Cost-effectiveness of paediatric central venous catheters in the UK

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2 Cost-effectiveness of paediatric central venous catheters in the UK: A secondary publication

3 from the CATCH clinical trial

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21

22   **Abstract**

23   **Background**: Antibiotic-impregnated central venous catheters (CVCs) reduce the risk of

24   bloodstream infections (BSIs) in patients treated in paediatric intensive care units (PICUs).

25   However, it is unclear if they are cost-effective from the perspective of the National Health

26   Service (NHS) in the UK.

27   **Methods:** Economic evaluation alongside the CATCH trial (ISRCTN34884569) to estimate

28   the incremental cost effectiveness ratio (ICER) of antibiotic-impregnated (rifampicin and

29   minocycline), heparin-bonded and standard polyurethane CVCs. The 6-month costs of CVCs

30   and hospital admissions and visits were determined from administrative hospital data and

31   case report forms.

32   **Results**: BSIs were detected in 3.59% (18/502) of patients randomized to standard, 1.44%

33   (7/486) to antibiotic and 3.42% (17/497) to heparin CVCs. Lengths of hospital stay did not

34   differ between intervention groups. Total mean costs (95% confidence interval) were:

35   £45,663 (£41,647 to £50,009) for antibiotic, £42,065 (£38,322 to £46,110) for heparin, and

36   £44,503 (£40,619 to £48,666) for standard CVCs. As heparin CVCs were not clinically

37   effective at reducing BSI rate compared to standard CVCs, they were considered not to be

38   cost-effective. The ICER for antibiotic versus standard CVCs, of £54,057 per BSI avoided,

39   was sensitive to the analytical time horizon.

40   **Conclusions**: Substituting standard CVCs for antibiotic CVCs in PICUs will result in reduced

41   occurrence of BSI but there is uncertainty as to whether this would be a cost-effective

42   strategy for the NHS.

43   **Key words:**

44   Cost-effectiveness analysis, bloodstream infection, central venous catheter, paediatric

45   intensive care, antibiotic, heparin

46

Introduction

Central venous catheters (CVCs) are a large yet potentially avoidable cause of health-care
associated infections in hospitals. In paediatric intensive care units (PICUs), catheter-related
bloodstream infections (BSIs) occur in 3% to 8% of all CVC insertions [1]. BSIs are
associated with increased morbidity, mortality, lengths of hospital stay and healthcare costs
[2,3]. Since between 40% and 60% [4] of the 16,000 annual admissions to English PICUs [5]
require CVCs, BSIs represent a major burden to patients and the National Health Service
(NHS) [3,6].

The incidence of BSI in adults may be reduced with CVCs impregnated with antibiotics,
antibacterial agents or heparin. These are recommended for use in adults at highest risk of
BSI [7], but evidence in children is lacking [8]. CVC use in children presents a greater
theoretical risk of BSI owing to the narrower lumens within which blood may thrombose more
readily. The CATheter Infections in Children (CATCH) trial (NCT01029717) was a pragmatic,
three-arm randomized controlled trial aimed to determine the clinical and cost-effectiveness
of antibiotic or heparin CVCs compared with standard CVCs in children requiring intensive
care. Both heparin-bonded and antibiotic-impregnated CVCs prevent biofilm formation which
prevents bacterial colonisation. Heparin inhibits thrombus formation and heparin-bonded
CVCs use benzalkonium chloride as an anti-infective bonding agent. The primary analyses
of CATCH, however, showed no effect of impregnated compared with standard CVCs [9,10];
but secondary analyses revealed antibiotic CVCs to be superior to heparin CVCs with a
hazard ratio (HR) for time to first BSI of 0.42 (95% CI, 0.19 to 0.93), and to standard
polyurethane CVCs (HR 0.43; 95% CI 0.20 to 0.96). Heparin CVCs were no different from
standard (HR 1.04; 95% CI, 0.53 to 2.03).

As impregnated CVCs are more expensive than standard, decisions on their broader use
within the NHS requires evidence of their cost-effectiveness. Existing economic analyses are
limited in their applicability to the PICU setting in the UK as they relate to adult populations

73   and, with one exception [1], apply to different healthcare systems (Australia [11], Germany

74   [12] and the USA [13-15]). These studies indicate, however, that antibiotic-impregnated

75   CVCs are associated with improved health outcomes and are cost saving.

76   Previous economic evaluations are reliant on modelled costs and consequences of BSI

77   using data from a range sources, often observational studies. As such, they rely on assumed

78   attribution of hospital lengths of stay (the main cost driver) and mortality to BSI. The

79   economic evaluation which adopted an NHS cost perspective assumed catheter-related

80   BSIs increase the length of hospital stay by 6 additional days in intensive care units (ICU)

81   and 5 additional days in a general medical ward [1]. A US cohort study of 1,339 paediatric

82   cases of catheter-related BSI matched to controls by propensity-score, identified a higher

83   mean attributable length of stay of 19 days [16]. While this is comparable with the 21 days

84   excess length of stay estimated for BSI in paediatric haematology/oncology patients [17],

85   studies of this nature are based on retrospective observational data and are prone to bias.

86   Patients who are more ill are more likely to develop BSI, making it difficult to separate the

87   contribution of BSI to excess length of stay from the underlying condition.

88   The aim of the present study was to assess the cost-effectiveness of antibiotic and heparin

89   CVCs relative to commonly used standard polyurethane CVCs in a UK PICU setting using

90   data collected as part of the CATCH randomized controlled trial.

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4

92 **Methods**

93 **Design and results of CATCH**

94 CATCH recruited 1,485 children <16 years who were admitted to any of 14 PICUs in

95 England and who were expected to require a CVC for ≥3 days. Children were randomized

96 equally to receive heparin-bonded, antibiotic-impregnated (rifampicin and minocycline) or

97 standard polyurethane CVCs. The intervention was blinded to everyone except the clinicians

98 responsible for inserting the catheter. The primary outcome was the time to first BSI

99 occurring between 48 hours after randomization and 48 hours after CVC removal. This

100 occurred in 3.59% (18/502) children randomized to standard CVC, 1.44% (7/486) to

101 antibiotic and 3.42% (17/497) to heparin CVCs. In the primary analysis, impregnated CVCs

102 (antibiotic and heparin) were no more effective than standard CVCs (HR 0.71; 95% CI 0.37,

103 1.34). Antibiotic CVCs were superior to standard CVCs in secondary analysis (HR 0.43;

104 0.20, 0.96) but heparin CVCs were not (HR 1.04; 0.53, 2.03). There were no differences

105 between intervention groups in other outcomes, including time to thrombosis, 30-day

106 mortality, or antibiotic resistance (minocycline or rifampicin). Trial results are presented in full

107 elsewhere [9,10].

108 The CATCH trial is registered with the ClinicalTrials.gov (Trial registration: NCT01029717

109 Registered 9 December 2009), and was conducted in accordance with the recommendations

110 of the Research Ethics Committee for South West England, with prospective or deferred

111 written informed consent obtained from all subjects in accordance with the Declaration of

112 Helsinki. The protocol was approved by the Research Ethics Committee for South West

113 England (reference number 09/H0206/69), and is available at

114 www.nets.nihr.ac.uk/projects/hta/081347.

115 **Economic evaluation**

116   We conducted a cost-effectiveness analysis as it is not possible to estimate health utilities in

117   children in a PICU setting [18]. While this precluded any evidence on allocative efficiency, it

118   allowed for an assessment of technical efficiency for selecting the most cost-effective CVC

119   for reducing the occurrence of BSIs.

120   **Resource use**

121   The economic analysis adopted the perspective of the NHS in England, with resource use

122   measurement focused on the principal cost drivers, which were PICU, High Dependency

123   Unit (HDU) and ward stays (including readmissions), outpatient clinic visits, Accident and

124   Emergency (A&E) admissions and the costs of the CVCs. The 6-month time horizon of the

125   base-case analysis was chosen to include the costs associated with managing BSIs and

126   associated complications. Shorter time horizons were explored in sensitivity analyses.

127   Patients' use of hospital services were obtained from trial case report forms (CRF), Hospital

128   Episode Statistics (HES), the Paediatric Intensive Care Audit Network (PICANet), and

129   hospital Patient Administration Systems (PAS). CRFs were accessed for data on dates of

130   hospital discharge, transfer to other hospitals and CVC removal. HES data on Healthcare

131   Resource Groups (HRGs) corresponding to the type of care patients receive at a ward-level,

132   outpatient visits and A&E admissions, were accessed from NHS Digital [19]. We accessed

133   the PICANet dataset [20] for the National Schedule of Reference Cost HRGs for HDU and

134   ICU stays [21], and for verifying the dates of hospital admission, transfer and discharge. The

135   finance offices of each participating hospital provided data from Patient Administration

136   Systems (PAS) on patients' lengths of stay in ICUs and wards, and on relevant HRGs.

137   These were used to supplement data that were otherwise missing from other sources.

138   **Costs analysis**

139   HRGs reflect NHS hospital payments for patients' use of hospital services. Unit costs from

140   the 2012-13 National Schedule of Reference Costs [21] were applied to all HRG codes; the

141   most significant being those associated with PICU, Neonatal Intensive Care Unit (NICU) and

6

142 HDU (Table 1). Basic HDU (XB07Z) or ICU (XB05Z) codes were applied in the 10% of

143 cases where HRG codes were missing.

144 Unit costs of ward, outpatient and A&E attendances are presented in the Supplementary

145 Appendix Tables 1 to 3. Any missing HRGs from HES or PAS data were replaced with ward

146 costs based on bed-day rates provided by hospital finance offices (Supplementary Appendix

147 Table 4). Bed-day rates were also applied to unassignable HRG codes appearing in the HES

148 and PAS data, but overall, bed-day rates were used to cost less than 1% of admissions.

149 Catheter list prices were provided by the supplier (Cook Medical, Bloomington, IN, USA).

150 The costs of care for the 6-months prior to randomization were calculated from HES and

151 PICANet data. Given that HRGs relate to episodes of care, we calculated patient costs for

152 the 6-months following randomization according to:

153 $$\text{Cost} = (N/n+N) \times (\text{ward cost} + \text{PICU cost} + \text{HDU cost})$$

154 $$+ (\text{outpatient costs} + \text{A\&E costs} + \text{CVC costs})$$

155 Where n and N are the number of days patients were hospitalised prior to, and following

156 randomization, respectively.

157 Patients' use of healthcare resources and total costs were calculated for the intention to treat

158 population, and summary statistics were generated by intervention group.

159 **Outcomes**

160 The health outcome for the cost-effectiveness analysis was the presence of a first BSI.

161 These were defined in CATCH by a positive blood culture from a sample that was clinically

162 indicated and taken more than 48 hours after CVC insertion and up to 48 hours after CVC

163 removal [9].

164 **Incremental analysis**

165 Each CVC was ranked in order of decreasing effectiveness and dominated interventions

166 (those which are less effective or ineffective) or extendedly dominated interventions

167 eliminated. The incremental cost effectiveness ratio (ICER) was calculated for remaining

168 CVCs as the difference in the means of total costs divided by the difference in the proportion

169 of bloodstream infections.

Uncertainty analysis

171 Bias-adjusted 95% central ranges for differences in costs and BSI were calculated from

172 10,000 replicate bootstrap analyses. The joint uncertainty in costs and BSI was depicted in a

173 cost-effectiveness acceptability curve (CEAC) which presented the probability of CVCs being

174 cost effective for different threshold willingness to pay for each BSI averted[22].

175 Uncertainty in total costs was further assessed by adjusting for the contribution of baseline

176 factors to overall variability [23].

Sensitivity analysis

178 Given the dependency of costs and therefore the ICER on the analytic time horizon, a

179 sensitivity analysis was performed in which costs were limited to those incurred during the

180 index hospitalization (that is, excluding any re-admissions that may have occurred over the

181 6-month period).

Regression analysis

183 Regression analyses were performed to control for possible baseline imbalances between

184 intervention groups [23] and, by including a variable to representing the presence of a BSI,

185 to estimate the value of healthcare resources associated with the management of BSI. The

186 following pre-specified variables were tested for their independent associations with total

187 costs: Age, body weight, 6-month pre-randomization costs (all log-transformed), gender, pre-

188 existing CVC 72 hours prior to randomization, health status before PICU admission, reason

189 for admission (cardiovascular, endocrine or metabolic, infection, neurological, oncology,

190   respiratory, trauma, other), suspected infection at randomization, immune compromised,

191   positive blood culture within 72 hours prior to randomization, numbers of devices in situ, and

192   admission type (elective or emergency). Where data were missing, we assumed: patients to

193   be healthy (n=1), not immunocompromised (n=19) and no positive blood culture (n=5).

194   Missing data for weight (n=2) were imputed with the mean (11.95 kg).

195   Variables that were significant at the 5% level were included using a stepwise approach in

196   multivariable generalized linear models (GLMs) that were specified using a combination of

197   families (e.g. gamma and poisson) and links (e.g. log, square root and identity). Modified

198   Park's test and Akaike Information Criterion were used to assess GLM goodness of fit but

199   were inconclusive. The identity link function performed best according to the Pearson

200   Correlation, Pregibon Link and the Modified Hosmer and Lemeshow tests. We therefore

201   specified an ordinary least squares regression based on the comparatively large sample size

202   which guaranteed near-normality of sample means [24].

203   All analyses were performed using STATA Version 10, and the economic analysis was

204   reported according to the Consolidated Health Economic Evaluation Reporting Standards

205   (CHEERS) statement [25].

206

207 **Results**

208 **Resource use and costs**

209 Cost data were available for all patients. Hospital ICU/HDU length of stay and total costs

210 were comparable between intervention groups during the 6-months prior to randomization.

211 In the 6-months following randomization, patients randomized to antibiotic-impregnated

212 CVCs were in PICU for a mean of 10.8 days (95% CI, 9.3 to 12.4), compared with 9.9 days

213 (95% CI, 8.6 to 11.4) for those randomized to heparin-bonded CVC and 10.5 days (95% CI,

214 9.2 to 11.9) for standard CVCs (Table 2). Mean durations of hospitalisation were 34.8 days

215 (95% CI, 31.2 to 38.5) for antibiotic-impregnated CVC, 31.4 days (95%CI, 28.2 to 34.7) for

216 heparin-bonded CVC and 31.7 (95% CI, 28.8 to 34.7) for the standard CVC group. Six

217 HRGs (from a total of 349) relating to congenital or other cardiac surgery and lower

218 respiratory tract disorders, accounted for 50% of ward costs.

219 Mean 6-month costs were £44,503 (median £28,952; range £1,786 to £360,983; 95% CI,

220 £40,619 to £48,666) for standard CVC, £45,663 (median £29,793; range £2,189 to

221 £442,365; 95% CI, £41,647 to £50,009) for antibiotic-impregnated CVC, £42,065 (median

222 £27,621; range £2,638 to £382,431; 95% CI, £38,322 to £46,110) for heparin-bonded CVC

223 (Table 3). Costs were not significantly different by CVC group over the 6-month timeframe.

224 Variables tested for the cost regression were evenly balanced between intervention groups

225 [8]. The residual variability in total cost could be explained, in part, by the following

226 significant explanatory variables: age (in days), 6-month pre-randomization costs (both log-

227 transformed), health status at randomization, reason for admission, immune status, and

228 admission type (elective or emergency). The adjusted incremental costs associated with

229 antibiotic CVCs, in relation to standard CVCs, were £1,220 (95% CI, -£4,332 to £6,773), and

230 with heparin CVCs, -£2,399 (95% CI, to -£7,914 to £3,120).

231 **Outcomes**

232 Seven patients from 486 randomized to antibiotic CVCs experienced a BSI, compared with

233 17/497 in the heparin CVC group and 18/502 in the standard CVC group. A statistically

234 significant absolute risk differences was found only for antibiotic versus standard CVCs (-

235 2.15%; 95% CI, -4.09 to -0.20). Heparin CVCs were not clinically effective with a risk

236 difference of -0.17% (95% CI, -2.45 to 2.12) versus standard CVC.

Value of healthcare resources associated with BSI

238 Patients who had a BSI (n=42) experienced 6.5 more days (95% CI, 1.4 to 11.6) in PICU

239 than those with no BSI (n=1,443), and 15.1 additional total days (95% CI, 4.0 to 26.2) of

240 hospitalization. The mean 6-month costs for patients with a BSI was £60,481 (95% CI,

241 £47,873 to £73,809) compared to £43,578 (95% CI, £41,185 to £45,970) for those without; a

242 difference of £17,263 (95% CI, -£3,076 to £31,450). The adjusted difference in mean costs

243 was £10,975 (95% CI, -£2,801 to £24,751).

Incremental and uncertainty analysis

245 Heparin CVCs were not clinically effective when compared to standard CVC, and are more

246 expensive, and so cannot be cost-effective by the same measure of BSI. The ICER for

247 antibiotic-impregnated versus standard CVCs was £54,057 per BSI averted (Table 4).

248 The probabilities of antibiotic CVCs being cost-effective at thresholds of £10,000, £50,000

249 and £100,000 per BSI averted, were 0.38, 0.49 and 0.62, respectively (Figure 1). There is a

250 probability of 0.650 for standard CVCs dominating antibiotic CVCs.

Sensitivity analysis

252 Considering only the index hospitalization, total costs in the antibiotic CVC group were

253 £33,073 (95% CI, £30,047 to £36,337) compared to £32,245 (95% CI, £29,013 to £35,823)

254 in the heparin CVC group and £35,165 (95% CI, £31,864 to £38,670) in the standard CVC

255 group. Antibiotic CVCs therefore dominated standard CVC with a difference of 2.15% in the

256 risk of BSI, and a saving of £97,543 per BSI averted.

Discussion

258   The results of the base-case analysis indicate that heparin-bonded CVCs are not cost-

259   effective while the incremental cost-effectiveness ratio of antibiotic-impregnated CVCs

260   versus standard CVCs is £54,057 per BSI averted. However, there is considerable

261   uncertainty in this estimate. Restricting costs to the index hospital stay resulted in an ICER

262   of £97,543 saved per BSI averted for antibiotic compared to standard CVCs. Antibiotic CVCs

263   are highly cost-effective when considering costs accruing over comparable periods to

264   events.

265   The economic analysis benefits from having been designed and executed as an integral part

266   of a pragmatic clinical trial that provided an unbiased comparison of CVCs in the context of

267   current practice in 14 UK PICUs. The cost-effectiveness analysis was conducted to

268   accepted methodological standards of trial-based economic evaluations [26]. Patient-level

269   HES data were used to reflect NHS payments to hospitals for their services, and we

270   exploited different sources to ensure a complete dataset.

271   However, there are limitations to the analysis. First, the CATCH trial was not powered to

272   demonstrate statistically significant differences in effectiveness or costs among each of the

273   three types of CVCs. However, differences in the rates of BSI were pre-specified in a

274   secondary analysis, and a lack of a difference in costs between intervention groups is less

275   relevant in the context of net benefits [27]. The joint uncertainty in costs and BSI is

276   considered in the CEAC which indicated antibiotic CVCs as having a probability of 0.35 of

277   dominating standard CVCs. Despite not being effective at reducing BSI rates, the mean

278   costs associated with heparin CVCs were lower than for either antibiotic or standard CVCs.

279   This is likely to be explained by BSI being a rare event, with associated costs diluted in the

280   overall costs of managing patients in intensive care.

281   A second limitation was in our choice of economic outcome. The quality-adjusted life-year

282   (QALY), which is the preferred measure of health outcome for cost-utility analyses [28],

12

283   could not be estimated in the study population [18]. The majority of trial participants (58%)

284   were aged less than one year, and even if utilities were measured by proxy, these would be

285   unreliable, especially in the context of intensive care. Using BSI averted as the denominator

286   of the ICER calculation also fails to fully capture other possible consequences of BSI,

287   including long term neurological defects, mortality, antibiotic resistance [29] and other

288   adverse events [30]. While neurological outcomes were not monitored in CATCH, there were

289   no differences in 30-day mortality for antibiotic versus standard (HR 0.96; 95% CI, 0.61 to

290   1.51) or for heparin versus standard CVC (HR 0.65; 95% CI, 0.40 to 1.07). There were also

291   no differences between intervention groups in microbial resistance to minocycline or

292   rifampicin, or in adverse event rates [9,10].

293   In contrast to QALYs, where an explicit threshold range has been defined (£20,000 to

294   £30,000 per QALY gained for most health technologies in the UK), there is no threshold for

295   BSIs averted. Interpretation may therefore be dependent on previous economic evaluations,

296   such as Shorr et al., [14] who considered US$9600 to be cost-effective, or assumptions

297   concerning the impact of BSI on health. For instance, if BSIs are assumed to impair patients'

298   quality of life by a year, (i.e. 1 QALY decrement on average), then antibiotic CVCs may not

299   be cost-effective.

300   The choice of analytical time horizon represents a further limitation. Six months was selected

301   to capture the costs of subsequent hospital readmissions and transfers to other hospitals.

302   However, as the cost-effectiveness calculation considered only the first BSI, costs accrued

303   over time with no corresponding change to the number of BSI (these all occurred within 30

304   days). Consequently, the ICER continued to increase over time.

305   Our estimates of the costs associated with the management of BSI are broadly in line with

306   other economic evaluations [1]; however there are appreciable differences in our estimate of

307   the ICER. Previous economic analyses indicated the dominance of antibiotic CVCs over

308   standard CVCs. Possible explanations for this discrepancy are that model-based analyses

309 are based on a synthesis of data from disparate sources, require strong assumptions on the

310 attribution of hospital lengths of stay and mortality to BSI and assume independence of the

311 cost of managing BSIs and CVC type.

312 In conclusion, the results of the economic evaluation indicate that replacing standard

313 polyurethane CVCs with antibiotic-impregnated CVCs in PICUs will result in reduced rates of

314 BSI. Given the low background rate of BSI, the variation in costs between CVCs and the

315 sensitivity of the ICER to the time-horizon of analysis, it remains uncertain if antibiotic-

316 impregnated CVCs are cost-effective from a UK NHS perspective. However, given the focus

317 of the evaluation, there is limited generalisability outside the UK to other payers, healthcare

318 systems or jurisdictions. Our economic findings from CATCH add to evidence on the

319 generalisability of trial participants in the UK, and on the cost implications of using antibiotic-

320 impregnated CVCs to the NHS [31].

321

322 **Author contributions**

323 DH and RG conceptualized the study; CR, RG and DH made substantial contribution to the

324 study design and acquisition of data; CR, CP, RG and DH made substantial contribution to

325 the analysis and interpretation of data, revised the paper critically for important intellectual

326 content and approved the final manuscript.

334 **Competing interests**

335 The authors declare that they have no competing interests.

370

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Table and figure titles and legends

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Table 1. Unit cost for intensive care and high dependency care, based on HRGs from the

National Schedule of Reference Costs (2012-13)

HRG code	HRG name	Description		Cost per day
XB01Z	Pediatric Critical Care, Intensive Care, ECMO/ECLS	Highly specialized intensive care treatment	ECMO, VAD and other highly complex procedures	£4,391
XB02Z	Pediatric Critical Care, Intensive Care, Advanced Enhanced		Unstable multi-system failure with other complications	£2,409
XB03Z	Pediatric 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	Pediatric Critical Care, Intensive Care, Basic Enhanced		Intensive ventilation with more than one system failure	£2,110
XB05Z	Pediatric 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	Pediatric 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	Pediatric Critical Care, High Dependency		Close monitoring, oxygen by mask, no invasive ventilation)	£886
XB08Z	Pediatric Critical Care, Transportation	Since pediatric critical care facilities are centralized in a small number of hospitals providing expert specialist care, specialist		£2,799

		transport teams are required to deliver clinical management during transfer of patients		
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

476   Abbreviations: ECMO extra-corporeal membrane oxygenisation, ECLS extracorporeal life

477   support, VAD Ventricular assist devices, CPAP Continuous Positive Airway Pressure, BiPAP

478   Bi-Level Positive Air Pressure, IV intravenous.

Table 2. Patients' lengths of stay from randomization to 6-months (including readmissions), according to place and intensity of care and by intervention group.

Unit	Antibiotic CVC		Heparin CVC		Standard CVC	
	Mean	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**
Days on ICU	10.79	9.28, 12.48	9.91	8.57, 11.44	10.50	9.17, 11.93
Pediatric Critical Care, Intensive Care, ECMO/ECLS (XB01Z)	0.30	0.07, 0.72	0.38	0.09, 0.80	0.40	0.17, 0.72
Pediatric Critical Care, Intensive Care, Advanced Enhanced (XB02Z)	0.16	0.09, 0.26	0.12	0.09, 0.15	0.16	0.10, 0.26
Pediatric Critical Care, Intensive Care, Advanced (XB03Z)	0.76	0.51, 1.05	0.61	0.43, 0.83	0.65	0.46, 0.87
Pediatric Critical Care, Intensive Care, Basic Enhanced (XB04Z)	2.30	1.92, 2.72	2.68	2.09, 3.44	2.75	2.14, 3.54
Pediatric Critical Care, Intensive Care, Basic (XB05Z)	6.96	5.65, 8.45	5.63	4.75, 6.59	6.40	5.42, 7.47
Neonatal Critical Care, Intensive Care (XA01C)	0.29	0.10, 0.55	0.46	0.13. 1.03	0.11	0.04, 0.20
Days on HDU	1.99	1.48, 2.62	1.59	1.28, 1.99	1.73	1.44, 2.05
Pediatric Critical Care, High Dependency, Advanced (XB06Z)	1.27	0.94, 1.70	1.08	0.80, 1.45	1.22	0.98, 1.49
Pediatric Critical Care, High Dependency (XB07Z)	0.71	0.42, 1.16	0.51	0.40, 0.64	0.51	0.40, 0.64
Days on ward	22.01	19.26, 24.80	19.84	17.40, 22.40	19.48	17.12, 21.94
Total days in hospital	34.80	31.21, 38.48	31.35	28.18, 34.65	31.71	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	

Abbreviations: CVC central venous catheter, CI confidence interval, ICU Intensive care unit, ECMO extra-corporeal membrane oxygenisation, ECLS extracorporeal life support, HDU High dependence unit, PICU Pediatric intensive care unit, HRGs Healthcare Resource Groups.

Table 3. Disaggregated and total costs (£) by intervention group from randomization to end of the six-month timeframe.

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

comorbidity (PA23A)						
Lower Respiratory Tract Disorders without acute bronchiolitis with length of stay ≥1 day with complication and comorbidity (PA14C)	858	593, 1157	668	454, 913	943	657, 1268
Implantation of Prosthetic Heart or Ventricular Assist Device (EA43Z)	273	0, 684	298	0, 762	548	103, 1155
Other inpatient HRG costs	10,316	8616, 12,231	8803	7524, 10,106	9930	7860, 12,409
Sub-total (inpatient)	19,766	17,934, 21,755	17,700	16,308, 19,182	18,814	16,649, 21,327
A&E cost	89	76, 104	85	73, 99	91	78, 104
Outpatient cost	1615	1412, 1838	1784	1496, 2109	1648	1453, 1871
CVC cost	78	78, 78	78	78, 78	43	43, 43
Total Cost (full 6 months)	45,663	41,647, 50,009	42,065	38,322, 46,110	44,503	40,619, 48,666

[a] National Schedule of Reference Costs 2012-2013; [b]Top 6 (of 349) HRGs ranked by cost, together contributing 50% of overall inpatient cost, <1% taken from bed day rates.

Abbreviations: CVC central venous catheter, CI confidence interval, ECMO extra-corporeal membrane oxygenisation, ECLS extracorporeal life support, HDU High dependence unit, PICU Pediatric intensive care unit, NICU Neonatal intensive care unit, HRGs Healthcare Resource Groups, A&E Accident and Emergency.

Table 4. Incremental analysis

	Antibiotic CVC	Heparin CVC	Standard CVC
Base-case analysis (6-month time horizon)			
Total costs	£45,663 (£41,647, £50,009)	£42,065 (£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 hospitalization)			
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)	-£97,543 per BSI averted [b]	-[a]	-

Values are means with 95% confidence intervals in parentheses.

[a]As heparin CVC was not deemed to be clinically effective in reducing BSI rates, it cannot be cost-effective by the same outcome measure

Abbreviations: BSI bloodstream infection, ICER incremental cost effectiveness ratio, CVC central venous catheter.

Figure 1. Cost-effectiveness acceptability curve presenting the probability of antibiotic and standard CVCs being cost-effective for a given values of ceiling ratio expressed as cost per bloodstream infection (BSI) averted