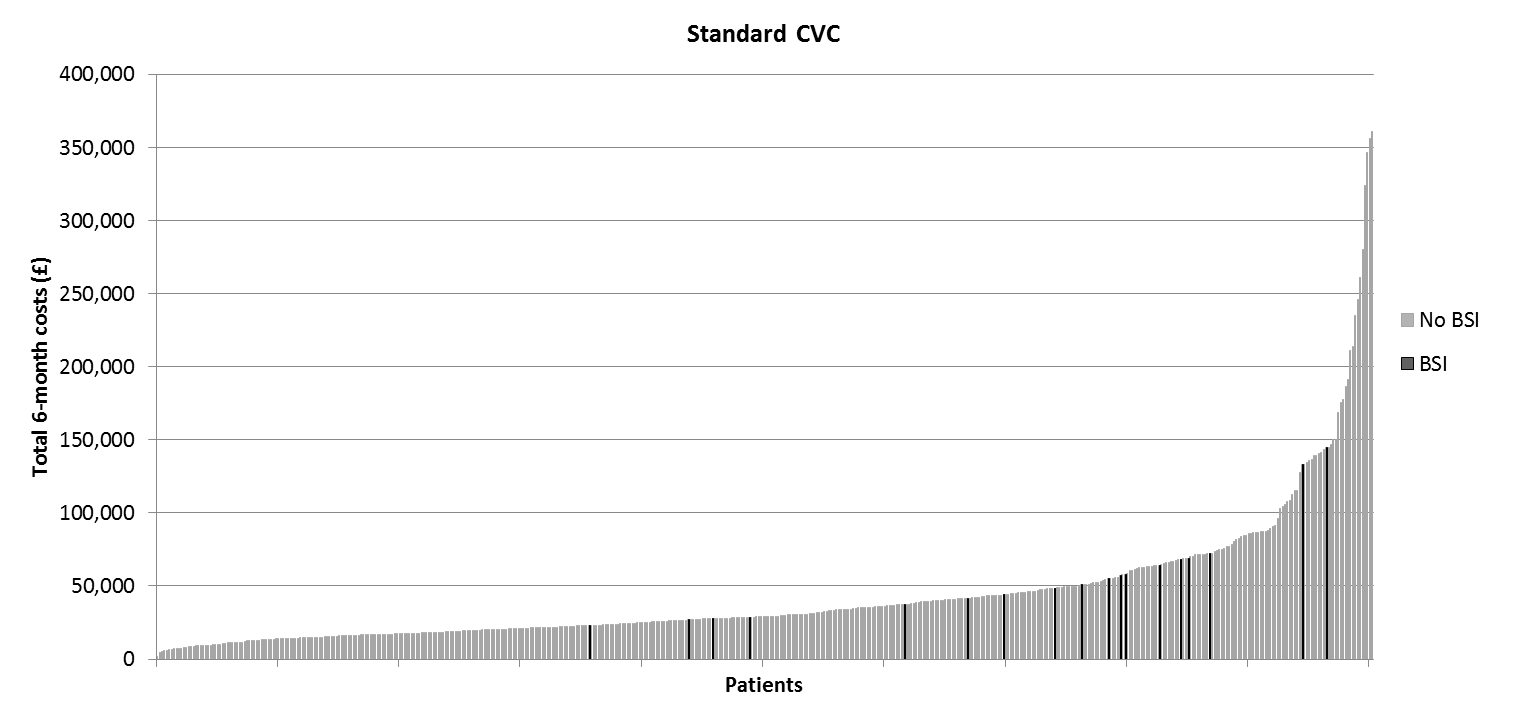
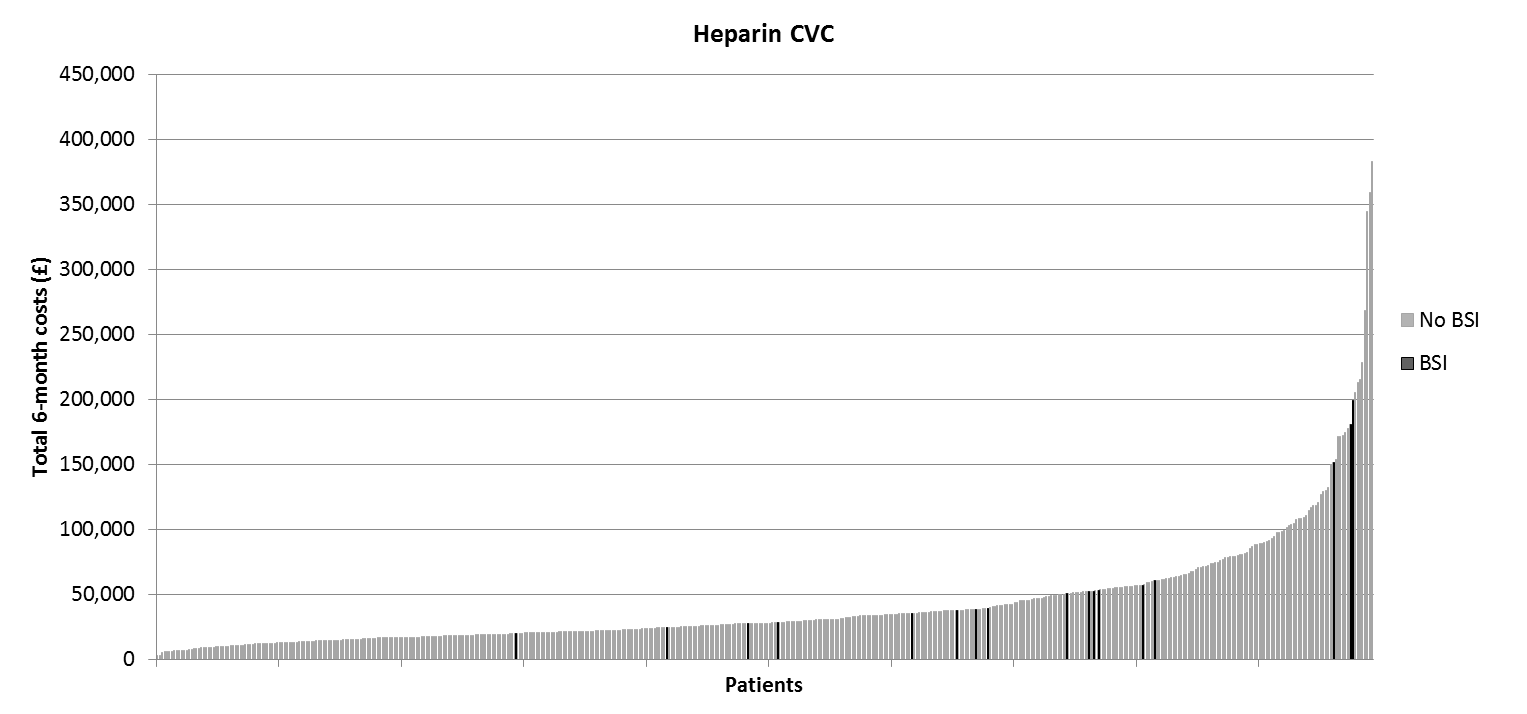
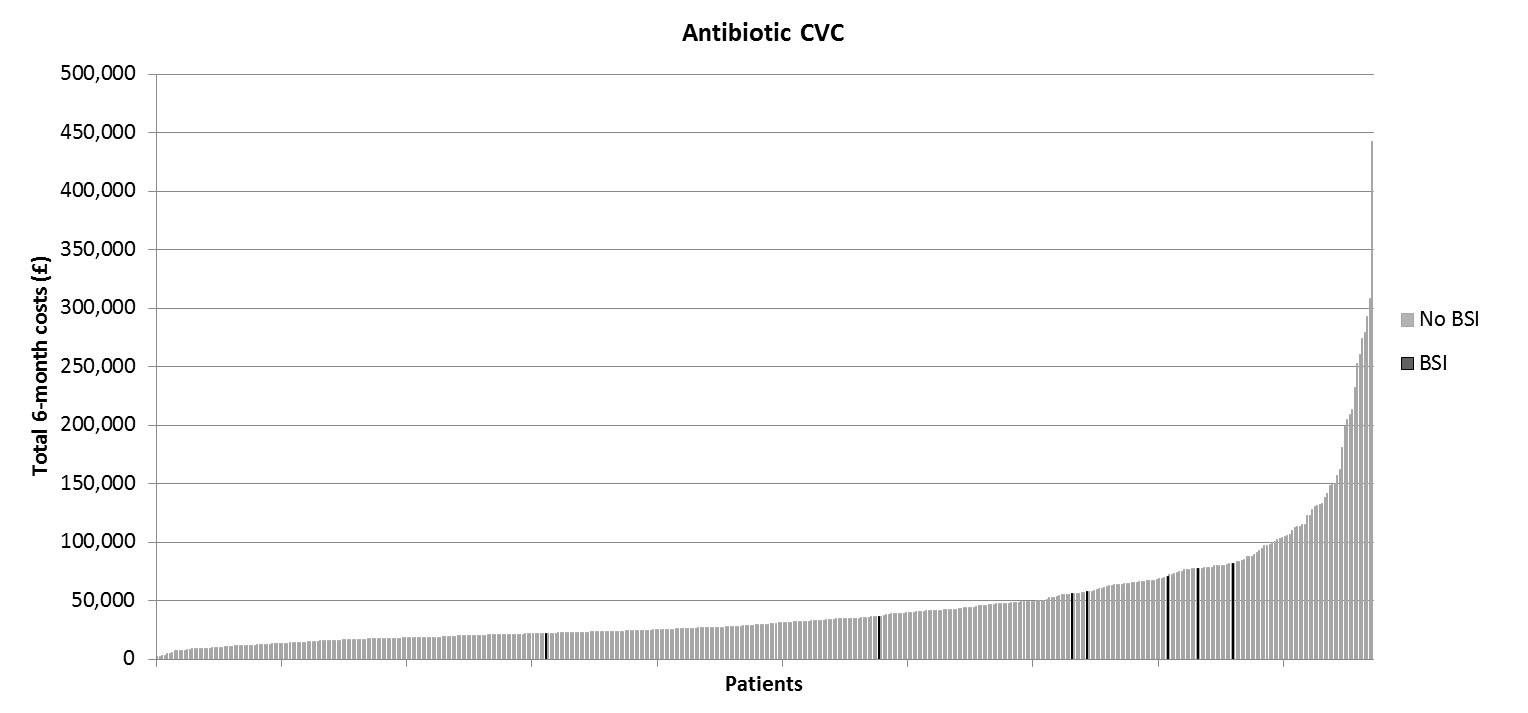


Figure 6: Cost-effectiveness acceptability curve based on a 6 month time horizon presenting the probability of antibiotic and standard CVCs being cost-effective for given values of ceiling ratio expressed as cost per bloodstream infection (BSI) averted

Figure 7: Relation between total costs (cumulative) and time since randomisation, according to intervention group

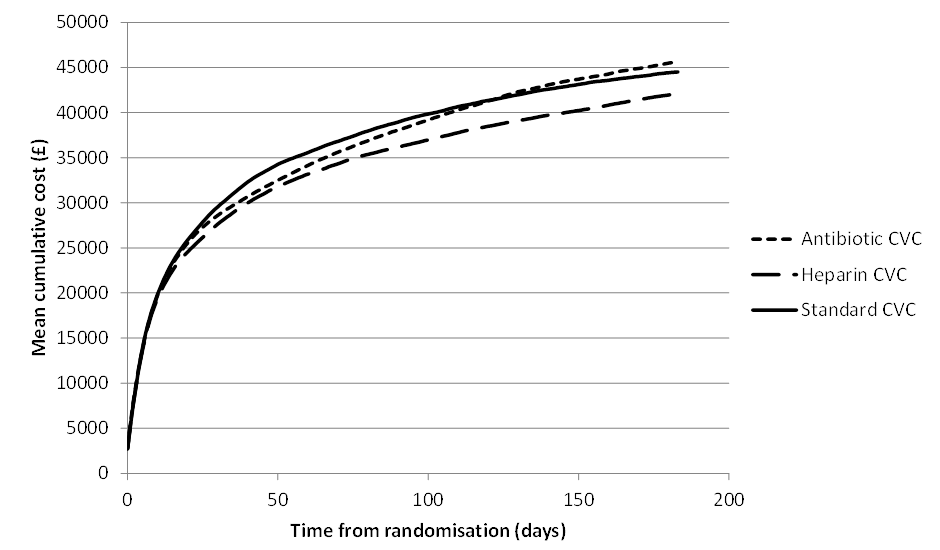


Figure 8: Relation between the ICER for antibiotic CVC versus standard CVC, and time since randomisation. Positive ICERs are cost-incurring, negative values represent incremental savings per BSI averted



# CHAPTER 5 GENERALISABILITY STUDY

## Introduction

CATCH was the largest trial in PICU 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 (2010-2012). However, if antibiotic-impregnated CVCs were adopted, it is likely that these CVCs would be bulk-purchased and used for all children requiring CVCs in PICU, not just children like those in the trial. Decisions on whether 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 those who receive the intervention in practice, for a variety of reasons.76 For CATCH, there were two specific reasons why those recruited might differ from those likely to receive impregnated CVCs outside the trial setting. Firstly, children recruited to CATCH were expected to require a CVC for three or more days, and would therefore have a higher risk of BSI than those staying less than three days. Secondly, the introduction of CVC care bundles and on-going 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, 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 healthcare resources.

We determined the generalisability of the CATCH trial findings by estimating risk-adjusted trends in BSI for children expected to require CVCs in PICU, based on a data linkage study including children not participating in CATCH.77 We determined the budget- and cost-impacts of adopting antibiotic-impregnated CVCs for all children required CVCs in PICU by synthesising the following evidence: i) the estimated risk of BSI using standard CVCs (derived from the data linkage study); ii) the number of BSI potentially averted by using antibiotic-impregnated CVCs (based on the relative treatment effect in the trial); iii) 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 iv) the value of the healthcare resources associated with each BSI (from the CATCH cost-effectiveness analysis).

## Methods

#### Rate of BSI using standard CVCs

Data sources

There is no single dataset from which the rate of BSI in PICUs across the NHS can be estimated for children requiring standard CVCs. Linkage between the national laboratory surveillance system coordinated by Public Health England (LabBase2) 78 and data from the Paediatric Intensive Care Audit Network (PICANet) 56 has provided an enhanced dataset from which to estimate the baseline rate of BSI.

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 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 were 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 datasets were produced and analysed separately, with results combined using Rubin’s rules.81

The resulting linked dataset 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 dataset to children expected to require a standard CVC in PICUs 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. Where no response was obtained or the PICU was not included in the survey, we assumed that standard CVCs were used.

Identifying children with CVCs

CVC use is not routinely captured for all admissions in PICANet, so we identified admissions likely to have 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 where CVC used was recorded. Presence of a CVC was recorded for 2488 admissions as part of two audits: Great Ormond Street Hospital (January 2006 - December 2010) and Cambridge 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 Bayesian Information Criterion (BIC).

The internal validity of the model was assessed using bootstrapping, accounting for any model over-fitting due to developing and testing the model in the same dataset.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 3.1.

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 PICU were equivalent to CVC-days, i.e. that CVCs were inserted at admission and removed at discharge from PICU. We defined an episode of BSI as any positive blood culture isolated from a blood sample taken from two days after admission to two days after discharge from 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 multi-level Poisson regression. We accounted for clustering of admissions within PICUs by including a random effect for PICU. 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 using standard CVCs for CATCH participants and non-participating admissions expected to require a CVC, and BSI rates for 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 BSI averted using antibiotic CVCs

We estimated the difference in the number of BSI if antibiotic CVCs were used in place of standard CVCs. We asked PICUs to provide the percentage of emergency and elective admissions receiving CVCs within a second PICU practice survey conducted in 2012.32 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 CVC-days for children expected to require CVCs 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 BSI, i.e. that the effect would be the same for children who would have been ineligible for the trial because they were expected to stay <3 days in 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). Randomised controlled trials of impregnated CVCs show similar results for long- and short-term CVCs, suggesting that effect is not modified in groups with different baseline risk or length of stay.3 In reality, 72% of children recruited in CATCH required a CVC for 3 or more days.

#### Budget-impact: additional costs of antibiotic CVCs

Antibiotic CVCs are more expensive than standard CVCs: £73 versus £42 for double lumen CVCs; £79 versus £43 for triple lumen CVCs. Total additional costs with antibiotic CVCs were calculated by multiplying the number of CVCs required by the maximum additional cost per CVC, i.e. £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 based on the additional costs of antibiotic CVCs only.

#### Cost-impact: value of resources associated with managing BSI

Assuming that any differences in costs between arms were due to differences in the number of BSI, the cost-impact analysis utilised the estimated difference in the 6-month risk-adjusted costs between patients who had a BSI versus those who did not (£10,975 per BSI; 95% CI -£2801 to £24,751) (cost-effectiveness analysis, Table 17).

The total number of BSI potentially averted was estimated by applying the BSI rate assuming all children in 2012 had used either standard or antibiotic CVCs. The cost-impact (total value of resources associated with managing BSI with standard CVCs) was calculated by multiplying the costs per BSI by the estimated number of BSI 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 with standard versus antibiotic CVCs. We also performed probabilistic sensitivity analysis using Monte Carlo simulation to reflect uncertainty in both costs and BSI. 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 BSI using standard CVCs

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 3.3). 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%; positive predictive value was 82% and negative predictive value was 61%. The predictive model identified 80% of the CATCH admissions as requiring a CVC.

Survey responses for the type of CVCs used prior to CATCH were obtained for 18 of the 23 PICUs in England (see Appendix 3.2). 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 dataset identified a subset of 21,381 admissions most likely to have received standard CVCs between 2003-2012. Characteristics of these admissions (based on PICANet data) are provided in Appendix 3.4. Risk-adjusted rates of BSI using standard CVCs decreased steadily between 2003 and 2012, and were greater for CATCH PICUs (5.27; 95% CI 5.06-5.49 per 1000 CVC-days in 2012) compared with non-participating PICUs (2.09; 95% CI 1.60-2.58 in 2012; Figure 9). Of the subset of admissions predicted to receive a CVC in 2012, 103/3021 (3.4%) experienced BSI, corresponding to an overall BSI rate using standard CVCs of 4.58 (95% CI 4.42, 4.74) per 1000 CVC-days (Table 20). This was non-significantly lower than the rate observed during the trial (8.24; 95% CI 4.7-11.8 per 1000 CVC days; Table 8), partially due to the inclusion of all children with CVCs (not just those requiring CVCs for 3 or more days). Further explanation for this difference are potentially incomplete reporting of BSI to the national infection surveillance system, use of bed days instead of CVC days in the estimated rate, or increased frequency of sampling in trial PICUs during CATCH.

Number of BSI averted using antibiotic CVCs

Survey responses indicated that on average, 60% of emergency admissions and 50% of elective admissions require CVCs (see Appendix 3.2). The estimated number of children using CVCs in 2012 was 8831, corresponding to a total of 85,971 CVC-days. The rate-ratio of BSI for impregnated versus standard CVCs was estimated as 0.40 (95% CI 0.17, 0.97; Table 9) in the trial. The point estimate of the number of BSI averted switching from standard to antibiotic CVCs for all children requiring CVCs in 2012 was therefore 232, with best and worst case scenarios of 338 and 11 respectively (Table 21).

#### Budget-impact: additional costs of antibiotic CVCs

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

#### 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 -£2,801, £24,751; Table 17). over 6 months, the value of resources made available in 2012 through averting BSI with standard CVCs (i.e. the total costs of managing these BSIs) would have been 232 x £10,975 = £2,541,397, with best and worst case scenarios of -£925,583 and £8,205,414 based on confidence intervals for both estimates. The probabilistic sensitivity analysis provided a 95% uncertainty interval of -£66,544 to £5,557,451 for total resources made available through averting BSI in 2012. There was a probability of 0.90 that the values of resources made available would be more than the additional costs of purchasing antibiotic CVCs (Figure 10).

The estimated cost-impact for a typical PICU with 350 admissions per year is shown for a range of BSI rates in Table 21. Figure 11 shows that costs of purchasing antibiotic CVCs for all children who require them will be less than costs of managing BSI with standard CVCs for PICUs with BSI rates above 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 4.7-11.8 per 1000 bed days), or the linked dataset for PICUs in England (4.58; 95% CI 4.42, 4.74).

Table 20: Parameter estimates for cost-impact analysis and sensitivity analysis

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Base case** | **Source** | **Sensitivity analysis** |
| *BSI rate using standard CVCs in 2012* | 4.58  (95% CI 4.42-4.74) | 3021 admissions in 15 PICUs:  Subset of admissions identified as most likely to have received standard CVCs by applying predictive model to linked dataset. Admissions identified by survey responses as receiving non-standard (heparin or antibiotic) CVCs were excluded. | Random sample taken with replacement from linked dataset, for the number of admissions expected to require CVCs. |
| *Rate ratio* | 0.40  (95% CI 0.17-0.97) | Trial clinical effectiveness analyses (Table 9) | *Ln\** N (-0.913, 0.415) |
| *Estimated BSI rate using antibiotic CVCs in 2012* | 1.83  worst case = 4.29  best case = 0.81 | Rate-ratio from the CATCH trial applied to estimated BSI rate using standard CVCs for PICUs in England | Derived from i) BSI rate using standard CVCs and ii) 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). | Emergency: Beta(60,40)  Elective:  Beta(50,50) |
| *Number of CVC days in 2012* | 85,971 | Average CVC-days per admission in subset of admissions identified as most likely to have received standard CVCs by applying predictive model to linked dataset, multiplied by number of admissions requiring CVCs in 2012. | Random sample taken with replacement from linked dataset, for admissions expected to require CVCs. |
| *Number of BSI averted in 2012* | 232 | BSI rates applied to CVC-days for admissions requiring CVCs in 2012 | Derived from i) number of admissions requiring CVCs in 2012 and ii) 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 (Table 17) | N(£10,975, £7,023) |

\*Ln Natural logarithm

Table 21: Cost impacted analysis of managing BSIs occurring with standard versus antibiotic CVCs with best and worst case scenarios\* and hypothetical scenarios for a typical PICU with 350 admissions per year

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **BSI per 1000 CVC-days using standard CVCs** | **Rate ratio** | **BSI per 1000 CVC-days using standard CVCs** | **N BSI with standard CVCs** | **N BSI with antibiotic CVCs** |  | **BSI averted *\*\**** | **Cost-impact** |
|  | Lower limit: Cost per BSI: -£2801 | Base case:  Cost per BSI: £10,975 | Upper limit:  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 |
| ***Hypothetical scenarios based on a typical PICU with 350 admissions per year*** | | | | | | |  |  |
|  | 1.00 | 0.40 | 0.40 | 3.5 | 1.4 | 3.5 | 3.5 | 3.5 |
|  | -£9,677 | £37,919 | £85,515 |
|  | 2.00 | 0.40 | 0.80 | 171.9 | 68.8 | 101.1 | 101.1 | 101.1 |
|  | -£283,234 | £1,109,780 | £2,502,795 |
|  | 3.00 | 0.40 | 1.20 | 257.9 | 103.2 | 151.7 | 151.7 | 151.7 |
|  | -£424,851 | £1,664,671 | £3,754,193 |
|  | 4.00 | 0.40 | 1.60 | 343.9 | 137.6 | 202.2 | 202.2 | 202.2 |
|  | -£566,468 | £2,219,561 | £5,005,590 |
|  | 5.00 | 0.40 | 2.00 | 429.9 | 171.9 | 252.8 | 252.8 | 252.8 |
|  | -£708,085 | £2,774,451 | £6,256,988 |
|  | 6.00 | 0.40 | 2.40 | 515.8 | 206.3 | 303.4 | 303.4 | 303.4 |
|  | -£849,703 | £3,329,341 | £7,508,385 |
|  | 7.00 | 0.40 | 2.80 | 601.8 | 240.7 | 353.9 | 353.9 | 353.9 |
|  | -£991,320 | £3,884,232 | £8,759,783 |
|  | 8.00 | 0.40 | 3.20 | 687.8 | 275.1 | 404.5 | 404.5 | 404.5 |
|  | -£1,132,937 | £4,439,122 | £10,011,181 |

\* Best and worst case scenarios assume a total of 8831 CVCs required in PICUs in England during 2012 (based on survey responses).

\*\* Positive values indicate the value of resources made available through averting BSI

Figure 9: Risk-adjusted rates in bloodstream infection for children expected to have central venous catheters based on linked PICANet-Labbase2 data for 16 PICUs in England; symbols=observed rates; lines=smoothed adjusted rates (log-scale)



CATCH recruitment period

Figure 10: Probability distribution for the value of resources made available by averting BSI using antibiotic CVC in all PICUs in England during 2012, 90% of the distribution represented costs greater than the additional cost of purchasing antibiotic CVCs

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Additional cost of antibiotic CVCs =£317,916

Figure 11: Cost-impact: Number of BSI averted and value of resources made available using antibiotic in place of standard CVCs for a range of baseline rates, assuming each BSI is associated with a mean cost of £10,975

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Break-even BSI rate: 1.2

BSI rate using standard CVCs in all PICUs 2012

# CHAPTER 6 DISCUSSION

## Introduction

We aimed to inform NHS policy regarding impregnated CVCs for intensive care of children. In order to address the question of whether impregnated CVCs should be adopted by PICUs in England and Wales, we undertook a large pragmatic randomised controlled trial to determine the clinical effectiveness and cost-effectiveness of impregnated versus 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 between time to first BSI for any impregnated CVCs (antibiotic-impregnated or heparin-bonded combined) versus standard CVCs. However, secondary analyses showed that antibiotic-impregnation reduced the risk of BSI 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 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.3, 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.54, 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 the country. 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

Potential limitations are firstly, the fact that clinicians inserting the CVCs could not be blinded to allocation. However, we found no evidence of differential sampling by trial arm (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 Secondly, due to 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 versus 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 – which showed that heparin-bonded and antibiotic-impregnated CVCs resulted in similar reductions in the risk of CR-BSI (70-80%).1Thirdly, resistance testing was not standardised across sites. This reflects local laboratory administration and processing, which centralised testing of all positive cultures could have mitigated. Where reported, resistance occurred in all trial arms, predominantly in gram negative isolates, as expected. The low rates are consistent with previous lack of evidence for the emergence of resistance.2

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 0.08-0.34).1 Although our finding of a clinically important reduction in any BSI with antibiotic-impregnated CVCs (HR 0.25; 95%CI: 0.07, 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 BSI or CR-BSI contradicts past evidence showing a pooled odds ratio for CR-BSI given heparin-bonded versus standard CVCs of 0.20 (95% CI 0.06-0.44).1 The difference in findings may reflect poor data quality in previous trials, highlighted by systematic reviews.43-45 Only one of the three trials comparing heparin with standard CVCs reported adequate concealment of randomisation, and this trial did not state whether clinicians were blinded to the intervention.3 A further explanation for the discrepancy may be the low baseline event rate observed in CATCH, 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 pair-wise 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 incremental cost-effectiveness ratio of antibiotic-impregnated CVCs versus standard CVCs was £54,057 per BSI averted over the 6 months after randomisation. Assuming the health impact of a BSI is no greater (on average) than a reduction of one year of full health (i.e. one QALY), then at the cost-effectiveness threshold of £30,000 per QALY, antibiotic CVC 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 cost accruing over comparable periods.

A secondary analysis of the CATCH trial indicated that heparin CVCs were not clinically effective with a risk difference for first BSI of -0.17 (95% CI, -2.45, 2.12) versus 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 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 due to random variation. A CMA 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, which 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 source to measure hospital use in order to ensure that cost data were complete.

However, there are limitations which 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, results are susceptible to random variation in costs between trial arms. While 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 both antibiotic and standard CVCs despite their ineffectiveness in avoiding BSI when compared with standard CVCs. Being a rare event, BSI costs were diluted in overall costs relating to the intensive care of patients.

Second, the economic evaluation did not consider quality-adjusted life-year (QALY), which is the standard metric for informing decisions on resource allocation. This was because estimation of utilities in paediatric ICU populations is empirically and conceptually challenging,92, 93 and the main long-term consequence of BSI, the long-term impact on neurological outcomes, is poorly measured in children and was not measured in the 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 differences in 30-day mortality for antibiotic versus standard (HR 0.96; 95% CI 0.61, 1.51) or for heparin versus standard CVC (HR 0.65; 95% CI 0.40, 1.07) and no differences in adverse events (Table 10).

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 index hospitalisation and transfers that may have occurred subsequently. This was intended to capture the costs of managing any longer-term complications from BSI, 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 to the number of BSI (these all occurred within 30 days), the ICER continued to increase over time.

Our findings are consistent with other studies in the estimation of the costs associated with the management of BSI, however our ICER differs considerably, and is inconclusive with regards to determining the cost-effectiveness of antibiotic CVCs. Published economic evaluations, including those which 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 BSI. In the evaluation by Hockenhull et al. 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 BSI.29 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 x 2.15%}. Extending this further, to calculate the ICER, gives a value of £9,326 saved per BSI averted {= £200.08 / 2.15%}, which differs appreciably from our base-case result. However, by analysing the data as a cohort study, separating the apparent costs of BSI 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 a policy of replacing standard CVCs with antibiotic-impregnated CVCs in paediatric ICUs will be more beneficial in terms of fewer patients developing BSI. 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 as to whether use of antibiotic CVCs represents a cost-effective use of NHS resources.

## Generalisability and cost-impact

We explored the generalisability of CATCH trial results and the cost-impact of changing practice in PICUs across England based on the trial results. In terms of generalisability, 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 CATCH had a higher risk of BSI than all children receiving CVCs in practice, as they were expected to require a CVC for 3 or more days. This means that children currently receiving CVCs in PICU are likely to have a lower BSI risk than those participating in the trial. This was reflected in the higher rate of BSI 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, Figure 9).

In terms of budget-impact, antibiotic CVCs are more expensive than standard CVCs. If adopted in PICU, antibiotic CVCs would likely be bulk-purchased for all children (including those with a lower risk of BSI than those participating in the trial). By estimating the number of BSI potentially averted using antibiotic CVCs for all children (including those with 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 CVCs. Another limitation was the possible error in estimating CVC-days: we assumed that for children in the linked dataset likely to have required CVCs, CVCs would remain in place for the entire PICU stay. There is no clear direction of bias as we may have over- or under-estimated 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 PICU, but we addressed this and uncertainty in other parameter estimate by performing sensitivity analyses.95, 96

The generalisability of RCT results can be assessed by accounting for differences in subgroup treatment effects, e.g. by re-weighting treatment effects based on population distributions.97, 98 In CATCH, the event rate was low and there was limited power to assess variation in the treatment effect according to the duration of CVC. However, due to 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 relative risks and for baseline incidence of CR-BSI as low as 0.2%.29 CATCH is the first trial to assess the effectiveness of antibiotic-impregnated versus standard CVCs in children, and our results adds to strong evidence of effectiveness in adults. Furthermore, as our cost estimates only consider use of hospital resources, the true cost of BSI and the benefits of antibiotic CVCs may be even greater when longer term outcomes of BSI 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.55, 101 As CATCH 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 CATCH could help to inform future studies.

In CATCH, deferred consent was obtained from 84% of families who were approached.61 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 CATCH after the intervention had taken place represented minimal burden to children (use of data already collected and follow-up data collection only). However, a proportion of parents chose not to consent, due to a perceived burden on the child. Ongoing in-depth research as part of the CONNECT study may help to explain further the experiences and choices of parents of children involved in CATCH.55, 104

One of the main concerns relating to deferred consent in CATCH was whether 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 CATCH, 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, where reasonable efforts to obtain consent have been made or are not feasible or considered to be harmful.61

There is still uncertainty about the most appropriate ways to approach bereaved parents of children randomised in an emergency.105 Our experience with CATCH highlights that further in-depth research should be incorporated into 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. CATCH was the largest RCT conducted in paediatric intensive care to date, and overlapped with the second largest RCT (the CHiP trial), which recruited 1369 children in 13 centres.108 Allowing co-enrolment into several trials at the same time can potentially enable efficient recruitment of children and has been successful in particular settings, e.g. for evaluating AIDS treatments.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 CATCH and CHiP, only two units decided to allow co-enrolment. Of the remaining three units, one delayed recruitment of elective patients for CATCH until CHiP had closed, resulting in a loss of six 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 due to overwhelming amounts of information 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 CATCH 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 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 healthcare data to support RCTs

This study provides a convincing example of how administrative and electronic healthcare 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 Office for National Statistics to allow evaluation of deaths within 30 days of randomisation; ii) PICANet data 56 to ascertain the primary diagnosis at admission and the Paediatric Index of Mortality score (PIM2).
2. Cost-effectiveness: Hospital Episode Statistics (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 healthcare data could be used to enhance and support RCTs.117 Firstly, in terms of capturing outcomes, we used administrative data up to six months post-randomisation. Ongoing linkage with administrative data could be useful to many RCTs for capturing further long-term outcomes and safety measures.118

Secondly, the sample size calculation in CATCH was based upon 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 made. 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.

Thirdly, 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 continued study of the safety and efficacy of new medicines and devices.

Barriers to realising the full potential for 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-to-trial basis. However, administrative data provides an opportunity to efficiently investigate short and long-term effectiveness in real healthcare setting, to assess the broader impact of treatments across the NHS, and to 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 for the paediatric setting.99, 119, 120

## Implications for practice

Our findings establish the effectiveness of antibiotic-impregnated CVCs compared with standard CVCs for use in children. For the first time, we directly demonstrate that antibiotic-impregnated CVCs are effective compared with heparin-bonded CVCs in this population. 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 low BSI rates and outweigh the current price differential between impregnated and standard CVCs. However, uncertainty remains as to whether antibiotic-impregnated CVCs represent a cost-effective use of NHS resources; careful monitoring of implementation would help to build up further evidence.

## Recommendations for future research

Implementation strategies to promote adoption of impregnated CVCs across the NHS should be developed and could be monitored through continued linkage of electronic healthcare 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 versus standard CVCs for children or adults in intensive care. However, further trials could be justified to determine whether 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 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 of interventions in contexts where outcomes are likely to change substantially over the lifetime of the trial, and to monitor implementation of effective interventions.117

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