NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology consultation:

Curos for preventing infections when using needleless connectors

Supporting documentation – Committee papers

The enclosed documents were considered by the NICE medical technologies advisory committee (MTAC) when making their draft recommendations:

1. **EAC assessment report** – an independent report produced by an external assessment centre who have reviewed and critiqued the available evidence.
2. **Assessment report overview** – an overview produced by the NICE technical lead which highlights the key issues and uncertainties in the company's submission and assessment report.
3. **Adoption scoping report** – produced by the adoption team at NICE to provide a summary of levers and barriers to adoption of the technology within the NHS in England.
4. **Sponsor submission of evidence** – the evidence submitted to NICE by the notifying company.
5. **Expert questionnaires** – expert commentary gathered by the NICE team on the technology.
6. **EAC correspondence log** – a log of all correspondence between the external assessment centre (EAC) and the company and/or experts during the course of the development of the assessment report.
7. **Company fact check comments** – the manufacturer's response following a factual accuracy check of the assessment report.

Please use the above links and bookmarks included in this PDF file to navigate to each of the above documents.

Curos disinfecting caps for infection prevention in needleless connectors

Produced by:	Cedar
Authors:	Dr Susan O'Connell, Senior Healthcare Researcher Megan Dale , Senior Healthcare Researcher Dr Helen Morgan, Senior Information Specialist and Systematic Reviewer Prof. Grace Carolan-Rees, Cedar Director
Correspondence to:	CEDAR Healthcare Technology Research Centre Cardiff and Vale University Health Board Cardiff Medicentre Heath Park, CARDIFF CF14 4UJ
Date completed:	08/11/2018

Declared interests of the authors

Description of any pecuniary relationship with the company, both personal and of the EAC. Please refer to NICE's Code of Practice for declaring and dealing with conflicts of interests.
http://www.nice.org.uk/niceMedia/pdf/Guidanceondeclarationsofinterest.pdf

None

Acknowledgements

Dr Elizabeth Pilling, Consultant Neonatologist, Royal Hallamshire Hospital

Ms Catherine Plowright, Acute Care Consultant Nurse, East Kent Hospitals University NHS Foundation Trust

Ms Jan Hitchcock, Gneral Manager (interim) Infection Prevention and Control, Imperial College Healthcare NHS Trust

Rider on responsibility for report

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

Contents

ABBREVIATIONS

Term	Definition
BSI	Bloodstream Infection
CASP	Critical Appraisal Skills Programme
CI	Confidence interval
CLABSI	Central Line Associated Bloodstream Infection
CRBSI	Catheter Related Bloodstream Infection
CBC	Contaminated Blood Culture
CVAD	Central Vascular Access Device
CVC	Central Venous Catheter
DH	Department of Health
EAC	External Assessment Centre
ICU	Intensive Care Unit
IQR	Interquartile range
MAUDE	Manufacturer and User Facility Device Experience
MHRA	Medicines & Healthcare products Regulatory Agency
MTEP	Medical Technologies Evaluation Programme
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICE CG	NICE clinical guideline
NICE MTG	NICE medical technology guidance
NICE QS	NICE quality standard
PICC	Peripherally Inserted Central Catheter
PID	Peripherally Inserted Device
PIV	Peripheral Intravenous Line
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QUORUM	Quality of Reporting of Meta-analyses
RCT	Randomised Controlled Trial
SD	Standard deviation
VAS	Visual Analogue Scale
vs	Versus

1 Executive Summary

The company submission included evidence from 5 published studies (5 before and after studies) and 5 unpublished abstracts. The EAC included one further before and after quality improvement study and 4 additional unpublished abstracts.

The quality of the published studies was considered to be very low and at high risk of bias by the EAC and there was not enough information to assess the quality of the unpublished abstracts.

Published studies showed a reduction in infection rates following the introduction of Curos but each study included elements of education and training which may have contributed to the reduction of infection rates. Alcohol wipes were still available for use as well as Curos in one study. Compliance with Curos was reported in the individual studies but compliance with manual disinfection is harder to assess and was reported in one study. The EAC concludes that it is not possible to attribute any reduction in infection rates to the use of Curos alone.

There was no published economic model comparing Curos with manual disinfection so the company submitted a de novo cost model. The model included two patient settings (a general hospital setting and an intensive care setting) and results of the submitted cost-analysis indicated that Curos was cost saving in both settings.

The EAC agreed with the model structure but did not agree with some inputs in the model in particular the nurse time for manual disinfection. The EAC believe nurse time for disinfection would be equal for both methods, as drying time during manual disinfection is time a nurse would be doing other things and is therefore not time to be saved.

The changes made by the EAC result in Curos becoming cost incurring in the ICU setting.

The EAC included a scenario analysis of patients in a burns unit taking data from one study (Martino, 2017). The results of the economic analysis in this patient group indicated that Curos was cost saving in this setting but this was based on data from a single study.

The company submission did not include any data on the environmental impact of Curos. The use of Curos is likely to increase plastic waste in the NHS both because the cap itself is plastic and because each cap is individually cased in plastic.

2.1 Overview and critique of company's description of clinical context

The background and clinical context provided in the company submission lacked detail. The company submission mentions only central venous catheters (CVCs) in relation to central line associated bloodstream infections (CLABSI) and catheter related bloodstream infections (CRBSI) although the scope includes all patients with vascular access devices. This would include peripheral intravascular devices (PIDs) and midline catheters. Types of CVC include peripherally inserted central catheters (PICCs), tunnelled central venous catheters, per-cutaneous non tunnelled cathers and implantable ports.

There was no information on the prevalence of CLABSI/CRBSI in patients with any type of vascular access device. NICE guidelines on the prevention of healthcare associated infections state that an estimated 300,000 patients a year in England acquire a healthcare-associated infection as a result of care within the NHS but there is no information as to the proportion of infections that are specifically bloodstream infections associated with vascular access devices [NICE CG139]. Therefore there is no information on the size of the population who may benefit from this device. The company submission estimates that 50% of general admissions and 100% of critical care admissions to hospital receive either an acture or longer term intravenous therapy via a needle free device attached to a vascular access device however they provide no evidence to support this estimate.

The company submission is appropriate and relevant to the decision problem. The company excluded studies in the community setting, although they were included in the scope. The EAC reviewed the evidence and identified only a single study conducted in the community setting which is currently completing data collection and will not have results reported within the time-frame necessary for inclusion in this assessment report. The EAC therefore agree that excluding the community setting is appropriate.

Infection prevention is a multifaceted process of which disinfection is only a part. As a result there is a 'bundle' of processes and interventions which make up an infection management protocol for staff. This bundle approach can include numerous elements such as hand hygiene, caps and gowns, disinfection of access ports with wipes or caps and regular education and training for staff. Currently manual disinfection using alcohol wipes is the considered standarad care in the NHS. The device is intended to replace alcohol wipes in the infection control bundle of care for patients with vascular access devices. The company claim that use of the device means that

healthcare staff do not need to spend time disinfecting and waiting for needless connectors to dry everytime they are used. The company claim that this may reduce bloodstream infections and as a result reduce the need for catheter tip cultures, freeing up laboratory time.

Table 1: Critique of company's definition of the decision problem

Decision Problem	Company Submission	Matches Decision Problem (Y/N)	EAC Comment
Population	People with vascular access devices in hospital and community settings	Partially	The scope included hospital and community settings but there was no evidence relating to the community setting therefore the company excluded this.
Intervention	Curos disinfecting cap	Y	
Comparator	• alcohol wipes • alcohol containing solution of chlorhexidine gluconate	Y	
Outcomes	• time taken to complete disinfect • overall staff time • infection rates (CLABSI and catheter-related bloodstream infections) • mortality • length of hospital stay • length of time vascular access device in place • device-related adverse events • improved consistency in disinfection protocols • reduced use of chlorhexidine • environmental impact of reduced number of wipes disposed and increased plastic waste	Partially	Outcomes of interest listed in the study selection criteria table (Table B1) of the company's submission include: • The number of catheter related bloodstream infections (CRBSI) or central line associated bloodstream infections (CLABSI) per 1000 catheter-days. In aggregate and separately by central lines and peripheral lines (if possible); • Bacteraemia rates for CRBSI and CLABSI; • Device related adverse events. Where studies report the number of infections and the number of catheter-days, the rate was calculated if possible. Communication with the company indicated that outcomes related to resource use (e.g. length of stay) would be included in the cost analysis and not in the clinical analysis. The EAC included all relevant outcomes, including those related to resource use, reported in the clinical submission. The EAC noted that compliance was not specifically included as an outcome in the scope nor did the company submission consider it in

			their selection criteria for published studies. The EAC noted that the outcome 'improved consistency in disinfection protocols' listed in the decision problem table (Table A1) could be interpreted as compliance rates. The company submission did report compliance rates from the included studies. The EAC agrees that compliance rates should be included as this may have an impact on the more important infection rate outcomes.
Cost Analysis	De Novo Cost Effectiveness Model	Partially	The model does not include mortality due to a lack of available data. The EAC agrees that this is an appropriate exclusion.
Subgroups	None	Y	

Special considerations, including issues related to equality

Curos disinfection caps are small medical devices and as such there is a potential choking hazard if ingested. The company considers this risk to be small but highlight the possibility that the risk may be higher in children.

Curos may be used with vascular access devices in people with chronic diseases who are considered disabled under the equality act. This will include people with cancer and may include people with chronic kidney disease, cystic fibrosis, sickle cell disease, thrombotic thrombocytopenic purpura, Sjogrens syndrome, Guillian-Barre syndrome, myasthenia gravis and lysosomal storage disorders.

No equality issues were highlighted by the company and the EAC consider there to be no specific equality issues relating to the use of Curos in addition to those highlighted in the scope.

2 Clinical evidence

2.1 Critique of and revisions to the company's search strategy

The EAC consider that the search strategy submitted was appropriate and comprehensive. Searches were conducted across a wide range of databases including: Medline, Medline In Process, Embase and The Cochrane Library. A single search strategy was developed to identify both clinical and economic evidence and the sensitivity of the strategy was tested against known publications. The company submission included searches for unpublished literature, ongoing clinical trials and clinical data on safety and adverse events of Curos.

As the original searches were conducted in September 2017, the EAC used the strategy developed by the company to carry out update searches to check for any new evidence in the period September 2017-September 2018.

2.2 Critique of the company's study selection

The EAC noted that the inclusion and exclusion criteria applied for study selection may have resulted in the exclusion of potentially relevant studies.

The company submission did not include any studies published before 2015. Communication with the company indicated that this decision was made due to there being a published systematic review (Voor in 't holt et al 2017) which they considered comprehensive and methodologically sound. As a result the company took the view that they need only update the systematic review. The EAC assessed the quality of the systematic review (Appendix C) and agreed that the literature searches were comprehensive and unlikely to have missed

evidence relevant to the decision problem being assessed. The searches in the systematic review were conducted up until May 2016 therefore by excluding anything pre-2015, the EAC consider that the company submission has allowed a sufficient overlap in search dates to ensure the risk of missing relevant studies is minimal.

The company submission states that retrospective studies were excluded as they considered there to be sufficient evidence from prospective studies. The EAC noted that the studies included in the submission were not true prospective studies. All studies were 'before and after' studies where only data on the intervention was collected prospectively. The EAC queried whether there was likely to be any relevant evidence in the retrospective studies. A review of the excluded studies by the EAC identified no additional published studies and 3 additional unpublished abstracts for inclusion.

Table 2: Critque of Company's Study Selection

	Company Inclusion	Company Exclusion	EAC Comment
Population	Studies of any hospitalized patients receiving a central or peripheral line.	Studies of non-hospitalized patients or patients who had not received a central or peripheral line.	This excludes any studies in the community setting which was part of the scope. The EAC did not identify any published data from studies in the community setting. The EAC has reviewed the excluded studies list for any relevant studies and identified 3 unpublished studies considered to be relevant.
Interventions	Studies that report on the use of Curos to cap central lines with access to the bloodstream or peripheral lines. Studies that report on Curos within bundles, as long as data on Curos are reported separately.	Studies that did not investigate Curos. Studies of the use of Curos with feeding tubes or for other purposes without access to the bloodstream.	The EAC agree with the inclusion of studies that report on the use of Curos to cap central lines with access to the bloodstream or peripheral lines. The EAC queried the exclusion of studies where Curos data are not reported separately. Infection prevention is a multifaceted process of which disinfection of ports is a part. Exclusion of bundle studies with Curos may mean that the impact of Curos is over-estimated by including only studies which assess Curos without making provisions for the impact of other aspects of the bundle such as on-going training/education. The EAC did not identify any studies which clearly assessed a bundle approach which included Curos as part of the bundle. One study (Martino, 2017) did include some data for a period of time following the introduction of Curos when the bundle approach changed.

	Company Inclusion	Company Exclusion	EAC Comment
Outcomes	• The number of CRBSI or CLABSI per 1000 catheter-days. In aggregate and separately by central lines and peripheral lines (if possible); • Bacteraemia rates for CRBSI and CLABSI; • Device related adverse events. Where studies report the number of infections and the number of catheter-days, the rate was calculated if possible.		The EAC agrees that the outcomes listed are appropriate however it is noted that they differ from the outcomes in the scope; the company stated there was no variation. A number of outcomes listed in the scope were not included, (e.g.environmental impact), although the EAC identified no evidence for these outcomes. The company's submission states that outcomes related to resource use have not been reported as part of the clinical submission but will be included in the economic analysis
Study design	Prospective studies. Published SRs and their included studies lists were checked to ensure that all relevant articles had been identified and assessed. These SRs were not data extracted.	Retrospective studies and any other study design that is not listed in the inclusion criteria.	The EAC considered that there may have been evidence in retrospective studies which could be useful and so requested the list of excluded studies to review. The EAC did not identify any retrospective studies for inclusion.
Language restrictions	English language studies.		The EAC agree with this filter
Search dates	Any dates.		The EAC suggest a limit from when Curos was made available would have been appropriate however it was not necessary therefore the EAC do not consider this to be a problem at this time.

2.3 Included and excluded studies

The company submission included 5 studies, four of which had been identified by the systematic review (Ramirez 2012, Sweet 2012, Merrill 2014 and Cameron-Watson 2016) and one additional study published after the systematic review (Martino 2017). One study identified by the EAC (Duncan et al, 2018) was not included in the company submission as it was published after completion of their searches.

The company included a number of abstracts in their submission which provided some evidence for the use of Curos. On review of the list of excluded studies provided by the company, the EAC identified a number of additional abstracts which were considered to have been excluded inappropriately (Alasmari et al, 2012; Madden et al, 2013; Budhiraja et al 2016) while an additional abstract was identified during the EACs own searches (Kwok et al, 2017).

A summary of the studies included by the company and the EAC is presented in tables 3 and 4. The EAC noted that one unpublished abstract that had been excluded by the company (Budhiraja, 2016) was a study which had been carried out with the support of the company in an NHS setting. This study, in a neonatal population reported no difference in the rate of infection following the introduction of Curos. A second abstract (Kwok et al, 2017) reported no change in rates of bloodstream infections despite compliance with Curos use of 95% or greater. Some of the abstracts are quite old and as none of them provide enough information to allow quality assessment, results from these abstracts should be considered and interpreted with caution.

Table 3: Published Studies

Included Studies	Design and intervention(s)	Participants and setting	Outcomes	EAC Comments
Sweet et al 2012 USA	Before and after introduction of quality improvement comprising a retrospective chart review for the period January 1-December 31, 2009 to identify rate of CLABSI per 1000 catheter days. Compared with prospective data collection in the 6-month period beginning January 11, 2010. Comparator period for CBCs was July 1 – December 31, 2009. Intervention: CUROS and needleless neutral-pressure connectors (MicroCLAVE) concurrently. Use of wipes was optional but no details on the use of wipes was recorded. ● Comparator: Alcohol wipes ●	Adult inpatients on the haematology and oncology floors of a hospital, who had a central venous catheter (CVC) ●	Change in incidence of CLABSI/1000 catheter days before vs after the introduction of the quality improvement programme Change in incidence of CBCs/1000 catheter days before vs after the introduction of the quality improvement programme. Compliance with the intervention, assessed by weekly point-prevalence observations, defined as the percentage of patients with catheter protectors. Indwelling time of catheters (days) was selectively reported for those cases in which CLABSIs were diagnosed ●	The EAC noted that data relating to the sample size was inconsistently reported in the paper. The EAC could not reconcile numbers presented in the text with numbers presented in tables. The EAC contacted the study authors who stated that the numbers in the paper were based on total patient encounters and not unique patients suggesting that there were a total of 282 patients with 436 patient encounters in the intervention period. The EAC queried whether any of these patients would leave hospital with a line still in place and the author reposnded that approximately 30% of lines were implanted ports so it is likely that some patients left hospital with lines in place but this was not specifically recorded in the study. Denominator data for the blood culture results section was based on the number of blood cultures analysed The EAC noted that the authors do not state what p-value is considered to indicate statistical significance. The reported results suggest the threshold for significance was $p < 0.05$. The EAC questioned whether the inclusion of needleless neutral pressure connectors concurrently was likely to have an effect on the outcomes for this study.

Included Studies	Design and intervention(s)	Participants and setting	Outcomes	EAC Comments
				The EAC contacted a clinical expert and information they provided suggest that the type of line and connector used may have an impact on the outcomes. The clinical expert indicated that they used negative pressure ports rather than neutral pressure ports and that there was some discussion around whether this impacted the effectiveness of Curos as they reported no difference in infection rates following introduction of Curos caps however this was not explored as part of their study.
Ramirez et al 2012 USA	Before and after introduction of quality improvement (including both prospective intervention data for period March 1 2011 – February 29 2012 and retrospective comparator data for period January 2010 – December 2010). Not clear if wipes were available ●	All patients in the intensive care unit (ICU) receiving IV treatments via an indwelling central line ●	Change in CLABSI rates in ICU before and after introduction of disinfectant caps. CLABSI was defined according to national guidelines. ● A survey tool was implemented to document compliance (100% compliance was a cap on every needleless connector). ●	The EAC noted that there are inconsistencies in the periods reported. The number of central line days appears to be reported per calendar year (January – December), whereas the intervention was introduced part way through in March 2011. The EAC considers this to be an inconsistency in reporting and does not think this will impact the results. Also of note, they report the average monthly number of central line days, not the actual number, and also don't state whether mean/median.
Merrill et al 2014 USA	Non-randomised interrupted time series study including both prospective intervention data for time period January 2012-December 2012 and retrospective comparator data for time period January 2011 to December 2011.	All patients with peripheral and central lines (including neonates, children and adults) in a >430 bed tertiary trauma care centre in the USA.	Rate of CLABSI per 1000 central line catheter days Compliance (monitored 1-2 times a week). The number of disinfectant caps present divided by the number of total available needleless connectors	The EAC noted that the results presented in this study are 'averages of averages' The monthly average infection rate was used to calculate a yearly average infection rate. This makes it difficult to compare actual number of actual infections and number of catheter in-line days, which of these is

Included Studies	Design and intervention(s)	Participants and setting	Outcomes	EAC Comments
	Not clear if wipes were available ●	No details on patient numbers ●	gave the compliance rate per central line patient. These data were then aggregated for each department. Impact of CLABSI (cost, estimated case fatality, length of ICU stay) ●	driving the average The EAC questions whether this was the most appropriate way to analyse the data and why the original infection data were not used to calculate the yearly average infection rate. It is possible that by calculating the rate of infection for the intervention period this way may result in the narrow confidence intervals observed but this cannot be confirmed.
Cameron-Watson et al 2016 UK	Before and after audit Alcohol wipes were removed from the trial area	1094 patients on four wards (oncology, acute care of the elderly, critical care and a surgical ward) across two sites with vascular access devices ●	Difference in rates of CLABSI pre and post introduction of Curos reported as mean CRBSI rates for the period before the intervention and the trial period● Compliance Intervention: measured as presence of Curos cap at time of audit Comparator: anonymous bench marking audit of disinfection technique including time to clean the IV and time left to dry after cleaning	The EAC noted that this study was conducted in an NHS setting.
Martino et al 2017 USA	Before and after assessment of a quality improvement intervention (including both prospective (intervention January 2012-June 2012) and retrospective (comparator July 2011-December 2011) data).	260 patients in a 16 bed Burns Intensive Care Unit in a regional burns centre. The burns unit is co-located with a level1 trauma centre. ●	Total number of CLABSI occurrences CLABSI rates per 1000 line days● Compliance (weekly audits to verify disinfection cap usage). On-going observational central line bundle surveillance was conducted	The EAC noted that there were some inconsistencies around the reporting time periods but cannot comment as to whether this would affect the results.
Duncan et al 2018 USA	Quasi-experimental before and after quality improvement study Data collection periods were for six months prior to intervention (January – June 2015)	Patients in a >900 bed tertiary care trauma 1 centre with a peripheral or central line with	Compliance with the use of disinfectant caps on needleless connectors and compliance with the	

Included Studies	Design and intervention(s)	Participants and setting	Outcomes	EAC Comments
	and a period of 7 months post intervention (November 2015-May 2016)	bloodstream access (located in the Midwest, USA) ●	use of disinfectant tips on disconnected IV tubing on all line types Primary BSI rates associated with PIV lines and with central lines●	

Table 4: Unpublished Studies/Abstracts

Study reference	Setting	Study design	intervention & comparator	Outcomes	EAC Comment
Pong A, 2011 USA	41 bed, neonatal intensive care unit	Before and after quality improvement study comparing CLABSI rate before and after the intervention	Curos cap vs. historic controls	CLABSI rate/1000 line days	The authors do not state that Curos was the port protector used. The authors comment that “used in conjunction with other CLABSI prevention measures has potential to help us reach our desired CLABSI rate of zero.”
Alasmari F, 2012 USA	Haematological ward	Before and after study with non-equivalent control comparison carried out between Jan 2010 and Decenber 2011	Curos vs no Curos on all CVC ports	CABSI rate	The reason for exclusion by the company was ‘Wrong Outcomes’. The EAC considers that the outcomes reported are relevant and should be included. This study appears to report data from a control ward for both the pre-intervention and intervention period hwever no information is provided about the control ward although there is a suggestion that all patients are acute leukaemia and stem cell transplant patients.

Study reference	Setting	Study design	intervention & comparator	Outcomes	EAC Comment
Danielson B, 2013 USA	47-bed level III neonatal ICU (NICU), Texas Health Presbyterian Hospital	A before and after study comparing CLABSI rate in a 12 month period before intervention (2010) with a 12 month intervention period (2011)	Curos cap vs. traditional 15-second catheter scrub with alcohol wipes	CLABSI rate/1000 catheter days	The intervention period (2011) included one quarter where port protectors were not available. No details regarding why they were not available was provided. The authors conclude that "in conjunction with other evidence-based CLABSI prevention components has a potential to help us reach our goal of zero CLABSIs."
Madden W, 2013	21 patients in a 16 bed, bone marrow transplant unit in a tertiary hospital (USA)	Before and after observational study comparing CLABSI rates between a six month intervention period (December 2011-June 2012) and a six months historical control period (June 2011-November 2011)	Curos caps on all line ports vs standard practice (no details given for what disinfection protocol was followed during this period) Noted that they scrubbed and used caps during the intervention period.	CLABSI rate/device days Compliance	The reason for exclusion by the company was 'Wrong Study Design. The EAC considers that this abstract suggests that the study design is a 'before and after' design and is therefore no different from other studies which have been included and should be included. The study suggests no difference in CLABSI rates before and after introduction of Curos however the number of patients included is small and there is not information to determine what intervention was put in place as the methods mention the use of best practice scrubbing techniques on neutral pressure hubs.

Study reference	Setting	Study design	intervention & comparator	Outcomes	EAC Comment
Sumner S, 2013 USA	Tertiary care hospital, Texas	Before and after quality improvement study comparing CLABSI rate and contaminated blood cultures pre-intervention (2011) with a 10 month intervention period (January 2012 to October 2012)	Curos cap vs. standard practice (alcohol wipes)	Compliance CLABSI Rate/1000 line days (reported as a mean) Rate of contaminated blood cultures (reported as a mean) Cost savings	The EAC noted that as well as the intervention (Curos being implemented) nurses were given vendor delivered or on-line training in the use of Curos caps. During audit processes nurses were also given education/training which included the proper care of secondary tubing
Shiber J, 2014 USA	Acute medical oncology unit. Ochsner Medical Center	Before and after quality improvement study comparing CLABSI rates before and after the introduction of disinfecting port protectors	disinfecting port protectors caps introduced as part of the central line bundle	CLABSI rate reduction (not quantified) Compliance	The EAC noted that the abstract did not state that the disinfection caps used were Curos however as this seems to be an industry publication on behalf of the company it can be assumed that the caps used were Curos. The study stated that disinfection caps were introduced on a single acute medical oncology unit however in the conclusions states that 'CLABSIs rates have decreased on both units' The study appears to measure the effect of a number of interventions including the port protector, hand hygiene and central line dressing changes.

Study reference	Setting	Study design	intervention & comparator	Outcomes	EAC Comment
Ventura R, 2015 UK	764 inpatients with a CVAD in place. Aintree University NHS Trust, Liverpool	Before and after quality improvement study comparing CRBSI rates during the intervention period (January 2015-October 2015), with CRBSI rate in the period prior to the intervention(January 2014-December 2014)	Curos caps vs. active hub disinfection by 2% chlorhexidine and 70% isopropyl	CRBSI rate/1000 catheter days	NHS Setting
Budhiraja S, 2016 UK	Babies admitted to the intensive care or high dependency rooms of a tertiary neonatal unit	Before and after quality improvement study comparing CLABSI rates for an eight month intervention period (December 2014-July 2015) and a 32 month baseline, pre-intervention period (April 2012-November 2014) with 3 months post intervention data also reported (August 2015-October 2015)	Intervention: Curos port protectors Comparator: 2% Alcohol wipes for 2 minutes	Mean CLABSI Rate Compliance	The reason for exclusion by the company was 'Wrong Study Design. The EAC considers that this abstract suggests that the study design is a 'before and after' design and is therefore no different from other studies which have been included and should be included. Contact with a member of the study team clarified the comparator. This study was conducted in an NHS setting.
Kwok M, 2017	All haematological patients with peripherally inserted central catheter (PICC), Hickman catheter and Hemostar catheter	Before and after quality improvement study comparing CRBSI rates for a 3 month intervention period (June 2016-August 2016) with a pre-intervention period (no details given)	Intervention: Curos caps Comparator: Standard practice (rub connectors with 2% chlorhexidine for 15 seconds).	Difference in CRBSI rates before and after Compliance	Identified by EAC

2.4 Overview of methodologies of all included studies

The published studies were uncontrolled before and after quality improvement studies (Sweet, 2012; Ramirez, 2014; Merrill, 2014, Cameron-Watson, 2016; Martino, 2017 and Duncan, 2018). In addition 8 abstracts from unpublished studies were included (table 5).

There were a number of differences between the included studies in relation to the study settings and populations. Settings included haematology ward, oncology wards, burns units, intensive care units, surgical units and paediatric intensive care units. One study was conducted in a UK setting (Cameron-Watson, 2016) while five studies were conducted in the USA (Sweet, 2012; Ramirez, 2014; Merrill, 2014; Martino, 2017and Duncan, 2018). The EAC cannot comment on how infection protocols in the USA might differ from those in the UK therefore some consideration should be given as to whether the results are generalisable between settings.

All studies introduced Curos in patients with central lines and two studies also included patients with peripheral lines (Cameron-Watson, 2016 and Duncan, 2018).

The main outcome reported was bloodstream infection rate with all studies reporting infection outcomes. Four studies reported change in CLABSI rates following the introduction of the device (Sweet, 2012; Ramirez, 2014; Merrill, 2014 and Martino, 2017). CLABSI rates were reported/1000 catheter days in 3 studies (Sweet, 2012; Ramirez, 2014 and Martino, 2017) and as mean rate/1000 days in one study (Merrill, 2014). One study reported mean catheter related bloodstream infections (Cameron-Watson, 2016) and one study reported bloodstream infection rates for peripheral and central lines separately (Duncan, 2018).

Compliance with the device use or disinfection bundle was also reported in all studies apart from two (Merrill 2014 and Duncan, 2018). Compliance with standard disinfection was reported in two studies (Cameron-Watson 2016 and Matino 2017) but this was largely based on retrospective data.

All published studies stated that education and training formed part of the process for introducing Curos however none of the studies accounted for the potential confounding effects of training/education.Education and training specific to the use of disinfection caps does not appear to be an integral part of the process of introduction of Curos although the company can provide training if required. Online training videos are available which clearly outline how Curos should be used but the available literature suggests that hospitals introduce Curos as part of broader strategies to reduce infection rates

providing their own training and education for staff around the whole infection prevention bundle of care and not just around the use of Curos specificially.

No studies were blinded as this would not be appropriate for an intervention of this sort.

None of the included studies reported on the environmental impact of Curos. The use of Curos is likely to increase plastic waste in the NHS both because the cap itself is plastic and because each cap is individually cased in plastic. While there is the capacity to recycle plastic waste it is possible that while the plastic cases could be recycled, the Curos cap itself might not be as it contains a sponge material inside which may not be compatible with recycling processes. There is the potential for increased storage requirements and possible cost implications for disposal particularly if disposal costs are based on weight or if waste collection increases in frequency due to an increase in volume of waste created by Curos caps and the plastic cases, particularly in parts of the hospital where numerous caps per patient are required.

2.5 Overview and critique of the company's critical appraisal

The EAC noted that the company submission did not consider the included studies to be assessments of the impact disinfection bundles but of Curos alone.

The EAC suggests that the included studies should be considered to be bundle studies as although there are data reported for Curos, that data relates specifically to compliance and as all of the included studies introduced an element of training, education and/or audit, it would not be accurate to say that the infection rate changes were entirely down to the use of Curos. It is possible that Curos compliance reported in the individual studies could be considered a surrogate measure for compliance with the whole disinfectction protocol.

The company submission included appropriate assessments of study quality for the individual studies included. The EAC conducted the same quality assessments on the included studies and while largely the EAC was in agreement with the company conclusions they highlighted some specific issues with the individual studies (Appendix C). Overall the EAC considered that the results of the individual studies could not be considered to be very precise. All the published studies were uncontrolled before and after studies and therefore high risk of bias particularly in relation to the 'before' due to the retrospective data collection and chart review and baseline population characteristics were largely unreported and assumed to be the same between group. Additionally all but one (Martino 2017) of the included studies acknowledged the potential for confounding factors such as education and

training were identified but did account for them analysis. In one study (Sweet 2012), alcohol wipes remained available for use, one study removed wipes from the study area (Cameron-Watson, 2016) while the remaining studies did not clarify whether wipes were available during the study period.

The company submission identified a systematic review (Voor, 2017) which they considered to address the decision problem and took the decision to update this review and identify any additional studies. The EAC consider that in this situation it would have been appropriate to include a quality assessment of the systematic review (Voor,2017) to highlight that it addressed the question in the scope, carried out appropriate searches and identified relevant studies. The EAC carried out a quality assessment for this review (Appendix C) and agreed that it addressed the decision problem and that updating the review was an appropriate approach. The results presented in this systematic review did not form part of the clinical evidence base nor were any of the results used in the economic submission. The company simply used the systematic review as a basis to identify relevant studies and performed their own critical appraisal and assessment of the individual studies. The EAC agreed with this approach.

2.6 Results

Table 5: summarises the results of the included studies by outcome including outcomes related to resource use where reported.

Overall the results of the published studies suggest that the use of Curos reduces the rate of bloodstream infections (table 5). Five studies reported a reduction in infection rates (Sweet 2012, Ramirez 2012, Merrill 2014, Cameron-Watson 2016 and Martino 2017) One study (Duncan, 2018) reported no difference in the rate of infections in central lines following introduction of Curos but did report an 81% reduction for peripheral lines.

However there are a number of issues which mean these results should be interpreted with caution; this might reduce confidence in the precision of the reported results. In one study (Sweet, 2012) reported a reduction in infection rates from 2.3/1000 line days to 0.3/1000 line days however alcohol wipes were available for use during the intervention period and it is possible that the effect of Curos might be over-estimated as a result.

Each of the studies introduced an element of training or education the impact of which was not assessed as part of the intervention. This again may result in an over-estimation of the effectiveness of Curos in infection reduction. One study (Martino, 2017) reported that, following the introduction of Curos, infection rates increased at a time when staff turnover was high which

indicates that Curos or any other port disinfection method is not solely responsible for any change infection rates.

A CLABSI as defined by CDC, is a primary (i.e., no apparent infection at another site) BSI in a patient that had a central line within the 48-hour period before the development of the BSI. BSI is defined using either laboratory confirmed bloodstream infection (LCBI) or clinical sepsis (CSEP) definitions. There is no minimum period of time that the central line must be in place in order for the BSI to be considered central line–associated. The culture of the catheter tip is not a criterion for CLABSI.

CRBSI Is a more rigorous clinical definition, defined by precise laboratory findings that identify the CVC as the source of the BSI and, used to determine diagnosis, treatment, and possibly epidemiology of BSI in patients with a CVC. Using the CRBSI definition requires more resources than use of the CLABSI definition as hospitals must have the capacity to correctly collect and label blood culture sets drawn from the CVC and a peripheral phlebotomy as well as culturing the CVC segment/ tips. Typically this rigorous approach requires a research study and staff.

Despite these standard definitions, there are variations in the way that bloodstream infections are reported with the term CLABSI and CRBSI being used interchangeabley throughout the literature and also in practice.

The base rate for CRBSI will always be lower than that of CLABSI due to the tighter testing criterion. The only way to know definitively whether a bloodstream infection is related to the cathether port is to carry out specific laboratory tests. Most of the published studies included the CDC definitions for CLABSI but one study (Cameron-Watson 2016) did not provide a definition and one study (Duncan 2018) used international definitions for bloodstream infections.

Compliance was measured in some format in five studies (Sweet 2012, Ramirez 2012, Merrill 2014, Cameron-Watson 2016 and Martino 2017) but in one study compliance was reported as bundle compliance (Martino 2017). Compliance with Curos use (measured as a Curos cap on any elegible port) ranged from 73% (Ramirez, 2012) to 85.2% (Sweet 2012).

One study reported that a 10% increase in compliance resulted in a 7% drop in CLABSI (Merrill 2014).

In addition the EAC noted that two unpublished abstracts which showed no impact on bloodstream infection rates were excluded from the company submission (Budhiraja, 2016 & Kwok, 2017).

Table 5: Study Outcomes and Results

Study	Bloodstream Infection	CBC rate	Compliance	Bed Days
Published Studies				

Study	Bloodstream Infection	CBC rate	Compliance	Bed Days
Sweet 2012	CLABSI rate/1000 catheter days 2.3 (pre-intervention) vs 0.3 (intervention) RR=0.14 (95% CI, 0.02 – 1.07; p=0.003)	2.5% (pre-intervention) vs 0.2% (intervention) RR=0.09 (95% CI, 0.01-0.65; p=0.002)	85.2% (Rate of adherence to the intervention)	N/R
Ramirez 2012	CLABSI rate/1000 catheter days 1.9/1000 catheter days in 2010 (pre-intervention) 0.5/1000 catheter days in 2011 (intervention)	N/R	73% (Average compliance through 12 month intervention period)	N/R
Merrill 2014	CLABSI rate/1000 catheter days 1.5±0.37 (pre-intervention vs 0.88±0.62 (intervention) –Reported as mean rate Incidence rate ratio=0.577 (pp=0.004) (indicating a reduction in the rate of patient infections of >40% with use of Curos)	N/R	10% increase in compliance resulted in a 7% drop in CLABSI (IRR=0.93, 95% CI 0.889-0.972; p=0.001) Compliance figures not reported	N/R
Cameron-Watson 2016	CRBSI rate 4.3 (pre-intervention) vs. 1.5 (intervention) reported as mean rate Mean rate reduction=2.8	N/R	53% increase in compliance with disinfection policy Pre-intervention (Scrub the hub)= 27% (54% were cleaning for 10 seconds or less; 75% accessed the needle-free device after 25 seconds or less). Intervention (Curos) = 80%	Estimated bed day saving was 198 (69.2% reduction)
Martino 2017	CLABSI rate/1000 catheter days 7.43 (pre-intervention) vs 2.36 (intervention)	N/R	92.5% (pre-intervention) vs 86.5% (intervention) Reported as bundle compliance	N/R

Study	Bloodstream Infection	CBC rate	Compliance	Bed Days
Duncan 2018	Intervention period: 17 (8 PIV; 0.11 infections/1000 patient-days) Pre-intervention period: 46 (39 PIV; 0.57 infections/1000 patient days) 81% reduction in peripheral BSI (p<0.001) Not significant difference between central line BSI (0.1/1000 patient days to 0.12/1000 patient days; p=0.72)	N/R	N/R	N/R
Unpublished Studies				
Pong A, 2011 USA Neonatal Intensive Care Unit	Pre-intervention: (October 2008-September 2009) 0.93 infections per1000 catheter days Intervention (October 2009-September 2010) 0.3 infections per 1000 catheter days	Number of blood isolates meeting criteria as contaminants Pre-intervention: 3.6/1000 line days Intervention: 2.7/1000 line days	N/R	N/R
Alasmari F, 2012 USA	Pre-intervention (2010): Median CABSI rate 5.3/1000 central line days versus 5.8/1000 days in a control unit Intervention (2011): Median CABSI rate 3.7/1000 central line days versus 5.4/1000 days in a control unit	N/R	N/R	N/R
Danielson B, 2013 USA	Pre intervention (2010): SIR 1.723 Post intervention (2011): SIR 1.013 Post intervention (2012): SIR 0.722	N/R	N/R	N/R
Madden W, 2013	3/21 patients acquired CLABSI during study 4/830 device days pre intervention (4.82/1000) 4/847 device days during intervention (4.72/1000)	N/R	95%	N/R
Sumner S, 2013 USA	Pre intervention: Mean = 2.4%, SD 1.5 Post intervention Mean = 0.87%, SD 0.63	Pre intervention: Mean = 2.5%, SD 0.45 Post intervention Mean = 1.4%, SD 0.32	Pre study, 55% of nurses scrub <5secs Study start: mean 73% SD 15.6 End: mean 88%, SD5.8	N/R

Study	Bloodstream Infection	CBC rate	Compliance	Bed Days
Shiber J, 2014 USA	CLABSI rates decreased	N/R	Curos: increased to over 90% Central line dressing changes: sustained 100% Hand hygiene: 8-90%	N/R
Ventura R, 2015 UK	Pre intervention: Mean 3.8 (range 0-9.71) Post intervention: Mean 0.23 (range 0-1.74)	N/R	N/R	N/R
Budhiraja S, 2016 UK	Pre intervention: Mean 21.3 (CI: 41,1.7) Intervention: Mean 27.5 (CI: 76.6,NA) Post intervention Mean 22.5 (CI: 31.6,13.5)	All CRBSI had postive blood culture.	95%	N/R
Kwok M, 2017	Authors report “no significant difference in CRBSI rate”	N/R	For nurses: 60% for rub 90% Curos For interns: 40% for rub 85% for Curos	N/R
BSI: Bloodstream infection; CBC: Contaminated blood culture; CLABSI: Central line associated bloodstream infection; CRBSI: Catheter related blood stream infection; CVC: Central Venous Catheter; NR: Not reported; PIV: Peripheral intravenous line SIR Standardized Infection Ratio				

2.7 Description of the adverse events

None of the included studies reported adverse events related to the use of Curos nor did they highlight any specific safety concerns.

The company included a search of the FDA Maude database which was conducted in September 2017 identifying 45 records. The search was updated by the EAC to cover the period to Septmeber 2018 identifying an additional 18 records (Appendix D). Following checks for duplication of reports, a total of 63 records were identified.

Leaking from the connection between the cap and the needleless connector in approximately 24 cases and breakage of the cap was reported in approximately 11 cases. A small number of records relate to problems using the cap. There was 1 report of a toddler removing the cap and putting it in their mouth.

The EAC is concerned that Curos may represent a choking hazard for some patients however the company has added a warning to the instructions for use so the EAC considers this concern to be adequately addressed.

There are are a number of reports of leakage or breakage when using Curos, although these have not resulted in any adverse patient effects. The EAC suggests reasons for leakages and breakages should be investigated if Curos was to be introduced across the NHS. It is possible that the caps are being used incorrectly or not checked by staff and training will be required. It is also possible that Curos caps are being used on unsuitable needleless connectors which may result in poor fit resulting in leakage and increased potential for breaking of caps. Poorly fitting caps may also impact the disinfection properties of the cap.

2.8 Description and critique of evidence synthesis and meta-analysis

The company submission included a meta-analysis of data from four of five included studies. Meta-analysis was conducted using 4 studies reporting CLABSI rates (Sweet, 2012; Ramirez, 2012; Merril, 2014 and Martino, 2017) and a second, subgroup including just the data from two studies carried out in the ICU setting (Ramirez, 2012 and Martino, 2017). Data from one study was excluded on the basis that this reported CRBSI rates rather than CLABSI rates (Cameron-Watson, 2016) however the EAC consider that there is some uncertainty around the outcome definition as the study makes no mention of carrying out tip cultures which is the only way to definitively diagnose CRBSI.

The company submission stated that the studies included in the meta-analysis were controlled before and after studies. The EAC note that none of the included studies were controlled which presents a risk to the internal validity of the studies particularly in relation to the potential risk of changes over time that are not due to intervention.

There was a lack of reporting or analysis of baseline patient characteristics in 3 studies (Sweet, 2012; Ramirez, 2012 and Merrill, 2014) making it unclear whether the patient populations are comparable in the pre-intervention and intervention periods.

The EAC identified a number of inaccuracies in the reporting of results in the individual studies as outlined in table 3.

The company submission excluded data from one paper (Cameron-Watson, 2016) on the basis that it did not report CLABSI. On review, the EAC consider that although this study claims to report CRBSI, it is not clear from the definition provided whether it was a CLABSI or a CRBSI rate that was reported.

Overall the EAC agrees with the individual studies included in the company submission however there are questions over the quality of the data reported in these studies.The EAC concluded that there were a number of issues identified which indicate the data from the individual studies is poor quality and that the results of the meta-analysis may be at risk of serious imprecision (Appendix E).

2.9 Ongoing studies

The company submission did not reference any ongoing studies or trials. The EAC identified three trials of interest which may result in additional evidence.

Table 6: Ongoing Studies

Trial Reference	Title	Aim	EAC Comment
NCT02351258	Community Central Line Infection Prevention Trial (CCLIP)	Evaluate whether use of 70% isopropyl alcohol embedded protective caps on central lines • reduces the rate of CLABSI in ambulatory pediatric hematology/oncology patients.reduces the rate of all positive blood cultures in ambulatory pediatric hematology/oncology patients.changes the distribution of bacteria isolated from blood cultures of pediatric hematology/oncology patients.	The EAC contacted the principal investigator for this study. The results of the study are likely to be ready for publication in late 2019 and the PI indicated that they would not be prepared to share any interim analysis or early results at this time. The EAC noted that this trial is being conducted in the USA and therefore may have limited applicability to the UK setting.
NCT03391960	Passive Disinfection Cap Compliance Study	To demonstrate that passive disinfecting caps can provide a patient safety practice that is easy for clinicians to follow, as well as providing easily auditable compliance, which may lead to lower CLABSI rates. The compliance rate for needleless connector disinfection will be evaluated after implementation of the passive disinfecting cap, and compared to the pre-intervention rate. The CLABSI rates before and after cap implementation will also be compared.	This trial is currently recruiting. The study is due to complete in January 2019 The EAC noted that this trial is being conducted in Brazil and therefore may have limited applicability to the UK setting.
NCT03486093	Port Protectors for Prevention of CLABSIs in Respiratory Semi-intensive Care Unit	To assess the efficacy of educational interventions alone and combined with port protector as adjuvant tool on rate of CLABSIs. Moreover, the investigators evaluated the effects of previously mentioned interventions on rates of CVC colonizations and contaminated blood cultures.	The EAC noted that this trial completed in 2014 but was not added to clinicaltrial.gov until 2018. No publications or results from this trail could be identified. The EAC had difficulty obtaining contact details for the principal investigator however an e-mail has been sent to the PI.

3 Economic evidence

3.1 Published economic evidence

Critique of the company's search strategy

The company carried out one search for both clinical and economic literature, adapting the search strategy for use in relevant economic databases including EconLit and CEA Registry. The EAC agreed with this approach.

Critique of the company's study selection

No relevant economic studies were identified by the company or the EAC.

3.2 Company de novo cost analysis

Patients

The user selects either hospitalized patients or ICU patients with vascular access devices in the model. Community settings (which were included in the scope) are excluded from the model. There is one sub-group analysis in the intensive care setting.

Technology

The technology is Curos disinfecting cap and this matches the scope.

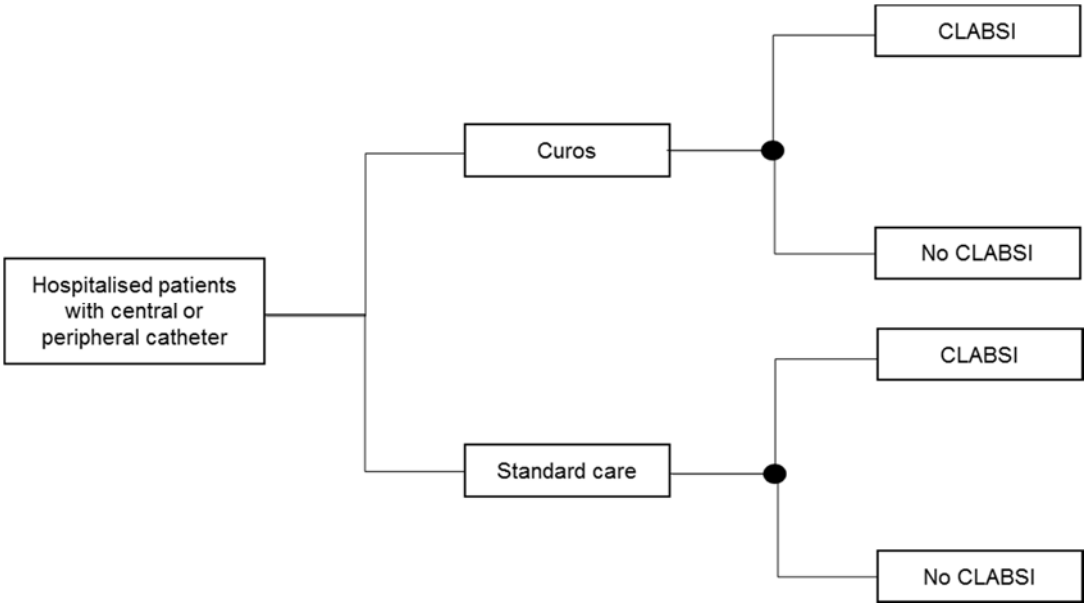
Comparator(s)

The comparator in the model is alcohol wipes, which matches the scope.

Model structure

The model is a decision tree with two main branches for CUROS and standard care. For each arm there is the possibility of CLABSI or no CLABSI. The user can select either the whole hospital population or the ICU population. The model does not include mortality. The model structure is simple because the introduction of Curos is an exchange of one method of disinfecting ports to another. There are no other changes to the care pathway.

Figure 1: Model Schematic



The EAC checked that the model calculations performed as expected and they did so (Appendix F).

Assumptions in the mode

Table 7: Model Assumptions

Assumption	EAC comment
Compliance with standard care is 100%	The company assumes that in standard care, the nursing staff always spend 15 seconds scrubbing the access port and 30 seconds just waiting for the port to dry. The company submission acknowledges that actual compliance is probably very low. Reported compliance with Curos ranges from 73% to 86.5% in the published literature (Sweet 2012, Ramirez 2012 and Martino 2017) while compliance with manual disinfection was 27% (Cameron-Watson, 2016) in one study and 92.5% in a second study (Martino, 2017). The EAC did not make any changes to compliance. In the submitted model, compliance only contributes to the total cost of the devices. In reality lower compliance would also mean less nurse time applying it, and possibly higher infection rates. There was no information available on the impact of lower compliance on infection rates.

All of the improvement in the before and after studies is due to Curos.	The studies include additional nurse education and monitoring of compliance when Curos is introduced which would itself be expected to reduce infection rates.
Baseline infection rates from parenteral feeding ports for patients mainly on gastric surgery wards is generalisable to the whole in-patient population.	Clinical expert communication (2 clinical experts) suggest that parenteral feeding lines may have a higher risk of infection than other types of catheter lines. The baseline infection rate used in the model was very low and the EAC did not identify an alternative value therefore kept the rate used in the company submission.
CRBSI and CLABSI are treated as interchangeable	The EAC requested that the data from Cameron-Watson be added to the meta-analysis, but this has not been received.
Environmental impact was not included.	Cost of NHS waste disposal not included. Alcohol wipes and curos caps are considered to be clinical waste and disposed of in orange bags to be heat treated to make the waste safe before going on for any further processing or disposal. Frequency of waste collection, costs and method of waste disposal is likely to vary across NHS trusts so would be difficult to include in the model. One clinical expert stated they had no knowledge of the impact but suspected that it would be similar to that of wipes.
Mortality is not included in the model although 'reduced mortality as a result of reduced risk of CLABSI' is given as a claimed benefit in the scope.	This exclusion was a result of the paucity of published literature relating to mortality from CLABSI. Overall the EAC agrees with the exclusion of mortality in this model given it is not concerned with long-term outcomes.
It is assumed that improved infection rates reported in short term before and after studies are sustainable.	Martino (2017) reported post-intervention data which suggested that rate of CLABSI might be impacted by confounders such as staff turnover or other changes to the disinfection bundle. For example a high nurse staff turnover in the post-intervention period reported a CLABSI rate of 9.0/1000 catheter days compared with 2.36/1000 catheter days during the active intervention period. A similar increase in infection rates would result in an increased cost per CLABSI avoided in the model.
Use of an alcohol containing solution of chlorhexidine gluconate is not included in the model.	The EAC agrees with this exclusion.

Summary of the base case

All hospital patients

Table 8: Company base case results for all hospital settings per patient

	CUROS	Wipes	Cost saving per patient
Disinfection method cost	£13.44	£0.84	-£12.60
Nurse cost	£6.13	£18.38	£12.25
Cost of CLABSI	£21.56	£50.15	£28.58
Total			**£28.23**

Table 9: Lowest and highest estimate from one-way sensitivitiy analysis using company base case results and company values for parameter variation

	Base-case	Lowest estimate	Highest estimate
Range of cost savings with CUROS	£28.23	-£0.35	£448.83

ICU patients

Table 10: Company base case results for ICU settings per patient

	CUROS	comparator	Cost saving per patient
Disinfection method cost	£208	£13	-£195
Nurse cost	£94.79	£284.38	£189.58
Cost of CLABSI	£57.10	£196.91	£139.80
Total			**£134.39**

Table 11: Lowest and highest estimate from one-way sensitivitiy analysis using company base case results and company values for parameter variation

	Base-case	Lowest estimate	Highest estimate
Range of cost-savings with CUROS	£134.39	-£7.80	£280.64

Clinical parameters and variables

General Hospital Setting

The EAC agree with the submission that there is a wide variation in infection rates and definitions used between different studies.

Baseline infection rates are not identified or reported in a standardised way in the UK, and are very variable between patient populations and sites. The choice of any single basline infection rate cannot reflect reality, but should be considered together with understanding of local conditions and sensitivity analysis. The same considerations will apply to the incidence rate ratio.

For this reason, the EAC did not make any changes to the clinical effectiveness data used in the model but have used sensitivity analysis to highlight cost impact of the wide variation in infection rates that is possible. The EAC also conducted a scenario analysis using published data to investigate the impact of a higher baseline rate of infection on the costs.

The baseline infection rate of 0.7 for the general hospital setting is taken from published literature (Hvas, 2014) The study population potentially represents a subset of the population defined in the submission as it includes only patients referred for parenteral nutrition on a general hospital ward and who will be assessed by a nutrition support team; clinical experts suggest that there is a possibility that the infection risk in parenteral nutrition lines is greater than in other line types. One clinical expert suggested that a number of places now use dedicated lines that are tunnelled to give this sort of nutrition. A second clinical expert stated that they record infection rates in patients receiving parenteral nutrition by the number of days they receive parenteral nutrition not the number of CVAD days (recorded as per 100 catheter days).

The incidence rate ratio used in the model is taken from the company's meta-analysis of a small number (n=4) of poor quality studies. The studies include different patient populations, a large number of ICU patients, are conducted in the USA and are taken from before and after studies which are subject to bias. Considering the results of one study (Merrill, 2014),which was conducted across a wider hospital setting including ICU, the risk ratio was 0.58 (0.4-0.84). A second study (Duncan, 2018) reports a rate ratio of 1.2 for central lines which would suggest no difference following the introduction of Curos. The results from these two studies provide an indication of how the infection rates can vary.

Where baseline infection rates are very low, a change of one less CLABSI infection can give a rate ratio that gives the appearance of a very effective

intervention. If a higher baseline infection rate was chosen, the rate ratio to reduce one CLABSI infection would be much closer to 1. The baseline infection rates are very low, so a very small change may result in a statistically significant reduction in infection which in turn can result in an over-estimation of the actual clinical benefit from using Curos.

Intensive Care Unit Population

The baseline infection rate for the ICU population is also taken from the published literature (Bion, 2012). The study reported the results of a quality improvement programme (Matching Michigan). Matching Michigan was a 2 year programme that aimed to minimise blood stream infections from central venous catheter. It was conducted in 223 ICUs in England, 176 of which were adult ICUs, 21 were paediatric ICUs and 26 were subspeciality ICUs.

The company submission used the infection rates reported in the last quarter of the study (1.48 per 1,000 catheter days) which seems appropriate.

The incidence rate ratio used in the model is taken from the meta-analysis of ICU studies included in the company's clinical submission (n=2 studies); one of the studies was conducted in a burns specific ICU and the second was conducted in 2 ICU units of a general hospital.

The EAC considers the clinical data used in the model for the ICU population to be appropriate.

Resource identification, measurement and valuation

Resources included in the model fall into three broad categories; the consumables used for the disinfection method (Curos caps or alcohol wipes), nurse time and resources due to subsequent infection.

The company calculates the number of Curos caps used by multiplying the 'average' number of ports per patient, by the number of accesses per port per day by the number of days with catheter in place per patient. The data source for the number of ports per patient and the number of accesses per port per day is a single nurse expert opinion and is therefore uncertain. The responses given by the expert are in the form of a range (for example, 1-2 ports for a patient in general hospital population and 10-15 ports for a patient in ICU). The EAC contacted 3 expert advisors and received responses from all three. One indicated that 10-15 ports for a patient in ICU was an accurate range while the second commentator responded that an ICU patient would have 'many' ports. A third clinical expert reported that in ICU 4-6 ports would be required but this was in a neo-natal population which would differ from an adult population. The EAC agrees with the ranges included in the model but

suggest that the company has selected from these responses in an inconsistent manner selecting the higer end of the range (n=2) for inclusion in the hospital population basecase and the lower end of the range (n=10) for inclusion in the ICU model basecase. The EAC therefore changed the ICU basecase value to 12 and kept the range in the sensitivity analysis as 10-15 caps in an attempt to represent an 'average' number of ports used in ICU. The EAC note that this change makes very little difference to the end result in the company submission.This is because CLABSI is per 1000 catheter days and is not related to number of ports. Number of ports will change equipment and nurse cost, but they are smaller costs.

The number of days with catheter in place per patient is taken from published literature (Dyson, 2017 & Tan, 2009) and verified by a clinical expert.

General Hospital Setting
The company submission indicated the literature reported a range of 7-244 days duration for cathethers in the general hospital population and this range was verified by a clinical expert. The EAC received responses from two clinical experts who also supported the range reported in the literature. One clinical expert suggested a range of 7-14 days based on clinical experience.

The model uses a median duration of 7 days which was taken from a study with the aim of examining the process of care of patients receiving paraenteral nutrition in hospital in order to identify remediable factors in the care received by these patients (Dyson, 2017). The median duration reported in the study was actually 7.5 days (1-62 days) so this was updated in the model by the EAC. This median value is the lower end of the range suggested by the literature and clinical experts and therefore is likely to represent a conservative estimate.

Intensive Care Units
The median duration of 13 days (2-100) was taken from a retrospective study with the aim of defining baseline data and complication rates and to inform future directions (Tan, 2009). The study included patients with PICCs in the ICU setting between April 2007 and March 2008. The median duration reported was 9 days (0-100) however lines removed after 0-1 days were considered failed insertions and removing them from the analysis resulted in the median line days of 13 which was included in the model. Using the adjusted median duration of 13 days seems appropriate as one attribute of CLABSI/CRBSI is that they occur after 48 hours following insertion.

The company's instructions for use indicate that Curos caps need to be changed at least every 7 days. If ports are in regular use this would not result in additional cap changes. The ports in less frequent use would need to have

their caps changed even if not used. This raises the practical concern that nurses would have to record whether caps had been changed on at least a weekly basis. Discussion with the company suggests that the needleless connectors are changed every 7 days therefore the Curos cap would be changed at the same time. This may result in changing Curos caps before there is a requirement increasing the number of Curos caps used. This has not been accounted for in the model and may lead to an underestimation of the cost of the intervention particularly in the ICU setting when there are numerous ports.

Nurse time included in the model is estimated as 15 seconds for each cap placement and 45 seconds of nurse time for each manual disinfection in standard care, to include 15 seconds cleaning and 30 seconds drying time. These times are supported by four clinical experts (three contacted by the EAC). All four clinical experts indicate that changing a cap would take a few seconds. Two experts suggest that manual disinfection should take 45 second (15 seconds cleaning and 30 seconds drying) and one clinical expert indicated that manual disinfection would take 20 seconds to “scrub the hub” plus time to get equipment required. One clinical expert indicated that both manual disinfection and changing a Curos cap would take less than 1 minute.

The EAC accepts that manual disinfection may take 45 seconds given a 30 second drying time however the EAC considers that the nurse would utilise the drying time to carry out associated tasks such as preparing the syringe or writing in the notes and this can therefore not be considered time saved when using Curos.

The model offers two options for the cost of CLABSI. One taken from NICE guidance (MTG25) and one micro-costing from published data. The company base case uses the CLABSI cost from NICE guidance (MTG25), and the EAC agree that this is appropriate.

In the micro-costing option using published data, evidence on additional length of hospital ward stay is referenced as Cooper(2014), but the original data was taken by Cooper from a paper by Warren (2006). The data was collected in 1998 to 2000 in the USA, therefore the applicability to the UK in 2018 is questionable. Evidence of additional days in ICU is also referenced as Cooper (2014), but Cooper reports the value was taken from a paper by Lambert (2011). The EAC cannot find anywhere in the paper by Lambert an additional length of stay in ICU of 1.5 days. Indeed Lambert reported that patients already in ICU did not have an increased length of stay resulting from blood stream infection acquired during their time in ICU.

The micro-costing takes in costs of diagnosis and treatment combined with any additional length of stay in ICU or on a ward due to the infection.

The resources associated with infections used in the micro-costing option are determined by the baseline rate of infection for the population and the risk ratio for Curos compared with the cost of CLABSI.

Technology and comparators' costs

The unit cost of CUROS caps is given as £0.32 and the unit cost per alcohol wipe used in standard care is £0.02 based on [redacted] The EAC agrees with these costs.

Sensitivity analysis

The company submission included a deterministic and a probabilistic sensitivity analysis which explored the impact of changing input parameters.

Two-way deterministic sensitivity analysis was conducted around the baseline rate of CLABSI and the incidence rate ratio with Curos and the cost per patient using Curos and manual disinfection. When varying the baseline infection rate and IRR, the two–way sensitivity analysis is reported as cost saving in all cases.

In the hospital setting the key drivers identified by the company included the baseline infection rate (higher infection rate resulted in greater saving) and number of catheter days (higher number of days at risk resulted in greater savings).

In the ICU setting, cost of nurse time for manual disinfection (higher nurse time cost resulted in greater savings) and the IRR associated with Curos (lower IRR the greater the savings) were identified as key drivers.

Probabilistic sensitivity analysis was conducted based on 2,000 iterations and reported to be cost saving in 96.4% of interations in the hospital population and in 86.3% of cases in the ICU population.

EAC changes to the model

The EAC does not agree with the additional 30 second drying time for manual disinfection included in the model. Nurses will be occupied with other tasks during this 30 second drying time. The EAC have changed the nurse time for manual disinfection to be equal to nurse time for Curos.

The EAC consider there to be considerable uncertainty around the infection rates used in the company submission due to the quality of the reported

literature. The EAC consider that this it is a reflection of the fact that infection rates will be variable across the NHS. For this reason, the EAC did not make any changes to the clinical parameters used in the company submission.

Table 12: EAC revisions to the company's model (Base Case)

Parameter	Company base-case	EAC value	Source	Cumulative Impact
Nurse Time	45 seconds in the manual disinfection (0.75 mins)	15 seconds (0.25 mins)	Epic3 guidelines which recommend 15 seconds disinfection and 30 seconds drying time. The EAC consider that the nurse time for manual disinfection should be equal to that of Curos as the 30 second drying time will be used by nurses to do other tasks and will therefore not be time that can be considered saved by using Curos.	Hospital: Change from -£28.23 to -£15.98 incremental cost ICU: Change from -£134.39 to +£55.20 . Decreases cost saving due to Curos, ICU becomes cost incuring
Nurse Cost per hour	£35	£37	The company submission used PSSRU 2016 for a band 5 nurse. The EAC updated this cost to reflect 2017 PSSRU costs for a band 5 nurse. Clincial experts indicate that all nurses should be a minimum band 5 and the EAC changed the lower value in the price range for this from £22 to £37 to reflect this information. There has been no change to the upper value in the range so this remains at £62 in the model.	No change to incremental cost, as nurse time equal.
Number of ports used in the ICU setting	10	12	Clinical experts suggest a range between 10-15 caps in the ICU setting. The EAC used 12 in the base case and a range of 10-15 in the sensitivity analysis.	ICU: Change to +£94.20 incremental cost Decreases cost saving.
Number of catheter days in the hospital setting	7	7.5	The EAC noted that the literature reported a median duration of 7.5 days not 7 as included in the company submission (Dyson, 2017).	Change to -£17.13incremental cost Decreases cost saving.

3.3 Interpretation of economic evidence

The EAC agrees that there is no published literature relevant to this topic and the decision of the company not to include any published studies.

3.4 EAC Interpretation of economic evidence

The EAC accept that the model functions as expected but disagreed with some of the assumptions regarding the data input in particular with regards to the nurse time for manual disinfection.

The EAC made some changes to the data input (table 12) and the results are presented below.

3.5 Results of EAC analysis

Base-case analysis results

General Hospital Setting

Table 13: EAC base case results in the general hospital setting

	CUROS	**Comparator**	**Cost saving per patient**
Disinfection method cost	£14.40	£0.90	-£13.50
Nurse cost	£6.94	£6.94	£0
Cost of CLABSI	£23.10	£53.73	£30.63
Total			**£17.13**

Table 14: Lowest and highest estimate from one-way sensitivitiy analysis using EAC base case results

	Base-case	**Lowest estimate**	**Highest estimate**
Range of cost-savings with CUROS (one way sensitivity analysis)	£17.13	-£13.50	£467.77

Intensive Care Unit

Table 15: EAC base case results in the ICU setting

	CUROS	**Comparator**	**Cost saving per patient**
Disinfection method cost	£249.60	£15.60	-£234
Nurse cost	£120.25	£120.25	£0
Cost of CLABSI	£57.10	£196.91	£139.80
Total			**-£94.20**

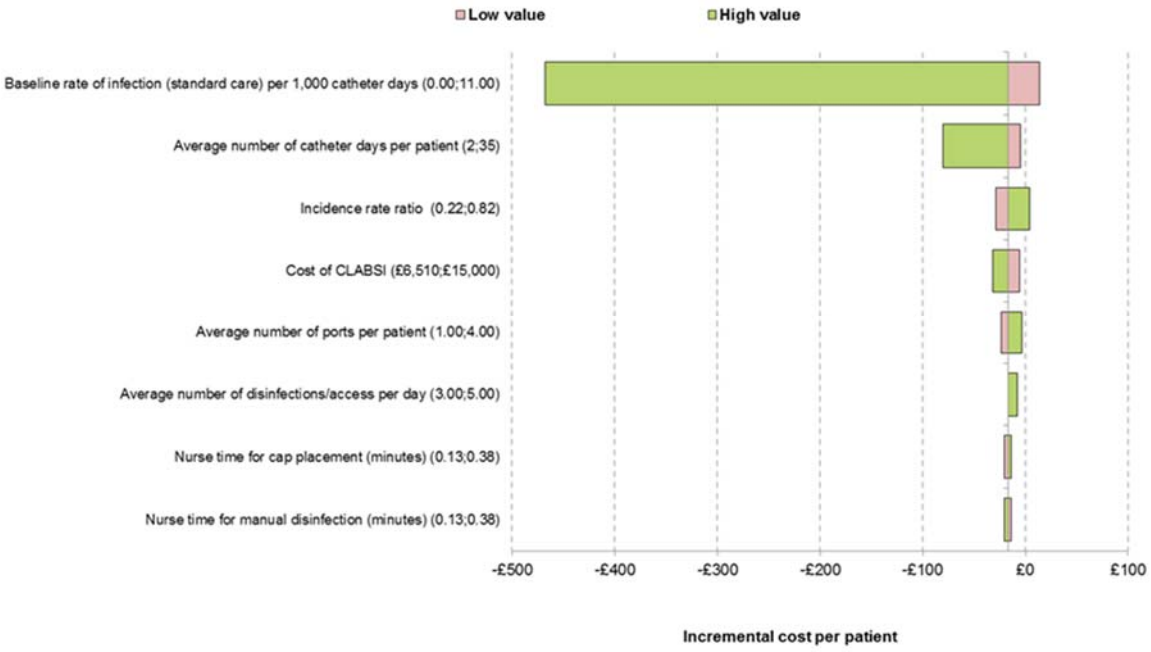
Table 16: Lowest and highest estimate from one-way sensitivitiy analysis using EAC base case results

	Base-case	Lowest estimate	Highest estimate
Range of cost-savings with CUROS (one way sensitivity analysis)	-£94.20	-£34.07	-£328.20

Sensitivity analysis results

Deterministic Sensitivity Analysis
For the hospital setting the key driver in the EAC basecase is the baseline rate of infection, as shown in figure 2. This is in part because we have maintained the large range between high and low values that was chosen by the company. However, the baseline rate will naturally be of key importance.

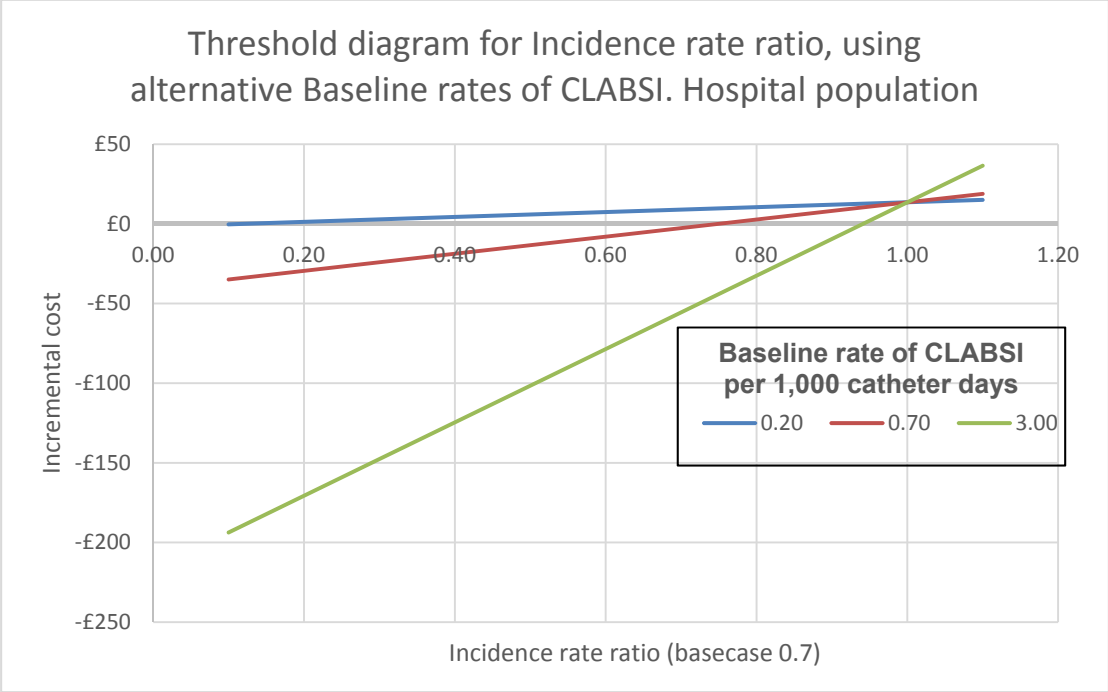
Figure 2: Tornado diagram showing univariate sensitivity analysis on basecase (any hospital setting)



Where the infection rate is already very low, any given rate reduction will result in less difference in CLABSI infections. Where there is a high baseline rate, any measure to improve infection control is likely to have a greater impact. The effect of the baseline rate and incidence rate on the incremental cost are shown in figure 3. It can be seen that for the 0.7 baseline rate used in the base case, Curos becomes cost incurring at approximately 0.75 incidence rate ratio. For the higher baseline rate illustrated, of 3.0, the

incidence rate ratio can be higher before Curos is cost incurring. For the lower baseline rate illustrated, of 0.2, Curos would almost always be cost incurring.

Figure 3: Threshold Diagram for hospital population



For ICU there is not as distinct a driver for the model. Baseline rate of infection appears to have less importance. This is partly due to the much smaller range being modelled, but also because the increased number of ports and access per day mean that the cost of the equipment is a larger part of the overall cost per patient, and the variables associated with this take on more importance.

Figure 4: Tornado diagram showing univariate sensitivity analysis on basecase (ICU)

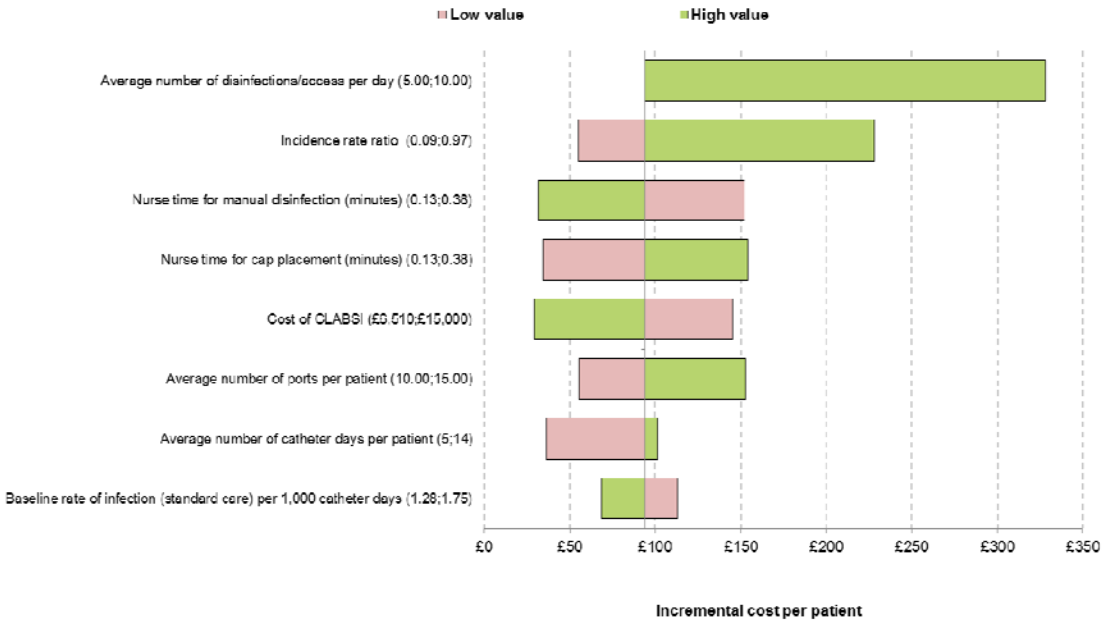
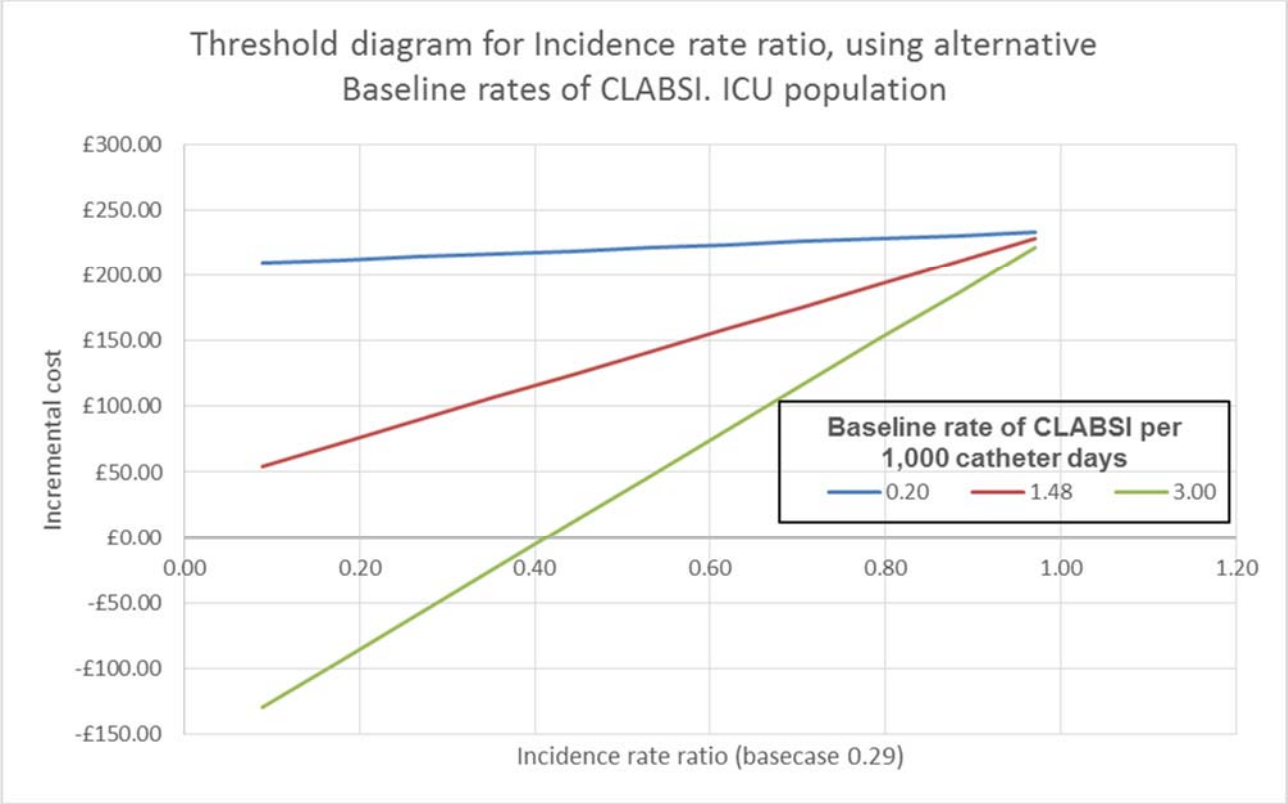


Figure 5 illustrates the impact of different baseline infection rates on the incidence rate ratio at which Curos becomes cost incurring. At the basecase value of 1.48, Curos is always cost incurring. At a higher baseline rate of infection, Curos may be cost saving.

Figure 5: Threshold Diagram ICU population



Probabilistic Sensitivity Analysis

Curos was cost saving in any hospital setting in 78.8% of iterations (2,000 iterations) and the average probabilistic cost was -£16.40 (cost saving).

Curos was cost saving in the ICU setting in 32.4% of iterations (2,000 iterations) and the average probabilisitic cost was £105.53 per patient (cost incurring).

3.6 Scenario analysis

The EAC conducted a number of analyses to assess the impact of possible clinical scenarios.

Table 17: EAC Scenario Analyses

Scenario	**Justification**	**Model Change**	**Impact**
Increased the cost of intervention to reflect the possible scenario where wipes and curos caps might be used together.	One study (Sweet, 2012) indicated that wipes remained available to staff for use throughout the study period. This scenario analysis therefore shows how adding the cost of wipes and curos impacts outcomes. A draft policy [redacted] recommends the use of both wipes and Curos indicating that this scenario is likely in the NHS.	Cost of Curos increased to £0.34 to reflect the possibility that alcohol wipes and curos caps are both used together.	The cost of disinfection increases resulting due to use of both wipes and Curos caps Hospital: Incremental cost changes to from -£17.13 to -£16.23 ICU: Incremental cost changes from £94.20 to £109.80
Increased number of ports in the hospital setting to reflect the likelihood of a mixed population.	The incidence rate ratio used in the model is from the results of a meta-analysis which includes 2 studies in the ICU setting, one study in a haematology/oncology unit and one study in a hospital setting which included ICU. Patients in ICU have a higher number of ports which will have an impact on the cost of the intervention.	Change number of ports in the hospital setting to: 3 4 5	Increasing the number of ports increased the cost of disinfection method and the cost of nurse time 3 ports: Incremental cost changes

			from -£17.13 to -£10.38 4 ports: Incremental cost changes from -£17.13 to -£3.63 5 ports: Incremental cost changes from -£17.13 to £3.12 (cost incurring)
Effectiveness data from a study in a subgroup of patients in a burns unit was used in the model comparing infection rates Pre-intervention vs intervention	The study in burn patients reported a higher basline infection rate compared with any of the other individual studies and much higher than the baseline rate used in the basecase (7.43/1000 days vs. 0.7/1000 days). An IRR was calculated using the infection rates for the pre-intervention period (5/673 days) and intervention period (3/1272 days) using the IRR calculator in STATA 15 This scenario analysis shows how a higher baseline infection rate impacts the cost savings due to Curos in a group of patients with a higher baseline infection risk.	Baseline CLABSI rate changed to 7.43 and IRR to 0.32 (0.49-1.63)	Incremental cost -£438.20
Pre-intervention vs post-intervention	Following the introduction of Curos there was a period of time where nursing staff turnover was 60% and infection rates increased to 9.0/1000 line days (10/1109 days). This was followed by a change to the bundle assessment protocol which resulted in a decrease in infection rates to 3.04/1000 line days (8/2624 days). The EAC used the combined infection data (18/3733 days) from these time periods to investigate how changes over time apart from Curos (compared with the initial baseline rate of 7.43) might impact the outcomes. A limitation of the scenario analysis is that it is based on a single before and after study.	Change the IRR to 0.65 (0.23-2.23)	Incremental cost -£111.98

CUROS and wipes are used compared with wipes alone

The additional cost of alcohol wipes (Curos+Wipes) changes the cost of the disinfection method as expected but overall does not impact the cost saving per patient significantly compared with the cost of Curos alone.

General Hospital setting

Table 18: Curos+Wipes

	CUROS+Wipes	Wipes	Cost saving per patient
Disinfection method cost	£15.30	£0.90	-£14.40
Nurse cost	£6.94	£6.94	£0
Cost of CLABSI	£23.10	£53.73	£30.63
Total			**£16.23**

Table 19: Curos+Wipes

	Base-case	Lowest estimate	Highest estimate
Range of cost-savings with CUROS+Wipes	£16.23	-£14.40	£466.87

ICU setting

Table 20: Curos+Wipes

	CUROS+Wipes	Wipes	Cost saving per patient
Disinfection method cost	£265.20	£15.60	-£249.60
Nurse cost	£120.25	£120.25	£0
Cost of CLABSI	£57.10	£196.91	£139.80
Total			**-£109.80**

Table 21: Curos+Wipes

	Base-case	Lowest estimate	Highest estimate
Range of cost-savings with CUROS+Wipes	-£109.80	-£42.23	-£359.40

Higher baseline rate of infection using a subgroup of burns patients

The baseline infection rate in the burns population was 7.43 compared with 0.7 in the basecase. The key driver of the cost results in this subgroup is the baseline rate of CLABSI. The higher baseline rate reported in the study (Martino, 2017) compared with other studies results in greater cost savings.Following the introduction of Curos there were two key changes within the burns unit which resulted in changes to the infection rates while Curos was being used. A high nursing staff turnover resulted in an increase in infection rates to 9.0. Following this a change to the bundle assessment resulted in the decrease in infection rates to 3.04. Comparing the combined impact of these two events with the baseline infection before in the introduction of Curos rate shows that although Curos remains cost saving, the cost saving is lower suggesting that Curos has some impact on infection rates but is not completely responsible for the reduction.

Table 22: Burns Population

	CUROS	Comparator	Cost saving per patient
Disinfection method cost	£249.60	£15.60	-£234.00
Nurse cost	£120.25	£120.25	£0
Cost of CLABSI	£316.33	£988.53	£672.20
Total			**£438.20**

Table 23: Burns Population (comparison of baseline (pre-curos) with infection rates after curos with other possible confounders)

	CUROS	Comparator	Cost saving per patient
Disinfection method cost	£249.60	£15.60	-£234.00
Nurse cost	£120.25	£120.25	£0
Cost of CLABSI	£642.54	£988.53	£345.98
Total			**£111.98**

Varying the number of ports in the hospital setting

Using the EAC base case, Curos remains cost saving in the hospital setting when increasing the number of ports to 3 and to 4. At 5 ports per patient, Curos becomes cost incurring. This will vary for different infection rates.

Table 24: Impact of increased ports per patient

Number of ports per patient	3	4	5
Cost Saving	£10.38	£3.63	-£3.12

Sensitivity analysis results

The key drivers in the both scenarios were the incidence rate ratio and the baseline risk of infection.

Probabilistic Sensitivity Analysis

Curos was cost saving in the burns population in 92.6% of iterations (4,000 iterations) and the average probabilistic cost was -£424.68 (cost saving).

Adjusting the effectiveness data to include a period of time with potential confounders (staff turnover and bundle assessment changes) indicated that Curos was cost saving in the burns population in 57.5% of iterations (4,000) and the average probabilistic cost was £2.64.

Model validation

There were no other health economic studies found in the literature to validate the structure of the de novo model. However it is a simple structure and the EAC considers the structure appropriate for the decision problem. Inputs were checked for accuracy and validated where possible by clinical experts. Remaining uncertainties are the baseline CLABSI rate for the hospital setting, and the incidence rate ratio for general hospital and ICU as this is based on poor quality before and after studies.

Impact on the cost difference between the technology and comparator of additional clinical and economic analyses undertaken by the External Assessment Centre

A summary of the impact of the changes made by the EAC is shown in table 20. The EAC basecase shows Curos to be cost saving in the hospital setting compared with manual disinfection but cost incurring in the ICU setting. Using

wipes and Curos together remained cost saving in the hospital setting and cost incurring in the ICU setting.

An increase in the baseline infection risk suggests that Curos is cost-saving even when the disinfection bundle is impacted by other factors such as a high staff turnover.

Increasing the number of ports per patient in the hospital setting to reflect the possible variation in the population suggests that Curos becomes cost incurring at 5 ports per patient.

Table 20: Impact of model changes

Setting	**Company Basecase**	**EAC Basecase**	**Curos+Wipes**	**Increased baseline infection rate**	**Other changes to bundle**	**Increase in port numbers per patient**
Hospital	£28.23	£17.13	£16.23			3 ports +£10.38 4 ports +£3.63 5 ports -£3.12
ICU	£134.39	-£94.20	-£109.80			
Burns Unit				£438.20	£111.98	

4 Conclusions

4.1 Conclusions on the clinical evidence

The clinical evidence is comprised of a small number of uncontrolled before and after studies which are low quality and potentially at high risk of bias due to the fact that the 'before' data are all retrospective record reviews and the 'after' introduces Curos while also including elements of education, disinfection protocol awareness and audit all of which may have an impact on the outcomes and were not assessed in the studies. Only one of the studies (Cameron-Watson, 2016) was carried out in a UK setting which may impact the generalisability of the study results.

The populations included in the studies were variable, including patients in ICU, general hospital wards, surgical wards and paediatric ward. All studies included central venous lines. One study that included both central and peripheral lines reported data for peripheral lines separately. The comparison was manual disinfection protocol using alcohol wipes in all studies but each study varied in how they introduced the disinfection caps (e.g. one study removed alcohol wipes from the ward while in one study nurses were wiping before putting on a disinfection cap).

The evidence reported outcome data only for bloodstream infection rates and compliance but there was no consistency in how infections were classified with some reporting CLABSI, some CRBSI and some BSI. In addition, the definitions provided in each study means that there is a question over whether the terms CLABSI, CRBSI and BSI are being used interchangeably in the literature.

The meta-analysis is based on data from these poor quality studies and doesnot the only study conducted in the UK setting. It would be more appropriate to consider the studies separately.

4.2 Conclusions on the economic evidence

The de Novo cost model used data from a very wide range of sources to determine the incremental cost of Curos in two settings; the general hospital setting and the intensive care setting.

The effectiveness data uses baseline CLABSI rates from studies in patients with central lines for parenteral nutrition which may not be reflective of the infection rate in all types of central or peripheral lines. The incidence rate ratio used in the model is derived from the meta-analysis in the clinical submission. The EAC did not identify an alternative source of effectiveness data and

acknowledges that the meta-analysis is the most appropriate source of clinical effectiveness data available, so did make any changes to the effectiveness data in the basecase. It is likely that the rate of infection in individual hospitals or trusts will be very variable. Infection rates will likely be impacted by a number of factors such as training, staff turnover and wider infection control policies. As a result in a setting with high baseline rates, if Curos is reducing infection, then it is likely to be cost saving but in a setting with very low infection rates, Curos needs to very effective at reducing infection to be cost saving. In any setting where infection control is already very good, even an effective intervention will have less impact. The EAC did conduct an additional scenario analysis using published data (Martino 2017) to investigate how a higher baseline infection rate affected the cost savings for Curos.

The amount of time for a nurse to carry out manual disinfection is assumed to be 3 times as long as for disinfection with Curos however this estimate includes a 30 second period of drying during which time the nurse will likely be carrying out other tasks.

The input data relating to the number of ports, number of caps and number of disinfections per patient is derived from clinical expert opinion in the absence of any published data.

The meta-analysis of data for the hospital setting includes 2 studies which were conducted in the ICU setting. Based on this, the number of ports/caps per patient in the model cannot be assumed to be as low as if the studies were only in the general hospital setting. The EAC conducted a scenario analysis where the number of ports per patient were increased in the model to investigate at what point Curos became cost incurring.

5 Summary of the combined clinical and economic sections

The EAC concludes that there will be variability in the baseline rates of infection which will be dependent on a number of factors including differences in infection control protocols including disinfection methods, patient populations and education and training. This variability is reflected in the published literature which is used in the economic analysis. The EAC concludes that there are scenarios where the introduction of Curos may lead to cost savings through a reduction in infection rates but that the decision to introduce Curos should be taken with consideration of local infection control protocols and baseline infection rates.

6 Implications for research

A study comparing bundle disinfection protocols using manual disinfection of ports or curos caps in clearly defined clinical settings would provide data on

whether the replacement of disinfection wipes with curos caps in the bundle has any impact on catheter related bloodstream infections.

Key information should include:

- bloodstream infections related to catheter lines usings a suitable definition and method of assessment. Infection details should be reported both on a per patient and per line day basis with the actual infection numbers used to calculate infection rates reported.

- compliance with both curos and alcohol wipes should be measured using clearly defined methods with results reported

- clearly defined and documented infection control protocols with any changes applied to both curos and to manual disinfection so that potential confounding can be assessed

- the study should include a clearly defined follow-up period for assessment to allow for the impact of natural changes and deviations from protocols to be assessed

- an assessment of the impact of increased plastic waste on waste storage and disposal including costs and potential environmental impact

References

Alasmari F. Impact of Alcohol Impregnated Protectors on Incidence of Catheter- Associated Blood Stream Infections Conference Abstract Availabe at https://idsa.confex.com/idsa/2012/webprogram/Paper37395.html [Last accessed: 24/10/2018]

Bion J, Richardson A, Hibbert P, Beer J, Abrusci T, McCutcheon M*, et al.* 'Matching Michigan': a 2-year stepped interventional programme to minimise central venous catheter-blood stream infections in intensive care units in England. BMJ Qual Saf. 2013;22(2):110-23.

Budhiraja S Impact of passive disinfection device on the rate of catheter related blood stream infections in neonates: A quality improvement initiative. Archives of Disease in Childhood 2016; 101(Suppl 1): A1-A374

Cameron-Watson C. Port protectors in clinical practice: an audit. Br J Nurs. 2016;25(8):S25-31.

Casey AL, Karpanen TJ, Nightingale P, Chaganti S, Elliott TSJ. Microbiologic contamination of a positive- and a neutral- displacement needleless intravenous access device in clinical use. Am J Infect Control. 2016;44(12):1678-80.

Cooper K, Frampton G, Harris P, Jones J, Cooper T, Graves N*, et al.* Are educational interventions to prevent catheter-related bloodstream infections in intensive care unit cost-effective? J Hosp Infect. 2014;86(1):47-52.

Danielson B, Willamson S, Kaur G, Brooks C, Scholl P, Baker A. Decreasing the incidence of central line-associated blood stream infections using alcohol-impregnated port protectors in a neonatal intensive care unit. Am J Infect Control. 2013;41(Suppl 6):S97-S98.

Dyson JK, Thompson N, Northern Nutrition N. Adult parenteral nutrition in the North of England: a region-wide audit. BMJ Open. 2017;7(1):e012663.

Duncan M. A bundled approach to decreasae the rate of primary bloodstream infections related to peripheral intravenous catheters. JAVA 2018;23(1):15-22

Hockenhull JC, Dwan K, Boland A, Smith G, Bagust A, Dundar Y*, et al.* The clinical effectiveness and cost-effectiveness of central venous catheters treated with anti-infective agents in preventing bloodstream infections: a systematic review and economic evaluation. Health Technol Assess. 2008;12(12):iii-iv, xi-xii, 1-154.

Hvas CL, Farrer K, Donaldson E, Blackett B, Lloyd H, Forde C*, et al.* Quality and safety impact on the provision of parenteral nutrition through introduction of a nutrition support team. Eur J Clin Nutr. 2014;68(12):1294-9.

Kwok MWN. Trial use and evaluation of disinfecting port protectors on central venous catheter in hematology ward in hong kong. Antimicrobial Resistance and Infection Control 2017;Conference(Supplement 2)

Lambert ML. Clinical outcomes of healthcare associated infections and antimicrobial resistance in patients admitted to European intensive care units: a cohort study. Lancet Infection 2011;11;30-38

Madden W Alcohol Impregnated Caps: Are They Effective for Preventing CLABSI? Biol Blood Marrow Transplant 2013;19:S370-S380

Martino A, Thompson L, Mitchell C, Trichel R, Chappell W, Miller J*, et al.* Efforts of a Unit Practice Council to implement practice change utilizing alcohol impregnated port protectors in a burn ICU. Burns. 2017;43(5):956-64.

Merrill KC, Sumner S, Linford L, Taylor C, Macintosh C. Impact of universal disinfectant cap implementation on central line-associated bloodstream infections. Am J Infect Control. 2014;42(12):1274-7.

National Institute for Health and Care Excellence. Healthcare-associated infections: prevention and control in primary and community care (CG139). London: National Institute for Health and Care Excellence; 2012. Available from: https://www.nice.org.uk/guidance/cg139

National Institute for Health and Care Excellence. The 3M Tegaderm CHG IV securement dressing for central venous and arterial catheter insertion sites (MTG25). (MTG25). London: National Institute for Health and Care Excellence; 2015. Available from: https://www.nice.org.uk/guidance/mtg25.

Personal Social Services Research Unit (PSSRU). Unit Costs of Health & Social Care 2016. Canterbury: PSSRU; 2016. Available from: http://www.pssru.ac.uk/project-pages/unit-costs/2017/.

Pong A, Salgado C, Speziale M, Grimm P, Abe C. Reduction of central line-associated bloodstream infection (CLABSI) in a neonatal intensive care unit with use of access site disinfection caps. In: ISDA Annual Meeting, Boston, MA; 21 October. 2011. P672Ramirez C, Lee AM, Welch K. Central venous catheter protective connector caps reduce intraluminal catheter-related infection. JAVA - Journal of the Association for Vascular Access. 2012;17(4):210-13.

Shiber J, Jolicoeur G, Crouchet T. Reducing central line-associated bloodstream infections through the addition of disinfecting port protector caps to the central line bundle. In: Ochsner Research Day, New Orleans, LA; 20 May. 2014. 8

Sumner S, Merrill KC, Linford L, Taylor C. Decreasing CLABSI rates and cost following implementation of a disinfectant cap in a tertiary care hospital. Am J Infect Control. 2013;41(Suppl 6):S37.

Sweet MA, Cumpston A, Briggs F, Craig M, Hamadani M. Impact of alcohol-impregnated port protectors and needleless neutral pressure connectors on central line-associated bloodstream infections and

contamination of blood cultures in an inpatient oncology unit. Am J Infect Control. 2012;40(10):931-4.

Tan R, Knowles D, Streater C, Johnston A. The use of peripherally inserted central catheters in intensive care: should you pick the PICC? JICS. 2009;10(2)

Ventura R. Passive disinfection port protector: effect on the reduction of catheter related bloodstream infections. In: Gavacelt Conference 2015, Milan, Italy; 2015. 7

Voor In 't Holt A. Antiseptic barrier cap effective in reducing central line-associated bloodstream infections: A systematic review and meta-analysis. [Erratum appears in Int J Nurs Stud. 2018 Aug;84:79-80; PMID: 29887034]. International Journal of Nursing Studies 2017 Apr;69:34-40.

Warren D. Attributable cost of catheter associated bloodstream infections among intensive cae patients in a non-teaching hospital. Critical Care Medicine 2006;34:8

Appendices

Appendix A: Prisma Diagram (Corrected Company Submission

Appendix B: Prisma Diagram (EAC updated literature search)

Appendix C: .Clinical Evidence Data Extraction Tables

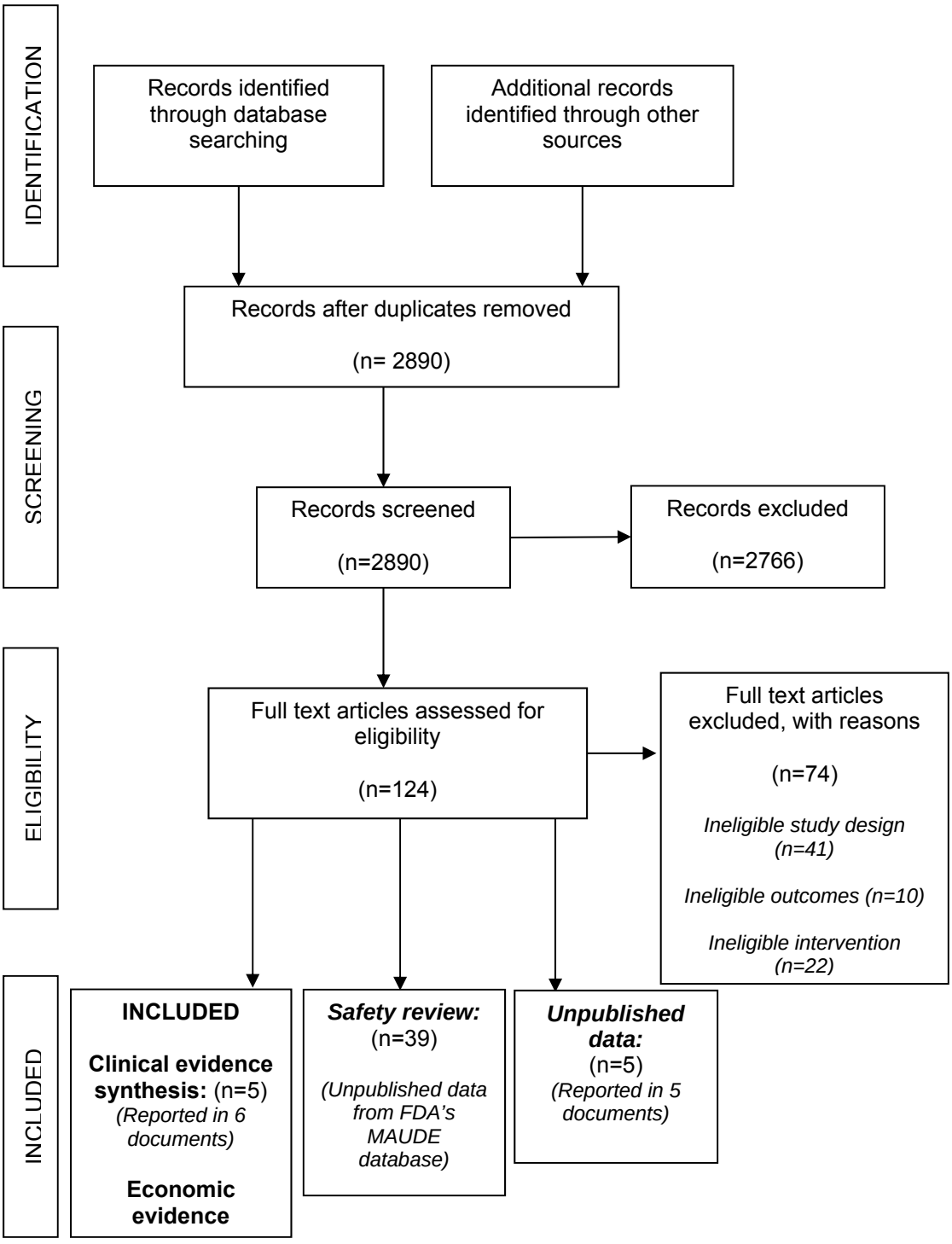
Appendix D: Adverse Events (EAC updated MAUDE search)

Appendix E: EAC Changes to Economic Model

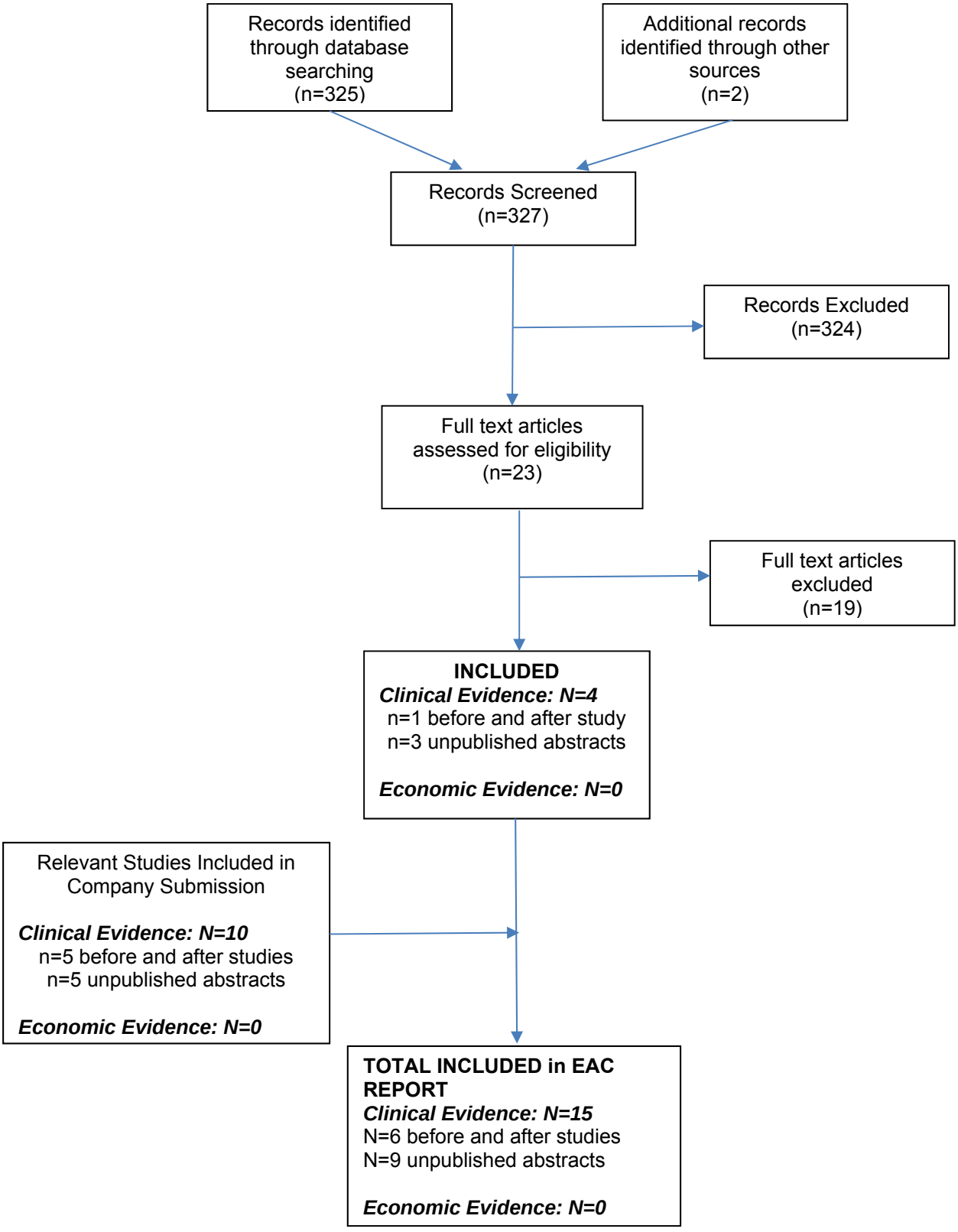
Appendix F: Sensitivity Analysis for EAC BaseCase

Appendix G: Sensitivity Analysis for Burns Population

Appendix A: PRISMA Diagram (Corrected Company Submission)



Appendix B: PRISMA Diagram (EAC updated searches)



Appendix C:Data Extraction Tables

PICO analysis of each study submitted by the company and all of those identified by extra EAC searches, description of bias for each study, detailed tables of results

Included Studies

Study name	Sweet 2012	Ramirez 2012	Merrill 2014	Cameron-Watson (2016)	Martino 2017	Duncan 2018
Objective	To assess the effect of optimising hub disinfection using a quality improvement intervention by measuring the rate of central line associated blood stream infections (CLABSI) and contaminated blood cultures (CBC) Pg 933 also states "The primary goals of our intervention were to decrease CLABSIs and CBCs by improving the maintenance care (after insertion) of central lines".	To reduce intraluminal contamination by minimising the introduction of contaminants through inadequately disinfected needleless connectors	To analyse the effect of universal IV needleless connector disinfectant cap on rate and type of CLABSI and estimated costs. Also to explore the relationship between disinfectant cap compliance and CLABSI rates.	To investigate the effect of a passive disinfection device on the incidence of vascular access device related bacteraemia	To investigate whether the use of alcohol impregnated port protectors while maintaining CDC central line Bundle compliance, decrease the rates of CLABSI in the burns intensive care unit compared with standard isopropyl alcohol swab cleansing.	To test whether peripheral intravenous maintenance bundle that includes the use of disinfection products (Curos caps and tips) could lower the rate of primary bloodstream infections.
Location	Hematology/oncology unit at West Virginia University Hospitals (USA)	2 intensive care units in a 214 bed community hospital in the USA	>430 bed tertiary trauma care centre (USA)	Four wards (oncology, acute care of the elderly, critical care and	16 bed Burns Intensive Care Unit in a regional burns centre. The burns unit is co-located with a level1 trauma centre.	>900 bed tertiary care trauma 1 centre in the Midwest (USA): • 37 bed adult medical/surgical ICU

Study name	Sweet 2012	Ramirez 2012	Merrill 2014	Cameron-Watson (2016)	Martino 2017	Duncan 2018
				a surgical ward) across two sites		• 16 bed trauma/neuro ICU • 12 bed burn ICU • Multiple medical/surgical units including oncology and a heart hospital with a cardiovascular ICU • 98 bed level III neonatal ICU • Paediatric ICU and a paediatric unit • Labour and birth and mother and baby unit
Design	Before and after introduction of a quality improvement intervention. Retrospective chart review for the period January 1-December 31, 2009 to identify rate of CLABSI per 1000 catheter days. Compared with prospective data	before and after quality improvement study (including both prospective intervention and retrospective comparator data). 12 months of data were collected prospectively and compared with 12	Non-randomised interrupted time series study (including both prospective (intervention) and retrospective	Audit	Before and after assessment of a quality improvement intervention (including both prospective (intervention) and retrospective (comparator) data).	Quasi-experimental before and after quality improvement study

Study name	Sweet 2012	Ramirez 2012	Merrill 2014	Cameron-Watson (2016)	Martino 2017	Duncan 2018
	collection in the 6-month period beginning January 11, 2010. Comparator period for CBCs was July 1 – December 31, 2009.	months of data collected in the previous 12 months prior to introduction of disinfectant caps	(comparator) data). 12 months of data were collected prospectively and compared with 12 months of data collected in the previous 12 months prior to introduction of disinfectant caps			
Duration of study	Retrospective data obtained for 1 year. Prospective study duration was a further 6 months.	Intervention: March 1 2011 – February 29 2012 Comparator: Unclear, states 12 months before the intervention. Figure 1 suggests that comparator data collection started in January 2010.	Intervention – 12 months prospective data (January 2012-December 2012) Comparator – 12 months retrospective data (January 2011-December 2011)	6 months (April 1, 2014 – September 30, 2014)	Intervention – 6 months prospective data (January 2012-June 2012). In addition12 months of post-implementation data are reported. Comparator – 6 months retrospective data (July 2011-December 2011)	Data collection periods were for six months prior to intervention (January – June 2015) and a period of 7 months post intervention (November 2015-May 2016)
Patient population	Adult inpatients on the haematology and oncology floors of a hospital, who had a	All patients in the intensive care unit (ICU) receiving IV treatments via an	All patients with peripheral and central lines (including	Patients with vascular access devices	Patients in a burns intensive care unit	Patients with a peripheral or central line with bloodstream access

Study name	Sweet 2012	Ramirez 2012	Merrill 2014	Cameron-Watson (2016)	Martino 2017	Duncan 2018
	central venous catheter (CVC)	indwelling central line	neonates, children and adults)			
Sample size	Pre-intervention period, patients with CVC n=836 Intervention period, patients with CVC n=436	Number of patients wasnot reported	Number of patients was not reported	1094	Pre-intervention: 673 catheter days Intervention: 1272 catheter days	Unclear 210 lines (43 central and 167 peripheral) during a 2 week pre-intervention period to establish a baseline 2355 lines (378 central and 1977 peripheral) during the 7 month study period Study also includes results from a six month pre-intervention period but no details of lines provided
Inclusion criteria	Patients having a CVC (e.g. PICC, tunnelled catheter, or implanted port) at the time of, or within 48 hours before a positive blood culture was obtained	All patients in the intensive care units (ICU) receiving IV treatments through an indwelling central line	All patients with peripheral and central lines in 13 inpatient units	Patients with vascular access devices including central venous catheters, peripheral IV catheters and arterial VADs	Thermal burns greater than 10% total body surface area, inhalation injuries, electrical injuries, skin injuries undergoing grafting and other dermatologic conditions requiring complex wound care.	All central or peripheral lines with bloodstream access
Exclusion criteria	Excluded culture results obtained within 48 hours of admission, to focus on hospital-acquired infections.	None reported. The authors imply that no patients were excluded.	Patients in emergency department, ambulatory care, surgical services,	None reported	None reported	Mother and baby unit, labour and birth unit and children's hospital

Study name	Sweet 2012	Ramirez 2012	Merrill 2014	Cameron-Watson (2016)	Martino 2017	Duncan 2018
			labour and delivery, wellbaby nursery, and patients who were postpartum			
Intervention(s) (n =) and comparator(s) (n =)	Intervention (n=436) use of Curos port protectors in addition to MicroCLAVE needleless neutral-pressure connectors, with optional use of alcohol wipes (at the nurse's discretion) Comparators (n=836) Traditional catheter hub care using alcohol wipes It is not clear how many patients were included within the 6-month pre-intervention period used as the comparator for rates of CBCs.	Intervention: Curos cap with 70% isopropyl alcohol Comparator: Current practice involved cleaning the hub with an alcohol sponge for 15 seconds	Intervention: Curos Caps Comparator: Standard Practice using alcohol wipes	Intervention: Curos Cap Comparator: Standard practice using alcohol wipes	Intervention (n=153): CDC central line bundle + Curos Comparator (n=107): CDC central line bundle (90% compliance required) The CDC central line bundle comprises optimal site selection, hand hygiene, cleaning the insertion site with chlorhexidine, maximum sterile barriers and prompt discontinuation of central line when no longer required.	Intervention: PIV maintenance bundle with Curos caps for needleless connectors and Curos tips for male leurs Comparator: PIV maintenance bundle with standard disinfection (alcohol wipes) for needleless connectors and male leurs.
Baseline differences	There were no statistically significant baseline differences (gender, age, type of oncologic disease, Charlson Comorbidity Index (CCI) score, or	Not reported/Not analysed There was an assumption that the patient mix during the study period would be	Not Reported	Not reported	No differences reported (comparisons included age, ICU days. Ventilator days, hospital days, thermal injury, inhalation injury, continuous renal replacement therapy and mortality)	Not assessed

Study name	Sweet 2012	Ramirez 2012	Merrill 2014	Cameron-Watson (2016)	Martino 2017	Duncan 2018
	receipt of systemic antibiotics). Also no significant differences in central line type. However, no details of the statistical tests used to compare baseline differences were reported.	comparable to the patient mix in the previous 3 years.				
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	No follow-up described beyond hospital discharge or study end date. It is not clear *how* any of the data (retrospective and prospective) were obtained/collected.	No follow-up described beyond hospital discharge or study end date. It is not clear *how* any of the data (retrospective and prospective) were obtained/collected, except that "the facility had reliable data".	Not Reported	Patients were not followed-up although while still in hospital, feedback regarding patient perception of the disinfectant caps formed part of the audit process.	Not reported although the study reports data for 2 years post implementation it is not clear whether any of these patients are the same patients.	Patients were not followed up
Statistical tests	Changes in CLABSI and CBC rates analysed by Fisher's exact test, with 2-tailed p-values and descriptive statistics	Unpaired t-tests (2-tailed) to compare data from 12 months before the intervention with 12 months of intervention data.	Generalised linear model using Poisson Distribution (adjusted for the number of line days per patient)	No statistical analysis carried out	Logistical regression analysis Anova Non-parametric tests	Control charts to observe/rest change in compliance end points from the pre-intervention period to the study intervention period Chi-squared tests to test average compliance between pre-intervention and intervention periods

Study name	Sweet 2012	Ramirez 2012	Merrill 2014	Cameron-Watson (2016)	Martino 2017	Duncan 2018
						Fisher's exact test to test for differences in BSI rates between pre-intervention and intervention time points.
Primary outcomes (including scoring methods and timings of assessments)	Change in incidence of CLABSI/1000 catheter days before vs after the introduction of the quality improvement programme	Change in CLABSI rates in ICU before and after introduction of disinfectant caps. CLABSI was defined according to national guidelines.	Rate of CLABSI per 1000 central line catheter days.	Difference in rates of CLABSI pre and post introduction of Curos reported as mean CRBSI rates for the period before the intervention and the trial period	Total number of CLABSI occurrences CLABSI rates per 1000 line days	Compliance with the use of disinfectant caps on needleless connectors and compliance with the use of disinfectant tips on disconnected IV tubing on all line types
Secondary outcomes (including scoring methods and timings of assessments)	Change in incidence of CBCs/1000 catheter days before vs after the introduction of the quality improvement programme. Compliance with the intervention, assessed by weekly point-prevalence observations, defined as the percentage of patients with catheter protectors. Indwelling time of catheters (days) was selectively reported for those cases in	A survey tool was implemented to document compliance (100% compliance was a cap on every needleless connector).	Compliance (monitored 1-2 times a week). The number of disinfectant caps present divided by the number of total available needleless connectors gave the compliance rate per central line patient. These data were then aggregated	Compliance Intervention: measured as presence of Curos cap at time of audit Comparator: anonymous bench marking audit of disinfection technique including time to clean the IV and time left to dry after cleaning	Compliance (weekly audits to verify disinfection cap usage). On-going observational central line bundle surveillance was conducted	Primary BSI rates associated with PIV lines and with central lines

<table>
<tr><th>Study name</th><th>Sweet 2012</th><th>Ramirez 2012</th><th>Merrill 2014</th><th>Cameron-Watson (2016)</th><th>Martino 2017</th><th>Duncan 2018</th></tr>
<tr><td></td><td>which CLABSIs were diagnosed.</td><td></td><td>for each department.
Impact of CLABSI (cost, estimated case fatality, length of ICU stay)</td><td></td><td></td><td></td></tr>
<tr><td>Results</td><td>Pre-intervention: 472 patients with CVCs accounted for 911 hospital admissions and 6851 line days
Intervention: 282 patients with CVC accounted for 479 hospital admissions and 3,005 line days

CLABSI Rates
Pre-intervention: 16 CLABSIs; 2.3/1000 central line days
Intervention: 1 CLABSI; 0.3/1000 central line days
Relative risk=0.14 (95% CI, 0.01-0.65; p=0.002)

CLABSI rate per 100/patient admissions</td><td>The average monthly number of central line days was
180 in 2011 (intervention) and 176 in 2010 (pre-intervention)

1 CLABSI reported during the intervention period
4 CLABSIs reported during the pre-intervention period
Standardised infection rate:
pre-intervention = 1.259; intervention = 0.308
CLABSI Rate:
1.9/1000 catheter days in 2010</td><td>Mean rate of CLABSI/1000 catheter days:
Intervention: 0.88±0.62
Pre-intervention: 1.5±0.37
Incidence rate ratio=0.577 (pp=0.004) (indicating a reduction in the rate of patient infections of >40% with use of Curos)
Compliance figures were not reported however the study reported that a 10% increase in compliance resulted in a</td><td>Compliance with disinfection policy increased by 53%
Pre-intervention (Scrub the hub)= 27% (54% were cleaning for 10 seconds or less; 75% accessed the needle-free device after 25 seconds or less).

Intervention (Curos) = 80%

CRBSI cases:
Pre-intervention=26
During intervention=8</td><td><table><tr><th></th><th>Total CVL days</th><th>Number of CLABSI</th><th>CLABSI rate/1000 catheter days</th><th>CVL Bundle Compliance</th></tr><tr><td>Jan-June 2011</td><td>950</td><td>9</td><td>9.47</td><td>91.7%</td></tr><tr><td>July-Dec 2011</td><td>673</td><td>5</td><td>7.43</td><td>92.5%</td></tr><tr><td>Jan-Jun 2012 (intervention period)</td><td>1272</td><td>3</td><td>2.36</td><td>86.5%</td></tr><tr><td>July-Nov 2012 (60% nursing staff turnover)</td><td>1109</td><td>10</td><td>9.0</td><td>74.3%</td></tr><tr><td>Dec 2012-Dec 2013: (bundle assessment changed)</td><td>2624</td><td>8</td><td>3.04</td><td>Not available</td></tr></table>Table reproduced from Martino et al (2017)

Rates of CLABSI for 2011 did not differ significantly to rates from 2012 (p=0.81) or 2013 (p=0.37).</td><td>Bloodstream Infections
Intervention period: 17 (8 PIV; 0.11 infections/1000 patient-days)
Pre-intervention period: 46 (39 PIV; 0.57 infections/1000 patient days)

81% reduction in peripheral BSI (p<0.001)
Not significant difference between central line BSI (0.1/1000 patient days to 0.12/1000 patient days; p=0.72)

Adverse Events associated with infection (these are not associated with the use of Curos)</td></tr>
</table>

Study name	Sweet 2012	Ramirez 2012	Merrill 2014	Cameron-Watson (2016)	Martino 2017	Duncan 2018
	decreased from 2.1-0.2 (p=0.01) CBC Rates decreased from 2.5% (17 of 692) to 0.2% (1 of 470) Relative Risk=0.09 (95% CI, 0.01-0.65; p=0.002) Before implementation, the average and median indwelling catheter time was 14 days. The majority of infected catheters were in place for at least 10 days (14/15) The only CLABSI recorded in the intervention period was associated with a catheter in place for 12 days. Adherence to the intervention was 85.2% (228 of 269)	0.5/1000 catheter days in 2011 Compliance varied from 25% early in the study to 100%. Reason for low compliance was thought to be access to caps. Cap strips were added to IV pole during month 5 and product education was done concurrently. Average compliance increased from 63% to 80% after adding strips. Average compliance through the 12 month intervention period was 73%.	7% drop in CLABSI (IRR=0.93, 95% CI 0.889-0.972; p=0.001) Total estimated cost of CLABSI: Pre-intervention = $1 million/year Post-intervention (2012) = $575,000/year Saving of $282,840/year when excluding cost of supplies Estimated a decrease of 68 patient hospital days and prevented one death.	Mean CRBSI rates: Pre-intervention=4.3 Intervention=1.5 Mean rate reduction=2.8 Costs of treating peripheral CRBSI @ £6209 per infection Cost of treating central catheter CRBSI @ £16,000 per infection Estimated cost of treating CRBSI for 1 year was £322,868 for peripheral and £832000 for central catheter related BSI (based on 26 CRBSI during the six month pre-intervention period).	Overall trend of CLABSI rates decreased from 2009 through 2014 (Data for 2014 not reported) (p=0.0045)	Pain, redness and swelling at the insertion sites was recorded in 8% of lines pre-intervention and 2% of lines during intervention (p<0.0001).

Study name	Sweet 2012	Ramirez 2012	Merrill 2014	Cameron-Watson (2016)	Martino 2017	Duncan 2018
				Based on this, the study reported that 3 dept. involved in the study saved a minimum of £105,5664 up to £281,802 Bed Days Bed days increase to treat 1 infection was 11 days Estimated bed days during pre-intervention was 286 (26*11) compared with 88 during the intervention period (8*11). Estimated bed day saving was 198 (69.2% reduction).		

Quality Assessment

Study	Was the cohort recruited in an acceptable way?	Was the exposure accurately measured to minimise bias?	Was the outcome accurately measured to minimise bias?	Have the authors identified all important confounding factors?	Have the authors taken account of the confounding factors in the design and/or analysis?	Was the follow-up of patients complete?	How precise (for example, in terms of confidence interval and p values) are the results?
Sweet 2012	***Not clear*** Presumably all adult inpatients with a central venous catheter (CVC) in a haematology/oncology unit were included. The authors do not report how data were obtained/collected. Table 1 indicates that 93 of the patients (40 in the intervention arm and 53 in the control group) had "no oncologic disease".	***Not clear*** Probably, but again we don't know how data were recorded. The rate of compliance (adherence to the intervention) was monitored. Compliance was assessed by the use of the intervention on all CVCs. Note that the numbers of patients in the entire sample were inconsistently reported, weakening confidence in the conclusions.	***Not Clear*** Each incidence of bacteraemia was reviewed by the hospital infection control department and an epidemiologist to determine if it met the National Healthcare Safety Network (NHSN) definition of a CLABSI. This assessment was not blinded and potentially open to biased interpretation.	***Yes*** Limitations mentioned are the lack of randomisation or blinding, and the possibility that awareness of the intervention changed other aspects of clinical practice. The authors state that "other temporary CVCs *could have* been placed by a physician at either the bedside or in the operating room. This uncertainty suggests that these data were not adequately recorded or accounted for. The authors also acknowledge that baseline CLABSI rates at their institution were above average, "likely due to suboptimal disinfection/maintenance".	***No*** Differences in baseline patient characteristics between the two study samples were tested and shown to be non-significant (Table 7.6.1 below). Also concurrent use of port protectors and neutral pressure connectors was checked using post-hoc testing (which confirmed that CUROS alone had an impact for patients with PICC). However, no adjustment was made to account for the increased education and regular monitoring of disinfection practice during the prospective	***N/A*** Outcomes were measured by period prevalence, rather than by following up individual patients.	***Not very precise*** Differences in baseline characteristics and central line characteristics were analysed and p-values are shown. Differences in the rate of CLABSI/1000 catheter days are reported with 95% confidence intervals and p-values. With a relative risk of 0.14, the 95% confidence intervals of 0.02 and 1.07 were close to zero, suggesting a relatively weak effect.

					data collection. Given that baseline practice was likely to have been sub-optimal, this is an important confounder which could easily be responsible for the overall reduction in infection rates. There did not appear to be any measurement of how many alcohol wipes were used in each arm, nor of duration (estimating disinfection times of 15 to 60 seconds).		
Ramirez 2012	***Unclear*** Not clear if study took place on one or two ICUs. States that "2 ICUs had all CVC and IV tubing covered with a protective cap" and that the study sample comprised "all patients in our ICU with an indwelling central line who were receiving IV treatments"	***Unclear*** Compliance with the intervention was measured by trained observers during rounds. The observers received consistent training on the use of the data collection tool. Compliance level may be affected if clinical staff were aware that an	***Yes*** Centre for Disease Control and Prevention National Healthcare Safety Network guidelines were used to define CLABSI	***No*** No discussion or identification of possible confounders. Baseline characteristics were assumed similar (no statistical analysis) No discussion/acknowledgement about blinding or about possible confounders such as staff training.	***No*** The authors state that training and encouragement to change practice were required throughout the trial period but do not account for this as a possible reason for reduction in CLABSI rates.	***N/A*** Outcomes were measured by period prevalence, rather than by following up individual patients.	***Not very precise*** Baseline characteristics were assumed to be the same between the pre-intervention cohort and the intervention cohort however the baseline characteristics were appear to have been assessed using 3 years of data pre intervention but only the most recent 12

	Also states that there was “migration to an oncology unit where staff members wanted to use the caps” but no indication of whether this use was assessed as part of the study results	assessment was underway in the unit. Nothing reported to indicate whether clinical staff were using alcohol wipes rather than disinfectant caps where there was non-compliance. The intervention was adapted during the trial in response to low compliance, which was attributed to lack of available caps at the bedside. During the fifth month, caps were made more accessible by adding cap strips (hung on IV poles) in patient rooms. This led to an increase in average compliance.		No measurement of alcohol wipe use or duration of use.			months of data pre intervention was used to make comparisons. Also the periods of outcome measurement were not fully concurrent with the periods of time before and after the intervention. The number of catheter days at risk was comparable between the two time periods; 2112/year and 2160/year. Results suggest that the CLABSI rate decreased from 1.9/1000 catheter days to 0.5/1000 catheter days however the number of CLABSI related infection recorded was very low both pre-intervention (n=4) and post-intervention (n=1). Several times the authors refer to there being a “significant” reduction in CLABSI rates, and claim that the intervention was effective. However,

							in the statistical methods section, the authors admit that p = 0.126 is not considered significant by conventional criteria.
Merrill 2014	***Yes*** All patients with peripheral and central lines in 13 units in a trauma centre were included in the study. Exclusion criteria were clearly identified in the study.	***Unclear*** Compliance was assessed 1-2 times a week throughout the study period and results were reported back to each unit to encourage compliance Nothing reported to indicate whether clinical staff were using alcohol wipes rather than disinfectant caps where there was non-compliance	***Unclear*** CLABSI was defined as a 'primary laboratory confirmed bloodstream infection in a patient with a central line at the time of (or within 48 hours prior to) the onset of symptoms and the infection is not related to infection from another site' (CDC definition). All positive blood cultures were reviewed to ensure they met the definition for CLABSI.	***Yes*** possible confounders were acknowledged including: Ongoing education implemented simultaneously Use of the disinfectant cap resulting in increased vigilance to compliance to central line bundle	***No*** Impact of possible confounders was not measured during the study	***N/A*** Patients were not followed up	***Not very precise*** The incidence rate ratio for implementing disinfection caps was 0.577 (95% CI, 0.396-0.842, p=0.004) indicating rate of infections decreased by >40% Rates of CLABSI per 1000 catheter line days decreased from a mean 1.5 (SD=0.37) before implementation to a mean 0.88 (SD= 0.62) after implementation
Cameron -Watson 2016	***Unclear*** Includes 1094 patients from 4 wards No indication whether this was all eligible patients No exclusion criteria	***Yes*** Anonymous benchmarking audit of standard practice was carried out before intervention implemented Compliance during the study period was measured by	***Unclear*** CLABSI rates were compared before and after intervention but no definition of CLABSI was provided	***Unclear*** Authors identified educational posters as a possible confounder but nothing else	***No*** Posters were provided to reinforce the use of disinfectant caps but the effect of these posters was not measured	***N/A*** Follow-up with patients formed part of the audit process but no follow up post discharge was reported	***Not very precise*** Number of catheter days at risk was not reported, results analysed on a per patient basis. Total number of infections for 6 months prior to

		counting the number of caps present on needle-free devices					implementation was 26 (27% compliance) compared with 8 (80% compliance) in the 6 months following implementation (69% reduction). Mean CLABSI rate reduced from 4.3 with standard care to 1.5 with disinfection caps (mean reduction of 2.8) but no standard deviations/standard errors reported. The authors state that CLABSIs started to increase on removal of disinfection caps at the end of the 6 month period but no statistical analysis presented
Martino 2017	***Yes*** Study population was clearly identified and all patients with a VAD on a burns ICU were included	***Unclear*** Weekly observational audits were conducted but no definition of compliance was reported. Simultaneous on-going observational central line bundle surveillance was	***Yes*** CLABSI was define using the CDC definition and identification and reporting were done by the Unit Infection Control Nurse	***Yes*** Acknowledged the limited patient population may not be representative. Highlights a number of changes which may impact CLABSI rates (e.g. location of unit, staff turnover,	***Partially*** Some confounding factors assessed. Baseline characteristics of patients in the study were assessed and no significant	***N/A*** Patients were not followed up	***Not very precise*** Baseline characteristics were analysed and p values presented. Overall the results and data being analysed and

		carried out by members of the infection control committee.		increased monitoring of the CLABSI bundle)	difference identified. Other potential confounding was not assessed statistically although some possible reasons for changes in compliance and CLABSI rates were put forward.		presented is not consistent or clear. Total CVL days and CLABSI rate/1000 line days are provided for • pre-intervention (presented as January-June 2011, July-December 2011) • intervention (presented asJanuary-June 2012) and • post-intervention periods (presented as July-November 2012 and December 2012-December 2013). No confidence intervals or p values presented. Results section compares CLABSI rates in 2014 (5.4/1000 line days; 2042 central line days) with averages in 2012 and 2013 providing p values but no other data.
Duncan 2018	***Unclear***	***Unclear***	***Unclear***	***No***	***No***	***N/A***	***Not very precise***

	Only exclusion criteria given related to hospital units excluded Number of lines in a two week pre-intervention period was given but study states that 6 months pre-intervention was assessed There is a gap in the study periods between pre-intervention and intervention. Pre-intervention was 6 month period (January-June 2015) while intervention period was 7 months (November 2015-June 2016)	Audits were carried out but no definition for compliance was given	Compliance was not defined BSI were defined according to international criteria	No confounding factors were identified, analysed or discussed	Baseline factors were not considered/assessed Both caps and tips were introduced simultaneously on peripheral lines while tips were introduced on central lines as caps had already been in use for 5 years. Analysis does not consider the possibility that either caps or tips alone may impact BSI rates.	Patients were not followed up	Overall the results and data being analysed and presented is not consistent or clear. No baseline characteristics were reported/analysed A pre-intervention 'baseline' assessment was carried out for 2 weeks but it is not clear what this was compared with. Timelines for reporting do not match through the text so it is unclear what data are being compared and how Number of primary BSIs during the intervention period was 17 on the units (8 from patients with PIV) that implemented the PIV maintenance bundle compared with 39 in the pre-intervention group but no details were given about the catheter days at

							risk/number of lines/number of patients assessed. It is not clear whether the 39 BSI's in the pre-intervention group were all primary BSI's or PIV associated BSI's. The study reports an 81% reduction in peripheral line associated BSIs compared with pre-intervention (0.57/1000 patient days to 0.11/1000 patient days; p<0.0001) suggesting the 30 BSI's in the pre-intervention period were PIV associated BSI's but this is not clear. 9 central line associated BSI's were reported during the intervention period compared with 7 in the pre-intervention period (0.1/1000 patient days to 0.12/1000 patient days p=0.72) Pain, redness and swelling at the

							insertion site was within define limits in 92% of patients pre-intervention and in 98% of patients during intervention (p<0.0001)
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study							

Systematic Review

Study name	**Voor in 't holt 2017**
Objective	To investigate the effect of antiseptic barrier caps compared with manual disinfection on the incidence of CLABSI
Location	Systematic Review of studies carried out in a hospital setting
Design	Systematic Review not limited by study methodology although reviews were excluded
Duration of study	Searches conducted up to May 10 2016
Patient population	N/A
Sample size	There were 4 studies included which had Curos as the antiseptic cap Sweet 2012 Ramirez 2012 Merrill 2014 Cameron-Watson 2016
Inclusion criteria	Any study which included the use of antiseptic barrier caps on the hubs of central lines with access to the blood stream
Exclusion criteria	Reviews (reference lists of reviews were searched for any additional studies) Studies of barrier caps on feeding tubes or tubes without access to the bloodstream Conference abstracts, abstracts only, letters Studies missing information about CLABSIs and the number of catheter days (after contacting the authors)
Intervention(s) (n =) and comparator(s) (n =)	Single use antiseptic barrier caps (including Curos) with the results analysis in totality and by antiseptic cap compared with standard care.
Baseline differences	Not analysed
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	No follow-up
Statistical tests	Study characteristics were summarised as frequencies and percentages Primary outcome (CLABSI Rates) expressed as Incidence Rate Ratio (IRR) Meta-analysis of the IRR (random effects model (DerSimonian and Laird) and I^2 statistic for heterogeneity)

Primary outcomes (including scoring methods and timings of assessments)	CLABSI Rates per 1000 catheter days
Secondary outcomes (including scoring methods and timings of assessments)	Compliance Costs and Savings

Study name: Voor in 't Holt 2017		
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Did the review have a focused question	Yes	Review Question: What is the effect of antiseptic barrier caps compared to manual disinfection on the incidence of CLABSIs The question was clear however it excluded the community setting
Were the right type of papers searched	Yes	The review did not exclude any studies based on study design which was appropriate in this case
Were the right type of papers included	Yes	Searches were comprehensive covering a number of key databases. Unpublished literature was identified and hand searching of reference lists carried out.
Was study quality assessed appropriately	Yes	Study quality was assessed using a 27 item scoring list
Were study data combined appropriately	Yes	Meta-analysis was carried out using appropriate methodology and subgroup analysis. The company did not use this meta-analysis in their submission.
What were the overall results	N/A	The results of the review were not used in the assessment report – only the relevant individual studies.
Were the results precise	N/A	The results of the review were not used in the assessment report – only the relevant individual studies.
Are the results applicable	N/A	The results of the review were not used in the assessment report – only the relevant individual studies.
Were all outcomes considered	Yes	
Are the benefits worth the harms and costs	N/A	The results of the review were not used in the assessment report – only the relevant individual studies.
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a Systematic Review		

Appendix D: Adverse Events (EAC Updated Searches)

Event Date	Event Type	Manufacturer	Date Received	Product Code	Brand Name	Device Problem	Event text
2018/05/25	Malfunction	3M COMPANY	2018/06/07	LKB	CUROS JET		Event Description: GREEN CUROS CAPS BROKE WHEN PLACED ONTO LUER LOCK. THIS OCCURRED ON TWO DIFFERENT PATIENTS WITH TWO DIFFERENT NURSES. BOTH WERE ABLE TO BE REMOVED AND A NEW CAP PLACED. THERE WAS NO HARM TO THE PATIENT. Manufacturer Narrative: .
2018/04/11	Malfunction	3M HEALTH CARE	2018/05/31	LKB	3M¿ CUROS JET¿ DISINFECTING CAP FOR NEEDLELESS CONNECTORS	Fluid Leak	Event Description: A CUSTOMER REPORTED THE FOLLOWING INFORMATION VIA A MEDWATCH REPORT: "A 3M¿ CUROS JET¿ CAP MALFUNCTIONED, LEAVING PATIENT'S DAILY FLUID LINE LEAKING ON THE PATIENT AND NOT THROUGH IV LINE. THE CAP WAS REMOVED AND PLACED IN A BIOHAZARD BAG TO SEND TO PURCHASING. NUMBER ON CAP WAS (B)(4). THE TUBING WAS NOT PRESERVED." Manufacturer Narrative: THE 3M¿ CUROS JET¿ DISINFECTING CAP NUMBER WAS REPORTED AS: (B)(4). NO PRODUCT CATALOG NUMBER WAS PROVIDED. WITHOUT A CATALOG NUMBER, A LOT NUMBER COULD NOT BE DETERMINED. NO SAMPLE HAS BEEN RECEIVED TO DATE. (B)(4) WAS RECEIVED FROM THE FACILITY AND THE FDA. 3M HAS RECENTLY IMPLEMENTED A LABELING CHANGE INFORMING USERS OF THE POTENTIAL FOR INTERMITTENT LEAKING WITH BAXTER® CONTINU-FLO¿ SOLUTION SET WITH CLEARLINK¿ LUER ACTIVATED VALVE IN ADDITION TO BD MAXZERO¿ NEEDLE-FREE CONNECTORS. PLEASE SEE THE EXACT WORDING BELOW: CAUTION: THERE IS A POTENTIAL FOR INTERMITTENT LEAKING WHEN BAXTER® CONTINU-FLO¿ SOLUTION SET WITH CLEARLINK¿ LUER ACTIVATED VALVE OR BD MAXZERO¿ NEEDLE-FREE CONNECTORS ARE USED UNDER PRESSURE WITH 3M¿ CUROS JET¿ DISINFECTING CAPS (CFJ1-270 AND CFJ5-250.) MONITOR THESE CONNECTORS IF USED UNDER PRESSURE. ALTERNATIVELY, 3M¿ CUROS¿ DISINFECTING CAP FOR NEEDLELESS CONNECTORS (CFF1-270 AND CFF10- 250) MAY BE USED. END OF REPORT.

2018/04/19	Malfunction	3M HEALTH CARE	2018/05/31	LKB	3M¿ CUROS JET¿ DISINFECTING CAP FOR NEEDLELESS CONNECTORS	Fluid Leak	Event Description: A CUSTOMER REPORTED THE FOLLOWING INFORMATION VIA A MEDWATCH REPORT: "PATIENT WAS RECEIVING TPN. GREEN CAP (3M¿ CUROS JET¿ CAP) CREATED A LEAK IN THE PORT WHICH LEAKED ON THE PATIENT'S BED. WHEN LEAK WAS FOUND, CAP WAS REPLACED AND THE SAME LEAK OCCURRED. WHEN THE CAP WAS REMOVED, IV PUMP ALERTED FOR OCCLUSION AND WHEN NEW GREEN CAP APPLIED, ALERT WAS REMOVED AND FLOW CONTINUED. AMOUNT OF TPN THE PATIENT DIDN'T RECEIVE WAS NOT KNOWN." Manufacturer Narrative: UPON FOLLOW-UP, THE CUSTOMER REPORTED THERE WAS NO HARM TO THE PATIENT. THE TPN WAS RESTARTED AND DID NOT REQUIRE REDOSING. THE 3M¿ CUROS JET¿ DISINFECTING CAP NUMBER AND LOT NUMBER WAS NOT AVAILABLE. WITHOUT A CAP OR LOT NUMBER, THE EXPIRATION DATE AND MANUFACTURER DATE COULD NOT BE DETERMINED. NO SAMPLE HAS BEEN RECEIVED TO DATE. INITIAL REPORTER: (B)(4) WAS RECEIVED FROM THE FACILITY AND THE FDA. 3M HAS RECENTLY IMPLEMENTED A LABELING CHANGE INFORMING USERS OF THE POTENTIAL FOR INTERMITTENT LEAKING WITH BAXTER® CONTINU-FLO¿ SOLUTION SET WITH CLEARLINK¿ LUER ACTIVATED VALVE IN ADDITION TO BD MAXZERO¿ NEEDLE-FREE CONNECTORS. PLEASE SEE THE EXACT WORDING BELOW: CAUTION: THERE IS A POTENTIAL FOR INTERMITTENT LEAKING WHEN BAXTER® CONTINU-FLO¿ SOLUTION SET WITH CLEARLINK¿ LUER ACTIVATED VALVE OR BD MAXZERO¿ NEEDLE-FREE CONNECTORS ARE USED UNDER PRESSURE WITH 3M¿ CUROS JET¿ DISINFECTING CAPS (CFJ1-270 AND CFJ5-250.) MONITOR THESE CONNECTORS IF USED UNDER PRESSURE. ALTERNATIVELY, 3M¿ CUROS¿ DISINFECTING CAP FOR NEEDLELESS CONNECTORS (CFF1-270 AND CFF10- 250) MAY BE USED. END OF REPORT.
2018/04/26	Malfunction	3M HEALTH CARE	2018/05/31	LKB	3M¿ CUROS JET¿ DISINFECTING CAP FOR NEEDLELESS CONNECTORS	Fluid Leak	Event Description: A CUSTOMER REPORTED THE FOLLOWING INFORMATION VIA A MEDWATCH REPORT: "ADMINISTERED MEDICATION TO SPECIFIED {SICU} PATIENT AND CUROS JET¿ CAP MALFUNCTION OCCURRED. MEDICATION WAS NOT PROPERLY ADMINISTERED TO THE PATIENT, BUT FOUND TO LEAK ONTO THE FLOOR. CUROS JET CAP WAS KEPT AND WILL BE RETURNED TO COMPANY PER MANAGEMENT REQUEST. MEDICATION THEN ADMINISTERED LATE TO PATIENT. NO PATIENT IMPACT OCCURRED." Manufacturer Narrative: NO SAMPLE HAS BEEN RECEIVED TO DATE. (B)(4) WAS RECEIVED FROM THE FACILITY AND THE FDA. 3M HAS RECENTLY IMPLEMENTED A LABELING CHANGE INFORMING USERS OF THE POTENTIAL FOR INTERMITTENT LEAKING WITH BAXTER® CONTINU-FLO¿ SOLUTION SET WITH CLEARLINK¿ LUER ACTIVATED VALVE IN ADDITION TO BD MAXZERO¿ NEEDLE-FREE CONNECTORS. PLEASE SEE THE EXACT WORDING BELOW: CAUTION: THERE IS A POTENTIAL FOR INTERMITTENT LEAKING WHEN BAXTER® CONTINU-FLO¿ SOLUTION SET WITH CLEARLINK¿ LUER ACTIVATED

							VALVE OR BD MAXZERO¿ NEEDLE-FREE CONNECTORS ARE USED UNDER PRESSURE WITH 3M¿ CUROS JET¿ DISINFECTING CAPS (CFJ1-270 AND CFJ5-250.) MONITOR THESE CONNECTORS IF USED UNDER PRESSURE. ALTERNATIVELY, 3M¿ CUROS¿ DISINFECTING CAP FOR NEEDLELESS CONNECTORS (CFF1-270 AND CFF10- 250) MAY BE USED. END OF REPORT
2018/04/26	Malfunction	3M COMPANY	2018/05/14	LKB	CUROS JET¿		Event Description: ADMINISTERED MEDICATION TO SPECIFIED {SICU} PATIENT, AND CUROS MALFUNCTION OCCURRED. MEDICATION WAS NOT PROPERLY ADMINISTERED TO THE PATIENT, BUT FOUND TO LEAK ONTO THE FLOOR. CAP WAS KEPT AND WILL BE RETURNED TO COMPANY PER MANAGEMENT REQUEST. MEDICATION THEN ADMINISTERED LATE TO PATIENT. NO PATIENT IMPACT. Manufacturer Narrative: .
2018/04/19	Malfunction	3M COMPANY	2018/05/14	LKB	CUROS JET¿		Event Description: PATIENT RECEIVING TPN. GREEN CAP CREATED A LEAK IN THE PORT WHICH LEAKED ON PATIENTS BED. WHEN LEAK WAS FOUND, CAP REPLACED AND SAME LEAK OCCURRED. WHEN CAP WAS REMOVED, IV PUMP ALERT FOR OCCLUSION AND WHEN NEW GREEN CAP APPLIED, ALERT WAS REMOVED AND FLOW CONTINUED. AMOUNT OF TPN THE PATIENT DIDN'T RECEIVE NOT KNOWN. Manufacturer Narrative: .
2018/03/01	Malfunction	3M HEALTH CARE	2018/05/09	LKB	3M¿ CUROS JET¿ DISINFECTING CAP FOR NEEDLELESS CONNECTORS	Fluid Leak	Event Description: A CUSTOMER REPORTED VIA A MEDWATCH THAT "A PATIENT WAS INFUSING HIS GEMCITABINE AND HE NOTICED A WET SPOT ON HIS PANTS. ON FURTHER INSPECTION HE NOTICED "THE LIQUID" WAS COMING OUT OF THE HUB OF THE TUBING. NURSE INSPECTED AND IT WAS NOTICED THAT WHERE THE CUROS CAP WAS ATTACHED TO THE SECOND HUB ON BAXTER TUBING WAS LEAKING. CHEMO STOPPED, CUROS REMOVED, PORT FLUSHED, PATIENT SKIN CLEANED AND CHEMO THEN RESTARTED AND FINISHED WITHOUT ISSUE." Manufacturer Narrative: CUSTOMER REPORTED THE DATE OF EVENT WAS (B)(6) 2018. (B)(6) 2018 WAS USED FOR THE DATE OF EVENT IN THIS REPORT. CUSTOMER REPORTED THE 3M¿ CUROS JET¿ DISINFECTING CAP FOR NEEDLELESS CONNECTORS FROM THIS REPORT WAS NOT SAVED. THE CUSTOMER REPORTED THE PRODUCT COULD HAVE BEEN EITHER CFJ1-270 OR CFJ5-250. THE CUROS JET¿ DISINFECTING CAP LOT NUMBER FOR THIS EVENT WAS UNKNOWN. WITHOUT A LOT NUMBER, THE EXPIRATION DATE AND MANUFACTURE DATE COULD NOT BE DETERMINED. (B)(4) RECEIVED FROM THE FACILITY. 3M RECEIVED A REPORT FROM THIS FACILITY IN (B)(6) 2018

							ALLEGING FOUR PATIENTS (NO SPECIFIC PATIENT INFORMATION PROVIDED) EXPERIENCED LEAKING OF MEDICATION AND MW2110898-2018-00040 WAS SUBMITTED TO THE FDA ON 9APR2018 FOR THIS REPORT. (B)(4) RECEIVED FROM THE FACILITY ON 7MAY2018 AND IT WAS CONFIRMED THAT THIS REPORT CONTAINED INFORMATION ABOUT ONE OF THE FOUR PATIENTS. THIS REPORT, MW2110898-2018-00052 WAS SUBMITTED SINCE INDIVIDUAL PATIENT INFORMATION WAS RECEIVED. 3M HAS RECENTLY IMPLEMENTED A LABELING CHANGE INFORMING USERS OF THE POTENTIAL FOR INTERMITTENT LEAKING WITH BAXTER® CONTINU-FLO¿ SOLUTION SET WITH CLEARLINK¿ LUER ACTIVATED VALVE IN ADDITION TO BD MAXZERO¿ NEEDLE-FREE CONNECTORS. PLEASE SEE THE EXACT WORDING BELOW: CAUTION: THERE IS A POTENTIAL FOR INTERMITTENT LEAKING WHEN BAXTER® CONTINU-FLO¿ SOLUTION SET WITH CLEARLINK¿ LUER ACTIVATED VALVE OR BD MAXZERO¿ NEEDLE-FREE CONNECTORS ARE USED UNDER PRESSURE WITH 3M¿ CUROS JET¿ DISINFECTING CAPS (CFJ1-270 AND CFJ5-250.) MONITOR THESE CONNECTORS IF USED UNDER PRESSURE. ALTERNATIVELY, 3M¿ CUROS¿ DISINFECTING CAP FOR NEEDLELESS CONNECTORS (CFF1-270 AND CFF10- 250) MAY BE USED. END OF REPORT
2018/04/01	Malfunction	3M HEALTH CARE	2018/05/09	LKB	3M¿ CUROS JET¿ DISINFECTING CAP FOR NEEDLELESS CONNECTORS	Fluid Leak	Event Description: A NURSE REPORTED CUROS JET¿ DISINFECTING CAPS WERE PLACED ON THE NEEDLELESS CONNECTORS OF A PATIENT'S IV TUBING. THE PATIENT HAD MEDICATION/FLUID INFUSING VIA AN IV PUMP CONNECTED TO AN EXTENSION SET WITH A Y ADAPTOR. THE PATIENT REPORTEDLY EXPERIENCED LEAKING OF MEDICATION/FLUID (CIRCLE OF WETNESS NOTICED ON THE PATIENT'S PILLOW). THE CUROS JET¿ CAP WAS REPLACED AND THE LEAK REOCCURRED. THE CUROS JET¿ CAPS WERE REPORTEDLY REMOVED AND NO FURTHER LEAKING OCCURRED. Manufacturer Narrative: EVENT DATER: (B)(6) 2018 WAS USED FOR THE DATE OF THE EVENT IN THIS REPORT. CUSTOMER REPORTED THE EVENT OCCURRED APPROXIMATELY 1- 11/2 WEEKS PRIOR TO (B)(6) 2018. THE 3M¿ CUROS JET¿ DISINFECTING CAP FOR NEEDLELESS CONNECTOR FROM THIS REPORT WAS NOT SAVED. THE PRODUCT CATALOG NUMBER WAS NOT PROVIDED. THE CUROS JET¿ DISINFECTING CAP LOT NUMBER FOR THIS EVENT WAS UNKNOWN. WITHOUT A LOT NUMBER, THE EXPIRATION DATE AND MANUFACTURE DATE COULD NOT BE DETERMINED. E1 EMAIL AND PHONE NUMBER FOR THE NURSE WHO PROVIDED THE INFORMATION IN THIS REPORT WAS NOT PROVIDED. 3M RECEIVED A REPORT FROM THIS FACILITY IN MARCH 2018 ALLEGING FOUR PATIENTS (NO SPECIFIC PATIENT INFORMATION PROVIDED) EXPERIENCED LEAKING OF MEDICATION AND MW2110898-2018-00040 WAS SUBMITTED TO THE FDA ON 9APR2018 FOR THIS REPORT. A 3M TEAM VISITED THE FACILITY ON 11APR2018. A NURSE WAS INTERVIEWED AND PROVIDED SOME INFORMATION ABOUT

							ONE OF THE FOUR PATIENTS IN MW2110898-2018-00040. THIS REPORT, MW2110898-2018-00053, WAS SUBMITTED WITH THE PATIENT/EVENT INFORMATION THAT WAS RECEIVED. 3M HAS RECENTLY IMPLEMENTED A LABELING CHANGE INFORMING USERS OF THE POTENTIAL FOR INTERMITTENT LEAKING WITH BAXTER® CONTINU-FLO¿ SOLUTION SET WITH CLEARLINK¿ LUER ACTIVATED VALVE IN ADDITION TO BD MAXZERO¿ NEEDLE-FREE CONNECTORS. PLEASE SEE THE EXACT WORDING BELOW: CAUTION: THERE IS A POTENTIAL FOR INTERMITTENT LEAKING WHEN BAXTER® CONTINU-FLO¿ SOLUTION SET WITH CLEARLINK¿ LUER ACTIVATED VALVE OR BD MAXZERO¿ NEEDLE-FREE CONNECTORS ARE USED UNDER PRESSURE WITH 3M¿ CUROS JET¿ DISINFECTING CAPS (CFJ1-270 AND CFJ5-250.) MONITOR THESE CONNECTORS IF USED UNDER PRESSURE. ALTERNATIVELY, 3M¿ CUROS¿ DISINFECTING CAP FOR NEEDLELESS CONNECTORS (B)(4) MAY BE USED. END OF REPORT
2018/04/11	Malfunction	3M COMPANY	2018/05/07	LKB	CUROS		Event Description: CUROS JET CAP MALFUNCTIONED, LEAVING PATIENTS DAILY FLUID LINE LEAKING ON THE PATIENT AND NOT THROUGH IV LINE. CAP WAS REMOVED AND PLACED IN BIOHAZARD BAG TO SENT TO PURCHASING. NUMBER ON CAP IS (B)(4). THE TUBING WAS NOT PRESERVED. Manufacturer Narrative: .
2018/03/28	Malfunction	3M HEALTH CARE	2018/04/09	LKB	3M¿ CUROS JET¿ DISINFECTING CAP FOR NEEDLELESS CONNECTORS	Fluid Leak	Event Description: A NURSE REPORTED CFJ5-250 CUROS JET¿ DISINFECTING CAPS WERE PLACED ON THE NEEDLELESS CONNECTORS OF THEIR IV TUBING. FOUR PATIENTS REPORTEDLY EXPERIENCED LEAKING OF MEDICATION BETWEEN THE CONNECTION OF THE CUROS JET¿ DISINFECTING CAP AND THE Y- SITE NEEDLELESS CONNECTOR OF THEIR BAXTER CONTINU-FLO IV TUBING. THE NURSE REPORTED NO PATIENT INJURIES OCCURRED AND NO ADDITIONAL MEDICAL TREATMENT WAS REQUIRED. Manufacturer Narrative: EVENT DATE: (B)(6) 2018 WAS USED FOR THE DATE OF EVENT. CUSTOMER REPORTED THE FOUR EVENTS OCCURRED OVER A THREE WEEK PERIOD AND SPECIFIC DATES WERE NOT KNOWN. CUSTOMER REPORTED THE 3M¿ CUROS JET¿ DISINFECTING CAP FOR NEEDLELESS CONNECTORS FROM THE REPORTS WERE NOT SAVED. THE CUROS JET¿ DISINFECTING CAP LOT NUMBER WAS UNKNOWN. WITHOUT A LOT NUMBER, THE EXPIRATION DATE AND MANUFACTURE DATE COULD NOT BE DETERMINED. END OF REPORT

2017/08/13	Malfunction	3M HEALTH CARE	2017/12/13	LKB	3M CUROS JET DISINFECTING CAP FOR NEEDLELESS CONNECTORS	Fluid Leak	Event Description: A CUSTOMER REPORTED CUROS JET CAPS WERE PLACED ON THE NEEDLELESS CONNECTORS OF THEIR IV TUBING. THE IV TUBING WAS CONNECTED TO A STOPCOCK THAT WAS TURNED TO THE OFF POSITION TOWARDS THE PATIENT. IV FLUID WAS OBSERVED TO BE LEAKING FROM ONE OF THE NEEDLESS CONNECTOR Y-SITES ALONG THE IV TUBING. NO PATIENT HARM OCCURRED AND NO MEDICAL INTERVENTION WAS REQUIRED. Manufacturer Narrative: NO SAMPLES HAVE BEEN RECEIVED TO DATE. (B)(4) WAS RECEIVED FROM THE FDA. CUSTOMER INITIALLY REPORTED "THE STOPCOCK WAS OFF TO INFUSE MEDICATION. THE PUMP DID NOT ALARM A DOWNSTREAM OCCLUSION. FLUID WAS NOTICED TO BE BACK FLOWING FROM PORT ON PRIMARY LINE. NEW MODEL OF GREEN CUROS CAP WAS ON THE PORT." 3M MADE SEVERAL ATTEMPTS TO OBTAIN ADDITIONAL INFORMATION ABOUT THIS REPORTED EVENT. ADDITIONAL INFORMATION WAS RECEIVED ON (B)(6) 2017. CUSTOMER REPORTED THEIR FACILITY USES BAXTER IV PUMPS AND BAXTER CONTINU-FLO TUBING WITH INTEGRATED CLEARLINK NEEDLELESS CONNECTORS. CUSTOMER REPORTED A CUROS JET CAP WAS ON ONE OF THE CLEARLINK PORTS (Y-SITE) ALONG THE IV TUBING. THE IV TUBING WAS THEN CONNECTED TO A STOPCOCK THAT WAS TURNED IN THE OFF POSITION TOWARDS THE PATIENT. LEAKING OF IV FLUID WAS REPORTEDLY OBSERVED AT A NEEDLELESS CONNECTOR Y-SITE ALONG THE IV TUBING. NO PATIENT INJURY OCCURED AND THERE WAS NO MEDICAL INTERVENTION REQUIRED.
2017/10/03	Malfunction	3M COMPANY	2017/11/13	LKB	CUROS¿		Event Description: TIP BROKE AFTER USE OF CUROS TIP. Manufacturer Narrative: .
2017/08/13	Malfunction	3M COMPANY, 3M HEALTH CARE	2017/09/27	LKB	CUROS JET		Event Description: THE STOP COCK WAS OFF TO INFUSE MEDICATION. THE PUMP DID NOT ALARM A "DOWNSTREAM OCCLUSION". FLUID WAS NOTICED TO BE BACK FLOWING FROM PORT ON PRIMARY LINE. NEW MODEL OF GREEN "CUROS CAP" WAS ON THE PORT. Manufacturer Narrative: .

2017/08/17	Malfunction	3M HEALTH CARE	2017/09/26	LKB	3M CUROS DISINFECTING CAP FOR NEEDLELESS CONNECTORS	Use of Device Problem	Event Description: AN INTERVENTIONAL RADIOLOGIST REPORTED AN OUTPATIENT PRESENTED WITH A NONFUNCTIONING HICKMAN CATHETER LINE. A SPONGE FROM A CUROS CAP WAS FOUND IN THE FEMALE LUER CATHETER HUB AND WAS REMOVED. NO INJURY WAS REPORTED, THE PATIENT WAS BEING MONITORED FOR SIGNS AND SYMPTOMS OF INFECTION. Manufacturer Narrative: CUSTOMER REPORTED THE CATALOG NUMBER FOR THIS REPORT WAS CFF1-270 (OR CFF 10-250). CFF1-270 ARE INDIVIDUAL CAPS AND CFF10-250 ARE STRIPS(10 CAPS /STRIP). OPERATOR OF DEVICE WAS UNKNOWN. CUSTOMER REPORTED THE PATIENT'S HICKMAN CATHETER WAS USED FOR DAILY HOME INFUSIONS OF TPN. TYPE OF REPORTABLE EVENT. THIS REPORT DID NOT INVOLVE A DEATH, SERIOUS INJURY OR A MALFUNCTION. MALFUNCTION WAS SELECTED FOR THIS REPORT BECAUSE A SELECTION WAS REQUIRED FOR THIS SECTION OF THE REPORT. THE CUSTOMER REPORT NOTED THAT CUROS CAPS ARE NOT INTENDED TO ATTACH TO A FEMALE LUER HUB AND ARE DESIGNED TO BE USED ON NEEDLELESS CONNECTORS. THE PRODUCT PACKAGING INCLUDES THE FOLLOWING WARNING AND CAUTIONARY STATEMENTS: WARNING: TO AVOID POTENTIAL INJURY - USE ONLY ON NEEDLELESS CONNECTORS. THE PACKAGE INSERT STATES THE FOLLOWING INFORMATION RELATED TO INTENDED USE AND INSTRUCTIONS FOR USE: INTENDED USE: THE CUROS¿ DISINFECTING CAP IS INTENDED FOR USE ON NEEDLELESS CONNECTORS ONLY AS A DISINFECTING CLEANER PRIOR TO I.V. ACCESS AND TO ACT AS A COVER BETWEEN LINE ACCESSES..... INSTRUCTIONS FOR USE: WARNING: TO AVOID POTENTIAL FOR INJURY - USE ONLY ON NEEDLELESS CONNECTORS..... IN ADDITION, 3M PROVIDES TRAINING MATERIALS (INCLUDING GRAPHICS) INSTRUCTING CUSTOMERS TO APPLY THE CUROS CAP ONLY TO NEEDLELESS CONNECTORS AND NOT TO APPLY THE CUROS CAP DIRECTLY TO A CATHETER HUB. IN SUMMARY, THE PRODUCT PACKAGING AND INSTRUCTIONS FOR USE CLEARLY STATE VIA A WARNING THAT THE PRODUCT SHOULD ONLY BE USED ON NEEDLELESS CONNECTORS.
	Malfunction	3M HEALTH CARE	2017/09/26	LKB	3M CUROS DISINFECTING CAP FOR NEEDLELESS CONNECTORS	Use of Device Problem	Event Description: AN INTERVENTIONAL RADIOLOGIST REPORTED IN THE PAST TWO YEARS, TWO PATIENTS WERE FOUND TO HAVE A CUROS CAP SPONGE IN THEIR FEMALE LUER CATHETER HUBS. THESE EVENTS WERE NOT PREVIOUSLY REPORTED. NO ADDITIONAL INFORMATION WAS AVAILABLE FOR THESE REPORTS. Manufacturer Narrative: INFORMATION WAS NOT PROVIDED BY REPORTER. NO DATE OF OCCURRENCE WAS PROVIDED FOR THIS REPORT. THE INTERVENTIONAL RADIOLOGIST INITIALLY REPORTED A SPECIFIC PATIENT ADVERSE EVENT OCCURRED ON (B)(6) 2017 AND REPORT NUMBER 2110898-2017-00128 WAS SUBMITTED FOR THAT PATIENT ADVERSE EVENT. IN HIS REPORT, THE INTERVENTIONAL RADIOLOGIST

							NOTED THIS IDENTICAL INCIDENT OCCURRED TWO OTHER TIMES IN THE PAST TWO YEARS. NO ADDITIONAL INFORMATION WAS PROVIDED. THIS REPORT, 2110898-2017-00129, WAS SUBMITTED TO CAPTURE THE TWO ADDITIONAL EVENTS WHERE NO SPECIFIC INFORMATION WAS PROVIDED. CUSTOMER REPORTED THE CATALOG NUMBER FOR THIS REPORT WAS CFF1-270 (OR CFF 10-250). CFF1-270 ARE INDIVIDUAL CAPS AND CFF10-250 ARE STRIPS (10 CAPS /STRIP). OPERATOR OF DEVICE WAS UNKNOWN. TYPE OF REPORTABLE EVENT. THIS REPORT DID NOT INVOLVE A DEATH, SERIOUS INJURY OR A MALFUNCTION. MALFUNCTION WAS SELECTED FOR THIS REPORT BECAUSE A SELECTION WAS REQUIRED FOR THIS SECTION OF THE REPORT. THE CUSTOMER REPORT NOTED THAT CUROS CAPS ARE NOT INTENDED TO ATTACH TO A FEMALE LUER HUB AND ARE DESIGNED TO BE USED ON NEEDLELESS CONNECTORS. THE PRODUCT PACKAGING INCLUDES THE FOLLOWING WARNING AND CAUTIONARY STATEMENTS: WARNING: TO AVOID POTENTIAL INJURY - USE ONLY ON NEEDLELESS CONNECTORS. THE PACKAGE INSERT STATES THE FOLLOWING INFORMATION RELATED TO INTENDED USE AND INSTRUCTIONS FOR USE: INTENDED USE: THE CUROS¿ DISINFECTING CAP IS INTENDED FOR USE ON NEEDLELESS CONNECTORS ONLY AS A DISINFECTING CLEANER PRIOR TO I.V. ACCESS AND TO ACT AS A COVER BETWEEN LINE ACCESSES. INSTRUCTIONS FOR USE: WARNING: TO AVOID POTENTIAL FOR INJURY - USE ONLY ON NEEDLELESS CONNECTORS. IN ADDITION, 3M PROVIDES TRAINING MATERIALS (INCLUDING GRAPHICS) INSTRUCTING CUSTOMERS TO APPLY THE CUROS CAP ONLY TO NEEDLELESS CONNECTORS AND NOT TO APPLY THE CUROS CAP DIRECTLY TO A CATHETER HUB. IN SUMMARY, THE PRODUCT PACKAGING AND INSTRUCTIONS FOR USE CLEARLY STATE VIA A WARNING THAT THE PRODUCT SHOULD ONLY BE USED ON NEEDLELESS CONNECTORS.
	Malfunction	3M HEALTH CARE	2017/09/18	LKB	3M CUROS DISINFECTING CAP FOR NEEDLELESS CONNECTORS	Break	Event Description: A PEDIATRIC ICU DEPARTMENT IN (B)(6) REPORTED A SMALL GREEN PARTICLE BROKE OFF FROM A CFF1-270R CUROS CAP AND WAS ASPIRATED OUT OF A PATIENT'S IV TUBING LUMEN. NO PATIENT INJURY WAS REPORTED. Manufacturer Narrative: NO INFORMATION WAS PROVIDED REGARDING USE OF A NEEDLESS CONNECTOR. Manufacturer Narrative: INFORMATION WAS NOT PROVIDED BY REPORTER. DATE OF EVENT: INFORMATION WAS NOT PROVIDED BY REPORTER.

2017/08/24	Malfunction	3M HEALTH CARE	2017/09/13	LKB	3M CUROS JET DISINFECTING CAP FOR NEEDLELESS CONNECTORS	Fluid Leak	Event Description: A NURSE REPORTED LEAKING OF BLOOD AND SALINE FROM THE CFJ5-250 CUROS JET CAP AND THE NEEDLELESS CONNECTOR WHEN FLUSHING THE PORT CATHETER/IV TUBING FOLLOWING BLOOD DRAWS. THE NURSE REPORTED THIS HAS BEEN A RECURRING ISSUE. NO PATIENT INJURY OR MEDICAL INTERVENTION HAS BEEN REPORTED. THE CUROS JET CAP AND THE NEEDLELESS CONNECTOR WERE REPLACED WHEN THE ISSUE OCCURRED. Manufacturer Narrative: PT INFO: INFORMATION WAS NOT PROVIDED BY REPORTER. DATE OF EVENT: (B)(6) 2017 WAS USED FOR THE DATE OF INCIDENT. NO SPECIFIC DATE OF OCCURRENCE WAS PROVIDED. NO LOT NUMBER WAS PROVIDED FOR THE REPORT. SAMPLE HAS NOT BEEN RECEIVED FOR THIS REPORT TO DATE.
2017/08/06	Injury	3M HEALTH CARE	2017/09/13	LKB	3M CUROS JET DISINFECTING CAP FOR NEEDLELESS CONNECTORS	Fluid Leak	Event Description: A CUSTOMER REPORTED A (B)(6) FEMALE, INSULIN DEPENDENT DIABETIC, TERMINAL CANCER PATIENT, EXPERIENCED LEAKING OF INSULIN AT THE PROXIMAL Y- SITE CONNECTION BETWEEN A CFJ5-250 CUROS JET CAP AND THE NEEDLELESS CONNECTOR ON HER PRIMARY IV TUBING. IT WAS UNCLEAR HOW LONG THE TUBING HAD BEEN LEAKING. THE PATIENT'S BLOOD SUGARS WERE ELEVATED AFTER THE LEAK WAS FOUND AND A NURSE REPORTED THE PATIENT EXPERIENCED DIABETIC KETOACIDOSIS. CONTINUATION OF THE INSULIN DRIP TITRATION AND PATIENT MONITORING WAS REQUIRED. THE CUSTOMER REPORTED IT WAS UNCLEAR IF THE LEAK CONTRIBUTED TO THE PATIENT'S ELEVATED BLOOD SUGARS. Manufacturer Narrative: CUSTOMER REPORTED THE PATIENT EXPIRED (B)(6) 2017 UNRELATED TO THIS INCIDENT. CAUSE OF DEATH REPORTED AS: CVA, METASTATIC BREAST CANCER. RISK MANAGER REPORTED THE CATALOG NUMBER AS CFJ1-270. SAMPLES WERE RECEIVED FOR THIS REPORT AND APPEAR TO BE FROM CATALOG NUMBER CFJ5-250. LOT NUMBER WAS REPORTED AS 03200429 WHICH IS THE CAP CODE. PRODUCT LOT NUMBER FOR THIS CAP CODE IS: (B)(4) THE INITIAL REPORTER WAS LISTED IN THIS SECTION. ADDITIONAL INFORMATION FOR THIS REPORT WAS RECEIVED FROM THE RISK MANAGER. DEVICE EVALUATION IN PROGRESS, NOT YET COMPLETED.

Appendix E: GRADE Assessment for Curos versus Manual Disinfection

Certainty assessment							№ of Catheter Days at Risk		Effect	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Curos Disinfection Caps**	**Alcohol Wipes**	**Relative (95% CI)**		
Catheter Related Bloodstream Infections/Catheter Associated Bloodstream Infections (assessed with: rate/1000 days)											
Refs. 1. Sweet (2012) 2. Ramirez (2012) 3. Merrill (2014) 4.Martino (2017)											
3 [1,2,3, 4]	observational studies [a]	very serious [b,c,d]	not serious	serious [e]	very serious [f]	all plausible residual confounding would reduce the demonstrated effect	5/6437 [g, h] 1/1000	25/9636 [g, h] 3/1000	**Rate ratio 0.43** (0.22 to 0.82),	⨁◯◯◯ VERY LOW	Critical

Abbreviations: CI: Confidence interval

Explanations

a. All studies were before and after studies
b. None of the studies were controlled before and after studies. They all used retrospective chart data to inform the 'before'.
c. Baseline characteristics of patients were not reported
d. Potential confounding factors were not accounted for
e. One Study (Sweet, 2012) includes a change of needleless connector as part of the intervention
f. Inconsistencies in the data reported (Sweet, 2012). Lack of clarity in the reporting periods in two studies (Ramirezl, 2012 and Martino, 2017).
g. Mean monthly infection rates used to calculate the mean annual infection rates (mean of means) rather than using the original infection numbers (Merrill, 2014) so the data from this study could not be included in the number of catheter days at risk.
h. Rate Ratio denominator is number of catheter line days at risk

Appendix F: Model Behaviour Test

Test	Intervention cost	Comparator cost	Difference	Comment
Disinfection Method in the Hospital Setting	£13.44	£0.84	-£12.60	
Set patients to 0				Costs reset to £0
Set patients to 2000				Everything (infection rates, costs of infections etc) doubles but the incremental costs stay the same – as expected
Set cost of Curos to £0	£0	£0.84	£0.08	Cost of Curos sets to £0 as expected which impacts the incremental cost by making Curos more cost saving as expected (-£41.67)
Set Cost of Curos to £1	£42.00	£0.84	£41.16	Cost of Curos increases which in turn increases the incremental cost per patient making Curos cost incurring (£0.33)
Set Cost of Wipes to £0	£13.44	£0.00	-£13.44	Cost of wipes is £0 in the model but Curos remains cost saving (-£27.39) although slightly less so due to the wipes now being 'free'. This is expected as the driver in this setting is the cost of CLABSI and the cost of wipes is so low in the basecase.
Cost of CLABSI in the hospital setting	£21.01	£50.15	-£28.58	
Increase the baseline infection rate	£77.01	£179.10	-£102.09	Increasing the baseline infection rate should make Curos more cost saving because increasing the baseline infection rate should result in more patients in the both groups getting a CLABSI but the number getting a CLABSI will be much increase more in the alcohol wipes group which will increase the cost per CLABSI.
Reduce the IRR (make it closer to 1)	£40.12	£50.15	-£10.03	Reducing the IRR to reflect the possibility that Curos does not have such an impact on infection rates will increase the number of infections in the CUROS group but should not affect the wipes group. This should increase the cost per

				CLABSI for Curos but have no impact on wipes
Make the rate of infection equal in both groups (IRR=1)	£50.15	£50.15	£0.00	Making the infection rate equal in both group should make the cost per CLABSI equal in both groups. With a baseline rate of 0.7 the number of infections in both groups should be 2.45 based on 500 patients with an average 7 catheter days at risk. The model does not allow for a situation where the infection rates are the same so it does not calculate an incremental cost per patient in this scenario because it cannot divide by 0 which is the differnec in the number of CLABSI per patient
Make the IRR 1.01	£50.20	£50.15	£0.05	This should allow check to see how model performs when the infections rates are as close to equal in the two groups as we can get it given an IRR of 1 does not give an incremental cost. The result is that Curos is less cost effective if the infection rates are same which would be expected due to the additional cost of curos caps
Make the IRR 0.999	£50.10	£50.15	-£0.05	Changes in the cost of CLABSI were as expected but the model appeared to suggest that Curos saved £61,194 per CLABSI avoided however review of the formula and calculations indicate that this the minus is due to the decimal places and that Curos in fact costs and additional £61,194 for every CLABSI avoided.
Cost of Nurse Time in the hospital setting	£6.13	£18.36	-£12.25	
Increase the amount of time for nurse disinfection in the Curos group	£12.25	£18.38	-£6.13	Increases the cost of nurse time for disinfection in the curos group which then impacts the incremental cost per patient. For example increasing nurse time to 0.5 mins means curos is still cost saving but the cost saving is less than when nurse time is 0.25 mins
Make the nurse time equal in both groups				This should make the cost of nurse time equal for both groups which it does. In the hospital setting Curos remains

				cost saving which would be expected as the cost of CLABSI is where the biggest diference is in the hospital population

Appendix G: EAC Changes to Model

EAC Basecase for general hospital and ICU settings

Sheet Title	Cell	Company Value	EAC Value	Comment
Nurse Time, standard care				
Costs and Resources, comparator	E35	0.75	0.25	Nurse time assumed equal in both due to the 30 second waiting time being utilised for other purposes in manual disinfection
Tornado Table Low Range	*F19*	*0.38*	*0.13*	*Change the range around nurse time for manual disinfection to be the same as Curos*
Tornado Table High Range	*H19*	*1.13*	*0.38*	*Change the range around nurse time for manual disinfection to be the same as Curos*
Nurse Cost (applies to both arms)				
Costs and Resources	E17	£35	£37	To reflect PSSRU 2017 cost of band 5 nurse
Tornado Table Low Range	*F17*	*£22*	*£37*	*Clinical expert suggests that all nurses accessing ports should be a band 5 minimum*
Tornado Table High Range	*H17*	*£62*	*£62*	*No change, PSSRU 2017 cost of band 8a*
Number of catheter days (applies to both arms)				
Cost and Resources	G27	7	7.5	To reflect the median duration of catheters reported in the literature (Dyson, 2017)
Number of ports per patient (ICU population, both arms)				
Costs and Resources	E30	10	12	To reflect the fact that the clinical experts suggest a range of 10-15 ports in the ICU setting. The range for sensitivity analysis remains 10 (lower) to 15 (higher)

EAC Scenario Analysis Curos + Wipes

Sheet Title	Cell	Company Value	Change	Comment
Costs and Resources	E13	£0.32	£0.34	To reflect the fact that in some areas disinfection protocol may include both wipes and caps

EAC Scenario Analysis (Burns Patients)

Sheet Title	Cell	Company Value	Change	Comment
Live	A4	ICU patients with either centrally and peripherally inserted catheters	Burns Patients	The choice of population is hospital or burns on the set-up sheet
Effectiveness	E17	1.48	7.43	Baseline infection rate for the six month pre-intervention period reported in Martino, 2017
Effectiveness	F17	0.29	0.32	Rate Ratio for pre-intervention/intervention period (calculated using STATA)
Costs & Resources	E17	£35	£37	To reflect PSSRU 2017 cost of band 5 nurse
Tornado Table	F17	£22	£37	Clinical expert suggests that all nurses accessing ports should be a band 5 minimum
Costs and Resources	E35	0.75	0.25	Nurse time assumed equal in both due to the 30 second waiting time being utilised for other purposes in manual disinfection
Tornado Table	D63	ICU	Burns	
Tornado Table	E63	0.09	0.49	Lower CI for IRR (Martino, 2017; calculated using STATA)
Tornado Table	F63	0.97	1.63	Upper CI for IRR (Martino, 2017; calculated using STATA)
PSA Distributions	F34	0.09	0.49	Lower CI for IRR (Martino, 2017; calculated using STATA)

PSA Distributions	G34	0.97	1.63	Upper CI for IRR (Martino, 2017; calculated using STATA)

EAC Subgroup Analysis (Possible Confounders in Burns Setting)

Sheet Title	Cell Number	Company Value	EAC Value	Comment
Effectiveness	F17	0.32	0.65	This change reflects the fact that the infection rate changed in the period post Curos due to other possible confounders such as staff turnover.
Tornado Table	D63	ICU	Burns	
Tornado Table	E63	0.49	0.23	Lower CI for IRR (Martino, 2017; calculated using STATA)
Tornado Table	F63	1.63	2.23	Upper CI for IRR (Martino, 2017; calculated using STATA)
PSA Distributions	F34	0.49	0.23	Lower CI for IRR (Martino, 2017; calculated using STATA)
PSA Distributions	G34	1.63	2.23	Upper CI for IRR (Martino, 2017; calculated using STATA)

Appendix H: Sensitivity Analyses

Deterministic Sensitivity Analysis

Baseline rate of infection and IRR (any hospital setting)

		Incidence rate ratio (basecase: 0.4)										
	-£17.13	0.22	0.28	0.34	0.40	0.46	0.52	0.58	0.64	0.70	0.76	0.82
Baseline rate of CLABSI per 1,000 catheter days (standard care) (basecase: 0.7)	0.20	£1.53	£2.45	£3.37	£4.29	£5.21	£6.13	£7.05	£7.97	£8.89	£9.82	£10.74
	0.33	-£6.26	-£4.74	-£3.22	-£1.70	-£0.18	£1.34	£2.86	£4.38	£5.90	£7.42	£8.94
	0.46	-£14.04	-£11.92	-£9.80	-£7.68	-£5.57	-£3.45	-£1.33	£0.79	£2.91	£5.03	£7.14
	0.59	-£21.82	-£19.11	-£16.39	-£13.67	-£10.95	-£8.24	-£5.52	-£2.80	-£0.09	£2.63	£5.35
	0.72	-£29.61	-£26.29	-£22.97	-£19.66	-£16.34	-£13.03	-£9.71	-£6.40	-£3.08	£0.24	£3.55
	0.85	-£37.39	-£33.48	-£29.56	-£25.65	-£21.73	-£17.82	-£13.90	-£9.99	-£6.07	-£2.16	£1.76
	0.98	-£45.17	-£40.66	-£36.15	-£31.63	-£27.12	-£22.61	-£18.09	-£13.58	-£9.07	-£4.55	-£0.04
	1.11	-£52.96	-£47.84	-£42.73	-£37.62	-£32.51	-£27.40	-£22.28	-£17.17	-£12.06	-£6.95	-£1.84
	1.24	-£60.74	-£55.03	-£49.32	-£43.61	-£37.90	-£32.19	-£26.47	-£20.76	-£15.05	-£9.34	-£3.63
	1.37	-£68.52	-£62.21	-£55.90	-£49.59	-£43.28	-£36.98	-£30.67	-£24.36	-£18.05	-£11.74	-£5.43
	1.50	-£76.31	-£69.40	-£62.49	-£55.58	-£48.67	-£41.76	-£34.86	-£27.95	-£21.04	-£14.13	-£7.22

Baseline rate of infection and IRR (ICU)

		Incidence rate ratio (basecase: 0.3)										
	£94.20	0.09	0.18	0.27	0.35	0.44	0.53	0.62	0.71	0.79	0.88	0.97
Baseline rate of CLABSI per 1,000 catheter days (standard care) (basecase: 1.48)	1.28	£79.03	£94.02	£109.00	£123.99	£138.97	£153.96	£168.95	£183.93	£198.92	£213.90	£228.89
	1.33	£73.34	£88.88	£104.41	£119.95	£135.48	£151.02	£166.56	£182.09	£197.63	£213.17	£228.70
	1.37	£67.65	£83.73	£99.82	£115.91	£132.00	£148.08	£164.17	£180.26	£196.34	£212.43	£228.52
	1.42	£61.96	£78.59	£95.23	£111.87	£128.51	£145.14	£161.78	£178.42	£195.05	£211.69	£228.33
	1.47	£56.27	£73.45	£90.64	£107.83	£125.02	£142.20	£159.39	£176.58	£193.77	£210.95	£228.14
	1.52	£50.58	£68.31	£86.05	£103.79	£121.53	£139.27	£157.00	£174.74	£192.48	£210.22	£227.95
	1.56	£44.89	£63.17	£81.46	£99.75	£118.04	£136.33	£154.61	£172.90	£191.19	£209.48	£227.77
	1.61	£39.20	£58.03	£76.87	£95.71	£114.55	£133.39	£152.23	£171.06	£189.90	£208.74	£227.58
	1.66	£33.51	£52.89	£72.28	£91.67	£111.06	£130.45	£149.84	£169.23	£188.61	£208.00	£227.39
	1.70	£27.82	£47.75	£67.69	£87.63	£107.57	£127.51	£147.45	£167.39	£187.33	£207.26	£227.20
	1.75	£22.13	£42.61	£63.10	£83.59	£104.08	£124.57	£145.06	£165.55	£186.04	£206.53	£227.02

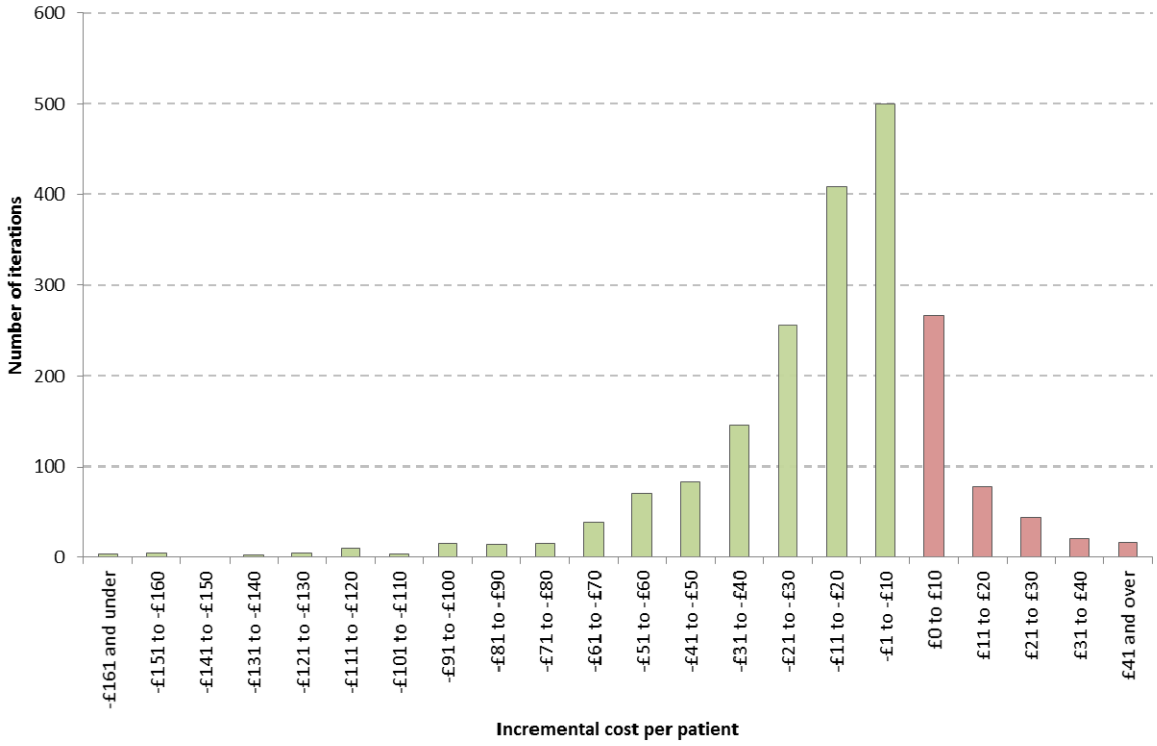
Cost of Standard Care and Curos (any hospital setting)

		Cost of standard care per patient (basecase: £0.90)										
	-£17.13	£0.11	£1.40	£2.69	£3.98	£5.27	£6.56	£7.85	£9.14	£10.43	£11.72	£13.01
Cost of Curos per patient (basecase: £14.40)	£1.90	-£28.84	-£30.13	-£31.42	-£32.71	-£34.00	-£35.29	-£36.58	-£37.87	-£39.16	-£40.45	-£41.74
	£23.86	-£6.87	-£8.16	-£9.45	-£10.74	-£12.03	-£13.32	-£14.61	-£15.90	-£17.19	-£18.48	-£19.77
	£45.82	£15.09	£13.80	£12.51	£11.22	£9.93	£8.64	£7.35	£6.06	£4.77	£3.48	£2.19
	£67.78	£37.05	£35.76	£34.47	£33.18	£31.89	£30.60	£29.31	£28.02	£26.73	£25.44	£24.15
	£89.74	£59.01	£57.72	£56.43	£55.14	£53.85	£52.56	£51.27	£49.98	£48.69	£47.40	£46.11
	£111.71	£80.97	£79.68	£78.39	£77.10	£75.81	£74.52	£73.23	£71.94	£70.65	£69.36	£68.07
	£133.67	£102.93	£101.64	£100.35	£99.06	£97.77	£96.48	£95.19	£93.90	£92.61	£91.32	£90.03
	£155.63	£124.89	£123.60	£122.31	£121.02	£119.73	£118.44	£117.15	£115.86	£114.57	£113.28	£111.99
	£177.59	£146.85	£145.56	£144.27	£142.98	£141.69	£140.40	£139.11	£137.82	£136.53	£135.24	£133.95
	£199.55	£168.81	£167.52	£166.23	£164.94	£163.65	£162.36	£161.07	£159.78	£158.49	£157.20	£155.91
	£221.51	£190.77	£189.48	£188.19	£186.90	£185.61	£184.32	£183.03	£181.74	£180.45	£179.16	£177.87

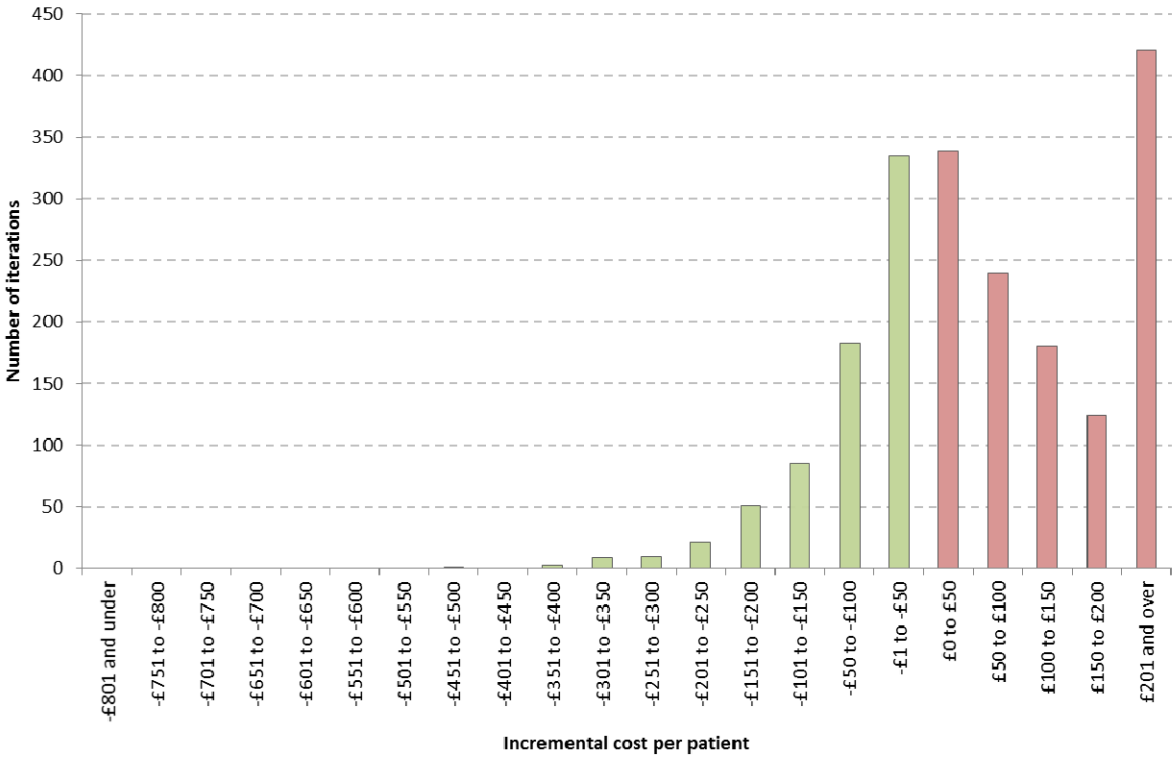
Cost of Standard Care and Curos (ICU)

		Cost of standard care per patient (basecase: £15.60)										
	£94.20	£4.65	£8.09	£11.53	£14.97	£18.41	£21.85	£25.28	£28.72	£32.16	£35.60	£39.04
Cost of Curos per patient (basecase: £249.60)	£79.11	-£65.34	-£68.78	-£72.22	-£75.66	-£79.10	-£82.54	-£85.98	-£89.42	-£92.86	-£96.29	-£99.73
	£137.65	-£6.80	-£10.24	-£13.68	-£17.12	-£20.56	-£24.00	-£27.44	-£30.88	-£34.31	-£37.75	-£41.19
	£196.19	£51.74	£48.30	£44.86	£41.42	£37.98	£34.54	£31.10	£27.67	£24.23	£20.79	£17.35
	£254.73	£110.28	£106.84	£103.40	£99.96	£96.52	£93.08	£89.65	£86.21	£82.77	£79.33	£75.89
	£313.27	£168.82	£165.38	£161.94	£158.50	£155.06	£151.63	£148.19	£144.75	£141.31	£137.87	£134.43
	£371.82	£227.36	£223.92	£220.48	£217.04	£213.61	£210.17	£206.73	£203.29	£199.85	£196.41	£192.97
	£430.36	£285.90	£282.46	£279.02	£275.59	£272.15	£268.71	£265.27	£261.83	£258.39	£254.95	£251.51
	£488.90	£344.44	£341.00	£337.57	£334.13	£330.69	£327.25	£323.81	£320.37	£316.93	£313.49	£310.05
	£547.44	£402.98	£399.55	£396.11	£392.67	£389.23	£385.79	£382.35	£378.91	£375.47	£372.03	£368.59
	£605.98	£461.53	£458.09	£454.65	£451.21	£447.77	£444.33	£440.89	£437.45	£434.01	£430.57	£427.14
	£664.52	£520.07	£516.63	£513.19	£509.75	£506.31	£502.87	£499.43	£495.99	£492.55	£489.12	£485.68

Probabilistic Sensitivity Analysis: Any Hospital Setting



Probabilistic Sensitivity Analysis: ICU


Number of iterations
450
400
350
300
250
200
150
100
50
0
-£801 and under
-£751 to -£800
-£701 to -£750
-£651 to -£700
-£601 to -£650
-£551 to -£600
-£501 to -£550
-£451 to -£500
-£401 to -£450
-£351 to -£400
-£301 to -£350
-£251 to -£300
-£201 to -£250
-£151 to -£200
-£101 to -£150
-£50 to -£100
-£1 to -£50
£0 to £50
£50 to £100
£100 to £150
£150 to £200
£201 and over
Incremental cost per patient

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

Assessment report overview

Curos for preventing infections when using needleless connectors

This assessment report overview has been prepared by the Medical Technologies Evaluation Programme team to highlight the significant findings of the External Assessment Centre (EAC) report. It includes **brief** descriptions of the key features of the evidence base and the cost analysis, any additional analysis carried out, and additional information, uncertainties and key issues the Committee may wish to discuss. It should be read along with the company submission of evidence and with the EAC assessment report. The overview forms part of the information received by the Medical Technologies Advisory Committee when it develops its recommendations on the technology.

Key issues for consideration by the Committee are described in section 6, following the brief summaries of the clinical and cost evidence.

This report contains information that has been supplied in confidence and will be redacted before publication. This information is highlighted in yellow. This overview also contains:

- Appendix A: Sources of evidence
- Appendix B: Comments from professional bodies
- Appendix C: Decision problem from scope

1 The technology

The Curos disinfecting cap (3M) is a single-use device used to protect the needleless connectors of vascular access devices. The Curos cap contains a foam that is impregnated with 70% isopropyl alcohol which acts as an antiseptic. Curos is twisted onto the end of a needleless connector point (port) and, according to the instructions for use, should be left in place for a minimum of 1 minute. The company claims that, after 1 minute, the antiseptic will kill 6 micro-organisms commonly associated with bloodstream infections. Curos can be removed to give access to the needleless connector. If access is not needed, the cap can remain in place to provide a physical barrier to contamination for up to 7 days. After each removal, the used Curos cap must be discarded, and a new one applied. Curos is supplied individually or in strips of 10 for ease of use. Curos received a class IIa CE mark in September 2016.

2 Proposed use of the technology

2.1 Disease or condition

Curos is intended to prevent bloodstream infections from bacteria introduced via vascular access devices. Vascular access devices are inserted to allow the administration of drugs, nutrition or fluids directly into the bloodstream and may be required to remain in place for many days. During this time treatments are frequently administered through the line, each time this happens there is a risk of introducing microorganisms that can cause bloodstream infection. Bloodstream infection causes fever and red skin and soreness around the access site and is associated with the need for additional treatment that may include line changes and prolonged antibiotic treatment. The consequences of a bloodstream infection include increased morbidity and mortality, length of stay and healthcare costs.

2.2 Patient group

The Curos disinfecting cap is intended for use on needless connectors of vascular access devices (such as peripherally inserted central catheters and

tunnelled and non-tunnelled central venous catheters) which may be used in the management of a wide range of conditions in any care setting.

NICE guidelines on the prevention of healthcare associated infections (CG139) state that an estimated 300,000 patients a year in England acquire a healthcare-associated infection as a result of care within the NHS but there is no information on to the proportion of infections that are specifically bloodstream infections associated with vascular access devices.

2.3 Current management

According to NICE clinical and public health, and other national, guidelines (CG139, PH36 and Epic 3) needleless connectors should be disinfected for at least 15 seconds using alcohol wipes or an alcohol containing solution of chlorhexidine gluconate, before and after use. This method requires the disinfected needleless connector to dry before it can be used which takes an additional 30 seconds.

2.4 Proposed management with new technology

Curos would be used as part of a bundle of infection prevention measures to reduce the risk of bloodstream infections from bacteria introduced via vascular access devices. It is intended to replace the use of alcohol wipes or solution. A new Curos cap is placed over the connector every time the needleless connector is used. The company provides online training videos for staff using Curos, and further training is offered by the company if required.

3 Company claimed benefits and the decision problem

Table 1 Changes to the decision problem

Decision problem	Variation proposed by company	EAC view of the variation
Population, vascular access devices in any setting	The company excluded use of the device in the community setting	The EAC viewed this as a valid change as there was no evidence available for the use of Curos in this population

Outcomes	The company proposed a number of changes including: • number of catheter related bloodstream infections (CRBSI) or central line associated bloodstream infections (CLABSI) per 1000 catheter-days. In aggregate and separately by central lines and peripheral lines (if possible) • bacteraemia rates for CRBSI and CLABSI • exclusion of improved consistency in disinfection protocols (compliance rate) • exclusion of alcohol containing solution of chlorhexidine gluconate comparator, mortality and environmental impact from cost model	Outcomes related to resource use (e.g. length of stay) were included in the company cost analysis and not in the clinical analysis. The EAC noted that all relevant outcomes, including those related to resource use, should be considered as part of the clinical evidence. Although the company did not include compliance as a selection criteria for its literature search it did include compliance outcomes where reported in studies. The EAC agreed that compliance rates should be considered as these may have an impact on infection rate outcomes. The EAC agreed with the exclusions from the cost model due to unavailable data.

4 The evidence

4.1 Summary of evidence of clinical benefit

The company submitted 5 before and after studies and 5 unpublished abstracts, the EAC agreed with the study selection and included 1 more before and after study and another 4 unpublished abstracts. The evidence included by the EAC totalled 6 before and after studies and 9 unpublished abstracts. The rationale for this decision is in section 2.2 and 2.3 of the EAC assessment report.

Table 2 Included studies

Studies included by both EAC and company	
Publication and study design	5 before and after studies (published as full papers) and 5 unpublished abstracts
Reference	Before and after studies: Ramirez 2012, Sweet 2012, Merrill 2014, Cameron-Watson 2016, Martino 2017

	Unpublished abstracts: Pong 2011, Danielson 2013, Sumner 2013, Shiber 2014, Ventura 2015
Additional studies not in submission but included by EAC	
Publication and study design	1 before and after study (published as a full paper) and 4 unpublished abstracts
Reference	Before and after study: Duncan 2018 Unpublished abstracts: Alasmari 2012, Madden 2013, Budhiraja 2016, Kwok 2017

The EAC noted that the clinical evidence for Curos is comprised of a small number of uncontrolled before and after studies which are low quality and potentially at high risk of bias. All studies introduce Curos while also including elements of education, disinfection protocol awareness and audit, all of which may have an impact on the outcomes. The populations included in the studies were variable, including patients in ICU, general hospital wards, surgical wards and a paediatric ward. Only one of the studies and 2 of the unpublished abstracts were carried out in a UK setting which may limit the generalisability of the study results.

The EAC summarised the unpublished abstracts in tables 4 and 5 of the assessment report but the lack of information precluded further critical appraisal. The unpublished abstracts detail studies done in a range of settings including neonatal intensive care, haematology, bone marrow transplant unit, oncology ward and more general hospital settings.

There were no studies which used an alcohol containing solution of chlorhexidine gluconate as the comparator. There was inconsistency in how bloodstream infections were classified and defined between the studies.

The company submission included 2 meta-analyses, the first of 4 studies reporting CLASBI rates and the other used data from only 2 of these studies, which were conducted in an intensive care setting. Due to the poor quality of the individual studies and the differences between them, the EAC concluded that the meta-analyses may be at risk of serious imprecision (please see appendix E of the assessment report for further details).

Table 3 Summary of key studies

Study and design	Participants/ population	Intervention & comparator	Outcome measures	Results	Comments
Ramirez (2012) before and after study Retrospective period Jan-Dec 2010. Prospective period Mar 2011-Feb 2012.	All patients in the intensive care unit receiving treatments via an indwelling central line. Location: USA	Curos compared with retrospective data for alcohol wipes.	Change in CLABSI rates in ICU before vs after introduction of Curos. A survey tool was implemented to document compliance.	CLABSI rate: 1.9/1000 catheter days in 2010, 0.5/1000 catheter days in 2011 Average compliance 73%.	The authors do not state if alcohol wipes were still available to staff during the prospective data collection period. The EAC noted some inconsistencies in reporting of study time period and that average number of central line days are reported, but it is not stated if this is mean or median.
Sweet (2012) before and after study Retrospective period Jan-Dec 2009 (CLABSI) and Jul-Dec 2009 (CBCs). Prospective period Jan-Jul 2010.	Adult inpatients on the haematology and oncology floors of a hospital, who had a central venous catheter. Location USA	Curos and needleless neutral-pressure connectors (MicroCLAVE) concurrently, compared with retrospective data for alcohol wipes.	Change in incidence of CLABSI and CBCs per 1000 catheter days before vs after the introduction of Curos and MicroCLAVE. Compliance (weekly observations, % of ports with Curos caps). Indwelling time of catheters (days)	CLABSI rate per 100/patient admissions decreased from 2.1-0.2 (p=0.01) CBC rate decreased from 2.5% (17 of 692) to 0.2% (1 of 470) Compliance 85.2%	Use of wipes during the prospective data collection period was optional but no further information is provided. The EAC noted some inconsistencies in the number of patients reported and that the authors did not state the p-value for statistical significance. The EAC sought clinical expert opinion on whether the inclusion of the neutral-pressure connector is likely to have affected the

			was selectively reported for people diagnosed with CLABSI.		outcomes. The expert was not aware of any evidence to answer this question.
Merrill (2014) non-randomised interrupted time series study. Retrospective period Jan-Dec 2011. Prospective period Jan-Dec 2012.	All patients with peripheral and central lines (including neonates, children and adults) in a >430 bed tertiary trauma care centre. Location: USA	Curos compared with retrospective data for alcohol wipes.	Rate of CLABSI per 1000 central line catheter days. Impact of CLABSI (cost, estimated case fatality, length of ICU stay). Compliance rate per central line patient (monitored 1-2 times a week), reported by department.	Mean rate of CLABSI/1000 catheter days, pre-intervention: 1.5±0.37, with Curos: 0.88±0.62 Incidence rate ratio: 0.577 (95% CI, 0.396-0.842, p=0.004) indicating a reduction in the rate of patient infections of >40% with use of Curos.	The authors do not state if alcohol wipes were still available to staff during the prospective data collection period. The EAC noted that the results presented in this study are 'averages of averages' and questions the methodology of this, it is possible that this analysis may result in the narrow confidence intervals observed but this cannot be confirmed.
Cameron-Watson (2016) before and after audit. Retrospective period Oct 2013-Apr 2014 Prospective period Apr-Sep 2014	1094 patients on 4 wards (oncology, acute care of the elderly, critical care and a surgical ward) across 2 sites with vascular access devices. Location: UK	Difference in rates of CLABSI pre and post introduction of Curos reported as mean CRBSI rates for the period before the intervention (alcohol wipes only) and the trial period.	Rate of CLABSI before and after. Compliance was measured during audit (and compared with anonymous bench marking). Disinfection technique including time to clean and time dry the	Mean CRBSI rates, pre-intervention: 4.3, with Curos: 1.5, mean rate reduction: 2.8 Compliance with disinfection policy increased by 53%	The authors state that alcohol wipes were removed from the ward during the trial period. The EAC noted that this study was conducted in an NHS setting. The 3 departments involved in this study saved a minimum of £105,5664 up to £281,802

			connector was also recorded.		
Martino (2017) before and after study. Retrospective period Jul-Dec 2011. Prospective period Jan-Jun 2012.	260 patients in a 16 bed burns intensive care unit. Location: USA	Curos compared with retrospective data for alcohol wipes.	Total number of CLABSI occurrences CLABSI rates per 1000 line days. Compliance (weekly audits).	Rates of CLABSI for 2011 did not differ significantly to rates from 2012 (p=0.81) or 2013 (p=0.37). Overall trend of CLABSI rates decreased from 2009 through 2014 (Data for 2014 not reported) (p=0.0045)	The authors state that there was on-going observational central line bundle surveillance during the prospective data collection period. The EAC noted that there were some inconsistencies around the reporting time periods but was unable to comment as to whether this would affect the results.
Duncan (2018) quasi-experimental before and after study. Retrospective period Jan-Jun 2015. Prospective period Nov 2015-May 2016.	Patients in a >900 bed tertiary care trauma centre with a peripheral or central line. Location: USA	Curos compared with retrospective data for alcohol wipes.	Bloodstream infection rates associated with peripheral and central lines. Compliance with the use of Curos on needleless connectors and disconnected tubing on all line types.	81% reduction in peripheral bloodstream infection (p<0.001)	The EAC note that the results and data being analysed and presented is not consistent or clear. No baseline characteristics were reported or analysed.

4.2 Summary of economic evidence

No published relevant economic studies were identified by the company or by the EAC.

De novo analysis

The model is a decision tree with two main branches for Curos and standard care (alcohol wipes). For each branch there is the possibility of CLABSI or no CLABSI. The model can be set to report results for either the whole hospital population or the intensive care population. The model does not include mortality. The model structure is simple because the introduction of Curos is an exchange of one method of disinfecting ports to another and there are no other changes to the care pathway. The EAC agreed with the model structure and when tested it performed as expected.

The model includes a number of assumptions, as described in table 4.

Table 4 Model assumptions

Assumption	EAC comment
Compliance with standard care is 100%, nursing staff always spend 15 seconds scrubbing the access port and 30 seconds just waiting for the port to dry	In reality, compliance is probably low. Reported compliance with Curos ranges from 73% to 86.5% in the published literature (Sweet 2012, Ramirez 2012 and Martino 2017) while compliance with manual disinfection was 27% (Cameron-Watson, 2016) in one study and 92.5% in a second study (Martino, 2017). The EAC did not make any changes to compliance. In the submitted model, compliance only contributes to the total cost of the devices. Lower compliance would mean less nurse time applying it, and possibly higher infection rates.
Baseline infection rates from parenteral feeding ports for people recovering from gastric surgery are generalisable to the whole in-patient population.	Two clinical experts advised that parenteral feeding lines may have a higher risk of infection than other types of catheter lines. The baseline infection rate used in the model was very low but the EAC was unable to identify an alternative value.

It is assumed that improved infection rates reported in short term before and after studies are sustainable.	Martino (2017) reported post-intervention data which suggested that rate of CLABSI might be impacted by confounders such as staff turnover or other changes to the disinfection bundle.

Model parameters

General hospital setting

The baseline infection rate (0.7 per 1,000 days) was taken from one study conducted in people with parenteral feeding ports. However, it is acknowledged that in a general hospital setting there is wide variation in infection rates as well as the definitions used between different studies, patient populations and sites. For this reason, the EAC did not make any changes to the clinical effectiveness data used in the model but have used sensitivity analysis to highlight cost impact of the wide variation in infection rates and higher baseline rate of infection that is possible.

The incidence rate ratio (0.43 per 1,000 days) used in the model for the generable hospital setting is taken from the company's meta-analysis of 4 studies. The studies include different patient populations, a large number of intensive care patients, are conducted in the USA and are taken from before and after studies which are subject to bias.

Intensive care setting

The baseline infection rate for the intensive care population (1.48) is also taken from a single study which was conducted in 223 intensive care units in England. The incidence rate ratio (0.29) used in the model is taken from the company's meta-analysis of 2 intensive care unit studies. The EAC considers the clinical data used in the model for the ICU population to be appropriate.

Table 5 Model parameters

Parameter	Hospital setting	Intensive care setting
Cost of CLABSI (MTG25)	£10,234	
Nurse cost per hour	£37	
Average number of ports per patient	2	12
Average number of disinfections/accesses per port per day	3	5
Average number of days with catheter	7.5	13

Costs and resource use

The number of Curos caps is calculated in the model by multiplying the 'average' number of ports per patient, by the number of accesses per port per day by the number of days with catheter in place per patient. The estimates for the number of ports per patient and the number of accesses per port per day were provided by a clinical expert as ranges (for example, 1-2 ports for a patient in general hospital population and 10-15 ports for a patient in ICU). The EAC contacted 3 further expert advisers who agreed with these estimates but noted that the number of ports would likely be lower for neonatal ICU patients.

The instructions for use for Curos state that the caps must be changed at least every 7 days. The model does not account for any ports in less frequent use that would need to have their caps changed even if not used. This could lead to an underestimation of the costs, particularly in the intensive care setting where there are many ports.

Nurse time included in the company model is estimated as 15 seconds for each Curos cap placement and 45 seconds of nurse time for each disinfection with alcohol wipes (15 seconds cleaning and 30 seconds drying time). These times are supported by 4 clinical experts (3 contacted by the EAC and 1 by the company). While the EAC accepts that disinfection with alcohol wipes takes 45 seconds it considers that the nurse would utilise the 30 second drying time to carry out other tasks (such as preparing the syringe or writing notes) and this therefore should not be considered time saved when using

Curos. In the EAC base case the nurse time for manual disinfection has been changed to be equal to nurse time for Curos.

In the model, the unit cost of Curos is given as £0.32 and the unit cost per alcohol wipe is £0.02. The EAC agreed with these costs.

Results

The results of the company and the EAC base case are shown in table 6.

Table 6 Company and EAC base case results

	Company base case				*EAC base case*			
Hospital setting		**Curos**	**Alcohol wipes**	**Cost saving per patient**		**Curos**	**Alcohol wipes**	**Cost saving per patient**
	Disinfection cost	£13.44	£0.84	-£12.60	**Disinfection cost**	£14.40	£0.90	-£13.50
	Nurse cost	£6.13	£18.38	£12.25	**Nurse cost**	£6.94	£6.94	£0
	Cost of CLABSI	£21.56	£50.15	£28.58	**Cost of CLABSI**	£23.10	£53.73	£30.63
	Total cost saving			**£28.23**	**Total cost saving**			**£17.13**
	Sensitivity analysis*	-£0.35 (lowest)		£448.83 (highest)	**Sensitivity analysis***	-£13.50 (lowest)		£467.77 (highest)
Intensive care setting		**Curos**	**Alcohol wipes**	**Cost saving per patient**		**Curos**	**Alcohol wipes**	**Cost saving per patient**
	Disinfection cost	£208	£13	-£195	**Disinfection cost**	£249.60	£15.60	-£234
	Nurse cost	£94.79	£284.38	£189.58	**Nurse cost**	£120.25	£120.25	£0
	Cost of CLABSI	£57.10	£196.91	£139.80	**Cost of CLABSI**	£57.10	£196.91	£139.80
	Total cost saving			**£134.39**	**Total cost saving**			**-£94.20**
	Sensitivity analysis*	-£7.80 (lowest)		£280.64 (highest)	**Sensitivity analysis***	-£34.07 (lowest)		-£328.20 (highest)

Positive values indicate cost saving
*One-way sensitivity analysis of total cost saving per patient

The EAC performed deterministic sensitivity analyses which showed that in the general hospital setting, the baseline infection rate was the key driver of cost savings. Where there is a high baseline rate, any measure to improve infection control is likely to have a greater impact. For the baseline infection rate (0.7 per 1,000 catheter days) used in the base case, Curos becomes cost incurring at approximately 0.75 incidence rate ratio. However, at a lower baseline infection rate of 0.2 per 1,000 catheter days, Curos would almost always be cost incurring.

For the intensive care setting there is no single driver of costs. In this setting, there is an increased number of ports and accesses per day meaning that the cost of equipment is a larger part of the overall cost per patient. In the EAC base case using Curos in the intensive care setting is always cost incurring at the baseline infection rate (1.48 per 1,000 catheter days). If the baseline infection rate were higher (>3) Curos may be cost saving.

The EAC modelled 3 additional scenarios for Curos; to estimate the cost of using both Curos and alcohol wipes, using data from a burns subgroup (high baseline risk of infection) and a scenario that varied the number of ports per patient in the hospital setting.

The EAC base case shows Curos to be cost saving in the hospital setting compared with manual disinfection but cost incurring in the ICU setting. Using wipes and Curos together remained cost saving in the hospital setting and cost incurring in the ICU setting. An increase in the baseline infection risk (7.43 per 1,000 catheter days from a burns intensive care unit subgroup) suggests that Curos is likely to lead to higher cost-savings (£438.20 per patient). This study from which these data were obtained also considered the impact of other factors, such as a high staff turnover, and found that Curos is likely to still be cost saving (reduced to £111.98 per patient) even when the disinfection bundle is impacted by other factors.

Increasing the number of ports per patient in the hospital setting (EAC base case) to reflect the possible variation in the population suggests that Curos becomes cost incurring at 5 ports per patient.

5 Ongoing research

The company submission did not reference any ongoing studies or trials. The EAC identified 3 trials related to Curos, 2 of these studies are expected to publish in 2019. Both of these studies are being conducted outside of Europe and so are likely to have limited generalisability to the NHS. The third study was completed in 2014 but it has not been possible to obtain any further information on this. Please see section 2.9 of the EAC assessment report for further details.

The EAC recommend that there should be further research conducted comparing bundle disinfection protocols using alcohol wipes with bundle disinfection protocols using Curos. Please see section 6 of the assessment report for further details.

6 Issues for consideration by the Committee

Clinical evidence

The clinical evidence shows that Curos may reduce bloodstream infections, however, the size of this effect is difficult to estimate as:

- The evidence is comprised of low quality studies with a high risk of bias because of their before and after study design.
- The studies include heterogeneous populations.
- Study results likely reflect the implementation of the new disinfection bundle rather than Curos alone.
- Limited or no analysis and reporting of baseline characteristics of people included in the trials.
- The terms bloodstream infection, CLABSI and CRBSI are used interchangeably in the literature, clinical experts advised that this inconsistency was an internationally recognised problem.
- The studies were mostly done in centres in the USA.

The effectiveness of Curos is dependent on the baseline infection rate and this may be higher in particular subgroups. For example clinical experts and

evidence note that infection rates are higher in people receiving parenteral nutrition. People may receive parenteral nutrition through an in-dwelling line if they have a gastrointestinal disorder (e.g. short bowel syndrome or ulcerative colitis) or cancer.

Training for staff using Curos is not expected to take any longer than training for manual disinfection with alcohol wipes. However, there may be a need to ensure regular training updates particularly if there is a high staff turnover or if the centre employs staff on temporary contracts. As a high number of Curos caps will be required it may also be necessary to include the hospital stock management and procurement teams in any training and development plans.

Curos may present a choking hazard for some patients if left within their reach. There is also a safety concern regarding the reuse of Curos caps. The device is single-use as the antiseptic liquid within the cap is only sufficient for one disinfection. It is possible to replace a Curos cap after use, training staff in the proper use of Curos will be essential to avoid this.

There is no evidence for the use of Curos in the community setting. However, the committee may wish to discuss the generalisability of studies done under hospital conditions to the community setting. In particular this would include people who are sent home with a central or peripheral line (either for parenteral feeding of for infrequent drug administration). Curos may be useful to these people as it acts as a physical barrier over the needleless connector.

Cost evidence

The company base case showed that Curos was likely to be cost saving in both the general hospital and intensive care setting. Although the EAC broadly agreed with the company model structure and inputs they made some changes which resulted in the intensive care setting becoming cost incurring. The EAC modelled additional scenarios that showed that using Curos and alcohol wipes together could still lead to costs savings due to reduced bloodstream infections and that higher cost savings can be expected if the baseline infection rate is higher.

The EAC disagrees with the company that there is potential to save staff time as it takes 3 times longer to clean a port with alcohol wipes than with Curos. The EAC state that the 30 seconds drying time would be used by the staff member to carry out other tasks. This change reduces the cost saving in the general hospital setting and makes Curos cost incurring in the intensive care setting.

In the general hospital setting, the key driver of the cost model for Curos is the baseline infection rate. While there is expected to be high variance between hospital bloodstream infection rates it may be possible to identify subgroups who are at a higher risk of bloodstream infection (such as people receiving parenteral feeding).

7 Authors

Kimberley Carter, analyst

Bernice Dillon, technical adviser

NICE Medical Technologies Evaluation Programme

December 2018

Appendix A: Sources of evidence considered in the preparation of the overview

A Details of assessment report:

- O'Connell S, Dale M, Morgan H and Carolan-Rees G, Curos disinfecting caps for infection prevention in needleless connectors, November 2018

B Submissions from the following sponsors:

- 3M

C Related NICE guidance

- Healthcare-associated infections: prevention and control in primary and community care (2012) NICE Clinical guideline CG139
- Healthcare-associated infections: prevention and control (2011) NICE Public health guideline PH36
- Curos disinfecting cap for needleless connectors (2018) NICE Medtech innovation briefing MIB143

D References

Alasmari F. Impact of Alcohol Impregnated Protectors on Incidence of Catheter- Associated Blood Stream Infections Conference Abstract Availabe at https://idsa.confex.com/idsa/2012/webprogram/Paper37395.html [Last accessed: 24/10/2018]

Bion J, Richardson A, Hibbert P, Beer J, Abrusci T, McCutcheon M, et al. 'Matching Michigan': a 2-year stepped interventional programme to minimise central venous catheter-blood stream infections in intensive care units in England. BMJ Qual Saf. 2013;22(2):110-23.

Budhiraja S Impact of passive disinfection device on the rate of catheter related blood stream infections in neonates: A quality improvement initiative. Archives of Disease in Childhood 2016; 101(Suppl 1): A1-A374

Cameron-Watson C. Port protectors in clinical practice: an audit. Br J Nurs. 2016;25(8):S25-31.

Casey AL, Karpanen TJ, Nightingale P, Chaganti S, Elliott TSJ. Microbiologic contamination of a positive- and a neutral- displacement needleless intravenous access device in clinical use. Am J Infect Control. 2016;44(12):1678-80.

Cooper K, Frampton G, Harris P, Jones J, Cooper T, Graves N, et al. Are educational interventions to prevent catheter-related bloodstream infections in intensive care unit cost-effective? J Hosp Infect. 2014;86(1):47-52.

Danielson B, Willamson S, Kaur G, Brooks C, Scholl P, Baker A. Decreasing the incidence of central line-associated blood stream infections using alcohol-impregnated port protectors in a neonatal intensive care unit. Am J Infect Control. 2013;41(Suppl 6):S97-S98.

Dyson JK, Thompson N, Northern Nutrition N. Adult parenteral nutrition in the North of England: a region-wide audit. BMJ Open. 2017;7(1):e012663.

Duncan M. A bundled approach to decrease the rate of primary bloodstream infections related to peripheral intravenous catheters. JAVA 2018;23(1):15-22

Hockenhull JC, Dwan K, Boland A, Smith G, Bagust A, Dundar Y, et al. The clinical effectiveness and cost-effectiveness of central venous catheters treated with anti-infective agents in preventing bloodstream infections: a systematic review and economic evaluation. Health Technol Assess. 2008;12(12):iii-iv, xi-xii, 1-154.

Hvas CL, Farrer K, Donaldson E, Blackett B, Lloyd H, Forde C, et al. Quality and safety impact on the provision of parenteral nutrition through introduction of a nutrition support team. Eur J Clin Nutr. 2014;68(12):1294-9.

Kwok MWN. Trial use and evaluation of disinfecting port protectors on central venous catheter in hematology ward in hong kong. Antimicrobial Resistance and Infection Control 2017;Conference(Supplement 2)

Lambert ML. Clinical outcomes of healthcare associated infections and antimicrobial resistance in patients admitted to European intensive care units: a cohort study. Lancet Infection 2011;11;30-38

Madden W Alcohol Impregnated Caps: Are They Effective for Preventing CLABSI? Biol Blood Marrow Transplant 2013;19:S370-S380

Martino A, Thompson L, Mitchell C, Trichel R, Chappell W, Miller J, et al. Efforts of a Unit Practice Council to implement practice change utilizing alcohol impregnated port protectors in a burn ICU. Burns. 2017;43(5):956-64.

Merrill KC, Sumner S, Linford L, Taylor C, Macintosh C. Impact of universal disinfectant cap implementation on central line-associated bloodstream infections. Am J Infect Control. 2014;42(12):1274-7.

National Institute for Health and Care Excellence. Healthcare-associated infections: prevention and control in primary and community care (CG139). London: National Institute for Health and Care Excellence; 2012. Available from: https://www.nice.org.uk/guidance/cg139

National Institute for Health and Care Excellence. The 3M Tegaderm CHG IV securement dressing for central venous and arterial catheter insertion sites (MTG25). (MTG25). London: National Institute for Health and Care Excellence; 2015. Available from: https://www.nice.org.uk/guidance/mtg25.

Personal Social Services Research Unit (PSSRU). Unit Costs of Health & Social Care 2016. Canterbury: PSSRU; 2016. Available from: http://www.pssru.ac.uk/project-pages/unit-costs/2017/.

Pong A, Salgado C, Speziale M, Grimm P, Abe C. Reduction of central line-associated bloodstream infection (CLABSI) in a neonatal intensive care unit with use of access site disinfection caps. In: ISDA Annual Meeting, Boston, MA; 21 October. 2011. P672Ramirez C, Lee AM, Welch K. Central venous catheter protective connector caps reduce intraluminal catheter-related infection. JAVA - Journal of the Association for Vascular Access. 2012;17(4):210-13.

Shiber J, Jolicoeur G, Crouchet T. Reducing central line-associated bloodstream infections through the addition of disinfecting port protector caps to the central line bundle. In: Ochsner Research Day, New Orleans, LA; 20 May. 2014. 8

Sumner S, Merrill KC, Linford L, Taylor C. Decreasing CLABSI rates and cost following implementation of a disinfectant cap in a tertiary care hospital. Am J Infect Control. 2013;41(Suppl 6):S37.

Sweet MA, Cumpston A, Briggs F, Craig M, Hamadani M. Impact of alcohol-impregnated port protectors and needleless neutral pressure connectors on central line-associated bloodstream infections and contamination of blood cultures in an inpatient oncology unit. Am J Infect Control. 2012;40(10):931-4.

Tan R, Knowles D, Streater C, Johnston A. The use of peripherally inserted central catheters in intensive care: should you pick the PICC? JICS. 2009;10(2)

Ventura R. Passive disinfection port protector: effect on the reduction of catheter related bloodstream infections. In: Gavacelt Conference 2015, Milan, Italy; 2015. 7

Voor In 't Holt A. Antiseptic barrier cap effective in reducing central line-associated bloodstream infections: A systematic review and meta-analysis. [Erratum appears in Int J Nurs Stud. 2018 Aug;84:79-80; PMID: 29887034]. International Journal of Nursing Studies 2017 Apr;69:34-40.

Warren D. Attributable cost of catheter associated bloodstream infections among intensive care patients in a non-teaching hospital. Critical Care Medicine 2006;34:8

Appendix B: Comments from professional bodies

Expert advice was sought from experts who have been nominated or ratified by their Specialist Society, Royal College or Professional Body. The advice received is their individual opinion and does not represent the view of the society.

Dr Alag Raajkumar
Consultant anaesthetist, NHS Worcestershire acute hospitals

Mr Roy Ventura
Lead vascular access clinical nurse specialist anaesthetics, university hospital Coventry and Warwickshire

Dr Elizabeth Pilling
Consultant neonatologist, royal Hallamshire hospital

Ms Corinne Cameron-Watson
Infection control nurse, North East London NHS treatment centre

Ms Jan Hitchcock
General manager (interim) infection prevention and control, Imperial college healthcare NHS trust

Ms Doreen Crawford
Critical care nurse, royal college of nursing

Ms Catherine Plowright
Acute care consultant nurse, urgent care and long term conditions division, East Kent hospitals university NHS foundation trust

Appendix C: decision problem from scope

	Scope issued by NICE	
Population	People with vascular access devices in hospital and community settings	
Intervention	Curos disinfecting cap	
Comparator(s)	• alcohol wipes • alcohol containing solution of chlorhexidine gluconate	
Outcomes	The outcome measures to consider include: • time taken to complete disinfect • overall staff time • infection rates (CLABSI and catheter-related bloodstream infections) • mortality • length of hospital stay • length of time vascular access device in place • device-related adverse events • improved consistency in disinfection protocols • reduced use of chlorhexidine • environmental impact of reduced number of wipes disposed and increased plastic waste	
Cost analysis	Comparator(s): Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.	
Subgroups to be considered	People who are at high risk of infection	
Special considerations, including those related to equality	Curos may be used with vascular access devices in people with chronic diseases who are considered disabled under the equality act. This will include people with cancer and may include people with chronic kidney disease, cystic fibrosis, sickle cell disease, thrombotic thrombocytopenic purpura, Sjogrens syndrome, Guillian-Barre syndrome, myasthenia gravis and lysosomal storage disorders.	
Special considerations, specifically related to equality issues	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristics?	Yes
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure MTAC will have relevant information to consider equality issues when developing guidance?	No
	Curos might present a choking risk for children and people with cognitive difficulties if left within reach.	

NICE National Institute for Health and Care Excellence

Adoption scoping report

MT396 Curos disinfecting cap for needleless connectors

Summary

Adoption levers

- Possible reduction in line-associated infections
- Increased staff compliance for disinfecting needleless connectors
- Time saving
- Convenient
- Already well established with high volume usage across some trusts

Adoption barriers

- Perceived poor quality of evidence to support its use
- Real world experiences include a reported increase in infection rates
- Technology specification not consistent with current RCN and EPIC3 guidelines
- Insufficient education may compromise safety, efficacy and resource impact (some staff reusing caps and some using the cap plus wipes)
- Patient safety – choking hazard in paediatric setting

1. Introduction

The adoption team collated information from healthcare professionals working within NHS organisations. This adoption scoping report includes some of the benefits and difficulties that may be faced by organisations when planning to adopt the technology into routine NHS use.

The technology described in this report is the Curos disinfecting cap (3M). It is used on needleless connectors on vascular access devices.

2. Contributors

Adoption information was gathered from 12 NHS staff in the following areas:

- 3 consultants (intensive care, neonatologist and a paediatric anaesthetist)
- 6 nurses (5 infection prevention specialists and 1 trainee advanced practitioner)
- 1 clinical research scientist
- 2 directors or deputy directors in infection prevention control

3. Use of the technology in practice

The 6 non-users and 1 previous user of the technology are experts in the field of needleless connectors.

The 5 users of the technology have used either hundreds or thousands of Curos caps in line with the manufacturer's instructions. A majority have used the technology for over 2 years in the following settings:

- Neonatal unit
- Intensive care unit for patients testing positive for healthcare-associated infections, such as MRSA
- Hematology and critical care unit
- High infection risk clinical areas, such as chemotherapy
- Acute hospital and in the community
- Patients requiring parenteral nutrition and chemotherapy regardless of location

One trust is using Curos with a closed needle free access system which does not require a cap. Staff are trained to disinfect connectors and the line with a 2% chlorhexidine gluconate (CHG) in 70% alcohol wipe prior to using the technology as there is a concern with line contamination.

There was a general consensus among contributors that most lines with needleless connectors not being used may be removed within a few days according to local protocols.

The manufacturer reported that as of August 2018, 238 NHS trusts, clinical commissioning groups and social enterprises in England are currently using the technology.

4. Reported benefits

The benefits of adopting the technology, as reported to the adoption team by healthcare professionals are:

- A possible reduction in line-associated infections.
- Associated increase in staff compliance versus manual disinfection of needleless connectors using a wipe, particularly in an emergency setting.
- Time saving particularly when access is required to the connector in an emergency.
- Convenient for staff as strips of the technology can be hung on IV poles.

5. Insights from the NHS

The considerations for adoption highlighted through discussions with contributors are:

Care pathway

There was some concern the technology did not contain the 2% CHG in 70% alcohol as recommended by RCN and EPIC3. This conflict with guidance is reported to be a barrier to adoption.

A potential user expressed concern that current practice in aseptic non touch technique (ANTT) may lapse if the technology was introduced.

Patient selection

Some contributors use the technology on patients who have an increased risk of developing line-associated infections, such as patients having chemotherapy treatment. Another contributor uses the caps on patients who may be difficult to treat if a line-associated infection developed, such as those who test positive for MRSA. However, a potential user commented use of the technology in specific settings may cause confusion if the patient is moved to a different care setting where staff are not aware of the technology.

Clinician confidence/acceptance

There was no consensus on the real world impact of the technology on line-associated infections rates by users. One contributor observed an increase in line-associated infection rates. Another saw a dip in line-associated infection rates over 2 months, but rates increased again to pre-intervention rates in month 3. Further users could not quantify the impact of the technology on line-associated infection rates as they were either not measured or were not clearly identifiable because the technology had been adopted as part of a new bundle of care. All agreed the evidence available for the benefits of the technology is of limited quality and would benefit from a randomised controlled trial.

Some users provided positive feedback on the technology due to convenience and reassurance on safe practice.

Resource impact

None of the users of the technology have measured the local resource impact but commented the cost of the Curos caps probably have a minimal impact on their budget.

Using Curos caps plus wipes compromises realisation of any potential cost benefits.

Training
Training and support was provided by the manufacturer to 4 sites using the technology. The training took 5-10 minutes over a few weeks on several occasions.

Ongoing training may be required to prevent staff complacency as was experienced by one contributor. Refresher training reinvigorated use of the technology. In addition ongoing training to prevent misuse (such as reusing the caps) may support safe adoption.

Patient/clinician safety
Some contributors either do not use or stopped using the caps because they were a perceived choking hazard in the peadiatric setting. A previous user commented that the caps screw on but don't lock on to the end of the connector which was of concern.

A hematology unit stopped using the technology after staff were found to be reusing the caps on the same patient.

6. Comparators

Clinell® alcoholic 2% CHG is a disposable disinfection wipe for medical devices presaturated with 70% alcohol and 2% CHG used to disinfect medical devices specifically designed for needle free devices.

PDI manufacture Sani-Cloth® CHG 2% sachets which contain 2% CHG and 70% alcohol. PDI also manufacture Prevantics® which contains 3.15% CHG and 70% alcohol which disinfects needleless access sites prior to use by scrubbing for 5 seconds and has a 5 second dry time. It can be hung from an IV pole.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical Technologies Evaluation Programme

Sponsor submission of evidence:

Evaluation title: MT396 Curos Caps

Sponsor: 3M UK PLC

Date sections A and B submitted: 11th Sept 2018

Contents

List of tables and figures

Section A – Decision problem

Section A describes the decision problem, the technology and its clinical context. There is also information about ongoing studies, regulatory information and equality issues.

Sponsors should submit section A before the full submission (for details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

1 Statement of the decision problem

The decision problem is specified in the final scope issued by NICE. The decision problem states the key parameters that should be addressed by the information in the evidence submission. All statements should be evidence based and directly relevant to the decision problem.

Table A1 Statement of the decision problem

	Scope issued by NICE	Variation from scope	Rationale for variation
Population	People with vascular access devices in hospital and community settings	None	
Intervention	Curos disinfecting cap	None	
Comparator(s)	• alcohol wipes • alcohol containing solution of chlorhexidine gluconate	None	
Outcomes	1. time taken to complete disinfect 2. overall staff time 3. infection rates (CLABSI and catheter-related bloodstream infections) 4. mortality 5. length of hospital stay 6. length of time vascular access device in place 7. device-related adverse events 8. improved consistency in disinfection protocols 9. reduced use of chlorhexidine 10. environmental impact of reduced number of wipes disposed and increased plastic waste	None	
Cost analysis	Comparator(s): Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which	None	
Subgroups to be considered	People who are at high risk of infection	None	
Special considerations, including issues related to equality	Curos may be used with vascular access devices in people with chronic diseases who are considered disabled under the equality act. This will include people with cancer and may include people with chronic kidney disease, cystic fibrosis, sickle cell disease, thrombotic thrombocytopenic purpura, Sjogrens syndrome, Guillian-Barre syndrome, myasthenia gravis and lysosomal storage disorders.	None	

2 Description of technology under assessment

2.1 Give the brand name, approved name and details of any different versions of the same device.

Brand name:

3M™ Curos™ Disinfecting Cap for Needleless Connectors (available as singles and strips)

3M™ Curos™ Disinfecting Cap for Tego® for haemodialysis connectors (available as singles only)

3M™ Curos™ Stopper Disinfecting Cap for open female Luers (available as singles and strips)

2.2 What is the principal mechanism of action of the technology?

The Curos Disinfecting Cap is a patented sterile needle free device protector with an impregnated sponge interior of 70% Isopropyl alcohol. It is intended for use on needleless connectors as a disinfecting cleaner prior to I.V. access and to act as a cover between line accesses. The cap will disinfect the needleless connector after one minute following application and protect from contamination between accesses for up to seven days if not removed

3 Clinical context

3.1 Provide a brief overview of the disease or condition for which the technology is being considered in the scope issued by NICE.

Central line associated blood stream infection (CLABSI) causes fever and red skin and soreness around the access site and is associated with the need for additional treatment that may include line changes and prolonged antibiotic treatment. The patient consequences of CLABSI are increased morbidity and mortality. Catheter related blood stream infection (CRBSI) is a more specific term sometimes used when the actual cause of infection has been confirmed following catheter tip bacterial cultures.

Hospital Episode statistics for 2016-17 indicated there were 16.5 million patients admitted to hospital and 293,170 into critical care. 3M company estimates suggest 50% of general admissions and 100% of critical care admissions receive a either acute or longer term intravenous therapy via a needle free device that is attached to the end of a vascular access device. There are no available data to indicate the number of community patients who receive such devices.

3.2 Give details of any relevant NICE or other national guidance or expert guidelines for the condition for which the technology is being used. Specify whether the guidance identifies specific subgroups and make any recommendations for their treatment. If available, these should be UK based guidelines.

Related NICE guidance:

1. Healthcare-associated infections: prevention and control in primary and community care (2012) NICE Clinical guideline CG139:
    - recommends that the access ports on needleless connectors should be decontaminated with either alcohol or an alcoholic solution of chlorhexidine gluconate before and after use.
2. Healthcare-associated infections: prevention and control (2011) NICE Public health guideline PH36
3. Curos disinfecting cap for needleless connectors (2018) NICE Medtech innovation briefing MIB143

Guidance from other organisations:

4. Epic 3 guidelines for preventing healthcare associated infections (2017) NHS Improvement
    - recommend that a single-use application of 2% chlorhexidine gluconate in 70% isopropyl alcohol (or povidone iodine in alcohol for people with sensitivity to

chlorhexidine) should be used to decontaminate access ports and catheter hubs. It also recommends that a hub is cleaned for a minimum of 15 seconds and allowed to dry before accessing the system.

3.3 Describe the clinical pathway of care that includes the proposed use of the technology.

When access is required the cap is removed, access gained, and a new cap placed in situ meaning the requirement for alcohol/CHG impregnated wipes and mechanical scrubbing of the port is no longer required

3.4 Describe any issues relating to current clinical practice, including any uncertainty about best practice.

None known.

3.5 Describe the new pathway of care incorporating the new technology that would exist if the technology was adopted by the NHS in England.

If Curos is used, a new Curos cap is placed over the connector each time it is used. Healthcare staff do not have to spend time disinfecting the connector and waiting for it to dry every time the needleless connector is used

3.6 Describe any changes to the way current services are organised or delivered as a result of introducing the technology.

None

3.7 Describe any additional tests or investigations needed for selecting or monitoring patients, or particular administration requirements,

associated with using this technology that are over and above usual clinical practice.

None

3.8 Describe any additional facilities, technologies or infrastructure that need to be used alongside the technology under evaluation for the claimed benefits to be realised.

None

3.9 Describe any tests, investigations, interventions, facilities or technologies that would no longer be needed with using this technology.

If there are fewer blood stream infections there will be less need for diagnostic tip cultures in settings where they are routinely performed.

3.10 Describe how the NHS in England can disinvest from tests, investigations, interventions, facilities or technologies described in section 3.9 that would no longer be needed with using this technology.

. In the case of fewer tip cultures being required this will also free up time in the labs.

4 Regulatory information

4.1 Provide PDF copies of the following documents:

- instructions for use
- CE mark certificate or equivalent UK regulatory approval such as EC declaration of conformity
- quality systems (ISO 13485) certificate (if required).

4.2 Does the technology have CE mark for the indication(s) specified in the scope issued by NICE? If so, give the date that authorisation

was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Curos is CE marked and has an EC Declaration of Conformity – 27th September 2016 and 20th April 2017

4.3 Does the technology have regulatory approval outside the UK? If so, please provide details.

The technology is available in all territories that accept the CE mark for medical devices (EU, Australia), plus other territories including Canada, USA, Japan, China, South Africa, Brazil and Mexico,

4.4 If the technology has not been launched in the UK provide the anticipated date of availability in the UK.

NA

4.5 If the technology has been launched in the UK provide information n the use in England.

Curos is currently marketed within the UK by a distributor (Vygon) who have company sensitive data regarding account usage. These data were sent to Tara Chernick under separate e-mail cover as part of the notification.

5 Ongoing studies

5.1 Provide details of all completed and ongoing studies on the technology from which additional evidence relevant to the decision problem is likely to be available in the next 12 months.

None

5.2 If the technology is, or is planned to be, subject to any other form of assessment in the UK, please give details of the assessment, organisation and expected timescale.

None known of.

6 Equality

NICE is committed to promoting equality of opportunity and eliminating unlawful discrimination on the grounds of age, disability, gender reassignment, race, religion or belief, sex, and sexual orientation, and to comply fully with legal obligations on equality and human rights.

Equality issues require special attention because of NICE's duties to have due regard to the need to eliminate unlawful discrimination, promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others.

Any issues relating to equality that are relevant to the technology under assessment should be described. This section should identify issues described in the scope and also any equality issues not captured in the final scope.

Further details on equality may be found in section 11.3 of this document.

6.1.1 Describe any equality issues relating to the patient population and condition for which the technology is being used.

As with many small medical devices there is a potential choking hazard with Curos. This risk, albeit small, will be higher in children.

6.1.2 Describe any equality issues relating to the assessment of the technology that may require special attention.

None

6.1.3 How will the submission address these issues and any equality issues raised in the scope?

The review of adverse events included in the submission identifies the reported incidence of choking. There is a caution for possible choking stated in the IFU.

Section B – Clinical evidence

7 Published and unpublished clinical evidence

Section B requires sponsors to present published and unpublished clinical evidence for their technology.

Sponsors should read section 6 of the Medical Technologies Evaluation Programme methods guide on published and unpublished evidence, available from www.nice.org.uk/mt

All statements should be evidence-based and directly relevant to the scope. Reasons for deviating from the scope should be clearly stated and explained in table A1.

Sponsors are required to submit section B in advance of the full submission (for details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

7.1 Identification of studies

Published studies

7.1.1 Describe the strategies used to retrieve relevant clinical data from the published literature. Exact details of the search strategy used should be provided in section 10, appendix 1.

A literature search was conducted in Ovid MEDLINE (Appendix 1) to identify studies reporting on the use of antiseptic barrier caps for the reduction of central and peripheral line associated infections. The strategy has three concepts:

- Central or peripheral lines (search lines 1 – 22);
- Antiseptics (search lines 23 – 33);
- Barrier caps (search lines 34 – 37)

The strategy was structured:

(Central or peripheral lines) **AND** antiseptics **AND** barrier caps

The strategy also included focused, stand-alone search lines that used terms that appeared to be highly relevant to antiseptic caps (search lines 39 – 43). These lines were intended to retrieve any relevant records that might have been missed by the three-concept approach, and therefore enhance sensitivity. Stand-alone search lines on a number of named caps, including Curos, were also included (search lines 44 – 49).

The strategy does not restrict by outcome or study design. This sensitive approach also ensured that a single strategy could identify both clinical and economic evidence.

The search strategy was devised using a combination of subject indexing terms and free text search terms in the title, abstract and "keyword heading word" fields. The search terms were identified through discussion within the research team, scoping searches, browsing database thesauri, and use of the PubMed PubReminer tool (http://hgserver2.amc.nl/cgi-bin/miner/miner2.cgi [accessed 04 October 2017]). Before running the final searches, the sensitivity of the strategy was tested by checking retrieval against a sample of relevant clinical studies known to the sponsor. The draft strategy successfully retrieved all of those relevant studies that were present in MEDLINE or MEDLINE In-Process.

The Ovid MEDLINE strategy excluded animal studies using a standard algorithm and non-English language records. No date or publication type limits were used.

The MEDLINE strategy was translated appropriately for each of the databases searched. The search was conducted in a range of relevant databases of published research including those databases specified as a minimum in Section 10.1 of the NICE MTEP Sponsor Submission Template:

- MEDLINE including MEDLINE In-Process (Ovid);

- Embase (Ovid);
- The Cochrane Library (Wiley):
    - Cochrane Database of Systematic Reviews (CDSR);
    - Cochrane Central Register of Controlled Trials (CENTRAL);
    - Database of Abstracts of Reviews of Effects (DARE);
    - Health Technology Assessment Database (HTA Database);
    - NHS Economic Evaluation Database (NHS EED).

The reference lists of any included studies and relevant systematic reviews were also checked to identify any additional studies that might have been missed by database searches.

The titles and abstracts of bibliographic records were downloaded and imported into EndNote bibliographic management software and duplicate records were removed using several algorithms.

Unpublished studies

7.1.2 Describe the strategies used to retrieve relevant clinical data from unpublished sources.

We sought to identify unpublished evidence that had been presented at relevant conferences or meetings. The searches for unpublished evidence included the use of Embase (Ovid) and the Conference Proceedings Citation Index – Science (Web of Knowledge) which both index the proceedings of conferences and meetings.

The following clinical trials registries were searched to identify any ongoing, recently completed, or other unpublished research:

- Clinicaltrials.gov (https://clinicaltrials.gov/);
- WHO ICTRP search portal (http://apps.who.int/trialsearch/).

We searched the Medicines and Healthcare Products Regulatory Agency (MHRA) webpages and the US Food and Drug Administration (FDA) Manufacturer and User Facility Device Experience (MAUDE) database for unpublished clinical data related to safety or adverse events.

To identify any further unpublished studies not retrieved through database searching, the reference lists of included studies and relevant systematic reviews were checked.

The searches for both published and unpublished evidence were conducted in September 2017. The full search strategies for all search sources, both published and unpublished, including search dates and result numbers are included in Appendix 1.

The combined searches (including documents obtained from non-database sources) for published clinical evidence, unpublished clinical evidence, and economic evidence retrieved **4108** records. After duplicates were removed, **2896** unique records remained. A PRISMA flow diagram is provided in Section 7.2.2 below.

7.2 Study selection

Published studies

7.2.1 Complete table B1 to describe the inclusion and exclusion criteria used to select studies from the published literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table B1 Selection criteria used for published studies

Inclusion criteria	
Population	Studies of any hospitalized patients receiving a central or peripheral line.
Interventions	Studies that report on the use of Curos to cap central lines with access to the bloodstream or peripheral lines. Studies that report on Curos within bundles, as long as data on Curos are reported separately.
Outcomes	• The number of catheter related bloodstream infections (CRBSI) or central line associated bloodstream infections (CLABSI) per 1000 catheter-days. In aggregate and separately by central lines and peripheral lines (if possible); • Bacteraemia rates for CRBSI and CLABSI; • Device related adverse events. Where studies report the number of infections and the number of catheter-days, the rate was calculated if possible.
Study design	Prospective studies. Published SRs and their included studies lists were checked to ensure that all relevant articles had been identified and assessed. These SRs were not data extracted.
Language restrictions	English language studies.
Search dates	Any dates.
Exclusion criteria	
Population	Studies of non-hospitalized patients or patients who had not received a central or peripheral line.
Interventions	Studies that did not investigate Curos. Studies of the use of Curos with feeding tubes or for other purposes without access to the bloodstream.
Outcomes	
Study design	Retrospective studies and any other study design that is not listed in the inclusion criteria.
Language restrictions	Non-English language studies.
Search dates	Not applicable

CLABSI = Central Line Associated Blood Stream Infections; CRBSI = Catheter-Related Blood Stream Infections; SR = Systematic Review

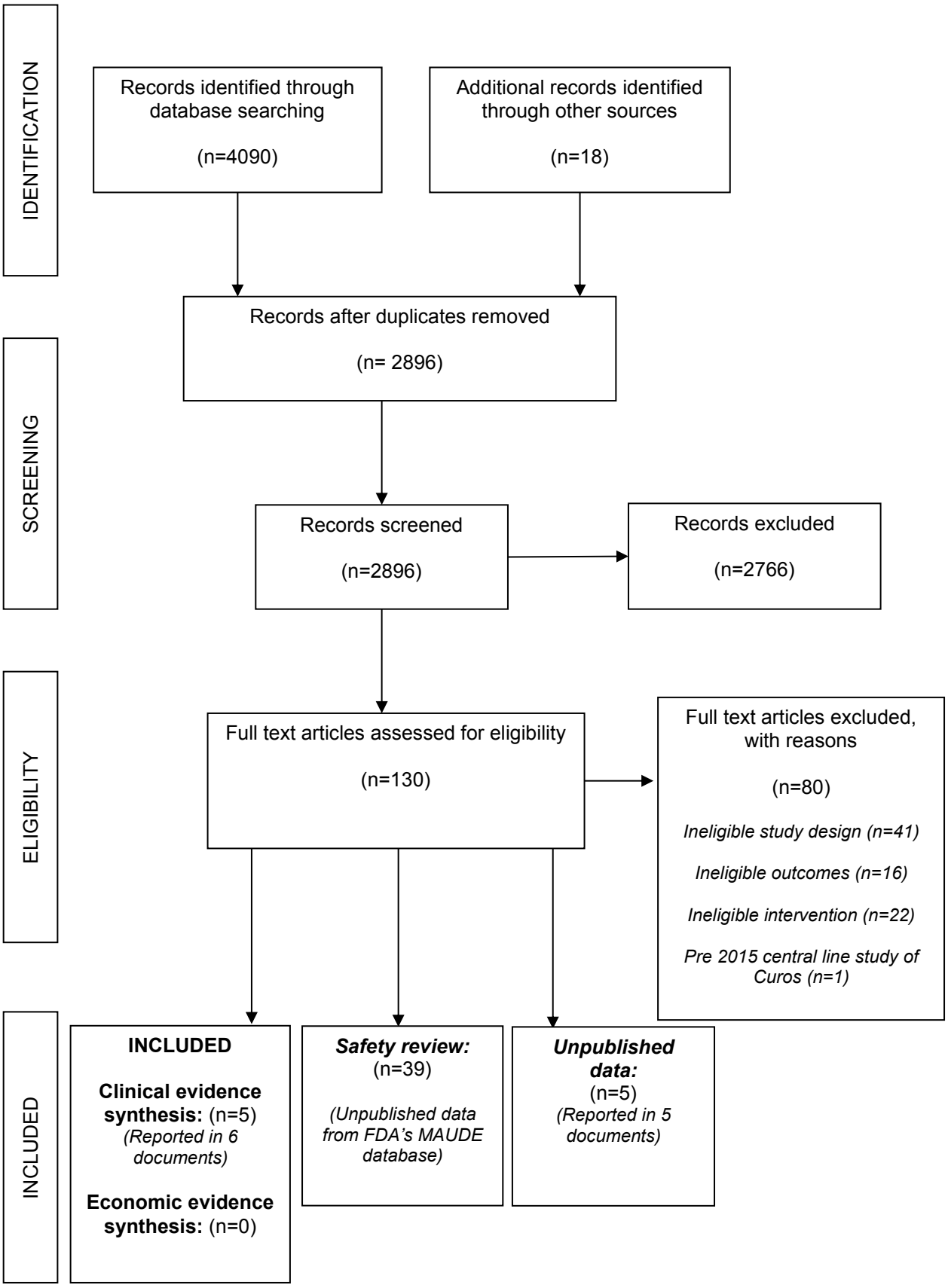
7.2.2 Report the numbers of published studies included and excluded at each stage in an appropriate format.

A total of 2896 records were screened for relevance, based on their title and abstract. 2766 records were excluded based on title and abstract screening and 130 full text reports were assessed for relevance against the pre-defined eligibility criteria and, from these, a further 80 records were excluded with reasons.

5 studies, reported in 6 publications, were included in the clinical evidence review (see Table B3).

The full record selection process for this review is shown as a PRISMA flow diagram in Figure 7.2.2 below.

Figure 7.2.2 Record selection process (PRISMA flow chart)



Unpublished studies

7.2.3 Complete table B2 to describe the inclusion and exclusion criteria used to select studies from the unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

The same eligibility criteria, presented in Table B1, were used to assess unpublished literature.

7.2.4 Report the numbers of unpublished studies included and excluded at each stage in an appropriate format.

5 unpublished studies are included in this review. The full record selection process is presented as a PRISMA flow diagram in Figure B1.

7.3 Complete list of relevant studies

The sponsor should provide a PDF copy of all studies included in the submission if the sponsor is either the copyright owner or has adequate copyright clearance to permit the intended use by NICE. If the sponsor does not have sufficient copyright clearance, they are asked to submit references or links only, or details of contacts for unpublished studies. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

7.3.1 Provide details of all published and unpublished studies identified using the selection criteria described in tables B1 and B2.

Table B3 List of relevant published studies

Study reference	Setting	Study design	intervention & comparator	Outcomes
Sweet MA, 2012 USA [1]	Hematology/ oncology unit in a university hospital	Retrospective review of patient records in calendar year 2009 compared with 6-month intervention period (Jan-June 2010)	Curos cap vs. traditional catheter hub care using alcohol wipes	CLABSI rates per 1000 Compliance rate
Ramirez C, 2012 USA [2]	2 ICUs within a 214-bed community hospital	12-months pre-intervention compared with the intervention period (12 months March 2011-April 2012)	Curos cap vs. current practice/ traditional catheter hub care	CLABSI rates/1000 catheter days Compliance rate
Merrill KC, 2014 USA [3]	13 inpatient units in a 430-bed tertiary care trauma centre.	Pre-intervention period (calendar 2011)compared with the intervention period (calendar 2012)	Curos cap vs. historic controls (not specified)	CLABSI rate per 1000 central line days
Cameron-Watson C, 2016 UK [4]	4 inpatient wards in an acute hospital: oncology, acute care of the elderly, critical care, surgical.	Pre-intervention period (6-months, Oct 2013-March 2014) compared with the intervention period (6 months April-September 2014)	Curos cap vs. current practice /traditional catheter hub care	CRBSI - number of cases Compliance rate
Martino A, 2017 & 2014 conference abstract USA [5]	16-bed ICU in a regional burn centre.	Pre-intervention period (July-Dec. 2011) compared with the intervention period (Jan-June 2012)	CDC recommended bundle excluding swabbing and including Curos vs. CDC recommended bundle	CLABSI rate per 1000 catheter days Compliance rate

CDC = Centers for Disease Control and Prevention; ICU = Intensive Care Unit

Table B4 List of relevant unpublished studies

Study reference	Setting	Study design	intervention & comparator	Outcomes
Pong A, 2011 USA [6]	Neonatal intensive care unit	CLABSI rate before and after the intervention	Curos cap vs. historic controls	CLABSI rate/1000 catheter days
Danielson B, 2013 USA [7]	47-bed level III neonatal ICU (NICU), Texas Health Presbyterian Hospital	CLABSI rate after the intervention in Q1, 2011 compared with estimate for 2010	Curos cap vs. traditional 15-second catheter scrub with alcohol wipes	CLABSI rate/1000 catheter days
Sumner S, 2013 USA [8]	Tertiary care hospital, Texas	CLABSI rate and contaminated blood cultures 2011 compared with 2012 after the introduction of the intervention	Curos cap vs. historic controls	Cost savings
Shiber J, 2014 USA [9]	Acute medical oncology unit. Ochsner Medical Center	CLABSI rates before and after the introduction of the intervention	Curos caps introduced as part of the central line bundle	CLABSI rate reduction (not quantified) Compliance
Ventura R, 2015 UK [10]	Inpatients with a CVAD in place. Aintree University NHS Trust, Liverpool	CRBSI rates in 764 patients with the intervention, compared with rate prior to the intervention	Curos caps vs. active hub disinfection by 2% chlorhexidine and 70% isopropyl	CRBSI rate/1000 catheter days

CVAD = Central Venous Access Device; NICU = Neonatal Intensive Care Unit

7.3.2 State the rationale behind excluding any of the published studies listed in tables B3 and B4.

7.4 Summary of methodology of relevant studies

7.4.1 Describe the study design and methodology for each of the published and unpublished studies using tables B5 and B6 as appropriate. A separate table should be completed for each study.

Study design and methodology is summarised for all of the published studies in Table B6. For unpublished studies no information is available beyond what is reported in an abstract. What details are available are summarised in Table

B4 above.

Table B5 Summary of methodology for randomised controlled trials

There are no randomised controlled trials.

Table B6 Summary of methodology for observational studies

Study name	**Sweet, 2012**
Objective	To assess the effect of optimising hub disinfection using a quality improvement intervention by measuring the rate of central line associated blood stream infections (CLABSI) and contaminated blood cultures (CBC)
Location	Hematology/oncology unit at West Virginia University Hospitals (USA)
Design	Retrospective chart review for the period January 1-Decemer 31 2009 to identify rate of CLABSI per 1000 catheter days. Compared with prospective data collection in the 6-month period beginning January 11 2010
Duration of study	Prospective study duration 6 months
Patient population	Adult oncology patients with a central venous catheter (CVC)
Sample size	Pre-intervention period, patients with CVC n=836 Intervention period, patients with CVC n=436
Inclusion criteria	Patients having a CVC (e.g. peripherally PICC, tunnelled catheter, or implanted port) at the time of, or within 48 hours before a positive blood culture was obtained
Exclusion criteria	None cited
Intervention(s) (n =) and comparator(s) (n =)	Traditional catheter hub care using alcohol wipes in the pre-intervention period compared with use of Curos in addition to, or in place of, alcohol wipes
Baseline differences	There were no statistically significant baseline differences (gender, age, type of oncologic disease, Charlson Comorbidity Index (CCI) score, or receipt of systemic antibiotoics)
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	No follow-up described beyond hospital discharge
Statistical tests	Changes in CLABSI and CBC rates analysed by Fisher's exact test, with 2-tailed p-values and descriptive statistics

Primary outcomes (including scoring methods and timings of assessments)	Reduction in CLABSI/1000 catheter days after the introduction of the quality improvement programme
Secondary outcomes (including scoring methods and timings of assessments)	Reduction in CBCs after the introduction of the quality improvement programme

CBC = Contaminated Blood Cultures; CCI = Charlson Comorbidity Index; CLABSI = Central Line Associated Blood Stream Infections; CVC = Central Venous Catheter; PICC = Peripherally Inserted Central Catheter

Study name	**Ramirez, 2012**
Objective	To evaluate an intervention designed to decrease intraluminal contamination by minimising the introduction of contaminants through inadequately disinfected needless connectors
Location	2 ICUs in a 214-bed community hospital in the USA
Design	Retrospective chart review for the 12-months before the start of the trial compared with data collected prospectively during the trial period
Duration of study	Prospective study: March 1, 2011 to February 29, 2012
Patient population	All ICU patients with an indwelling central line
Sample size	Pre-intervention period 2112 catheter days at risk Intervention period 2160 catheter days at risk
Inclusion criteria	ICU patients with an indwelling line who were receiving IV treatment through the line
Exclusion criteria	None described
Intervention(s) (n =) and comparator(s) (n =)	Current practice for disinfecting connectors involved cleaning the hub with an alcohol sponge for 15 seconds. The intervention involved replacing traditional cleaning with Curos caps
Baseline differences	Not analysed
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	No follow-up is described beyond hospital discharge
Statistical tests	Unpaired t-tests to compare the 12-month pre-intervention period with the 12-month intervention period
Primary outcomes (including scoring methods and timings of assessments)	Difference in rates of CLABSI pre- and post-intervention. CLABSI defined according to Centers for Disease Control (CDC) and National Healthcare Safety Network Guidelines

Secondary outcomes (including scoring methods and timings of assessments)	Compliance, defined as 100% if there was a cap on every needless connector

CDC = Centers for Disease Control; CLABSI = Central Line Associated Blood Stream Infections; ICU = Intensive Care Unit

Study name	**Merrill, 2014**
Objective	To evaluate the effect of implementation of universal IV needless connector disinfection cap on rates of CLABSI and estimated costs. And to examine the relationship between compliance and CLABSI rates
Location	430-bed tertiary care trauma 1 centre in the USA
Design	Rates of CLABSI and costs were compared for the 12-month pre-intervention period (2011) and the 12-month intervention period (2012)
Duration of study	Prospective data collection January-December 2012
Patient population	All patients (newborn to adult) with peripheral and central lines in 13 inpatient units.
Sample size	Not reported
Inclusion criteria	As above
Exclusion criteria	Patients in the emergency department, ambulatory care, surgical services, labour and delivery, and well-baby nursery and patients who were postpartum
Intervention(s) (n =) and comparator(s) (n =)	Traditional catheter disinfection methods compared with Curos cap applied to all needless connectors (central, peripheral and IV tubing)
Baseline differences	None reported
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	None reported beyond hospital discharge
Statistical tests	Generalised linear model using a Poisson distribution fitted to test for significant differences between pre- and post-intervention rates
Primary outcomes (including scoring methods and timings of assessments)	Rates of CLABSI/1000 catheter days
Secondary outcomes (including scoring methods and timings of assessments)	Compliance assessed 1-2 times weekly from February 2012 throughout the study period

CLABSI = Central Line Associated Blood Stream Infections; IV = Intravenous

Study name	Cameron-Watson, 2016
Objective	The aim was to evaluate the effectiveness of the Curos port protector in reducing rates of CRBSI compared with traditional practice
Location	Four wards (oncology, acute care of the elderly, critical care, surgery) in an acute hospital in the UK
Design	Retrospective chart review in the 6 months pre-intervention (October 2013-March 2014) compared with audit completed during the 6-month trial period.
Duration of study	6-months , April-September 2014
Patient population	Patients with vascular access devices in situ covering all needle free devices, including central venous catheters, peripheral IV catheters and arterial VADs
Sample size	1094 patients
Inclusion criteria	As above
Exclusion criteria	Not defined
Intervention(s) (n =) and comparator(s) (n =)	Traditional port disinfecting practice using 2% CHG in 70% isopropyl alcohol pads ('scrub the hub') compared with Curos cap
Baseline differences	Not reported
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	No follow-up reported beyond hospital discharge
Statistical tests	No statistical analysis is presented
Primary outcomes (including scoring methods and timings of assessments)	Difference in catheter-related blood stream infections (CRBSI) pre-and post-intervention. Outcomes are reported as the difference in the number of CRBSI cases in the two periods, and in terms of the difference in number of cases per month.
Secondary outcomes (including scoring methods and timings of assessments)	Compliance. Measured in an anonymous benchmarking audit by a) the normal amount of time spent cleaning the IV hub, and b) the length of time allowed for the hub to dry after cleaning before access. Measured during the intervention by unannounced monthly audits.

CRBSI = Catheter-Related Blood Stream Infections; IV = Intravenous; VAD = Vertebral Artery Dissection

Study name	Martino, 2017
Objective	To evaluate the effectiveness of the introduction of a central venous line port protector in reducing the rates of CLABSI.
Location	16-bed ICU in a regional burn centre co-located with a level 1 trauma centre in the USA

Design	Comparison of the 6-month pre-intervention period (July-December 2011) with the 6-months of the intervention
Duration of study	Prospective data collection January-June 2012
Patient population	Hospital inpatients with thermal burns greater than 10% total body surface area (TBSA), inhalation injuries, electrical injuries, skin injuries undergoing grafting, and other dermatological conditions necessitating complex wound care.
Sample size	Pre-intervention = 673 catheter days Intervention = 1272 catheter days
Inclusion criteria	All patients with central venous catheters
Exclusion criteria	Not reported
Intervention(s) (n =) and comparator(s) (n =)	Centers for Disease Control (CDC) recommended bundle, including cleaning the insertion site with chlorhexidine (CHX), compared with the same practice excluding cleaning with CHX, and with the addition of the Curos cap port protector
Baseline differences	No statistically significant differences in baseline characteristics (age, ICU days, ventilator days, hospital days, thermal injury (%), Inhalation injury (%), continuous renal replacement therapy (CRRT (%), mortality)
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	None reported beyond hospital discharge
Statistical tests	Descriptive statistics, linear regression, analysis of variance (ANOVA) , and non-parametric statistics.
Primary outcomes (including scoring methods and timings of assessments)	Rates of CLABSI per 1000 catheter days
Secondary outcomes (including scoring methods and timings of assessments)	Compliance. Measured by weekly observation audits to verify usage of the Curos caps

ANOVA = Analysis of Variance; CDC = Centers for Disease Control; CHX = Chlorhexidine; CLABSI = Central Line Associated Blood Stream Infections; CRRT = Continuous Renal Replacement Therapy; ICU = Intensive Care Unit; TBSA = Total Body Surface Area

7.4.2 Provide details on data from any single study that have been drawn from more than one source (for example a poster and unpublished report) and/or when trials are linked this should be made clear (for example, an open-label extension to randomised controlled trial).

Martino was also provided as a conference abstract.

7.4.3 Highlight any differences betweden patient populations and methodology in all included studies

All of the studies adopted a single-centre controlled before-and-after design, with historical controls drawn from the same inpatient units as the intervention. All relate to inpatients with central or peripheral lines in-situ, and all report a comparison between traditional catheter hub cleansing procedures and a passive disinfecting cap fitted to the access port (Curos). Outcomes were measured by the difference in CLABSI rates per 1000 catheter days at risk (or in two cases CRBSI rates (Cameron-Watson [4];Ventura [10]), and by compliance with prevention protocols.

The main differences between study populations are in sample size (measured by catheter days at risk), disease characteristics and the inpatient units from which subjects were drawn. Study settings included one or more general hospital wards (Sweet, 2012 [1]; Merrill, 2014 [3]; Cameron-Watson, 2016 [4]), two ICU wards (Ramirez, 2012 [2]), and an intensive care unit in a regional burn centre (Martino, 2017 [5]). Pre-intervention CLABSI rates in most studies are comparable (range 1.5-2.34/1000 catheter days). The exception is the study carried out in an ICU in a regional burns centre (7.43/1000 catheter days).

7.4.4 Provide details of any subgroup analyses that were undertaken in the studies included in section 7.4.1. Specify the rationale and state whether these analyses were pre-planned or post-hoc.

NA

7.4.5 If applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each treatment in an appropriate format.

NA

7.4.6 If applicable provide details of and the rationale for, patients that were lost to follow-up or withdrew from the studies.

NA

7.5 Critical appraisal of relevant studies

7.5.1 Complete a separate quality assessment table for each study. A suggested format for the quality assessment results is shown in tables B7 and B8.

A quality assessment is provided in Table B8 for all of the published studies. No assessment is possible for the unpublished studies because of the lack of detail available.

Table B7 Critical appraisal of randomised control trials

There are no randomised controlled trials

Table B8 Critical appraisal of observational studies

Study name: Sweet, 2012		
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	All adult inpatients with a central venous catheter (CVC) in a hematology/oncology unit were included.
Was the exposure accurately measured to minimise bias?	Yes	The rate of compliance (adherence to the intervention) was monitored. Compliance was assessed by the use of the intervention on all CVCs
Was the outcome accurately measured to minimise bias?	Yes	Each incidence of bacteremia was reviewed by the hospital infection control department to determine if it met the National Healthcare Safety Network (NHSN) definition of a CLABSI
Have the authors identified all important confounding factors?	Yes	Limitations mentioned are the lack of randomisation or blinding, and the possibility that awareness of the intervention changed other aspects of clinical practice.
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Differences in baseline patient characteristics between the two study samples were tested and shown to be non-significant (Table 7.6.1 below)
Was the follow-up of patients complete?	NA	Patients were not followed-up. The outcome measure was the number of CLABSI cases
How precise (for example, in terms of confidence interval and p values) are the results?	Yes	Differences in baseline characteristics and central line characteristics were analysed and p-values are shown. Differences in the rate of CLABSI/1000 days are reported with 95% confidence intervals and p-values
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

CLABSI = Central Line Associated Blood Stream Infections; CVC = Central Venous Catheter; NHSN = National Healthcare Safety Network

Study name: Ramirez, 2012		
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	All patients in the 2 intensive care units (ICU) with an indwelling central line were included in the study
Was the exposure accurately measured to minimise bias?	Yes	The rate of compliance (adherence to the intervention) was monitored. Compliance was assessed by trained observers and was measured by how many of the connectors were covered with a cap
Was the outcome accurately measured to minimise bias?	Yes	CLABSI was defined by National Healthcare Safety Network Guidelines, confirmed by blood cultures
Have the authors identified all important confounding factors?	No	No discussion of the limitations of the study
Have the authors taken account of the confounding factors in the design and/or analysis?	No	Patient characteristics in the pre-intervention and intervention populations are assumed to be the same, but this assumption is not tested
Was the follow-up of patients complete?	NA	There is no follow-up. Outcomes are measured by the number of CLABSI cases
How precise (for example, in terms of confidence interval and p values) are the results?	Yes	95% confidence intervals and p-values are presented for the difference in CLABSI rates between pre-intervention and intervention periods. The difference is not statistically significant (p=0.126), but is assumed to be clinically significant
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

CLABSI = Central Line Associated Blood Stream Infections; ICU = Intensive Care Unit

Study name: Merrill, 2014		
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	All inpatients with peripheral or central lines in 13 inpatient wards in the hospital were included; with some exceptions. Exclusion criteria are clearly stated
Was the exposure accurately measured to minimise bias?	Yes	Compliance with the intervention was monitored 1 or 2 times a week throughout the study period. Compliance was measured by the proportion of connectors covered by a cap
Was the outcome accurately measured to minimise bias?	Yes	The presence of a CLABSI was defined by Centers for Disease Control (CDC) criteria. All positive blood cultures were reviewed against the CDC definition
Have the authors identified all important confounding factors?	Yes	A possible confounder was the fact that ongoing education was implemented at the same time as the study, and this may have had an independent effect on compliance
Have the authors taken account of the confounding factors in the design and/or analysis?	No	There is no analysis to test for differences in baseline characteristics
Was the follow-up of patients complete?	NA	There was no follow-up. The outcome measure was the incidence of CLABSI
How precise (for example, in terms of confidence interval and p values) are the results?	Yes	Estimates of the difference in rates of CLABSI and the connection between compliance and the CLABSI rate are tested using a generalised linear model. 95% confidence intervals and p-values are reported
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

CDC = Centers for Disease Control; CLABSI = Central Line Associated Blood Stream Infections

Study name: Cameron-Watson, 2016		
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	All inpatients with vascular access devices (VAD) in four wards in the hospital were included
Was the exposure accurately measured to minimise bias?	Yes	Monthly audits were carried out throughout the study to ascertain compliance with the intervention
Was the outcome accurately measured to minimise bias?	Not clear	No description is given of how the presence of a positive blood culture was verified as a catheter-related infection (CRBSI), in line with the Health Protection Agency (HPA) definition
Have the authors identified all important confounding factors?	No	No limitations are discussed
Have the authors taken account of the confounding factors in the design and/or analysis?	No	There is no analysis of possible differences in baseline population characteristics. The study does not report the number of catheter days at risk, or the number of patients with VADs in the pre-intervention period.
Was the follow-up of patients complete?	NA	No follow-up. The outcome measure was the incidence of CRBSI
How precise (for example, in terms of confidence interval and p values) are the results?	No	The study reports the number of cases occurring in the sample periods but does not report the number of catheter days at risk. It is therefore not possible to calculate the change in the CRBSI rate. No statistical analysis is reported
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

CRBSI = Catheter-Related Blood Stream Infections; HPA = Health Protection Agency; VAD = Vertebral Artery Dissection

Study name: Martino, 2017		
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	All inpatients with vascular access devices (VAD) in the burn intensive care unit (BICU) in a regional burn centre were included
Was the exposure accurately measured to minimise bias?	Yes	Weekly audits were carried out to monitor use of the intervention
Was the outcome accurately measured to minimise bias?	Yes	CLABSI was defined according to the Centers for Disease Control (CDC) definition. Identification and reporting of cases was done by the infection control nurse
Have the authors identified all important confounding factors?	Yes	Results from one hospital unit may not be generalizable to other settings. Over time changes in education and awareness may have contributed to the reduction in rates of CABSI
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Differences in baseline patient characteristics were tested and shown to be non-significant (Table 7.6.5 below)
Was the follow-up of patients complete?	NA	There was no follow-up. The outcome was the number of CABSI cases
How precise (for example, in terms of confidence interval and p values) are the results?	Yes	Differences in baseline patient characteristics were analysed and p-values are shown. Differences in the rate of CLABSI/1000 days are reported, but confidence intervals and p-value are not reported for the difference between the defined study periods (pre-intervention July-December 2011; intervention January-June 2012).
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

BICU = Burn Intensive Care Unit; CABSI = Catheter-Associated Blood Stream Infections; CDC = Centers for Disease Control; CLABSI = Central Line-Associated Bloodstream Infection; VAD = Vascular Access Devices

7.6 Results of the relevant studies

7.6.1 Complete a results table for each study with all relevant outcome measures pertinent to the decision problem. A suggested format is given in table B9.

The outcomes relevant to the scope are a) baseline rates of central line-associated blood stream infections (CLABSI) or catheter-related blood stream infections (CRBSI); b) the Incidence Rate Ratio (IRR) associated with a switch to Curos from standard practice; and c) compliance with procedures to reduce the risk of infection. Table B9 provides a summary of these outcomes for the included studies, together with cost savings where these are reported. Where further details are available for each study these details are presented in Tables 7.6.1a-7.6.1f.

Table B9 Outcomes from published and unpublished studies

Study	CLABSI/CRBSI rate			Compliance rate	
	Control	Curos		Control	Curos
Published Studies					
Sweet, 2012 [1]	16 CLABSI cases in 6851 catheter days = 2.34/1000 days	1 case in 3005 catheter days = 0.33/1000 days	IRR=0.14 95% CI: 0.02,1.07 0; p=0.03	-	85.2% (228 of 269 patients)
Ramirez, 2012 [2]	4 CLABSI cases in 2112 catheter days = 1.89/1000 days	1 case in 2160 catheter days = 0.46/1000 days	IRR=0.24. Mean difference = 1.525. 95% CI -0.46,3.51; p=0.126	-	73% (63% initially increasing to 80% at the end of the trial)
	Estimated cost saving in the 1-year trial period $39,050				
Merrill, 2014 [3]	CLABSI rate = 1.5/1000 days (sd = 0.37)	Rate = 0.88/1000 (sd = 0.62)	IRR = 0.577 95% CI 0.396,0.8 42; p=0.004	-	Increase in compliance associated with a reduction in CLABSI. IRR =0.93 (95% CI 0.889,0.972); p=0.001
	Estimated annual cost saving $282,840				

Cameron-Watson, 2016 [4]	26 CRBSI cases in the 6-month period, expressed as cases per month (4.3)	8 cases in the 6 month period, expressed as cases per month (1.5)	-	54% of staff cleaning for 10 seconds or less	80%
	Estimated savings for the 6-month intervention period £281,802				
Martino, 2017 [5]	5 CLABSI cases in 673 catheter days = 7.43/1000 days	3 cases in 1272 catheter days = 2.36/1000 days	IRR=0.32	92.5% compliance with complete CDC bundle, incl.swabbing with CHG	86.5% compliance with CDC bundle ex. swabbing and inc. Curos
Unpublished Studies					
Pong A, 2011 [6]	2008 CLABSI rate 7/7533 days = 0.93/1000	2009 rate 2/6782 days = 0.3/1000	IRR = 0.32		
Danielson B, 2013 [7]	2010 CLABSI rate = 1.723/1000	2011 rate = 1.013/1000 2012 rate = 0.722/1000	IRR = 0.59 (2011) IRR = 0.42 (2012)		
Sumner S, 2013 [8]	Decrease in CLABSI and contaminated blood cultures (not quantified)				
	Estimate annual cost saving $732,840				
Shiber J [9]	CLABSI rates reduced (not quantified)				Compliance >90%
Ventura R, 2015 [10]	CRBSI rate = 3.8/1000	0.23/1000	IRR = 0.06 94% decrease		

CDC = Centers for Disease Control; CHG = Chlorhexidine Gluconate; CI = Confidence Interval; CLABSI = Central Line-Associated Bloodstream Infection; IRR = Incidence Rate Ratio; SD = Standard Deviation

TABLE 7.6.1a Sweet, 2012 [1]: Patient characteristics, central line characteristics and CLABI organisms

Patient characteristics

	Preintervention	Intervention	*P* value*
Patients with CVC, n	836	436	
Male sex, % (n)	48.9 (409)	49.0 (214)	.90
Age, years, mean (range)	56.3 (20-91)	56.4 (19-92)	.90
Oncologic disease, % (n)			
Acute leukemia	24.5 (205)	23.4 (102)	.70
Chronic leukemia	2.4 (20)	2.5 (11)	.89
Lymphoma	17.7 (148)	14.7 (64)	.20
Myeloma	5.1 (43)	5.9 (26)	.60
Other	5.0 (42)	6.2 (27)	.46
Solid tumor	38.9 (325)	38.1 (166)	.80
No oncologic disease	6.3 (53)	9.2 (40)	.08
Charlson Comorbidity Index score, mean (range)	4.1 (0-13)	4.3 (0-14)	.23
Receipt of systemic antibiotics, % (n)	75.8 (634)	76.6 (334)	.81

*All values statistically nonsignificant.

Central line characteristics

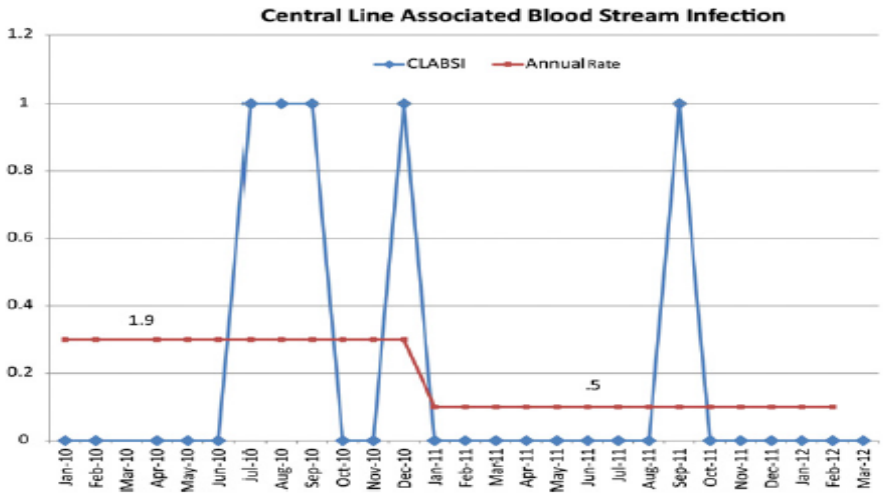
Central line type	Preintervention, % (n)	Intervention, % (n)	*P* value*
PICC	47.8 (400)	50.9 (222)	.30
Implanted port	30.9 (259)	29.4 (128)	.59
Subclavian	11.0 (92)	10.5 (46)	.80
Internal jugular	0.95 (6)	1.8 (8)	.13
Femoral	2.3 (19)	2.5 (11)	.90
Multiple	7.2 (60)	4.8 (21)	.13

*All statistically nonsignificant.

Distribution of CLABSI organisms

Organism	Preintervention	Intervention
Coagulase-negative staphylococci	4	
MRSA	2	1
Escherichia coli	2	
Streptococcus viridans	1	
Klebsiella pneumoniae	1	
Mixed	6	
Total	16	1

TABLE 7.6.1b Ramirez, 2012 [2]: CLABSI incidence rate and Monthly compliance



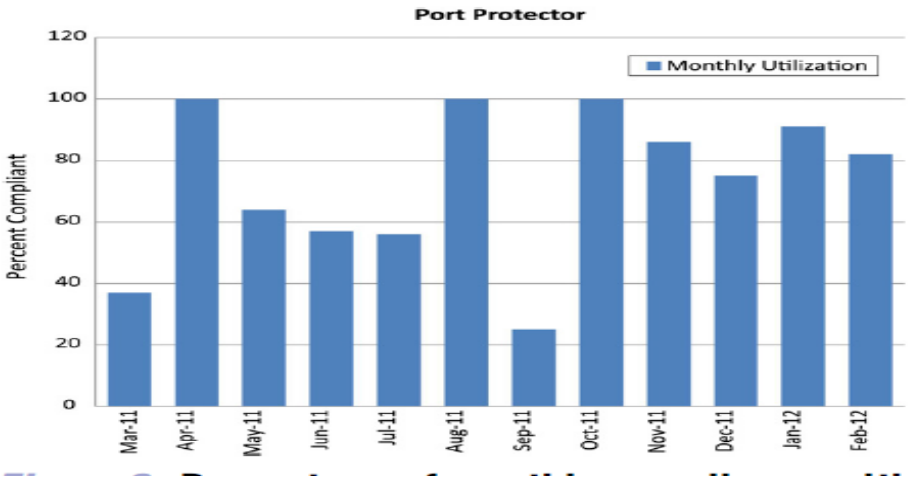
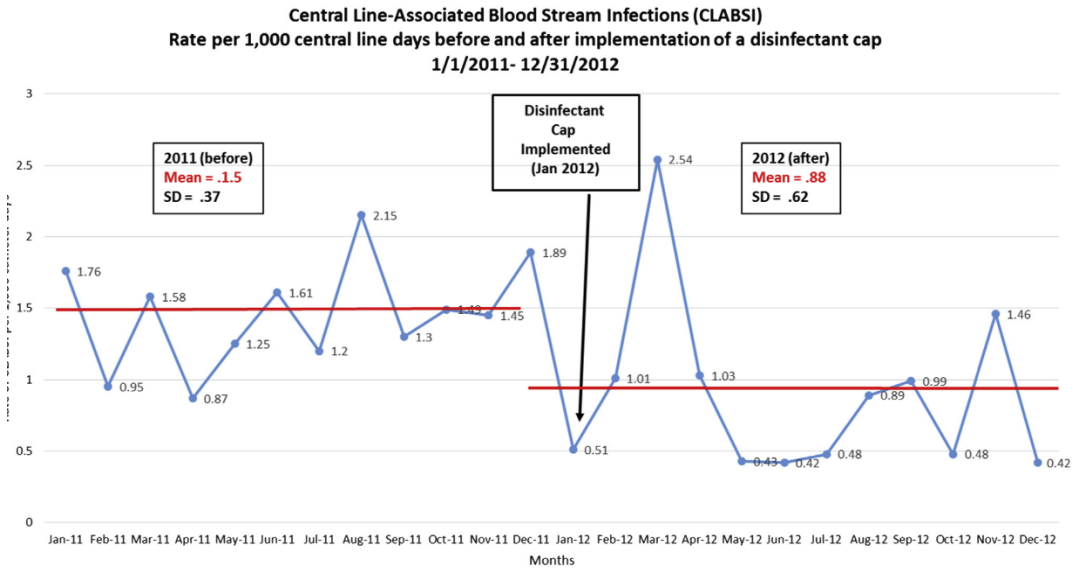


TABLE 7.6.1c Merrill, 2014 [3]: CLABSI rates and compliance parameter estimates



Disinfectant cap intervention, CLABSI rates, and compliance parameter estimates

Model	Parameter	B	SE	*P*	IRR	95% CI for IRR
CLABSI	Intercept	−2.161	0.073	.000*	0.115	.100-.133
Intervention	Intervention = 1	−0.55	0.193	.004*	0.577	.396-.842
CLABSI	Intercept	−2.19	0.0877	.000*	0.112	.094-.133
Compliance	Compliance %	−0.073	0.0228	.001*	0.93	.889-.972

CI, confidence interval; *CLABSI*, central line–associated bloodstream infection; *IRR*, incidence rate ratio.
*Statistically significant result.

TABLE 7.6.1d Cameron-Watson [4]: Results of a 2014 audit of IV cleansing practice in a UK hospital, and results of a UK national survey carried out in 2014 (Rawlinson, 2014 [11])

"I normally clean IV hubs for this amount of time."

	National survey	Trust audit
5 seconds or less	30%	28%
10 seconds or less	54%	54%
15 seconds or less	70%	69%
More than 15 seconds	30%	31%

"I normally let the IV hubs dry for this long before accessing."

	National survey	Trust audit
5 seconds or less	22%	28%
15 seconds or less	42%	55%
25 seconds or less	63%	75%
More than 25 seconds	37%	25%

Table 7.6.1e Cameron-Watson [4] Table 2: Costs and savings

	6 months before intervention	6 months during intervention	improvement achieved
Infection rate	26	8	-18 (-69%)
Disinfection compliance rate	27% (scrub the hub)	80% (with Curos)	+ 53%
Estimated blocked bed-days (infections x 11 days)	286	88	198 (-69.2%)
Estimated cost to treat PIV-CRBSIs (£6209)	£161,434	£49,672	-£111,762
Estimated cost to treat CLA-CRBSIs (£16000)	£416,000	£128,000	-£288,000
Cost of product	£659.35	£6,857.24	+ £6,197.89
Estimated total cost to treat PIV-CRBSIs	£162,093.35	£56,529.24	-£105,564.11

	Estimated total cost to treat CLA-CRBSIs	£416,659.35	£134,857.24	-£281,802.11

TABLE 7.6.1f Martino, 2017 [5]: Patient demographics and CLABSI rates

Table 1 – Patient demographics. (CRRT=continuous renal replacement therapy; ICU=intensive care unit; SD=standard deviation).

	Baseline	Implementation	Post-implementation		p
	July–December 2011	January–June 2012	July–December 2012	January–December 2013	
n	107	153	136	287	
Age years mean±SD (range)	42±16 (17–87)	44±18 (17–97)	46±19 (16–87)	45±19 (15–93)	0.36
ICU days mean±SD (range)	10±25 (1–182)	11±22 (1–147)	10±18 (1–117)	12±23 (1–143)	0.78
Ventilator days mean±SD (range)	4.2±12 (0–89)	6±17 (0–147)	3±10 (0–83)	6±17 (0–133)	0.21
Hospital days mean±SD (range)	17±28 (1–185)	19±26 (1–160)	15±22 (1–128)	19±27 (1–154)	0.46
Thermal injury % (n)	96% (103)	99% (152)	99% (135)	97% (278)	0.14
Inhalation injury % (n)	17% (17/103)	26% (39/153)	16% (22/135)	15% (43/279)	0.07
CRRT % (n)	11% (12)	10% (16)	7% (9)	8% (22)	0.44
Mortality % (n)	12% (13)	13% (20)	10% (13)	10% (30)	0.75

Table 2 – Central line associated blood stream infection (CLABSI) rates. CVL, central venous line.

Time period	Total CVL days	# of CLABSI	CLABSI rate per 1000 line days	CVL bundle compliance	Notes
January–June 2011	950	9	9.47	91.7%	
July–December 2011	673	5	7.43	92.5%	Baseline
January–June 2012 intervention period	1272	3	2.36	86.5%	May 2012: relocated burn unit
July–November 2012	1109	10	9.0	74.3%	July 2012: 60% nursing staff turnover
December 2012–December 2013	2624	8	3.04	Data unavailable	Bundle assessment changed

7.6.2 Justify the inclusion of outcomes in table B9 from any analyses other than intention-to-treat.

NA

7.7 Adverse events

In section 7.7 the sponsor is required to provide information on the adverse events experienced with the technology being evaluated in relation to the scope.

For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator.

7.7.1 Using the previous instructions in sections 7.1 to 7.6, provide details of the identification of studies on adverse events, study selection, study methodologies, critical appraisal and results.

The search approach and strategies described in Section 7.1 (reproduced in full in Appendix 1) were designed to retrieve adverse events, as well as effects and economic evidence.

The searches described in Section 7.1 include those of the Medicines and Healthcare Products Regulatory Agency (MHRA) webpages and the US Food and Drug Administration (FDA) Manufacturer and User Facility Device Experience (MAUDE) database to identify unpublished data related to safety or adverse events.

7.7.2 Provide details of all important adverse events reported for each study. A suggested format is shown in table B10

None of the included studies reported any adverse events associated with or related to the use of the Curos cap. A summary of device-related adverse events recorded in the FDA MAUDE dataset is provided in Section 7.7.3. (Table B10).

7.7.3 Describe all adverse events and outcomes associated with the technology in national regulatory databases such as those maintained by the MHRA and FDA (Maude).

As reported in section 10.1.4, the search strategy retrieved 45 records from the FDA MAUDE database and 0 records from the MHRA webpages. Six of the records from the MAUDE database relating to patients receiving parenteral nutrition were excluded. Section 10.5, Appendix 5 reports the MAUDE database records in detail. Table B10 provides a summary.

Table B10 Adverse events: Summary of reports in the MAUDE database

Report number and date	Description
MW5070690 (05/2017)	Concern regarding the use of isopropyl alcohol-embedded caps in neonates on the basis that it may lead to isopropyl toxicity. No specific case is cited
2110898-2017-00083 (05/2017)	Curos caps were removed to connect IV/fluids/medication. Leakage was reported from the needless connectors when fluids/ medications were being infused or being disconnected. No patient harm occurred
2110898-2017-00062 (02/2017)	Leaking from the needless connector with Curos cap in place. No patient harm occurred
2110898-2017-00058 (01/2017)	Leaking from the needless connector with Curos cap in place. No patient harm occurred
2110898-2017-00059 (02/2017)	Leaking from a connection between the needless connector and Curos cap when IV tubing was accidentally left clamped. No patient harm occurred
2110898-2017-00060 (02/2017)	Leaking from the connection between the needless connector and Curos cap located in the mid portion of the IV tube. No patient harm occurred
2110898-2017-00061 (02/2017)	IV tubing set with three needless connectors. Leaking from one of the needless connectors with Curos cap in place. No patient harm occurred
2110898-2017-00055 (01/2017)	Leaking from the connection between needless connector and Curos cap located in the middle of the IV tubing. No patient harm occurred
2110898-2017-00056 (01/2017)	Leakage from the needless connector/Curos cap located at the distal end of the IV tubing. No patient harm occurred
2110898-2017-00057 (01/2017)	Six reports of leaking at the connection between the needless connector and Curos cap in past 2 weeks of use. No patient harm occurred
2110898-2011-00053 (01/2017)	Infusion pump did not recognise a downstream occlusion because it was leaking under the Curos cap.No patient harm occurred
6456187 (02/2017)	Fluid leaking from a Baxter Clearlink IV tubing access port with Curos cap in place, when tubing was accidentally left clamped Second report of a Curos cap screwed on at an angle causing fluid to leak from the port. Damaged hospira microclave suspected to be associated with the Curos cap
2110898-2017-00021 (01/2017)	Periodic leaking from injection ports where Curos caps were used. Two reports in past 2 weeks where IV chemotherapy was piggybacked into infusion tubing. No patient harm occurred
2110898-2017-00026 (02/2017)	Leaking from an injection port with Curos cap in place. The patient required a blood level check to ensure the therapeutic dose had been received. No re-dosing was required
2110898-2017-00020 (02/2017)	ICU patient's blood pressure was observed to be dropping. Found that IV fluids were leaking from an injection port where Curos cap

	was in place. Patient did not suffer any adverse consequences as a result of the incident.
2110898-2017-00025 (02/2017)	Approximately 150cc of chemotherapy infusion was found to be leaking from connector with Curos cap in place. The patient required re-dosing and was given an estimated amount of chemotherapy lost due to leakage
2110898-2017-00050 (03/2017) 6431666 (03/2017)	Mother of a toddler reported that her son removed one of the Curos caps from the fluid line and put it in his mouth. Mother reported the son was choking and she removed it. Toddler was evaluated and lungs were clear, 100% oxygen saturation and easy breathing Patient found by parent to have pulled the Curos caps off his fluid lines and put them in his mouth. The parent stated that the patient was choking and removed the cap. Patient was evaluated, lungs sound clear, oxygen saturation 1005 and easy breathing
6493194 (03/2017)	Male end of tubing breaks off when Curos tips are applied
2110898-2017-00066 (04/2017)	Plastic film from Curos male tips staying on the end of the male tip when removed from the strip. No patient harm occurred
6529588 (04/2017)	Plastic strip that covers the tip in between the foil and the tip remained on the tip. The plastic strip could be forced into the IV line
2110898-2017-00012 (01/2017) 2110898-2017-00013 (01/2017) 2110898-2017-00014 (01/2017)	Curos cap was incorrectly applied directly to the hub of a PICC catheter which resulted in the separation of the sponge. A warning was added in March 2017 to product literature that Curos caps are not to applied directly to a catheter hub Cutros cap was incorrectly applied directly to the hub of a midline catheter which resulted in the separation of the sponge. The sponge was retrieved Curos cap was incorrectly applied directly to the hub of a catheter which resulted in separation of the sponge. Sponge was later found.
2110898-2016-00041 (02/2016)	Patient was receiving antibiotics through an internal jugular, triple lumen central line catheter. Nurse incorrectly disconnected the IV setup down to the catheter hub. Central line lumen was not clamped when the IV was disconnected and a Curos cap placed directly on the central line catheter hub/ the patient subsequently died
2110898-2016-00022 (11/2015) and 5406449	Curos cap was incorrectly placed over a three-way stopcock to cover the access port. A part of the Curos cap became detached and lodged in the access port. The patient required a non-rebreather mask and medications to manage rising systolic blood pressure
6325422 (02/2017)	Curos cap broke while nurse was screwing the cap on to a PICC line
6275607 (01/2017)	Internal ring of cap disconnected from the external cap
4253141 (09/2014)	Curos cap was unscrewed from IV line and the inside of the cap was still around the line. A hemstat clamp was required to remove it
3008142801-2014-00001 (07/2014)	Curos caps breaking while patients move around in bed and also break apart when the cap is removed. There was no patient safety issue

3008142801-2014-00002 (08/2014)	Curos cap broke apart. Green ring stayed on the IV port when the cap was removed
4253190 (09/2014)	Curos cap broke while being fitted to the line
4023072 (08/2014)	Curos cap broke and part stayed on the port
4023073 (07/2014)	Curos cap breaks when patient move around in bed and when the cap is removed
2412604 (01/2012)	Curos cap broke after being attached to the port
MW5021324 (05/2011) and MW5021325 (05/2011) and MW5021326	Some patients with lines fitted with Curos caps developed candida infections. No causal link has been identified between the caps and the infections.

7.7.4 Provide a brief overview of the safety of the technology in relation to the scope

There are no significant safety issues with Curos caps when applied in line with the manufacturer's recommended use. As with any small medical device there is a potential choking hazard. The adverse event reports contained in the MAUDE database are all minor in the sense that they led to no harm to patients or staff. Many of the adverse event reports arose in circumstances where the product was not used in line with the manufacturer's indications for use.

One report raised a concern about the use of any isopropyl alcohol impregnated product in neonates because of a potential risk of isopropyl alcohol toxicity. No cases related to the use of Curos have been reported. Another reported a series of candida infections in patients with IV lines protected by a Curos cap. No specific cause for the infections was identified, and no link was established to the use of the cap. Two reports refer to the cap being swallowed by a child. Neither case resulted in harm to the child. Many of the reports refer to leakage of fluids from the connection between a needless connector and the cap. In most cases the leak was small and quickly rectified, with no patient safety issues. In a small number of cases it was necessary to carry out checks to ensure that a therapeutic dose had been received. There were some early reports that the cap may break as it is being

applied, or when a patient moves around in bed. There are no reported safety issues. Other reports refer to incidents where the product was incorrectly applied, or was used outside of the manufacturer's recommended use. For example, where the cap is applied directly to a catheter hub or placed over a three-way stopcock.

7.8 Evidence synthesis and meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be considered.

Section 7.8 should be read in conjunction with the 'Medical Technologies Evaluation Programme Methods Guide', available from www.nice.org.uk/mt

7.8.1 Describe the technique used for evidence synthesis and/or meta-analysis. Include a rationale for the studies selected, details of the methodology used and the results of the analysis.

Summary

We conducted two meta-analyses of published Curos studies. Four of the five studies provided data on rates of infection. The outcome of interest is a comparison of rates of infections (number of infections per 1000 catheter days) pre- and post- the introduction of Curos. The comparison is made via incidence risk ratio (IRR) which is the ratio of the post- and pre-intervention infection rates. IRR = 1 means that no effect can be detected, while an IRR < 1 means that the risk of infection decreased after intervention.

The analysis was carried out twice: once including all studies that provided sufficient data, and once for a subset of studies that assessed an ICU population. In both cases the results are that the IRR is very likely to be <1 (see Figure 7.8.1a and Figure 7.8.1b). More details are given below

Figure 7.8.1a: Meta-analysis results - all studies

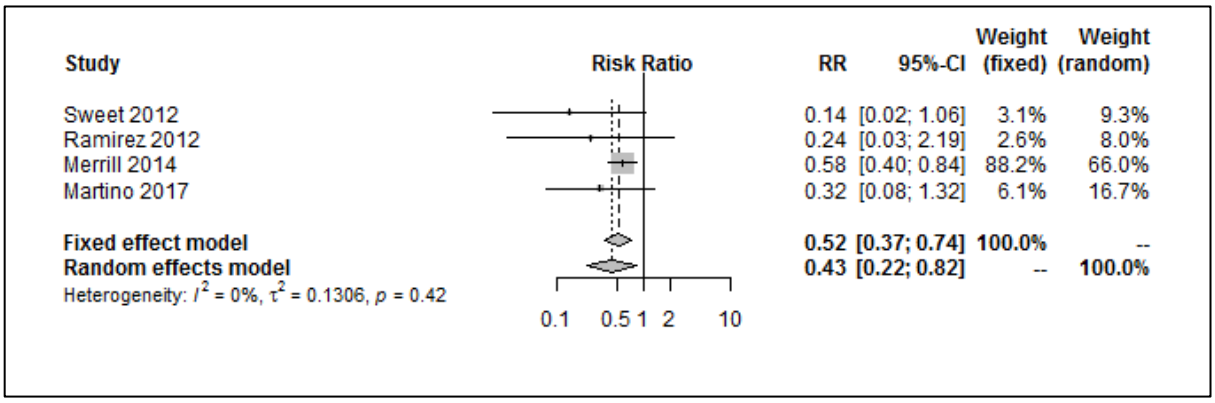
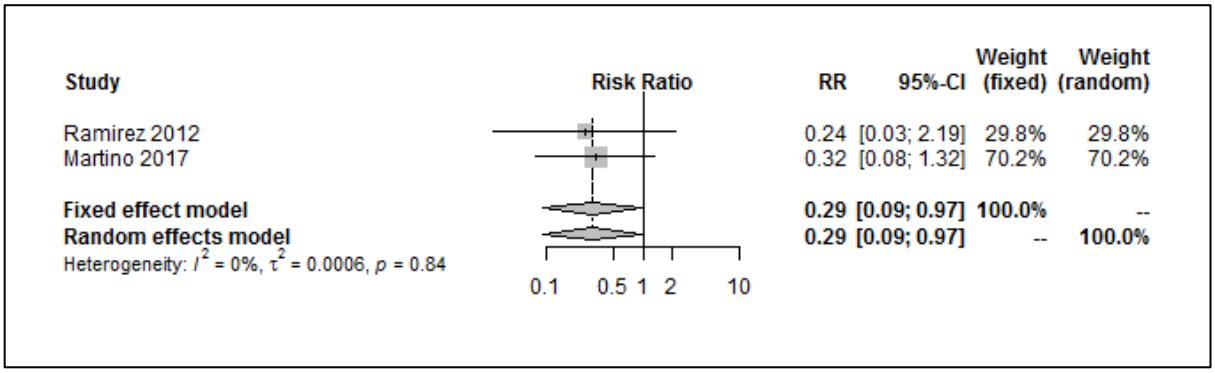


Figure 7.8.1b: Meta-analysis results – ICU population studies only



Data

Two of the five relevant studies reported number of infections and catheter days for pre-/post-intervention. One of these studies reported the incidence risk ratio with 95% confidence intervals, while one other study reported both number of infections and catheter days and incidence risk ratio with 95% confidence intervals. One study (Cameron-Watson 2016 [4]) included neither number of catheter days nor the incidence risk ratio with confidence intervals, and was therefore excluded from the meta-analysis.

Method

Two meta-analyses were undertaken, using the following sets of studies:

- All four studies which contained enough information to be used;
- A subset of two studies (Ramirez 2012 [2] and Martino 2017 [5]), referring to an ICU population.

All calculations were performed on the log scale. The results presented here have been back-transformed to the original scale. Where available, the incidence risk ratio (IRR) was used in the calculations. Where missing, the IRR was calculated based on number of infections and catheter days at risk for pre- and post-intervention.

The standard error for the log transformed IRR was calculated based on number of infections and catheter days for pre- and post-intervention whenever possible. When missing, the standard error was derived from the length of the confidence interval for the log transformed IRR.

A fixed effect model and a random effects model have been fitted to the data. Both give a summary effect of the IRR for all the studies including confidence intervals. The fixed effect model is appropriate under the assumption that the true effect of the intervention is the same in each study. Otherwise, the random effects model is appropriate. This could be the case, for example, if studies look at patient groups with different characteristics, or if the effect of an intervention is variable for other reasons. Results for both the fixed effect model and the random effects model are provided.

We note that during this process the confidence intervals for single studies have been recalculated. This led to one minor difference between calculated and reported upper confidence limit (UCL) probably due to rounding (Sweet 2012 [1]: reported UCL at 1.07, calculated UCL at 1.06).

Result

- **All studies (A)**

Both the fixed effect model and the random effects model produce an estimated risk ratio <1. Moreover, in both models the 95% confidence interval does not

include 1: there is a statistically significant reduction in the risk of infection post-intervention.

The fixed effect model summarizes the IRR to 0.52 (95% confidence interval: 0.37, 0.74). This implies that the number of infections per 1000 catheter days is almost halved post-intervention. The random effects model estimates the IRR as 0.43, although here the confidence interval (and as such the uncertainty of the IRR estimate) is wider.

In both models Merrill 2014 [3] largely dominates the result due to its narrow within-study confidence interval.

- **ICU population studies (B)**

For the meta-analysis of studies in the ICU population, the fixed effect model and the random effects model show a summary risk ratio <1, and the 95% confidence interval does not include 1. Therefore, there is a statistically significant reduction in the risk of infection post-intervention.

The fixed effect model and the random effects model yield the same results, indicating that it is reasonable to assume that the true effect of intervention in both studies is equal.

Both models estimate the IRR at 0.29 (95% confidence interval: 0.09, 0.97). This estimate is somewhat lower than the estimate in analysis (A). However, since the 95% confidence interval for (B) includes the value estimated in (A), it cannot be concluded from the results that the size of the effect for sets (A) and (B) are different.

7.8.2 If evidence synthesis is not considered appropriate, give a rationale and provide a qualitative review. The review should summarise the

overall results of the individual studies with reference to their critical appraisal.

7.9 Interpretation of clinical evidence

7.9.1 Provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and any risks relating to adverse events from the technology.

The evidence is consistent with the conclusion that using a Curos disinfecting cap on needless connectors is a safe and effective way to reduce the risk of catheter-associated infections compared with standard 'scrub the hub' procedures.

Recommended practice in the UK to prevent catheter-associated infections is to scrub the connector hub before and after access for a minimum of 15 seconds with 2% chlorhexidine gluconate (CHG) in 70% alcohol (unless contraindicated) and allow to dry (NICE, 2012 [12]; Loveday, 2014 [13]). Evidence suggests that compliance with this guideline in the UK is low. A 2014 audit carried out in one acute NHS hospital (Cameron-Watson, 2016 [4]) found that in 69% of observations (n=108) the connector was cleaned for less than 15 seconds. This compares with 70% cleaned for less than 15 seconds in a national UK audit (n=1237) (Rawlinson, 2014 [11]). The Curos cap avoids the need for manual cleaning and is expected to reduce rates of CLABSI, in part through improving compliance and in part through the passive disinfection action of the cap itself.

A previous systematic review and meta-analysis of the effectiveness of an antiseptic barrier cap as a means to reduce rates of CLABSI reviewed the literature published to May 2016 (Voor, 2017 [14]). Three Curos studies were identified and included in the meta-analysis (Sweet, 2012 [1]; Ramirez, 2012 [2]; Merrill, 2014 [3]). The pooled IRR was 0.48 (95% CI = 0.242; 0.954) in favour of Curos. Because of the expected clinical heterogeneity between studies, a random effects model was fitted to the data. We updated the search and meta-analysis to include studies published since 2015. One additional

study (Martino, 2017 [5]) was included. The pooled incidence rate ratio in the random effects model was 0.43 (95% CI = 0.22; 0.82) in favour of Curos (Figure 7.8.1a). In a high-risk sub-group of patients in intensive care the RR was 0.29 (95% CI = 0.09; 0.97) in favour of Curos (figure 7.8.1b).

Of the 39 adverse event incidents reported in the FDA MAUDE database, none resulted in harm to patients and most were either minor or a result of inappropriate use of the product (Table B10 and Appendix 5).

7.9.2 Provide a summary of the strengths and limitations of the clinical-evidence base of the technology.

All of the evidence comes from single-centre, controlled before and after observational studies. The strength is the fact that these studies were carried out in routine clinical practice, rather than in the highly controlled environment of a multi-centre randomised controlled trial (RCT). Two of the studies (Cameron-Watson, 2016 [4] and Ventura, 2015 [10]) were carried out in an English hospital. A potential weakness is the fact that none of the studies adopted a randomised design and none was explicitly blinded. Randomisation helps to ensure that patient characteristics are similar between treatment groups and avoids selection bias. Blinding helps to avoid investigator bias.

In the current context blinding is likely to be less of an issue because the primary outcome, incidence of a catheter-associated bloodstream infection, is usually confirmed by a laboratory test which is independent of the investigator. Similarly, the better studies test explicitly for relevant differences in baseline patient characteristics between the control and intervention groups.

7.9.3 Provide a brief statement on the relevance of the evidence base to the scope. This should focus on the claimed patient- and system-benefits described in the scope.

The evidence relates directly to the claimed benefits of the technology: improved patient safety and benefits to the NHS through a reduction in the rate of catheter-associated bloodstream infections.

7.9.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice.

All of the studies evaluate the technology in a routine clinical setting. The controlled before and after design standardises the setting and clinician and, in this sense, may be more applicable to routine practice than a randomised trial. Two of the studies (Cameron-Watson, 2016 [4] and Ventura, 2015 [10]) evaluate Curos in an English hospital and both show results which are consistent with the rest of the literature.

7.9.5 Based on external validity factors identified in 7.9.4 describe any criteria that would be used in clinical practice to select patients for whom the technology would be suitable.

The technology is suitable for use in all patients who require ether acute or long term intravenous therapy via a needle-free device that is attached to the end of a vascular access device.

Section C – Economic evidence

8 Existing economic evaluations

8.1 Identification of studies

8.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished data. The search strategy used should be provided as in section 10, appendix 3.

The search strategies to identify clinical evidence reported in Section 7.1 were not limited by outcome or study design and therefore they also identify economic studies. The required searches of MEDLINE and MEDLINE In-Process, Embase, and the NHS Economic Evaluation Database (NHS EED) were therefore carried out as part of the searches described in Section 7.1. The strategy reported in Section 7.1 was additionally translated for the following resources specific to economic research:

- Econlit (Ovid);
- CEA Registry (http://healtheconomics.tuftsmedicalcenter.org/cear4/Home.aspx).

The full search strategies for the economic specific searches (including search dates and result numbers) are included in Appendix 3.

The combined searches for published clinical evidence, unpublished clinical evidence, and economic evidence retrieved **4108** records. After duplicates were removed, **2896** unique records remained. A PRISMA flow diagram is provided in Section 7.2.2 above.

8.1.2 Describe the inclusion and exclusion criteria used to select studies from the published and unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table C1 Selection criteria used for health economic studies

Inclusion criteria	
Population	Studies of any hospitalized patients receiving a central or peripheral line.
Interventions	Studies that report on the use of Curos to cap central lines with access to the bloodstream or peripheral lines. Studies that report on Curos within bundles, as long as data on Curos are reported separately.
Outcomes	• CRBSI or CLABSI attributable inpatient length of stay (LOS); • CRBSI-attributable or CLABSI-attributable admissions to ICU/HDU; • CRBSI/CLABSI antibiotic use; • Total costs per patient episode; • Costs and numbers of caps per patient; • Impact of CRBSI/CLABSI on quality of life; • Incremental cost-effectiveness ratios (ICER).
Study design	Economic evaluations, cost studies, published economic models and HTA reports investigating the cost-effectiveness of treatments. Published SRs and their included studies lists were checked to ensure that all relevant articles had been identified and assessed. These SRs were not data extracted.
Language restrictions	English language studies.
Search dates	No restriction was applied.
Exclusion criteria	
Population	Studies of non-hospitalized patients or patients not receiving a central or peripheral line.
Interventions	Studies that did not investigate Curos. Studies of the use of Curos with feeding tubes or for other purposes without access to the bloodstream.
Outcomes	
Study design	Retrospective studies and case reports and any study design that is not listed in the inclusion criteria.
Language restrictions	Non-English language studies.
Search dates	Not applicable

CLABSI = Central Line Associated Blood Stream Infections; CRBSI = Catheter-Related Blood Stream Infections; HDU = High Dependency Unit; ICER = Incremental Cost-Effectiveness Ratio; ICU = Intensive Care Unit; LOS = Length of Stay; SR = Systematic Review

8.1.3 Report the numbers of published studies included and excluded at each stage in an appropriate format.

A total of 2896 records were screened for relevance, based on their title and abstract. 2766 records were excluded based on title and abstract screening and 130 full text reports were assessed for relevance against the pre-defined eligibility criteria and, from these, a further 80 records were excluded with reasons.

0 records were included in the economic assessments review.

As noted in 8.1.1 above, the search strategies identified both clinical and economic evaluation evidence. Therefore, the PRISMA flow diagram reported in section 7.2.2 also reports the outcomes of the economic evaluations search.

8.2 Description of identified studies

8.2.1 Provide a brief review of each study, stating the methods, results and relevance to the scope. A suggested format is provided in table C2.

No eligible studies were identified in this review. Separate searches were conducted for evidence on baseline rates of infection and the costs of infection in the UK (section 9 below).

8.2.2 Provide a complete quality assessment for each health economic study identified. A suggested format is shown in table C3.

No eligible studies were identified in this review.

9 De novo cost analysis

Section 9 requires the sponsor to provide information on the de novo cost analysis.

The de novo cost analysis developed should be relevant to the scope.

All costs resulting from or associated with the use of the technology should be estimated using processes relevant to the NHS and personal social services.

Note that NICE cites the price of the product used in the model in the Medical Technology guidance.

9.1 Description of the de novo cost analysis

9.1.1 Provide the rationale for undertaking further cost analysis in relation to the scope.

A *de novo* cost-effectiveness model was developed because no published studies were identified (Section 8) addressing the cost-effectiveness of the Curos cap. The aim of this analysis was to estimate the costs and consequences of using the Curos cap in a hospital setting, with benefit arising from a reduction in the rate of CLABSI.

Different terms are used in the literature to describe CVC-infections. CRBSI is a clinical definition that requires specific laboratory testing to confirm the catheter as the source of the infection. CLABSI is a simpler definition more often used for surveillance purposes. The economic model is based on the published clinical literature and meta-analysis, both of which report rates of CLABSI. However, some of the UK-based inputs used to populate the model for baseline rates of infection and costs had to be taken from data on CRBSI.

Patients

9.1.2 What patient group(s) is (are) included in the cost analysis?

Hospitalised patients requiring either an acute or longer term central venous catheter (CVC) inserted via the subclavian, internal jugular or femoral vein, or inserted peripherally via the cephalic, basilica or brachial vein (PICCs) are included within the analysis. Also included in the analysis were hospitalised patients with peripheral intravenous catheters (PIVC).

Two hospital settings were considered:

(i) A general inpatient hospital setting including all ward types (all hospitalised patients)

(ii) An intensive care unit setting (ICU), i.e. a subgroup of critically ill patients

Technology and comparator

9.1.3 Provide a justification if the comparator used in the cost analysis is different from the scope.

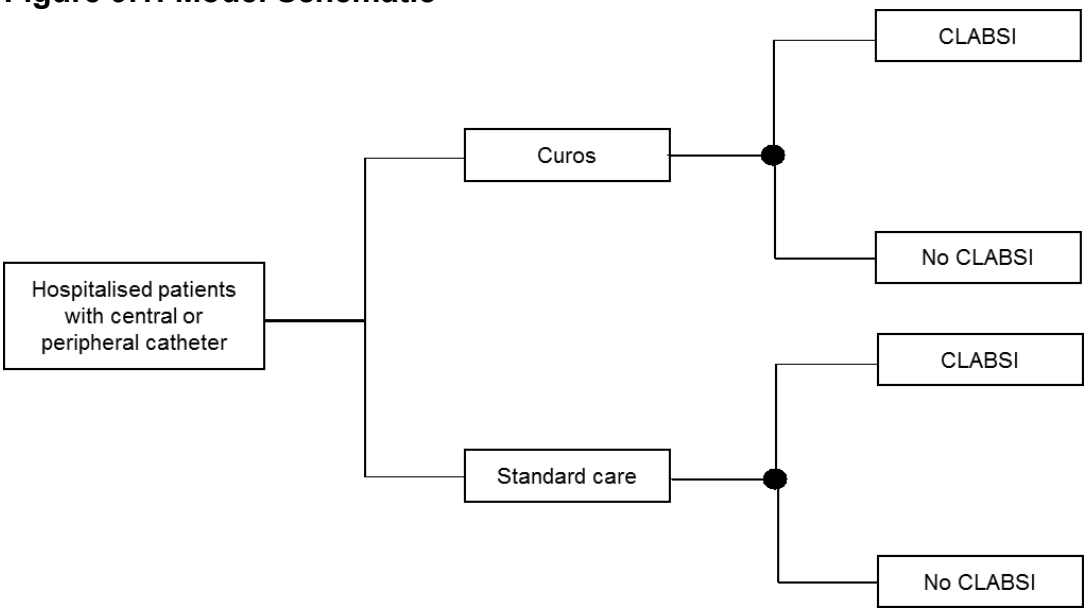
The comparator used in the main analysis is manual disinfection i.e. scrubbing of the needless connector hub for at least 15 seconds with a 2% CHG in alcohol wipe and then allowing the disinfectant to dry for 30 seconds. This occurs each time the port is accessed.

A simple cost comparison versus SwabCap is reported in Section 9.8.4. Due to the lack of comparative clinical data this was not included within the main analysis.

Model structure

9.1.4 Provide a diagram of the model structure you have chosen.

Figure 9.1: Model Schematic



9.1.5 Justify the chosen structure in line with the clinical pathway of care identified in response to question 3.3.

A *de novo* economic model was developed to estimate the costs and consequences associated with the use of the Curos cap and standard care for hospitalised patients requiring central venous or peripheral catheters from an NHS perspective. The structure of the model is shown in Figure 9.1.

Curos can be considered to be a disease prevention device. The meta-analysis showed a significant reduction in CLABSI rates with use of the Curos cap compared with manual disinfection (reported in Section 7.8). CLABSI can lead to significantly longer stays in hospital and increased costs, and this is reflected in an overall episode cost which includes treatment, diagnosis and additional length of stay.

The model assigns each patient in the standard care arm a baseline risk of infection. The infection risk for patients in the Curos arm was estimated by applying the IRR from the meta-analysis to the baseline risk. Costs include the cost of the intervention (Curos cap or alcohol wipe), nurse time for disinfection or placement of the Curos cap, and additional treatment costs for CLABSI.

Costs for training were not included. Clinical studies identified in the review referred to minimal training requirements for the introduction of the Curos cap such as focussed education, education fact sheets, online training or in-service lectures [2, 3, 15]. One study noted that adding devices to CVCs is fairly well established practice and is part of routine care [2]. Therefore, it was judged that any training requirement for the introduction of the Curos cap would be minor and the overall cost per patient would be negligible.

9.1.6 Provide a list of all assumptions in the cost model and a justification for each assumption.

- The studies used in the meta-analysis to derive the IRR were not used in the economic model for the baseline infection rate. This is because neither of the UK-based studies (Cameron-Watson [4] and Ventura [10]) report rates of CLABSI. The baseline infection rate was derived from a separate literature search to identify specific UK sources

- Adverse events were not included because none were identified in the published clinical literature. A search of FDA MAUDE did return results (Section 7.7), but the events reported were judged to be minor and it is not possible to estimate an event probability because there is no way of knowing the population at risk

- Compliance with Curos and with standard care was not explicitly considered. Studies have shown compliance with either in unlikely to be 100%, and the effectiveness data for both Curos and standard care will reflect actual compliance. For the purposes of the costing exercise, compliance with Curos and standard care is assumed to be 100%. The impact of this assumption is tested in sensitivity analysis

- No data were identified for the number of disinfections or accesses per day per port, so this input is an assumption validated by a UK clinical expert

- It is assumed that the cost of treating an infection occurring in general hospital patients and ICU patients is the same. No data were identified to be able to adjust this cost to specific patient groups

- There is likely to be an increase in mortality risk associated with a catheter-associated infection. Infection-associated mortality is not included in the model

9.1.7 Define what the model's health states are intended to capture.

Health outcomes in the economic model are designed to capture the difference in the incidence and costs of CLABSI between the intervention and comparator.

9.1.8 Describe any key features of the cost model not previously reported. A suggested format is presented below.

Table C4 Key features of model not previously reported

Factor	Chosen values	Justification	Reference
Time horizon of model	Under 1 year	Length of stay associated with CLABSI is assumed to be less than 10 days. All studies obtained from search for CLABSI baseline rate of infection considered patients with catheters in place for less than 1 year.	Cooper *et al*. 2014 [16]
Discount of 3.5% for costs	Discounting was not included	A time horizon of less than one year was used so discounting was deemed not necessary.	NA
Perspective (NHS/PSS)	The economic perspective taken was the UK NHS and PSS	In line with scope	NICE 2017 [17]
Cycle length	NA	NA	NA
NHS, National Health Service; PSS, Personal Social Services			

9.2 Clinical parameters and variables

9.2.1 Describe how the data from the clinical evidence were used in the cost analysis.

The clinical parameters required for the economic model are the baseline (standard care) rate of CLABSI and the Curos IRR.

Baseline rate of CLABSI per 1,000 catheter days

One UK unpublished study (Ventura [10]) reported a baseline rate of CRBSI of 3.8/1000 catheter days (Table B9). A supplementary literature search was conducted of studies post-2012 to identify additional UK specific baseline rates. Pre-2012 studies were excluded because improvements in UK infection control practice in that year are expected to have led to a general reduction in hospital-acquired infections.

Search strategy

A pragmatic search strategy was developed in MEDLINE (Ovid interface) to identify papers which reported on the following outcomes in hospitalised patients in the UK:

- Costs of treating catheter-associated or catheter-related bloodstream infections resulting from central venous catheters or PICC lines
- The baseline risk of CRBSI/CLABSI resulting from central venous catheters or PICC lines

The strategy comprised 2 concepts:

- CLABSI/CRBSI
- UK.

The strategy was structured: CLABSI/CRBSI AND UK.

The strategy was devised using a combination of subject indexing terms and free text search terms in the title, abstract and keyword heading word fields. The search terms for the CLABSI/CRBSI concept were identified through discussion within the research team, scanning background literature, analysis of records for known relevant studies, browsing database thesauri and use of the PubMed PubReminer tool (http://hgserver2.amc.nl/cgi-bin/miner/miner2.cgi). The search terms for the UK concept used the validated UK geographic search filter developed by the NICE guidance Information Services team. The strategy excluded animal studies using a standard algorithm. The strategy also excluded publication types unlikely to yield relevant study reports (news items, comments, editorials and letters). Searches were restricted to studies published in English from 2012 to date. The choice of date restriction was informed by company knowledge, and validated by nationally published sources from Health Protection Scotland [18] and Public Health Wales [19] which show reduced rates of CRBSI after 2011.

The search was not designed to be exhaustive, but to target papers which were most likely to be relevant to the research question. The strategy was therefore focused and pragmatic. Pragmatic search approaches used included:

- Limitations on the range of index terms and free text terms included in the strategy (the strategy required that retrieved studies were indexed with the most relevant subject headings and / or explicitly included relatively specific terms for each of the concepts in the database record);

- An emphasis on title searches, with search terms in the abstracts used in conjunction with narrow adjacency operators

The MEDLINE strategy was translated appropriately for the other databases searched. The full strategies (including search dates) are included in Appendix 4. The literature search was conducted using a range of relevant core bibliographic databases. The databases searched are shown in Appendix 4

In addition to the bibliographic database searches targeted searches of grey literature were performed. Nationwide CLABSI/CRBSI rates were identified for critically ill patients within the NHS for both Wales and Scotland in 2013 [18, 19].

Searching a number of databases produces a degree of duplication in the results. To manage this issue, the titles and abstracts of bibliographic records were downloaded and imported into EndNote bibliographic management software and duplicate records were removed using several algorithms.

Literature Search Results

The database searches identified 1866 records (Table C4b). Following deduplication 1416 records remained.

Table C4b: Literature search results

Resource	**Records identified**
Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)	514
Embase	978
Cochrane Database of Systematic Reviews (CDSR)	54
Cochrane Central Register of Controlled Trials (CENTRAL)	227
Health Technology Assessment Database (HTA)	23
Database of Abstracts of Reviews of Effects (DARE)	44
NHS Economic Evaluation Database (NHS EED)	23
Econlit	3
TOTAL	1866
TOTAL after deduplication	**1416**

Selection criteria

Studies were selected on the basis of the following selection criteria:

- Setting: UK hospital, including any specific wards, excluding any studies conducted only in children.

- Outcomes: CRBSI/CLABSI rate per 1,000 catheter days or cost of CRBSI/CLABSI (excluding studies only reporting incidence of infection without the number of catheter days, or reporting CRBSI due only to a specific bacteria e.g. MRSA)

Study selection was performed by a single reviewer. 60 studies were included after title and abstract screening, and this was reduced to 21 studies after full paper review. At full paper review, narrower inclusion criteria were used when assessing studies in an ICU population because the Bion *et al*. 2012 [20] paper had already been identified prior to the search, so the purpose of including ICU populations was to identify any studies with more robust or up to date data than this. Hence, for studies conducted outside of ICUs we included studies comparing an intervention to a comparator, recognising that neither will fully reflect practice across the NHS which will likely comprise a mixture of interventions for reducing rates of CLABSI/CRBSI. For studies conducted within the ICU setting, these comparative studies were excluded. Studies (such as those reporting on economic models) were included where relevant data were used.

Included studies

Studies included for data extraction are shown in Table C4c. Information on CLABSI/CRBSI rates and costs were both extracted. Where papers or abstracts reported on the same study, data were only extracted for the model from the complete source.

Table C4c: Included studies

Author and year	Setting	Definition of infection	CLABSI/CRBSI rate per 1,000 catheter days or treatment cost reported
Not specific to critically ill patients			
Ahmed 2012 [21]	Infectious endocarditis/cardiology patients, Leeds general infirmary, UK	A diagnosis of CRI required the correlation of clinical findings with laboratory results. Intravascular CRBSI: CRBSI was defined as isolation of an organism from at least one bottle of a pair of blood culture bottles plus: a semiquantitative culture of the removed catheter tip positive for the same organism (>15 colony-forming units) as the blood culture isolate; or a differential time to positivity of paired peripheral and through-line blood cultures >2 h in favour of throughline cultures (CVCs only)	Peripheral line: 0.0 Non tunnelled CVC: 7.1 Tunnelled CVC: 5.3
Aitken 2016 [22]	Dialysis patients, Renal surgery ward, Western infirmary, Glasgow, Scotland	Culture proven bacteraemia. Note this is for catheter related sepsis.	1.4 Cost of catheter related sepsis: £9,148 (based on Hockenhull 2008)
Austin 2016 [23]	Surgical, haemato-oncology and medical parenteral nutrition	Several definitions available:	10.2 (MM [23 infections])

Author and year	Setting	Definition of infection	CLABSI/CRBSI rate per 1,000 catheter days or treatment cost reported
	patients, Southampton teaching hospital, UK	Matching Michigan (MM) project definition Centers for disease control and prevention (CDC) 2008 definition Retrospective clinical diagnosis	8.4 (CDC [19 infections]) 11 (retrospective clinical diagnosis [25 infections])[1]
Dixon 2012 [24]	Patients with pulmonary arterial hypertension receiving IV iloprost, Royal Hallamshire Hospital, Sheffield, UK	CR-BSI was defined as a positive bacterial culture in blood associated with clinical and/or laboratory markers of infection (e.g. elevated C-reactive protein or leucocyte counts)	8.5 (Antibiotics only) 3.8 (Antibiotics and antibiotic lock)
Dyson 2017 [25]	Parenteral nutrition patients, 10 Northern nutrition network centres, UK	Definition of line infection adapted from the ESPEN guidelines and National Healthcare Safety Network (NHSN) surveillance definitions. Note catheter related sepsis.	1.5
Alexakis 2015 [26]	Parenteral nutrition patients, Royal Surrey county hospital, UK	Defined as positive blood cultures taken from a CVC during PN feed period	4.46

[1] Note these were calculated. Paper reports the number of catheter infections for each definition and the number of PN days as 2,259 so all rates are calculated using this figure. This may mean rates for CDC and MM definitions are underreported as not all patient data was available for all definitions.

Author and year	Setting	Definition of infection	CLABSI/CRBSI rate per 1,000 catheter days or treatment cost reported
Hvas 2014 [27]	Parenteral nutrition patients outside of intensive care and intestinal failure unit, Salford royal NHS foundation trust, UK	Diagnosis of a CRBSI was based on qualitative and quantitative assessment of central and peripheral blood cultures and pour plates, as recommended by European guidelines. All cases of a suspected CRBSI were evaluated by the NST Governance board and classified as a confirmed or disproved CRBSI.	6.8 (2009, before intervention) 0.7 (2012 after introduction of dedicated nutrition support team)
Jackson 2012 [28]	Hospitalised patients, District general hospital in the UK	Note CLABSI, definition not reported	0.85 (2009-2012) 0.97 (2010-2011) 0.00 (2011-2012)
Kanaa 2015 [29]	Haemodialysis patients, Yorkshire, UK	CDC definition used	0.28 (Intervention [Cathasept]) 0.68 (Control [Heparin])
Sammut 2013 [30]	Patients with pulmonary arterial hypertension receiving IV iloprost, Sheffield Royal Hallamshire hospital, UK	A catheter-related BSI was defined by positive culture of blood, not explained by another focus of sepsis, drawn either from a peripheral vein or from the indwelling central catheter, or a positive culture of the tip of a removed line.	0.65

Author and year	Setting	Definition of infection	CLABSI/CRBSI rate per 1,000 catheter days or treatment cost reported
Youssouf 2017 [31]	Dialysis patients, NHS greater Manchester renal units	Based on Epic3 guidelines	2.65 (before intervention) 0.5 (after intervention [bundle approach])
Francis 2014 [abstract only] [32]	Haematology/oncology patients, Wolverhampton, UK	Definition not reported	0.49
Appleton 2013 [abstract only] [33]	Type of patients not reported, Wirral hospital, UK	CRBSI was defined as positive paired qualitative blood cultures from a peripheral vein and PICC	0.1 (confirmed CRBSI) 1.7 (clinically suspected)
Kilner 2013 [abstract only] [34]	Haematology patiens, Newcastle upon tyne hospital, UK	Matching Michigan project definition used.	6.2 [pre intervention] 3.56 [post intervention] 0.2 Note: CRBSI and CLABSI combined.
Driver 2012 [abstract only] [35]	Parenteral nutrition patients, UK	CVC-associated infection was confirmed when the same organism was grown on central and peripheral blood cultures, or blood culture and CVC tip culture.	3.26 [>24hr group] 0.3 3.14 [<24hr group]

Author and year	Setting	Definition of infection	CLABSI/CRBSI rate per 1,000 catheter days or treatment cost reported
Critically ill patients (in ICU or CCU)			
Bion 2012 (Matching Michigan study) [20]	ICU patients in hospitals across England	Definitions used from the Hospital in Europe Link for Infection Control through Surveillance programme and the US National Nosocomial infection Surveillance System from the Centre for Disease Control & Prevention, and were piloted and refined to ensure applicability and ease of understanding for an English context	1.88 (after interventions) 1.48 (adults in last quarter)
Cooper 2014 [16]	ICU patients, NHS hospitals in England (Economic model based on Matching Michigan study)	As per Matching Michigan study	3.7 (Matching Michigan baseline rate before interventions) Cost of CRBSI £3,940
Jenks 2016 [36]	ICU patients, NHS hospitals in England (Economic model based on Matching Michigan study)	As per Matching Michigan study	1.48 (Matching Michigan rate after interventions) Cost of CRBSI £9,900 (based on Hockenhull, 2008)
Thokala 2016 [37]	ICU patients, NHS hospitals in England (Economic model based on Matching Michigan study)	As per Matching Michigan study	1.48 (Matching Michigan rate after interventions) Cost of CRBSI £9,900 (based on Hockenhull, 2008)

Author and year	Setting	Definition of infection	CLABSI/CRBSI rate per 1,000 catheter days or treatment cost reported
Ahmadnia 2016 [abstract only] [38]	Critically ill patients, Bristol, UK	Definition not reported. Note CLABSI	9.51 [without chlorhexidine bathing] 7.90 [with chlorhexidine bathing]
Fuerstenberg 2012 [abstract only] [39]	ICU patients with CRBSI, UK	Matching Michigan definition used.	Median LoS ITU was 42.5 [cases] vs 18.5 [controls]

In 2013, Welsh health boards reported 0.19 CRBSI per 1,000 catheter days and the rate in Scottish ICUs was reported as 0.3 (95% CI: 0.2-0.6) per 1,000 catheter days [18, 19]. However, the study authors in Scotland noted that this rate may underestimate the true CRBSI rate because of the lack of routine catheter tip culturing and hence the potential under-classification of blood stream infections as being catheter related. A rate of 2.4 CRBSI per 1,000 catheter days (95% CI: 1.9 to 3.0) was provided for 'probable and confirmed CRBSI' in patients with a CVC in Scottish ICUs in 2013 [18].

None of the identified studies was judged more robust or representative of the UK NHS than the Matching Michigan study [20] due to its large size and geographical spread. This study was chosen because the 'bundles' used in Matching Michigan are understood to have been widely implemented in the NHS, so this study was judged to be most representative of UK NHS practice.

- A baseline ICU rate of 1.48 CLABSI per 1,000 catheter days was used in the analysis. This was the rate in adults in the last quarter of the study (1.88/1000 was the overall average rate in adult ICU patients).
- A conservative assumption was made that the baseline rate in patients in any other ward would be lower than the rate in ICU patients, and this was validated with a clinical expert (Section 9.5.2). Three papers reported very similar rates: 0.7, 0.68 and 0.65 [27,29,30]. The rate reported in the paper by Hvas [27] (0.7/1000) was chosen because this had the largest study population (n=992 patients).

The pragmatic review demonstrated that there is wide variation in infection rates and in the definitions used between different settings. This was also shown in the studies included in the meta-analysis, which reported baseline rates between 1.5 and 7.3 CLABSI/1000 catheter days (Table C4d).

Table C4d: Meta-analysis study baseline CLABSI rates and IRR

Author and year	Setting	CLABSI rate per 1,000 catheter days	IRR with Curos
Sweet 2012 [1]	Haematology/ oncology unit in a university hospital, USA	2.3	0.14
Ramirez 2012 [2]	2 ICUs within a 214-bed community hospital, USA	1.9	0.24
Merrill 2014 [3]	13 inpatient units in a 430-bed tertiary care trauma centre, USA	1.5	0.58
Martino 2017 [5]	16-bed ICU in a regional burn centre, USA	7.3	0.32

CLABSI rate with Curos

The IRR from the meta-analysis as detailed in Section 7.8.1 was used to calculate the expected CLABSI rate with Curos. The rate from all studies was used to calculate the CLABSI rate for general hospital patients (0.43, CI: 0.22 to 0.82), and the rate from the ICU population studies was used to calculate the CLABSI rate for the ICU patient subgroup (0.29, CI: 0.09 to 0.97).

9.2.2 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

Extrapolation of costs and clinical outcomes was not necessary because of the 1-year time horizon.

9.2.3 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?

No surrogate or intermediate outcome measures were included in the model.

9.2.4 Were adverse events such as those described in section 7.7 included in the cost analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.

Adverse events were not included because none were identified in the published clinical literature. A search of FDA MAUDE did return results (Section 7.7), but the events reported were judged to be minor and it is not possible to estimate an event probability because there is no way of knowing the population at risk.

9.2.5 Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

This is a critical step and the names and professional titles of the clinical advisers should be included along with the following:

Expert adviser	Roy Ventura, RCN IV Access specialist nurse University Hospitals Coventry
Criteria for selection	The expert was selected based on his experience with the device and recent publication on the topic in scope
Number of experts approached	One
Number who participated	One
Declaration of potential conflict of interest	None
Background information provided and its consistency with the totality of the evidence provided n the submission	An explanation was given of the aims of the economic analysis and the reason why his opinions were being sought
Methods used to collect and collate opinions	A questionnaire was send by email
Medium used to collect opinions	His opinions were collected through a self-administered questionnare
Questions asked	Table C4e
Was iteration used	No
Was uncertainty around opinions addressed in sensitivity analysis	Yes

Table C4e: Questions and expert opinins

Question	*Opinion*
On average, how long would it take a nurse to replace a Curos cap?	*3 seconds*

On average, how long would a nurse typically spend on manual disinfection?	*30 seconds to scrub and 30 seconds to dry*
On average, how many ports/hubs would a patient in each of the following settings have: *(iii) A critically ill patient in ICU?* *(iv) A patient in hospital (on any ward)?*	*i. 10-15 ports* *ii. 1-2*
On average, how many times per day per port would replacement of a Curos cap be required? *(i) A critically ill patient in ICU?* *(ii) A patient in hospital (on any ward)?*	*i. 5-10 per day* *ii. At least 3 times per day*
On average, how many times per day per port would manual disinfection occur?	*Not answered*
What grade (or grades) of nurse would typically carry out replacement of a Curos cap or manual disinfection: *(i) In ICU?* *(ii) On a general hospital ward?*	*Generally band 5s and 6s., frontline staff for both wards*
The literature that we have identified suggests that patients are in ICU with a catheter for between 5 and 9.4 days. Does this range seem reasonable based on your experience? What would you consider to be the average duration?	*The range based on the literature is correct. But based on experience, patients normally have catheter between 7-14 days.*
The literature that we have identified suggests that patients are in hospital with a catheter for between 7 and 244 days. Does this range seem reasonable based on your experience? What would you consider to be the average duration?	*Yes, I agree with the range stated here in.*
Would you expect CRBSI rates to be lower or higher in a non-ICU setting compared with an ICU setting?	*Literature suggests higher rates in ICU*
We have assumed that manual disinfection is carried out using a 70% alcohol and 2% chlorhexidine gluconate wipe. Does this seem reasonable?	*Yes, it is reasonable. Current available disinfectant wipes contain both elements. The available disinfectant caps at the moment contain alcohol only. The rationale for this is that studies and results of the effectiveness of 70% ROH + 2% CHG focused on skin disinfection. There was just an automatic transference of the results to the NFC and hard surfaces. There is a limited amount of papers proving effectiveness of ROH+CHG on hard surfaces. However, it seems to work.*
Would ports typically be manually disinfected when the catheter is first inserted?	*It does not matter whether a catheter is newly inserted or it has been in situ for days, the ports will have to be manually*

	disinfected before access. Unless the port access is done during the "operative phase" under surgical ANTT, where the items are considered aseptic, then manual disinfection is not warranted.

9.2.6 Summarise all the variables included in the cost analysis. Provide cross-references to other parts of the submission. A suggested format is provided in table C5 below.

Table C5 Summary of variables applied in the cost model

Variable	Value	Range or 95% CI (distribution)	Source
CLABSI baseline rate of infection per 1,000 catheter days hospitalised patients	*0.7*	*Range: 1.2 to 1.5 (gamma)*	Hvas *et al.* 2014 [27]
CLABSI baseline rate of infection per 1,000 catheter days ICU patients	*1.48*	*CI: 1.28 to 1.75 (gamma)*	Bion *et al.* 2013 [20]
IRR for Curos – All studies (hospitalised patients)	0.43	*CI: 0.22 to 0.82 (Lognormal)*	Section 7.8.1
IRR for Curos – ICU studies (ICU patients)	0.29	*CI: 0.09 to 0.97 (Lognormal)*	Section 7.8.1
Cost of CLABSI/CRBSI	*£10,234*	*SE: £3,000 (gamma)*	NICE MTG25 costing template 2015 [40]. Inflated to 2015-16 prices.
Unit cost of Curos cap	*£0.32*	*Not varied*	3M
Unit cost per alcohol wipe used for standard care	*£0.02*	*Not varied*	NHS Supply Chain Product and Transaction Database, NHSBSA Copyright 2017 Weighted average of products VJT061, VJT120 and VJT516 by units sold in 2016 and 2017
Cost per hour of nurse time to disinfect catheters	*£35.00*	*SE: £17.50 (gamma)*	PSSRU 2016 [41] Band 5 nurse cost based on clinical opinion

Nurse time for cap placement (minutes)	*0.25*	*SE: 0.13 (gamma)*	Assumption. Clinical expert suggested 3 seconds, 15 seconds used to be conservative.
Nurse time for manual disinfection (minutes)	*0.75*	*SE: 0.38 (gamma)*	Cameron-Watson *et al.* 2016 [4] Epic3 guidelines [13]
Average number of ports per patient	*2 (any hospital ward patients)* *10 (ICU patients)*	*SE: 1 (any hospital ward)* *5 (ICU)* *(gamma)*	Casey *et al.* 2016 [42] and clinical expert opinion
Number of disinfections or accesses needed per day per port –	*3 (any hospital ward)* *5 (ICU patients)*	*SE: 1.5 (any hospital ward)* *2.5 (ICU)* *(gamma)*	Assumption informed by clinical expert
Average number of days with catheter per patient – hospitalised patients	*7*	*SE: 3.5* *(gamma)*	Dyson *et al.* 2017 [25]
Average number of days with catheter per patient – ICU patients	*13*	*SE: 6.5* *(gamma)*	Tan *et al.* 2009 [43] Range reported by clinical expert of 7 to 14 days.
CI, confidence interval			

9.3 Resource identification, measurement and valuation

NHS costs

9.3.1 Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.

Patients with CLABSI may be in hospital for a wide range of reasons and may be costed under many different HRGs. The following reference costs and PbR tariffs might apply to patients with CLABSI:

PA16A Major Infections with CC

PA16B Major Infections without CC

PA17A Intermediate Infections with CC

PA17B Intermediate Infections without CC

PA18A Minor Infections with CC

PA18B Minor Infections without CC

WA09W Other Non-Viral Infection with CC

WA09Y Other Non-Viral Infection without CC

WH07A Infections or Other Complications of Procedures, with Multiple Interventions, with CC Score 2+

WH07B Infections or Other Complications of Procedures, with Multiple Interventions, with CC Score 0-1

WH07C Infections or Other Complications of Procedures, with Single Intervention, with CC Score 2+

WH07D Infections or Other Complications of Procedures, with Single Intervention, with CC Score 0-1

WH07E Infections or Other Complications of Procedures, without Interventions, with CC Score 4+

WH07F Infections or Other Complications of Procedures, without Interventions, with CC Score 2-3

WH07G Infections or Other Complications of Procedures, without Interventions, with CC Score 0-1

9.3.2 State the Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS) codes for the operations, procedures and interventions relevant to

the use of the technology for the clinical management of the condition.

L911 Open insertion of central venous catheter

L912 Insertion of central venous catheter NEC

L913 Attention to central venous catheter NEC

L915 Insertion of tunnelled catheter

Resource identification, measurement and valuation studies

9.3.3 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria and consider published and unpublished studies.

A pragmatic systematic search was conducted to identify a UK specific cost of treating CLABSI/CRBSI. Studies were selected on the basis of being in the UK and in hospitalised patients with a catheter. UK studies were included if they reported either the cost of an episode of treatment or resource use. An additional study was identified via grey literature searches – MTG25 costing template [40]. A single reviewer selected and data-extracted the studies.

Six studies were identified which reported the cost of a CLABSI/CRBSI in the UK (Table C5b)

Table C5b: Cost of CLABSI/CRBSI, included studies

Author and year	Setting	CLABSI/CRBSI cost reported
Aitken 2016 [22]	Dialysis patients, Renal surgery ward, Western infirmary, Glasgow, Scotland	Cost of catheter related sepsis: £9,148 (based on Hockenhull 2008 [44])
Cooper 2014 [16]	ICU patients, NHS hospitals in England (Economic model based on Matching Michigan study)	Cost of CRBSI £3,940 based on an ICU stay of 1.5 days, ward stay of 5.13 days and a diagnosis and treatment cost of £500.

Jenks 2016 [36]	ICU patients, NHS hospitals in England (Economic model based on Matching Michigan study)	Cost of CRBSI £9,900 (based on Hockenhull, 2008 [44])
NICE, 2014 [40]	ICU patients, NHS hospitals in England (costing template)	Cost of CRBSI £9,900 (based on Hockenhull, 2008 [44])
Thokala 2016 [37]	ICU patients, NHS hospitals in England (Economic model based on Matching Michigan study)	Cost of CRBSI £9,900 (based on Hockenhull, 2008 [44])
Fuerstenberg 2012 [abstract only] [39]	ICU patients with CRBSI, UK	Median LoS ITU was 42.5 [cases] vs 18.5 [controls]

Four of the studies reported a cost based on a study by Hockenhull *et al,* [44] with one reporting only length of stay and the other reporting a cost based on a micro-costing approach using length of stay data for ICU and any hospital ward and a treatment and diagnosis cost. The cost identified from the MTG25 costing template [40] was used in the base case analysis because it has been published by NICE previously. This cost was inflated from 2012/13 to 2015/16 prices using the hospital and community health services (HCHS) pay and price index [41]. The episode cost of infection used in the model is £10,234 (Table C5). This figure includes diagnosis, treatment, additional length of stay and catheter replacement costs.

Cooper *et al.* [16] reported an additional length of stay in the ICU of 1.5 days plus an additional ward length of stay of 5.13 days, and a diagnosis and treatment cost of £518. This additional length of stay was combined with updated ICU and ward costs and the diagnosis and treatment cost inflated using HCHS pay and price index [41], to calculate a total cost of an episode of CLABSI/CRBSI. The cost of an ICU bed day was taken from a NICE costing report (CG83) for rehabilitation after critical illness [45], which reported the cost of an ICU bed day at £1,390 which was then inflated from 2008/9 costs to

2015/16 costs using HCHS pay and price index to £1,546. Two other sources were identified for the cost of an ICU bed day. First, £1,932 was reported by a Welsh government report [19], which when inflated (from 2011/12 to 2015/16) gave a cost per bed day of £2,031. Second, ISD Scotland [46] also reported a higher ICU bed day cost of £2,085, which when inflated (from 2013/14 to 2015/16) gave a cost per ICU bed day of £2,132. The lower cost of £1,546 was used to calculate the cost of additional stay to be conservative.

The cost of a ward bed day was calculated using NHS reference costs 2015-16 [47]. The unit cost for all HRGs for elective, non-elective long stay, and non-elective short stay was divided by the corresponding average length of stay. A one day stay for non-elective short stay was used. These were then weighted by the corresponding number of episodes for each HRG. This produced a cost of £722 per bed day. Combining all of these costs with the data from Cooper *et al.* 2014 [16] gave a total cost of £6,552.72 per episode (Table C5c).

Table C5c: Micro-costing of treatment for CLABSI/CRBSI

Component	Number	Cost	Total
Additional ICU length of stay	1.5	£1,546.18	£2,319.27
Additional ward length of stay	5.13	£722.00	£3,703.86
Diagnosis and treatment cost	1	£529.59	£529.59
Total			**£6,552.72**

Using the alternative length of stay assumptions from Wales and Scotland produced estimates of £7,280 and £7,431 respectively.

Clinical experts approached for a previous NICE guidance for Tegaderm CHG [40], considered the average length of stay for a CLABSI/CRBSI patient will vary between 6 days (first 2 days in ICU and rest in a general medical ward) and 10 days (first 3 days in ICU and rest in a general medical ward). Using these figures for length of stay would give an episode cost of between £6,510

and £10,222, so it was considered the cost used in the model was reasonable. Sensitivity analyses were conducted around this value.

9.3.4 Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model.

Length of stay estimates were provided by two clinical experts as part of submission for the NICE guidance produced for Tegaderm CHG IV securement dressing for central venous and arterial catheter insertion sites [MTG25] [40]. This was validated by a further group of experts during the external assessment centre's review and was therefore judged to be relevant and recent enough to use to verify the costs of CLABSI/CRBSI in this submission.

The experts were asked the following questions that were considered relevant to this submission:

- Average length of stay of patients in critical care.
- Extra length of stay where CLABSI/CRBSI occurs.
- Costs that are associated with CLABSI/CRBSI

The following input was provided by the experts:

Length of stay due to CLABSI/CRBSI: The experts considered that the average length of stay will vary between 6 days (first 2 days in ICU and rest in a general medical ward) and 10 days (first 3 days in ICU and the rest in a general medical ward)

Cost of CLABSI/CRBSI: The clinical experts judged the cost of an average day in a UK ICU to be between £1,800 to £2,400 with an additional £100 for consultant time and consumables. They also estimated that approximately 50% of intravascular catheters are removed due to suspected infection, and if they are subsequently replaced this results in an estimated additional cost of £140.

The values identified in Section 9.3.3 fall within the range reported by the external assessment centre during the Tegaderm CHG evaluation of £6,826 to £11,888.

Technology and comparator costs

9.3.5 Provide the list price for the technology.

The following information was provided by the NHS supply chain product and transaction database:

Table C5d Curos unit costs to the NHS

Description	Price per pack	Caps per pack	Price per cap	Proportion used*
Curos single cap	£85.44	270	£0.32	56%
Curos strip of 10 caps	£79.11	250	£0.32	44%

*figures calculated from sales figures provided by NHS supply chain

Three types of alcohol wipe sold in 2017 in the NHS were identified in the NHS supply chain product and transaction database to cost standard care, and they were as follows:

Table C5e Cost of alcohol wipes to the NHS

Description	Units sold	Percentage use	Cost per unit
70% alcohol sterile individual sachet 200mm x 125mm (PDI limited)	6,093,500	6%	£0.022
70% alcohol 2% chlorhexidine gluconate individual sachet 190mm x 105mm (Gama Healthcare Ltd)	41,717,800	38%	£0.019
70% alcohol 2% chlorhexidine gluconate individual sachet 25gsm 160mm x 128mm (PDI Limited)	61,844,400	56%	£0.018

Given the similarity of the costs, a weighted average was used and a cost of £0.02 was used in the economic analysis.

9.3.6 If the list price is not used in the de novo cost model, provide the alternative price and a justification.

9.3.7 Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost model. A suggested format is provided in tables C6 and C7. Table C7 should only be completed when the most relevant UK comparator for the cost analysis refers to another technology.

Table C6 Costs per treatment/patient associated with the technology in the cost model

Items	Value	Source
Price of the technology per treatment/patient	Average number of caps required per patient= 42 (any hospital ward patients) and 650 (ICU patients) Calculated as: [Number of days with catheter in place per patient x Number of disinfections or accesses needed per day per port] x Average number of ports per patient Hospitalised patients: [7 x 3] x 2 = 42 x £0.32 = £13.44 per patient ICU patients: [13 x 5] x 10 = 650 x £0.32 = £208.00 per patient	Price - NHS Supply Chain Product and Transaction Database, NHSBSA Average number of catheter days per patient (any hospital ward patients) - Dyson *et al.* 2017 [25], validated by clinical expert. Average number of catheter days per patient (ICU patients) - Tan *et al.* 2009 [43], validated by clinical expert Number of disinfections needed per day – Assumption validated by clinical expert Average number of ports per patient – Casey *et al.* 2016 [42], validated by clinical expert
Consumables (if applicable)	NA there are no further consumables	NA
Maintenance cost	NA	NA
Training cost	None	See Section 9.1.5
Other costs	Estimated 15 seconds of nurse time for each cap placement = 0.25 x (£35/60) = £0.15 Any hospital ward patients – 42 x £0.15 = £6.13 (differences due to rounding) ICU patients – 650 x £0.15 = £94.79 (differences due to rounding)	15 seconds – assumption validated by clinical expert Nurse cost per hour – PSSRU 2016 [41], p187, Band 5 taken based on clinical expert opinion
Total cost per treatment/patient	Any hospital ward patient = £19.57 ICU patients = £302.79	Calculation

Table C7 Costs per treatment/patient associated with the comparator technology in the cost model

Items	Value	Source
Cost of the comparator per treatment/patient	Average number of disinfectons/accesses required per patient= 42 (any hospital ward patients) and 650 (ICU patients) Calculated as: [Number of days with catheter in place per patient x Number of disinfections or accesses needed per day per port] x Average number of ports per patient Hospitalised patients: [7 x 3] x 2 = 42 x £0.02 = £0.84 per patient ICU patients: [13 x 5] x 10 = 650 x £0.02 = £13.00 per patient	Price - NHS Supply Chain Product and Transaction Database, NHSBSA Average number of catheter days per patient (any hospital ward patients) - Dyson *et al.* 2017 [25], validated by clinical expert. Average number of catheter days per patient (ICU patients) - Tan *et al.* 2009 [43], validated by clinical expert Number of disinfections needed per day – Assumption validated by clinical expert Average number of ports per patient – Casey *et al.* 2016 [42], validated by clinical expert
Consumables (if applicable)	NA it was assumed other treatment costs were the same and therefore not included in the model.	NA
Maintenance cost	NA	NA
Training cost	None	See Section 9.1.5
Other costs	Estimated 45 seconds of nurse time for each manual disinfection (15 seconds cleaning and 30 seconds to dry = £0.44 Any hospital ward patients – 42 x £0.44 = £18.38 (differences due to rounding) ICU patients – 650 x £0.44 = £284.38 (differences due to rounding)	45 seconds – Based on epic3 guidelines [13] and Cameron-Watson *et al.* 2016 [4], validated by clinical expert Nurse cost per hour – PSSRU 2016 [41], p187. Band 5 taken based on clinical expert opinion
Total cost per treatment/patient	Any hospital ward patient = £19.22 ICU patients = £297.38	Calculation

Health-state costs

9.3.8 If the cost model presents health states, the costs related to each health state should be presented in table C8. The health states should refer to the states in section 9.1.7. Provide a rationale for the choice of values used in the cost model.

Modelled outcomes are the rate of CLABSI/1000 catheter days and the associated resource use and costs.

Table C8 List of health states and associated costs in the economic model

Please refer to Section 9.3.3 for costs associated with CLABSI

Adverse-event costs

9.3.9 Complete table C9 with details of the costs associated with each adverse event referred to in 9.2.4 included in the cost model. Include all adverse events and complication costs, both during and after longer-term use of the technology.

Table C9 List of adverse events and summary of costs included in the cost model

No adverse events were included in the model as detailed in Section 9.2.4.

Miscellaneous costs

9.3.10 Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state.

No other costs were considered as part of the evaluation.

9.3.11 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

None were considered relevant to this evaluation.

9.4 Approach to sensitivity analysis

Section 9.4 requires the sponsor to carry out sensitivity analyses to explore uncertainty around the structural assumptions and parameters used in the analysis. All inputs used in the analysis will be estimated with a degree of imprecision. For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

9.4.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost analysis.

The impact of changing input parameters on the results of the model is explored through deterministic and probabilistic sensitivity analysis. Scenario analyses were also carried out around the baseline rate of infection and IRR.

9.4.2 Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied and what was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

Deterministic

Deterministic sensitivity analyses were undertaken around model parameters to assess the impact on the results and to identify key drivers of costs. Where the direction of results changed during the analysis, threshold values have been reported.

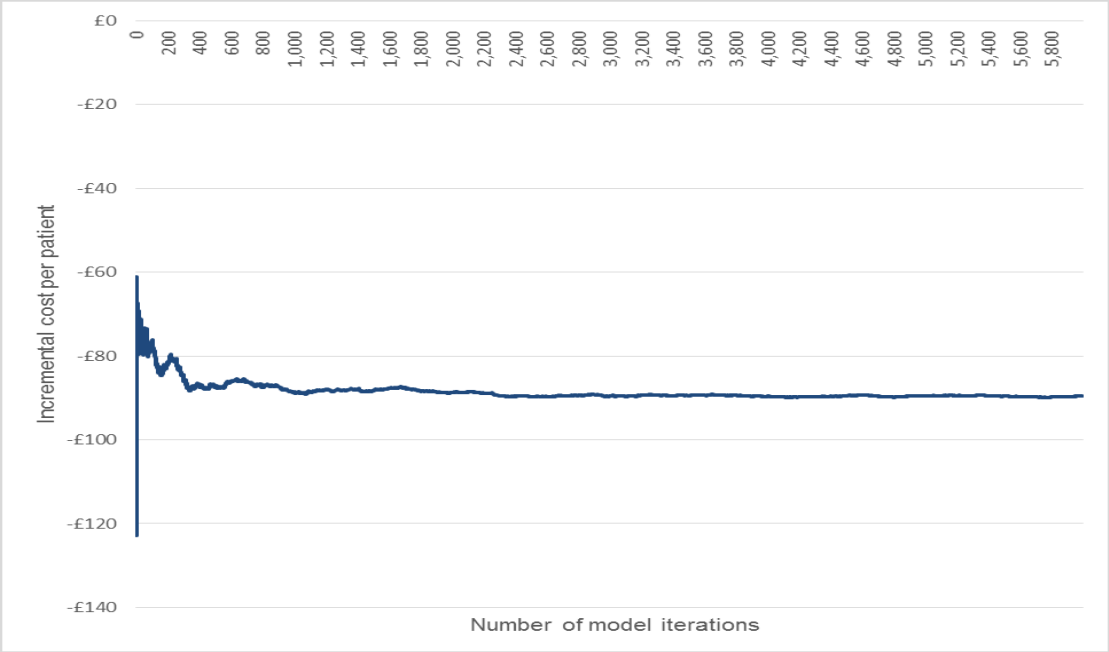
Ranges reported have, where possible, been taken from the literature. Where thes data were unavailable, clinical opinion or conservative assumptions have been used with a wide range of plausible values considered (Table C10.1).

Two-way deterministic sensitivity analyses were performed around the baseline rate of CLABSI and the IRR with Curos, and around the cost per patient of using the Curos cap and manual disinfection. A third scenario was also run to explore the impact of an alternative catheter management guideline.

An additional scenario analysis was undertaken around the time taken for manual disinfection based on a NICE guideline for primary and community care [12], whereby it was assumed that the catheter hub requires disinfection both prior to and after access. Although this guideline may not be directly applicable to the hospital setting, the scenario was run to explore the impact of increased nurse time and consumables for manual disinfection based on the possibility that this may also occur in a secondary care setting.

Probabilistic

Figure 9.2: Probabilistic results by number of model iterations



Probabilistic sensitivity analysis was performed using 2,000 iterations. This was the number of iterations that was found to produce stability in the results (see Figure 9.2). All parameters, as detailed in Table C10.3 were varied. The

ranges and distributions used are also reported in Table C10.3, with an explanation of ranges.

9.4.3 Complete table C10.1, C10.2 and/or C10.3 as appropriate to summarise the variables used in the sensitivity analysis.

Table C10.1 Variables used in one-way scenario-based deterministic

sensitivity analysis

Variable	Base-case value	Range of values	Explanation of range used
Cost of CRBSI	£10,234	£6,510 to £15,000	The ranges used were based on the alternative CRBSI cost paper by Cooper *et al.* 2014 [16], utilising the cost of treatment and diagnosis of CRBSI but with the lower value ranges for LoS expressed by the Tegaderm CHG experts. The lower value cost for ICU was also used in order to calculate a low value for cost of CRBSI. A higher value of £15,000 as it is expected that for some patients the cost of a CRBSI could be very high if it is associated with a long stay in ICU.
Baseline rate of infection per 1,000 catheter days	0.7 (any hospital ward) 1.48 (ICU)	0 to 11 (any hospital ward) 1.28 to 1.75 (ICU)	No CIs were reported by Hvas et al 2014 [27] so the range from all studies found in the CRBSI rate pragmatic review for non ICU patients was used. For ICU patients, confidence intervals reported by Bion et al 2012 [20] were used.
IRR	0.43 (any hospital ward) 0.29 (ICU)	0.22 to 0.82 (any hospital ward) 0.09 to 0.97 (ICU)	The IRR was varied between the confidence intervals for the two subgroups
Cost per hour of nurse time	£35.00	£23 to £62	Range from band 2 to 8a [41]
Nurse time for cap placement (minutes)	0.25	0.13 to 0.38	Conservative assumption
Nurse time for manual disinfection (minutes)	0.75	0.38 to 1.13	Conservative assumption
Average number of ports per patient	2 (any hospital ward) 10 (ICU)	1 to 4 (any hospital ward) 10 to 15 (ICU)	Conservative assumption based on expert opinion
Average number of disinfections/accesses per day	3 (any hospital ward) 5 (ICU)	3 to 5 (any hospital ward) 5 to 10 (ICU)	Conservative assumption based on expert opinion
Average number of catheter days per patient	7 (any hospital ward) 13 (ICU)	2 to 35 (any hospital ward) 5 to 14 (ICU)	Conservative assumption based on expert opinion

Table C10.2a Variables used in multi-way scenario-based sensitivity analysis

Variable	*Baseline rate of CRBSI per 1,000 catheter days*	*IRR*
Base case	0.7 (Any hospital ward) 1.48 (ICU)	0.43 (Any hospital ward) 0.29 (ICU)
Scenario 1 – Cost of CRBSI	Range between: 0.2 to 1.5 (Any hospital ward) 1.28 to 1.75 (ICU)	Range between: 0.22 to 0.82 (Any hospital ward) 0.09 to 0.97 (ICU)

Variable	*Cost of Curos per patient**	*Cost of standard care per patient**
Base case	£13.44 (Any hospital ward) £208.00 (ICU)	£0.84 (Any hospital ward) £13.00 (ICU)
Scenario 2 – Cost of intervention and comparator	Range between: £1.90 to £221.51 (Any hospital ward) £79.11 to £664.52 (ICU)	Range between: £0.11 to £13.01 (Any hospital ward) £4.65 to £39.04 (ICU)

*Note this excludes nurse costs

Variable	*Nurse time for manual disinfection (minutes)*	*Number wipes used for manual disinfection*
Base case	0.75	1
Scenario 3 – alternative catheter management guideline	1.5	2

The ranges used in two-way deterministic analysis for the cost of the Curos cap and the cost of manual disinfection were calculated by finding plausible ranges for the average number of ports per patient, the average number of disinfections or accesses per port per day and the average number of catheter days per patient. These inputs are assumed to be equal between the two treatment arms. The high and low estimates for each of these parameters are summarised in Table C10.2a, and were based on clinical opinion.

Table C10.2b: Estimating Curos and standard care costs

Any hospital ward	Low value	High value
Average number of ports per patient	1	4

Average number of disinfections or accesses per port per day	3	5
Average number of catheter days per patient	2	35
ICU	**Low value**	**High value**
Average number of ports per patient	10	15
Average number of disinfections or accesses per port per day	5	10
Average number of catheter days per patient	5	14

Table C10.3 Variable values used in probabilistic sensitivity analysis

Variable	Base-case value	Distribution (standard error)	Explanation of range used
Baseline rate of CRBSI per 1,000 catheter days	0.7 (Any hospital ward) 1.48 (ICU)	Gamma (0.33 [any hospital ward], 0.12 [ICU])	Confidence intervals from Bion et al 2012 [20] used to calculate standard error
IRR	0.43 (Any hospital ward) 0.29 (ICU)	Lognormal (0.34 [Any hospital ward], 0.61 [ICU])	Confidence intervals used from meta-analysis
Cost of CLABSI/CRBSI	£10,234	Gamma (£3,000)	Conservative assumption
Cost per hour of nurse time	£35.00	Gamma (£17.50)	Conservative assumption based on clinical opinion
Nurse time for cap placement (minutes)	0.25	Gamma (0.13)	Conservative assumption, validated by clinical opinion
Nurse time for manual disinfection (minutes)	0.75	Gamma (0.38)	Conservative assumption, validated by clinical opinion
Average number of ports per patient	2 (any hospital ward 10 (ICU)	Gamma (1 [any hospital ward], 5 [ICU])	Each of the parameters used to calculate the costs of Curos and standard care were varied individually in PSA to ensure costs for Curos and SC were correlated. Wide SEs were assumed.
Average number of disinfections/access per day	3 (any hospital ward) 5 (ICU)	Gamma (1.5 [any hospital ward], 2.5 [ICU])	
Average number of catheter days per patient	7 (Any hospital ward) 13 (ICU ward)	Gamma (3.5 [any hospital ward], 6.5 [ICU])	

9.4.4 If any parameters or variables listed in section 9.2.6 were omitted from the sensitivity analysis, provide the rationale.

All parameters were included in probabilistic sensitivity analysis with the exception of the cost of the Curos cap and the cost of standard care (alcohol wipe). The cost per patient of using Curos and standard care is still captured in PSA through varying the average number of ports per patient, the average number of disinfections per day and the average number of catheter days per patient. Compliance was not included in PSA ecause this is not considered in the base case.

9.5 Results of de novo cost analysis

Section 9.5 requires the sponsor to report the de novo cost analysis results. These should include the following:

- costs
- disaggregated results such as costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- a tabulation of the mean cost results
- results of the sensitivity analysis.

Base-case analysis

9.5.1 Report the total costs associated with use of the technology and the comparator(s) in the base-case analysis. A suggested format is presented in table C11.

Table C11 Base-case results (cohort size = 500)

All hospital patients	Curos	Standard care	Increment
Total costs Cost per patient Number of CLABSI cases	£20,564 £41.13 1.05	£34,681 £69.36 2.45	-£14,117 -£28.23 -1.40
Cost per case avoided			Curos dominant
ICU patient sub-group	Curos	Standard care	Increment
Total costs Cost per patient Number of CLABSI cases	£179.947 £359.89 2.79	£247,141 £494.28 9.62	-£67,194 -£134.39 -6.83
Cost per case avoided			Curos dominant

9.5.2 Report the total difference in costs between the technology and comparator(s).

Table C11

9.5.3 Provide details of the costs for the technology and its comparator by category of cost. A suggested format is presented in table C12.

Table C12 Summary of costs by category of cost per patient

Item	Cost *intervention (Curos)*	Cost *comparator (Standard care)*	Increment	Increment (%)
Disinfection method cost	*£13.44*	*£0.84*	*£12.60*	*>100%*
Nurse cost	*£6.13*	*£18.38*	*-£12.25*	*-66.7%*
Cost of CLABSI	*£21.56*	*£50.15*	*-£28.59*	*-57.0%*
Total	*£41.13*	*£69.36*	*-£28.23*	*-40.1%*

Item	Cost *intervention (Curos)*	Cost *comparator (Standard care)*	Increment	Increment (%)
Disinfection method cost	*£208.00*	*£13.00*	*£195*	*>100%*
Nurse cost	*£94.79*	*£284.38*	*-£189.58*	*-66.7%*
Cost of CLABSI	*£57.10*	*£196.91*	*-£139.80*	*-71.0%*
Total	*£359.89*	*£494.28*	*-£134.39*	*-27.2%*

9.5.4 If appropriate, provide details of the costs for the technology and its comparator by health state. A suggested format is presented in table C13.

Table C13 Summary of costs by health state per patient

Not applicable

9.5.5 If appropriate, provide details of the costs for the technology and its comparator by adverse event. A suggested format is provided in table C14.

Table C14 Summary of costs by adverse events per patient

Not applicable

Sensitivity analysis results

9.5.6 Present results of deterministic one-way sensitivity analysis of the variables described in table C10.1.

The results of the deterministic sensitivity analysis are presented in Figure 9.3-9.8. Threshold values for main cost drivers are shown in table C13.

Figure 9.3: Tornado diagram showing univariate sensitivity analysis on base case (any hospital ward)

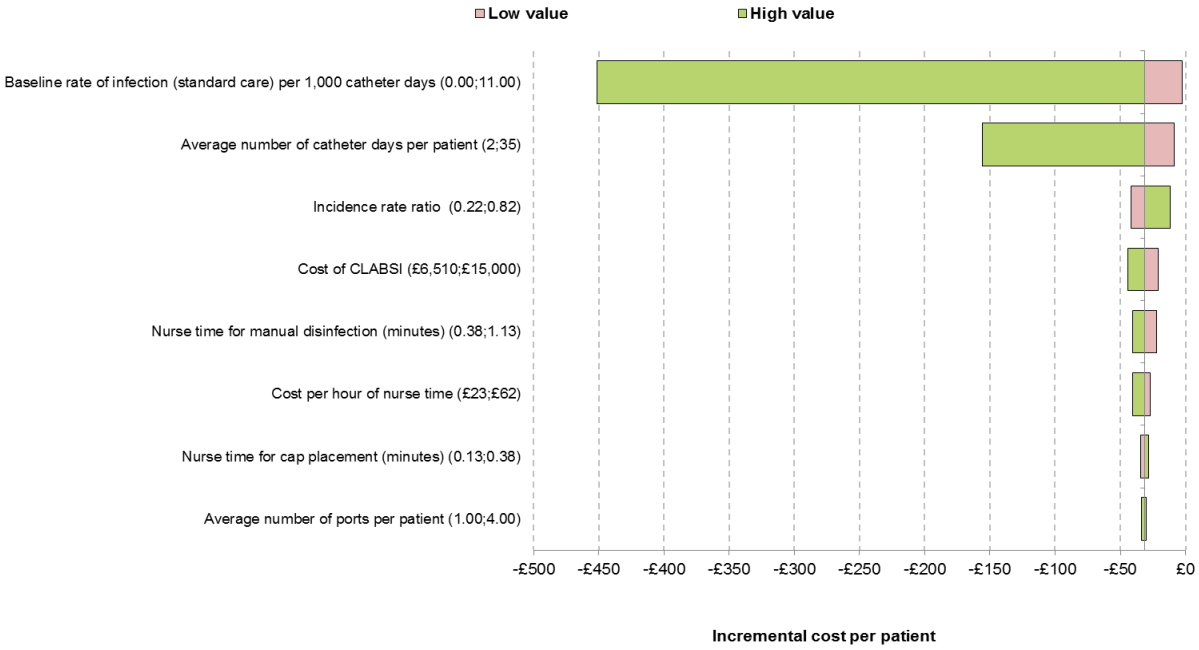


Figure 9.4: Tornado diagram showing univariate sensitivity analysis on base case (ICU ward)

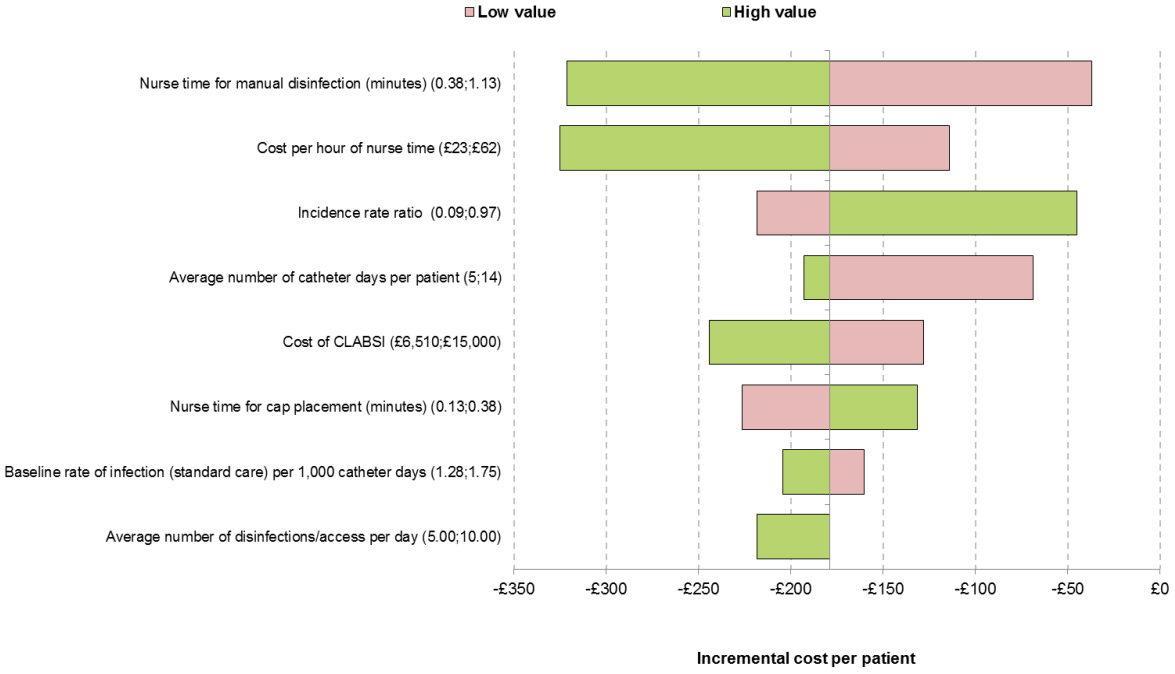


Table 15a Threshold values of main cost drivers

Parameter	Threshold value (any hospital ward)	Threshold value (ICU)
Average number of catheter days per patient	0 (i.e. input does not change the direction of results)	0 (i.e. input does not change the direction of results)
IRR	0.99	0.98
Baseline rate of infection per 1,000 catheter days	0.01	0.04
Cost of CRBSI	£93	£294
Nurse time for manual disinfection (minutes)	Input does not change the direction of results.	0.39 i.e.23 seconds
Cost per hour of nurse time	Input does not change the direction of results.	£9.93
Unit cost of Curos cap	£0.99	£0.53

Curos remains cost saving compared with standard care in all of the cases tested. The main drivers of the cost savings associated with a switch from standard care to Curos in the general hospital population are

- The baseline rate of CLABSI. The higher the baseline rate, the greater the savings
- The number of catheter days. The higher the number of days at risk, the greater the savings

In the ICU sub-population

- The cost of nurse time for manual disinfection. The higher the cost of nurse time, the greater the savings
- The IRR associated with Curos. The lower the value of the IRR, the greater the savings
- The number of catheter days at risk is also a cost driver in the ICU setting

9.5.7 Present results of deterministic multi-way scenario sensitivity analysis described in table C10.2.

Results are shown for a two-way SA varying the baseline rate of infection and the IRR: Figure 9.6 (general hospital population); Figure 9.7 (ICU population).

- Curos remains cost saving in all of the scenarios tested. Cost savings increase with the baseline rate of infection, and reduce with higher values of the IRR

Figure 9.5: Baseline rate of infection and IRR (any hospital ward)

		Incidence rate ratio (basecase: 0.4)										
	-£28.32	0.22	0.28	0.34	0.40	0.46	0.52	0.58	0.64	0.70	0.76	0.82
Baseline rate of CLABSI per 1,000 catheter days (standard care) (basecase: 0.7)	0.20	-£10.92	-£10.06	-£9.20	-£8.34	-£7.48	-£6.62	-£5.76	-£4.90	-£4.04	-£3.18	-£2.32
	0.33	-£18.18	-£16.76	-£15.34	-£13.92	-£12.51	-£11.09	-£9.67	-£8.25	-£6.83	-£5.41	-£4.00
	0.46	-£25.44	-£23.47	-£21.49	-£19.51	-£17.54	-£15.56	-£13.58	-£11.60	-£9.63	-£7.65	-£5.67
	0.59	-£32.71	-£30.17	-£27.64	-£25.10	-£22.56	-£20.03	-£17.49	-£14.96	-£12.42	-£9.88	-£7.35
	0.72	-£39.97	-£36.88	-£33.78	-£30.69	-£27.59	-£24.50	-£21.40	-£18.31	-£15.21	-£12.12	-£9.02
	0.85	-£47.24	-£43.58	-£39.93	-£36.28	-£32.62	-£28.97	-£25.32	-£21.66	-£18.01	-£14.35	-£10.70
	0.98	-£54.50	-£50.29	-£46.08	-£41.86	-£37.65	-£33.44	-£29.23	-£25.01	-£20.80	-£16.59	-£12.38
	1.11	-£61.77	-£56.99	-£52.22	-£47.45	-£42.68	-£37.91	-£33.14	-£28.37	-£23.60	-£18.83	-£14.05
	1.24	-£69.03	-£63.70	-£58.37	-£53.04	-£47.71	-£42.38	-£37.05	-£31.72	-£26.39	-£21.06	-£15.73
	1.37	-£76.29	-£70.41	-£64.52	-£58.63	-£52.74	-£46.85	-£40.96	-£35.07	-£29.18	-£23.30	-£17.41
	1.50	-£83.56	-£77.11	-£70.66	-£64.22	-£57.77	-£51.32	-£44.87	-£38.43	-£31.98	-£25.53	-£19.08

Figure 9.6: Baseline rate of infection and IRR (ICU)

		Incidence rate ratio (basecase: 0.3)										
	-£135.78	0.09	0.18	0.27	0.35	0.44	0.53	0.62	0.71	0.79	0.88	0.97
Baseline rate of CLABSI per 1,000 catheter days (standard care) (basecase: 1.48)	1.28	-£150.95	-£135.97	-£120.98	-£105.99	-£91.01	-£76.02	-£61.03	-£46.05	-£31.06	-£16.08	-£1.09
	1.33	-£156.64	-£141.11	-£125.57	-£110.03	-£94.50	-£78.96	-£63.42	-£47.89	-£32.35	-£16.81	-£1.28
	1.37	-£162.33	-£146.25	-£130.16	-£114.07	-£97.99	-£81.90	-£65.81	-£49.73	-£33.64	-£17.55	-£1.46
	1.42	-£168.02	-£151.39	-£134.75	-£118.11	-£101.47	-£84.84	-£68.20	-£51.56	-£34.93	-£18.29	-£1.65
	1.47	-£173.71	-£156.53	-£139.34	-£122.15	-£104.96	-£87.78	-£70.59	-£53.40	-£36.21	-£19.03	-£1.84
	1.52	-£179.40	-£161.67	-£143.93	-£126.19	-£108.45	-£90.72	-£72.98	-£55.24	-£37.50	-£19.77	-£2.03
	1.56	-£185.09	-£166.81	-£148.52	-£130.23	-£111.94	-£93.65	-£75.37	-£57.08	-£38.79	-£20.50	-£2.22
	1.61	-£190.78	-£171.95	-£153.11	-£134.27	-£115.43	-£96.59	-£77.76	-£58.92	-£40.08	-£21.24	-£2.40
	1.66	-£196.47	-£177.09	-£157.70	-£138.31	-£118.92	-£99.53	-£80.14	-£60.76	-£41.37	-£21.98	-£2.59
	1.70	-£202.17	-£182.23	-£162.29	-£142.35	-£122.41	-£102.47	-£82.53	-£62.59	-£42.66	-£22.72	-£2.78
	1.75	-£207.86	-£187.37	-£166.88	-£146.39	-£125.90	-£105.41	-£84.92	-£64.43	-£43.94	-£23.45	-£2.97

Results are shown for a two-way SA varying the costs of standard care and Curos: Figure 9.8 (general hospital population); Figure 9.9 (ICU population).

- Curos ceases to be cost saving at a cost per patient above approximately £24 compared with a baseline cost of £13.44 (general population); and above approximately £310 compared with £208 (ICU population)
- Cost savings with Curos increase as the cost of standard care increases

Figure 9.7: Cost of standard care and Curos per patient (any hospital ward)

		Cost of standard care per patient (£0.84)										
	-£28.32	£0.11	£1.40	£2.69	£3.98	£5.27	£6.56	£7.85	£9.14	£10.43	£11.72	£13.01
Cost of Curos per patient (basecase: £13.44)	£1.90	-£39.04	-£40.33	-£41.62	-£42.91	-£44.20	-£45.49	-£46.78	-£48.07	-£49.36	-£50.65	-£51.94
	£23.86	-£17.08	-£18.37	-£19.66	-£20.95	-£22.24	-£23.53	-£24.82	-£26.11	-£27.40	-£28.69	-£29.98
	£45.82	£4.88	£3.59	£2.30	£1.01	-£0.28	-£1.57	-£2.86	-£4.15	-£5.44	-£6.73	-£8.02
	£67.78	£26.84	£25.55	£24.26	£22.97	£21.68	£20.39	£19.10	£17.81	£16.52	£15.23	£13.94
	£89.74	£48.80	£47.51	£46.22	£44.93	£43.64	£42.35	£41.06	£39.77	£38.48	£37.19	£35.90
	£111.71	£70.76	£69.47	£68.18	£66.89	£65.60	£64.31	£63.02	£61.73	£60.44	£59.15	£57.86
	£133.67	£92.72	£91.43	£90.14	£88.85	£87.56	£86.27	£84.98	£83.69	£82.40	£81.11	£79.82
	£155.63	£114.68	£113.39	£112.10	£110.81	£109.52	£108.23	£106.94	£105.65	£104.36	£103.07	£101.78
	£177.59	£136.64	£135.35	£134.06	£132.77	£131.48	£130.19	£128.90	£127.61	£126.32	£125.03	£123.74
	£199.55	£158.60	£157.31	£156.02	£154.73	£153.44	£152.15	£150.86	£149.57	£148.28	£146.99	£145.70
	£221.51	£180.57	£179.28	£177.99	£176.70	£175.41	£174.12	£172.83	£171.54	£170.25	£168.96	£167.67

Figure 9.8: Cost of standard care and Curos per patient (ICU)

		Cost of standard care per patient (£13.00)										
	-£135.78	£4.65	£8.09	£11.53	£14.97	£18.41	£21.85	£25.28	£28.72	£32.16	£35.60	£39.04
Cost of Curos per patient (basecase: £208.00)	£79.11	-£254.93	-£258.37	-£261.81	-£265.24	-£268.68	-£272.12	-£275.56	-£279.00	-£282.44	-£285.88	-£289.32
	£137.65	-£196.39	-£199.83	-£203.26	-£206.70	-£210.14	-£213.58	-£217.02	-£220.46	-£223.90	-£227.34	-£230.78
	£196.19	-£137.85	-£141.28	-£144.72	-£148.16	-£151.60	-£155.04	-£158.48	-£161.92	-£165.36	-£168.80	-£172.24
	£254.73	-£79.30	-£82.74	-£86.18	-£89.62	-£93.06	-£96.50	-£99.94	-£103.38	-£106.82	-£110.26	-£113.69
	£313.27	-£20.76	-£24.20	-£27.64	-£31.08	-£34.52	-£37.96	-£41.40	-£44.84	-£48.28	-£51.71	-£55.15
	£371.82	£37.78	£34.34	£30.90	£27.46	£24.02	£20.58	£17.14	£13.70	£10.27	£6.83	£3.39
	£430.36	£96.32	£92.88	£89.44	£86.00	£82.56	£79.12	£75.68	£72.25	£68.81	£65.37	£61.93
	£488.90	£154.86	£151.42	£147.98	£144.54	£141.10	£137.66	£134.23	£130.79	£127.35	£123.91	£120.47
	£547.44	£213.40	£209.96	£206.52	£203.08	£199.64	£196.21	£192.77	£189.33	£185.89	£182.45	£179.01
	£605.98	£271.94	£268.50	£265.06	£261.62	£258.19	£254.75	£251.31	£247.87	£244.43	£240.99	£237.55
	£664.52	£330.48	£327.04	£323.60	£320.17	£316.73	£313.29	£309.85	£306.41	£302.97	£299.53	£296.09

The effect of an alternatve catheter management procedure in which the catheter is disinfected both before and after access only affects the cost of standard care. Increasing this cost substantially increases the expected savings with Curos (Table C15b)

Table C15b: Alternative catheter management guideline

	Curos	Standard care	Incremental
Base case cost per patient	Any hospital ward: £40.98 ICU: £357.58	Any hospital ward: £69.30 ICU: £493.37	Any hospital ward: -£28.32 ICU: -£135.78
Alternative guideline scenario: Any hospital ward	£40.98	£88.46	-£47.48
Alternative guideline scenario: ICU	£357.58	£789.82	-£432.24

The impact of varying compliance with standard care and Curos was also tested and found to have minimal impact on the results.

9.5.8 Present results of the probabilistic sensitivity analysis described in table C10.3.

Probabilistic sensitivity analysis was conducted based on 2,000 iterations. Curos was cost saving in any hospital ward setting in 96.4% of iterations and the average probabilistic cost saving was £28.95 per patient. In an ICU setting Curos was cost saving in 86.3% of iterations and the average probabilistic cost saving was £170.48 per patient. Figure 9.9: Probabilistic results (any hospital ward) and Figure 9.10 show the distribution of these results. The results in the ICU setting have greater uncertainty due to the wider confidence interval around the IRR calculated from the meta-analysis.

Figure 9.9: Probabilistic results (any hospital ward)

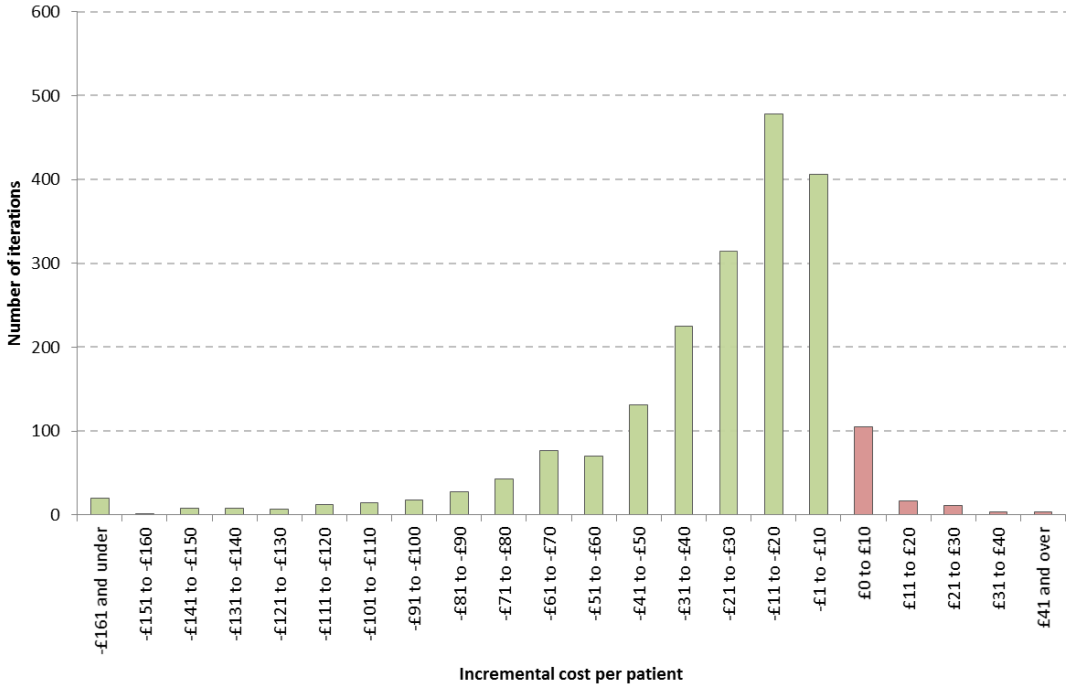
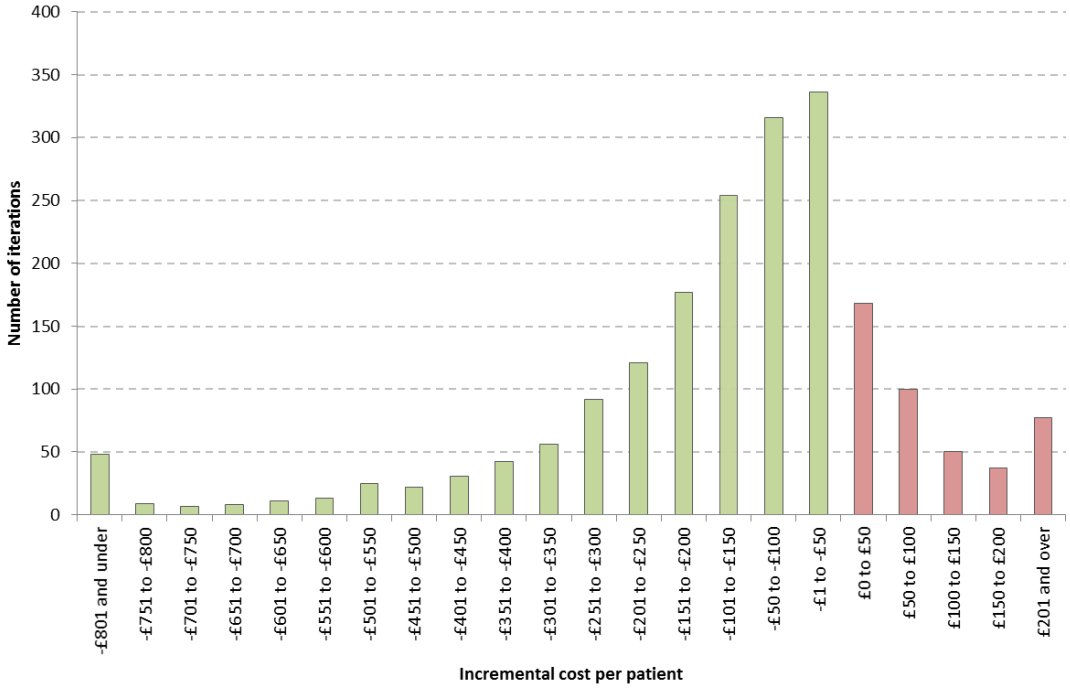


Figure 9.10: Probabilistic results (ICU)



9.5.9 What were the main findings of each of the sensitivity analyses?

- Curos remains cost saving compared with standard care in all of the one-way SA variations tested
- In a two-way SA varying the baseline rate of infection and the IRR, Curos remains cost saving in all of the scenarios tested. Cost savings increase with the basline rate of infection, and reduce with higher values of the IRR
- In a two-way SA varying the costs of standard care and Curos, Curos ceases to be cost saving at a cost per patient above approximately £24 compared with a baseline cost of £13.44 (general population); and above approximately £310 compared with £208 (ICU population)
- Curos was cost saving in any hospital ward setting in 96.4% of PSA iterations and the average probabilistic cost saving was £28.95 per patient. In an ICU setting Curos was cost saving in 86.3% of iterations and the average probabilistic cost saving was £170.48 per patient.
-

9.5.10 What are the key drivers of the cost results?

The main drivers of the cost savings associated with a switch from standard care to Curos in the general hospital population are

- The baseline rate of CLABSI. The higher the baseline rate, the greater the savings
- The number of catheter days. The higher the number of days at risk, the greater the savings

In the ICU sub-population

- The cost of nurse time for manual disinfection. The higher the cost of nurse time, the greater the savings
- The IRR associated with Curos. The lower the value of the IRR, the greater the savings
- The number of catheter days at risk is also a cost driver in the ICU setting

9.5.11 Describe any additional results that have not been specifically requested in this template. If none, please state.

There are no additional results.

9.6 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. Sponsors are required to complete section 9.6 in accordance with the subgroups identified in the scope and for any additional subgroups considered relevant.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, if the costs of facilities available for providing the technology vary according to location).

9.6.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in table A1 and sections 3.2 and 7.4.4.

Critically ill patients are considered as a subgroup but are included in the previous sections. This distibction was made on the basis that the risk of infection is likely to be higher in the ICU setting.

9.6.2 Define the characteristics of patients in the subgroup(s).

NA

9.6.3 Describe how the subgroups were included in the cost analysis.

NA

9.6.4 What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to that in section 9.5.1 (base-case analysis).

NA

9.6.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

NA

9.7 Validation

9.7.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

The economic model was built in Microsoft Excel by one health economist and checked for errors by a second health economist. Most of the input parameters were validated by an independent UK clinician.

No evidence of previous evaluations of Curos was identified in the systematic review. The accuracy of the Excel model was validated against a published NICE guidance for Tegaderm CHG [40]. Tegaderm CHG data were inputted into the Curos model to ensure the results matched.

9.8 Interpretation of economic evidence

9.8.1 Are the results from this cost analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

No evidence was identified in the systematic review with which to compare the results of this economic analysis.

9.8.2 Is the cost analysis relevant to all groups of patients and NHS settings in England that could potentially use the technology as identified in the scope?

The cost analysis is relevant to all groups included in the scope. However, studies showed heterogeneity in baseline infection rates between different settings and patient groups. For example, in a general hospital setting baseline rates of infection per 1,000 catheter days varied between 0 [21] and 11 [23]. Where infection rates are very low, there is less scope for benefit from the Curos device.

9.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

This is the first economic analysis of Curos, and inputs such as the IRR were identified through a systematic review and meta-analysis process. However, any modelling process involves simplification and assumptions that may not reflect real world clinical practice. Where possible, data were based on published literature and identified via a systematic review process, however this was not possible for all inputs. Further, there was wide variation reported in the literature for some inputs, but the impact of this was tested in sensitivity analysis. There may be a reduction in mortality from reducing CLABSIs which is not captured in the current analysis.

9.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

The results of the cost analysis are likely to provide a good reflection of the impact of Curos in routine NHS clinical practice. With the exception of the relative infection risk with Curos vs. standard of care, which was estimated from a meta-analysis of data from non-UK studies, other variables in the analysis are specific to the UK. However, estimates of baseline risk in particular, are subject to a high degree of uncertainty because of differences between studies in setting, patient characteristics and local clinical practice. For this reason, the magnitiude of potential cost savings will vary between

organisations, although the overall conclusion of cost savings with Curos is very robust.

One of the assumptions underlying the analysis is the assumption that compliance with standard care and Curos is complete. Compliance with standard care is difficult to measure but evidence from the UK suggests it is very likely to be quite low. Compliance with Curos reported in observational studies is significantly higher but this is not necessarily reflective of practice outside of a clinical trial. The effect of non-compliance on the cost analysis is difficult to assess, but a future study would ideally measure compliance and outcomes with standard care and Curos in parallel study cohorts to give a motre accurate estimate of relative costs of the two approaches.

Swabcap is a device available in the NHS with a similar objective to Curos. A simple unit cost comparison shows that the cost of the two is likely to be similar. The NHS Supply Chain catalogue gives a unit price of Curos of £0.32 and £0.30 for Swabcap. However, because of a lack of direct head-to-head evidence it is not possible to compare the two devices in terms impact on the overall costs of CLABSI.

References

Please use a recognised referencing style, such as Harvard or Vancouver.

1. Sweet MA, Cumpston A, Briggs F, Craig M, Hamadani M. Impact of alcohol-impregnated port protectors and needleless neutral pressure connectors on central line-associated bloodstream infections and contamination of blood cultures in an inpatient oncology unit. Am J Infect Control. 2012;40(10):931-4.
2. Ramirez C, Lee AM, Welch K. Central venous catheter protective connector caps reduce intraluminal catheter-related infection. JAVA - Journal of the Association for Vascular Access. 2012;17(4):210-13.
3. Merrill KC, Sumner S, Linford L, Taylor C, Macintosh C. Impact of universal disinfectant cap implementation on central line-associated bloodstream infections. Am J Infect Control. 2014;42(12):1274-7.
4. Cameron-Watson C. Port protectors in clinical practice: an audit. Br J Nurs. 2016;25(8):S25-31.
5. Martino A, Thompson L, Mitchell C, Trichel R, Chappell W, Miller J*, et al.* Efforts of a Unit Practice Council to implement practice change utilizing alcohol impregnated port protectors in a burn ICU. Burns. 2017;43(5):956-64.
6. Pong A, Salgado C, Speziale M, Grimm P, Abe C. Reduction of central line-associated bloodstream infection (CLABSI) in a neonatal intensive care unit with use of access site disinfection caps. In: ISDA Annual Meeting, Boston, MA; 21 October. 2011. P672
7. Danielson B, Willamson S, Kaur G, Brooks C, Scholl P, Baker A. Decreasing the incidence of central line-associated blood stream infections using alcohol-impregnated port protectors in a neonatal intensive care unit. Am J Infect Control. 2013;41(Suppl 6):S97-S98.
8. Sumner S, Merrill KC, Linford L, Taylor C. Decreasing CLABSI rates and cost following implementation of a disinfectant cap in a tertiary care hospital. Am J Infect Control. 2013;41(Suppl 6):S37.
9. Shiber J, Jolicoeur G, Crouchet T. Reducing central line-associated bloodstream infections through the addition of disinfecting port protector caps to the central line bundle. In: Ochsner Research Day, New Orleans, LA; 20 May. 2014. 8
10. Ventura R. Passive disinfection port protector: effect on the reduction of catheter related bloodstream infections. In: GavaceIt Conference 2015, Milan, Italy; 2015. 7
11. Rawlinson L. National IV Report Cleaning Survey Results. Swindon: Vygon UK; 2014. Available from: http://www.aim-at-zero.co.uk/wp-content/uploads/2016/04/PS304-EMAIL-National-Port-Cleaning-Survey-pages.pdf.
12. National Institute for Health and Care Excellence. Healthcare-associated infections: prevention and control in primary and community care (CG139). London: National Institute for Health and

Care Excellence; 2012. Available from: https://www.nice.org.uk/guidance/cg139.
13. Loveday HP, Wilson JA, Pratt RJ, Golsorkhia M, Tingle A, Baka J*, et al.* epic3: National Evidence-Based Guidelines for Preventing Healthcare-Associated Infections in NHS Hospitals in England. J Hosp Infect. 2014;86(Suppl. 1):S1-S70.
14. Voor In 't Holt AF, Helder OK, Vos MC, Schafthuizen L, Sulz S, van den Hoogen A*, et al.* Antiseptic barrier cap effective in reducing central line-associated bloodstream infections: A systematic review and meta-analysis. Int J Nurs Stud. 2017;69:34-40.
15. Martino AL, Mitchell C, Fields JL, Martinez DM, Hatem AM, Bang S*, et al.* Successful outcomes associated with implementing the use of alcohol impregnated port protectors in a burn unit. J Burn Care Res. 2014;35:S86.
16. Cooper K, Frampton G, Harris P, Jones J, Cooper T, Graves N*, et al.* Are educational interventions to prevent catheter-related bloodstream infections in intensive care unit cost-effective? J Hosp Infect. 2014;86(1):47-52.
17. National Institute for Health and Care Excellence (NICE). Medical technologies evaluation programme process guide. 2017.[cited 1st December 2017]. Available from: https://www.nice.org.uk/process/pmg34/chapter/introduction.
18. Health Protection Scotland. Surveillance of Healthcare Associated Infections in Scottish Intensive Care Units. Annual report of data from January - December 2013. 2014. Last updated August 2014 [cited 6th Jan 2015]. Available from: http://www.documents.hps.scot.nhs.uk/hai/sshaip/publications/icu-surveillance/icu-annual-report-2014.pdf.
19. Welsh Healthcare Associated Infection Programme. Central Venous Catheter (CVC) Infection and Ventilator Associated Pneumonia (VAP) in Critical Care - Annual Report. 2014. Last updated 25 July 2014 [cited 8th Jan 2015]. Available from: http://www2.nphs.wales.nhs.uk:8080/WHAIPDocs.nsf/($All)/28459C38515ACCAC80257D79005253C4/$File/Aneurin%20Bevan%20Critical%20Care%20CVC%20%26%20VAP%20Report%202013.pdf?OpenElement.
20. Bion J, Richardson A, Hibbert P, Beer J, Abrusci T, McCutcheon M*, et al.* 'Matching Michigan': a 2-year stepped interventional programme to minimise central venous catheter-blood stream infections in intensive care units in England. BMJ Qual Saf. 2013;22(2):110-23.
21. Ahmed SS, McCaskey MS, Bringman S, Eigen H. Catheter-associated bloodstream infection in the pediatric intensive care unit: a multidisciplinary approach (Provisional abstract). Pediatr Crit Care Med. 2012;13(2):e69-e72.
22. Aitken E, Iqbal K, Thomson P, Kasthuri R, Kingsmore D. Are early cannulation arteriovenous grafts (ecAVG) a viable alternative to tunnelled central venous catheters (TCVCs)? An observational "virtual study" and budget impact analysis. J. 2016;17(3):220-8.

23. Austin PD, Hand KS, Elia M. Impact of definition and procedures used for absent blood culture data on the rate of intravascular catheter infection during parenteral nutrition. J Hosp Infect. 2016;93(2):197-205.
24. Dixon JJ, Steele M, Makanjuola AD. Anti-microbial locks increase the prevalence of Staphylococcus aureus and antibiotic-resistant Enterobacter: observational retrospective cohort study. Nephrol Dial Transplant. 2012;27(9):3575-81.
25. Dyson JK, Thompson N, Northern Nutrition N. Adult parenteral nutrition in the North of England: a region-wide audit. BMJ Open. 2017;7(1):e012663.
26. Alexakis C, Malcolm L, Banks C. Central venous catheter associated sepsis in patients receiving parenteral nutrition: experience at a district general hospital. Clin Nutr ESPEN. 2015;10(5):e181-e82.
27. Hvas CL, Farrer K, Donaldson E, Blackett B, Lloyd H, Forde C*, et al.* Quality and safety impact on the provision of parenteral nutrition through introduction of a nutrition support team. Eur J Clin Nutr. 2014;68(12):1294-9.
28. Jackson A, Cooper S. Zero central-line infections in a 550-bedded district general hospital. Br J Nurs. 2012;21(14 SUPPL.):S24-S28.
29. Kanaa M, Wright MJ, Akbani H, Laboi P, Bhandari S, Sandoe JAT. Cathasept Line Lock and Microbial Colonization of Tunneled Hemodialysis Catheters: A Multicenter Randomized Controlled Trial. Am J Kidney Dis. 2015;66(6):1015-23.
30. Sammut D, Elliot CA, Kiely DG, Armstrong IJ, Martin L, Wilkinson J*, et al.* Central venous catheter-related blood stream infections in patients receiving intravenous iloprost for pulmonary hypertension. Eur J Clin Microbiol Infect Dis. 2013;32(7):883-9.
31. Youssouf S, Nache A, Wijesekara C, Middleton RJ, Lewis D, Shurrab AE*, et al.* Effect of a Quality Improvement Program to Improve Guideline Adherence and Attainment of Clinical Standards in Dialysis Care: Report of Outcomes in Year 1. Nephron. 2017;136(2):75-84.
32. Francis S, Cooper M, Jacob A, Jones H, MacWhannell A, Basu S. The impact of implementing matching michigan and EPIC3 recommendations to real life haemato-oncology patients: Results from a prospective uk based study. Haematologica. 2014;99:191.
33. Appleton ND, Corris A, Edwards C, Kenyon A, Walsh CJ. A dedicated peripherally inserted central catheter (PICC) line service: 2 year review. Int J Surg. 2013;11 (8):649.
34. Kilner M, Collins J, Price A, Richardson A, Samuel J, Straughan C*, et al.* Reducing central venous catheter infection rates amongst hematology patients: Real-life implementation of a 'Matching Michigan' approach in this patient population. Blood. Conference: 55th Annual Meeting of the American Society of Hematology, ASH. 2013;122(21)
35. Driver R, Mistry P, Swain D, Colinese E, Saich R. Timing of parenteral nutrition administration set changes: Impact on incidence of catheter associated infections. Gut. 2012;61:A100-A01.

36. Jenks M, Craig J, Green W, Hewitt N, Arber M, Sims A. Tegaderm CHG IV Securement Dressing for Central Venous and Arterial Catheter Insertion Sites: A NICE Medical Technology Guidance. Appl Health Econ Health Policy. 2016;14(2):135-49.
37. Thokala P, Arrowsmith M, Poku E, Martyn-St James M, Anderson J, Foster S*, et al.* Economic impact of Tegaderm chlorhexidine gluconate (CHG) dressing in critically ill patients. Journal of Infection Prevention. 2016;17(5):216-23.
38. Ahmadnia E, Hadley JS, Millar M, Hall D, Hewitt H. The effect of introduction of daily chlorhexidine bathing on healthcare-associated infections and acquisition of multi-drug resistant organisms. Intensive Care Medicine Experimental. Conference: 29th Annual Congress of the European Society of Intensive Care Medicine, ESICM. 2016;4(no pagination)
39. Fuerstenberg F, Spencer C, Reay M, Mohankumar L, Raybould S. Audit and antimicrobiogram of isolates of central venous catheter blood stream infections in a nine bed critical care unit. Intensive Care Med. 2012;38:S273-S74.
40. National Institute for Health and Care Excellence. The 3M Tegaderm CHG IV securement dressing for central venous and arterial catheter insertion sites (MTG25). (MTG25). London: National Institute for Health and Care Excellence; 2015. Available from: https://www.nice.org.uk/guidance/mtg25.
41. Personal Social Services Research Unit (PSSRU). Unit Costs of Health & Social Care 2016. Canterbury: PSSRU; 2016. Available from: http://www.pssru.ac.uk/project-pages/unit-costs/2016/.
42. Casey AL, Karpanen TJ, Nightingale P, Chaganti S, Elliott TSJ. Microbiologic contamination of a positive- and a neutral- displacement needleless intravenous access device in clinical use. Am J Infect Control. 2016;44(12):1678-80.
43. Tan R, Knowles D, Streater C, Johnston A. The use of peripherally inserted central catheters in intensive care: should you pick the PICC? JICS. 2009;10(2)
44. Hockenhull JC, Dwan K, Boland A, Smith G, Bagust A, Dundar Y*, et al.* The clinical effectiveness and cost-effectiveness of central venous catheters treated with anti-infective agents in preventing bloodstream infections: a systematic review and economic evaluation. Health Technol Assess. 2008;12(12):iii-iv, xi-xii, 1-154.
45. National Institute for Health and Care Excellence. Rehabilitation after critical illness in adults (CG83). London: National Institute for Health and Care Excellence; 2009. Available from: https://www.nice.org.uk/guidance/cg83.
46. Information Services Division Scotland. Scottish Tariffs for Cross Boundary Flow Costing. In; 2013/14.
47. Department of Health. NHS Reference Costs 2015-16 [webpage]. London: 2016. Last updated 15 December 2016.[cited 30th June 2017]. Available from: https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016.

48. Granstedt EM, Petrov P, Knapp K, Cordero M, Patel V. Fast imaging diagnostics on the C-2U advanced beam-driven field-reversed configuration device. Rev Sci Instrum. 2016;87(11):11D416.
49. Heidari Zare H, Juhart V, Vass A, Franz G, Jocham D. Efficacy of silver/hydrophilic poly(p-xylylene) on preventing bacterial growth and biofilm formation in urinary catheters. Biointerphases. 2017;12(1):011001.

Appendices

9.9 Appendix 1: Search strategy for clinical evidence (section 7.1.1)

The following information should be provided:

9.9.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Database / information source	**Interface / URL**
MEDLINE, MEDLINE In-Process and MEDLINE(R) Daily Epub Ahead of Print	Ovid SP
PubMed	http://www.ncbi.nlm.nih.gov/pubmed
Embase	Ovid SP
Science Citation Index	Web of Science
Conference Proceedings Citation Index (Science)	Web of Science
CINAHL	EBSCO
Cochrane Database of Systematic Reviews (CDSR)	Cochrane Library
Cochrane Central Register of Controlled Trials (CENTRAL)	Cochrane Library
Database of Abstracts of Reviews of Effects (DARE)	Cochrane Library
Health Technology Assessment Database (HTA Database)	Cochrane Library
NHS Economic Evaluation Database (NHS EED)	Cochrane Library
ClinicalTrials.gov	https://clinicaltrials.gov./
WHO International Clinical Trials Registry Portal (ICTRP)	http://apps.who.int/trialsearch/
US Food and Drug Administration (FDA) Manufacturer and User Facility Device Experience (MAUDE) database	https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm
Medicines and Healthcare products Regulatory Agency (MHRA) webpages	https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency

9.9.2 The date on which the search was conducted.

The searches were conducted between 19 and 22 September 2017.

9.9.3 The date span of the search.

The searches were not limited by date. The date coverage of each database searched is shown below in Section 10.1.4.

9.9.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

A.1: Source: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Interface / URL: Ovid SP
Database coverage dates: 1946 to current. Updated daily.
Search date: 19/09/17
Retrieved records: 476
Search strategy:

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
---

1 Catheterization/ (50771)
2 Catheterization, Central Venous/ (14219)
3 exp Catheterization, Peripheral/ (10542)
4 Cardiac Catheterization/ (46864)
5 exp Catheters/ (25839)
6 Catheter-Related Infections/ (3731)
7 (catheter$ or microcatheter$ or cannula$ or microcannula$ or canula$ or microcanula$).ti,ab,kf. (230643)
8 (CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs).ti,ab,kf. (13811)
9 ((PIC or CVP) adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kf. (120)
10 (central adj3 (venous or pressure)).ti,ab,kf. (26654)
11 ((central or subclavian or jugular or femoral) adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kf. (16745)
12 (peripheral adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kf. (6784)

13 ((venous or intravenous or vein$1 or vascular or intravascular or IV) adj3 (line$1 or access$ or site or sites or device$ or reservoir$)).ti,ab,kf. (28701)
14 ((arterial or intraarterial or artery or arteries) adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kf. (8363)
15 (art line$1 or a line$1 or IAC or IACs).ti,ab,kf. (11320)
16 (CA-BSI or CA-BSIs or CABSI or CABSIs or CR-BSI or CR-BSIs or CRBSI or CRBSIs or CLA-BSI or CLA-BSIs or CLABSI or CLABSIs).ti,ab,kf. (1334)
17 (access$ adj3 (device$ or site or sites or route$1)).ti,ab,kf. (11997)
18 ((invasive or percutaneous) adj3 device$).ti,ab,kf. (3137)
19 (CVA or CVAD or CVADs or VAD or VADs).ti,ab,kf. (10084)
20 (IVD or IVDs).ti,ab,kf. (2176)
21 (port a cath$1 or portacath$1 or hickman$1 or broviac$1 or cook$1 or seldinger$1 or punktion$1 or groshong$1 or quinton$1).ti,ab,kf. (8686)
22 or/1-21 (384446)
23 exp Anti-Infective Agents/ (1520380)
24 Disinfection/ (13081)
25 (antiinfect$ or anti-infect$ or antisep$ or anti-sep$ or antimicrob$ or anti-microb$ or antibacter$ or anti-bacter$).ti,ab,kf. (196555)
26 (disinfect$ or decontaminat$ or clean$ or barrier).ti,ab,kf. (251828)
27 exp Alcohols/ (634010)
28 Chlorhexidine/ (7599)
29 alcohol$.ti,ab,kf. (302651)
30 ethanol$.ti,ab,kf. (123114)
31 isopropyl$.ti,ab,kf. (20518)
32 chlorhexidine$.ti,ab,kf. (9315)
33 or/23-32 (2588482)
34 (cap or caps).ti,ab,kf. (43615)
35 (hub or hubs).ti,ab,kf. (8875)
36 (connector or connectors).ti,ab,kf. (4030)
37 or/34-36 (56315)
38 22 and 33 and 37 (322)
39 ((port or ports or hub or hubs) adj5 protect$).ti,ab,kf. (82)
40 ((catheter$ or connector or connectors or hub or hubs or protector or protectors or protection or protective or barrier or antiinfect$ or anti-infect$ or antisep$ or anti-sep$ or antimicrob$ or anti-microb$ or antibacter$ or anti-bacter$ or disinfect$ or decontaminat$ or clean$) adj1 (cap or caps)).ti,ab,kf. (166)
41 ((alcohol$ or ethanol$ or chlorhexidine or isopropyl$ or impregn$) adj3 (cap or caps)).ti,ab,kf. (77)
42 (passive adj5 disinfect$).ti,ab,kf. (13)
43 or/39-42 (322)
44 (swab cap$2 or swabcap$2).ti,ab,kf. (3)
45 (site scrub$2 or sitescrub$2).ti,ab,kf. (3)
46 (life shield$2 or lifeshield$2).ti,ab,kf. (2)
47 (EffectIV or EffectIVr or EffectIVtm).ti,ab,kf. (6)
48 (dual cap$2 or dualcap$2).ti,ab,kf. (1)

49 curos$2.ti,ab,kf. (5)
50 or/44-49 (20)
51 38 or 43 or 50 (618)
52 exp animals/ not humans/ (4585070)
53 51 not 52 (546)
54 limit 53 to english language (498)
55 remove duplicates from 54 (476)

A.2: Source: PubMed

Interface / URL: http://www.ncbi.nlm.nih.gov/pubmed
Database coverage dates: 1940s to current. Updated daily.
Search date: 20/09/17
Retrieved records: 626
Search strategy:

Search Query Items found
#56 Search #53 NOT #54 Filters: English 626
#55 Search #53 NOT #54 643
#54 Search medline[sb] 24307328
#53 Search #51 not #52 3972
#52 Search animals[mh] NOT humans[mh:noexp] 4372391
#51 Search #38 or #43 or #50 4744
#50 Search #44 OR #45 OR #46 OR #47 OR #48 OR #49 15
#49 Search curos[tiab] OR curosr[tiab] OR curostm[tiab] 1
#48 Search dualcap[tiab] OR dualcapr[tiab] OR dualcaptm[tiab] OR dual cap[tiab] OR dual capr[tiab] OR dual captm[tiab] 2
#47 Search EffectIV[tiab] OR EffectIVr[tiab] OR EffectIVtm[tiab] 6
#46 Search lifeshield*[tiab] 1
#45 Search site scrub*[tiab] OR sitescrub*[tiab] 3
#44 Search swabcap*[tiab] 2
#43 Search #39 OR #40 OR #41 OR #42 4491
#42 Search passive[tiab] AND disinfect*[tiab] 93
#41 Search (alcohol*[tiab] OR ethanol*[tiab] OR chlorhexidine[tiab] OR isopropyl*[tiab] OR impregn*[tiab]) AND (cap[tiab] OR caps[tiab]) 583
#40 Search (catheter*[tiab] OR connector[tiab] OR connectors[tiab] OR hub[tiab] OR hubs[tiab] OR protector[tiab] OR protectors[tiab] OR protection[tiab] OR protective[tiab] OR barrier[tiab] OR antiinfect*[tiab] OR anti-infect*[tiab] OR antisep*[tiab] OR anti-sep*[tiab] OR antimicrob*[tiab] OR anti-microb*[tiab] OR antibacter*[tiab] OR anti-bacter*[tiab] OR disinfect*[tiab] OR decontaminat*[tiab] OR clean*[tiab]) AND (cap[tiab] OR caps[tiab]) 3110
#39 Search (port[tiab] OR ports[tiab] OR hub[tiab] OR hubs[tiab]) AND protect*[tiab] 824
#38 Search #22 AND #33 AND #37 408
#37 Search #34 OR #35 OR #36 53309
#36 Search connector[tiab] OR connectors[tiab] 3900

#35 Search hub[tiab] OR hubs[tiab] 8305
#34 Search cap[tiab] OR caps[tiab] 41302
#33 Search #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 1790680
#32 Search chlorhexidine*[tiab] 8914
#31 Search isopropyl*[tiab] 19083
#30 Search ethanol*[tiab] 118339
#29 Search alcohol*[tiab] 289728
#28 Search "Chlorhexidine"[mesh:noexp] 7252
#27 Search "Alcohols"[mesh] 605189
#26 Search disinfect*[tiab] OR decontaminat*[tiab] OR clean*[tiab] OR barrier[tiab] 241379
#25 Search antiinfect*[tiab] OR anti-infect*[tiab] OR antisep*[tiab] OR anti-sep*[tiab] OR antimicrob*[tiab] OR anti-microb*[tiab] OR antibacter*[tiab] OR anti-bacter*[tiab] 189196
#24 Search "Disinfection"[mesh:noexp] 12562
#23 Search "Anti-Infective Agents"[mesh] 614278
#22 Search #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 752724
#21 Search port a cath*[tiab] OR portacath*[tiab] OR hickman*[tiab] OR broviac*[tiab] OR cook*[tiab] OR seldinger*[tiab] OR punktion*[tiab] OR groshong*[tiab] OR quinton*[tiab] 27913
#20 Search IVD[tiab] OR IVDs[tiab] 2054
#19 Search CVA[tiab] OR CVAD[tiab] OR CVADs[tiab] OR VAD[tiab] OR VADs[tiab] 9815
#18 Search (invasive[tiab] OR percutaneous[tiab]) AND device*[tiab] 19671
#17 Search access*[tiab] AND (device*[tiab] OR site[tiab] OR sites[tiab] OR route*[tiab]) 62181
#16 Search CA-BSI[tiab] OR CA-BSIs[tiab] OR CABSI[tiab] OR CABSIs[tiab] OR CR-BSI[tiab] OR CR-BSIs[tiab] OR CRBSI[tiab] OR CRBSIs[tiab] OR CLA-BSI[tiab] OR CLA-BSIs[tiab] OR CLABSI[tiab] OR CLABSIs[tiab] 1269
#15 Search art line[tiab] OR a line*[tiab] OR IAC[tiab] OR IACs[tiab] 12673
#14 Search (arterial[tiab] OR intraarterial[tiab] OR artery[tiab] OR arteries[tiab]) AND (line[tiab] OR lines[tiab] OR access*[tiab] OR site[tiab] OR sites[tiab] OR device*[tiab]) 75341
#13 Search (venous[tiab] OR intravenous[tiab] OR vein*[tiab] OR vascular[tiab] OR intravascular[tiab] OR IV[tiab]) AND (line[tiab] OR lines[tiab] OR access*[tiab] OR site[tiab] OR sites[tiab] OR device*[tiab] OR reservoir*[tiab]) 169955
#12 Search peripheral[tiab] AND (line[tiab] OR lines[tiab] OR access*[tiab] OR site[tiab] OR sites[tiab] OR device*[tiab]) 69765
#11 Search (central[tiab] OR subclavian[tiab] OR jugular[tiab] OR femoral[tiab]) AND (line[tiab] OR lines[tiab] OR access*[tiab] OR site[tiab] OR sites[tiab] OR device*[tiab]) 129737
#10 Search central[tiab] AND (venous[tiab] OR pressure[tiab]) 59254

#9 Search (PIC[tiab] OR CVP[tiab]) AND (line[tiab] OR lines[tiab] OR access*[tiab] OR site[tiab] OR sites[tiab] OR device*[tiab])1253
#8 Search CVC[tiab] OR CVCs[tiab] OR CVL[tiab] OR CVLs[tiab] OR PICC[tiab] OR PICCs[tiab] OR PIV[tiab] OR PIVs[tiab] OR PVC[tiab] OR PVCs[tiab] 13108
#7 Search catheter*[tiab] OR microcatheter*[tiab] OR cannula*[tiab] OR microcannula*[tiab] OR canula*[tiab] OR microcanula*[tiab] 219373
#6 Search "Catheter-Related Infections"[mesh:noexp] 3530
#5 Search "Catheters"[mesh] 24443
#4 Search "Cardiac Catheterization"[mesh:noexp] 44434
#3 Search "Catheterization, Peripheral"[mesh] 10017
#2 Search "Catheterization, Central Venous"[mesh:noexp] 13549
#1 Search "Catheterization"[mesh:noexp] 48389

A.3: Source: Embase

Interface / URL: Ovid SP
Database coverage dates: 1974 to 19/09/17
Search date: 20/09/17
Retrieved records: 906
Search strategy:

Database: Embase <1974 to 2017 September 19>
Search Strategy:
---
1 catheterization/ or exp blood vessel catheterization/ or heart catheterization/ (122501)
2 exp catheter/ (148541)
3 catheter infection/ (14649)
4 vascular access/ (20727)
5 (catheter$ or microcatheter$ or cannula$ or microcannula$ or canula$ or microcanula$).ti,ab,kw. (316354)
6 (CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs).ti,ab,kw. (20604)
7 ((PIC or CVP) adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kw. (221)
8 (central adj3 (venous or pressure)).ti,ab,kw. (37150)
9 ((central or subclavian or jugular or femoral) adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kw. (24456)
10 (peripheral adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kw. (8606)
11 ((venous or intravenous or vein$1 or vascular or intravascular or IV) adj3 (line$1 or access$ or site or sites or device$ or reservoir$)).ti,ab,kw. (41338)
12 ((arterial or intraarterial or artery or arteries) adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kw. (12262)
13 (art line$1 or a line$1 or IAC or IACs).ti,ab,kw. (12601)
14 (CA-BSI or CA-BSIs or CABSI or CABSIs or CR-BSI or CR-BSIs or CRBSI or CRBSIs or CLA-BSI or CLA-BSIs or CLABSI or CLABSIs).ti,ab,kw. (2501)
15 (access$ adj3 (device$ or site or sites or route$1)).ti,ab,kw. (16431)

16 ((invasive or percutaneous) adj3 device$).ti,ab,kw. (4760)
17 (CVA or CVAD or CVADs or VAD or VADs).ti,ab,kw. (17140)
18 (IVD or IVDs).ti,ab,kw. (3540)
19 (port a cath$1 or portacath$1 or hickman$1 or broviac$1 or cook$1 or seldinger$1 or punktion$1 or groshong$1 or quinton$1).ti,ab,kw. (12289)
20 or/1-19 (541963)
21 exp antiinfective agent/ (2763330)
22 disinfection/ or disinfection system/ (22578)
23 (antiinfect$ or anti-infect$ or antisep$ or anti-sep$ or antimicrob$ or anti-microb$ or antibacter$ or anti-bacter$).ti,ab,kw. (255216)
24 (disinfect$ or decontaminat$ or clean$ or barrier).ti,ab,kw. (304745)
25 alcohol/ (229780)
26 exp alcohol derivative/ (420836)
27 Chlorhexidine/ (14866)
28 alcohol$.ti,ab,kw. (393352)
29 ethanol$.ti,ab,kw. (158573)
30 isopropyl$.ti,ab,kw. (23762)
31 chlorhexidine$.ti,ab,kw. (10376)
32 or/21-31 (3692178)
33 (cap or caps).ti,ab,kw. (56129)
34 (hub or hubs).ti,ab,kw. (11163)
35 (connector or connectors).ti,ab,kw. (4777)
36 or/33-35 (71715)
37 20 and 32 and 36 (691)
38 port protector/ (21)
39 ((port or ports or hub or hubs) adj5 protect$).ti,ab,kw. (146)
40 ((catheter$ or connector or connectors or hub or hubs or protector or protectors or protection or protective or barrier or antiinfect$ or anti-infect$ or antisep$ or anti-sep$ or antimicrob$ or anti-microb$ or antibacter$ or anti-bacter$ or disinfect$ or decontaminat$ or clean$) adj1 (cap or caps)).ti,ab,kw. (229)
41 ((alcohol$ or ethanol$ or chlorhexidine or isopropyl$ or impregn$) adj3 (cap or caps)).ti,ab,kw. (116)
42 (passive adj5 disinfect$).ti,ab,kw. (20)
43 or/38-42 (469)
44 (swab cap$2 or swabcap$2).ti,ab,kw,dv. (19)
45 (site scrub$2 or sitescrub$2).ti,ab,kw,dv. (6)
46 (life shield$2 or lifeshield$2).ti,ab,kw,dv. (10)
47 (EffectIV or EffectIVr or EffectIVtm).ti,ab,kw,dv. (36)
48 (dual cap$2 or dualcap$2).ti,ab,kw,dv. (3)
49 curos$2.ti,ab,kw,dv. (25)
50 or/44-49 (97)
51 37 or 43 or 50 (1118)
52 (animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/ (5766699)
53 51 not 52 (1013)

54 limit 53 to english language (925)
55 remove duplicates from 54 (906)

A.4: Source: Science Citation Index (SCI) Expanded

Interface / URL: Web of Science
Database coverage dates: 1900-present. Last update 21/09/17
Search date: 22/09/17
Retrieved records: 907
Search strategy:

39 #25 OR #30 OR #37 Language Restriction: English 907
38 #25 OR #30 OR #37 957
37 #31 OR #32 OR #33 OR #34 OR #35 OR #36 37
36 TS=(“curos” OR “curosr” OR “curostm”) 3
35 TS=(“dual cap” OR "dualcap" OR “dual capr” OR "dualcapr" OR “dual captm” OR "dualcaptm") 4
34 TS=(“EffectIV” OR “EffectIVr” OR “EffectIVtm”) 18
33 TS=(“life shield*” OR lifeshield*) 3
32 TS=(“site scrub*” OR sitescrub*) 4
31 TS=(“swab cap*” OR swabcap*) 5
30 #26 OR #27 OR #28 OR #29 679
29 TS=(“passive” NEAR/5 disinfect*) 15
28 TS=((alcohol* OR ethanol* OR “chlorhexidine” OR isopropyl* OR impregn*) NEAR/3 (“cap” OR “caps”)) 93
27 TS=((catheter* OR “connector” OR “connectors” OR “hub” OR “hubs” OR “protector” OR “protectors” OR “protection” OR “protective” OR “barrier” OR antiinfect* OR anti-infect* OR antisep* OR anti-sep* OR antimicrob* OR anti-microb* OR antibacter* OR anti-bacter* OR disinfect* OR decontaminat* OR clean*) NEAR/1 (“cap” OR “caps”)) 416
26 TS=((“port” OR “ports” OR “hub” OR “hubs”) NEAR/3 protect*) 172
25 #16 AND #20 AND #24 280
24 #21 OR #22 OR #23 99,701
23 TS=("connector" OR "connectors") 10,104
22 TS=(“hub” OR “hubs”)13,690
21 TS=("cap" OR "caps")76,165
20 #17 OR #18 OR #19 1,403,023
19 TS=(alcohol* OR ethanol* OR isopropyl* OR chlorhexidine*) 683,782
18 TS=(disinfect* OR decontaminat* OR clean* OR “barrier”) 505,153
17 TS=(antiinfect* OR anti-infect* OR antisep* OR anti-sep* OR antimicrob* OR anti-microb* OR antibacter* OR anti-bacter*) 250,882
16 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 585,838
15 TS=(“port a cath*” OR portacath* OR hickman* OR broviac* OR cook* OR seldinger* OR punktion* OR groshong* OR quinton*) 56,007
14 TS=(“IVD” OR “IVDs”)2,103

13 TS=(“CVA” OR “CVAD” OR “CVADs” OR “VAD” OR “VADs”) 10,257
12 TS=((“invasive” OR “percutaneous”) NEAR/3 device*) 3,513
11 TS=(access* NEAR/3 (device* OR “site” OR “sites” OR route*)) 17,426
10 TS=(“CA-BSI” OR “CA-BSIs” OR “CABSI” OR “CABSIs” OR “CR-BSI” OR “CR-BSIs” OR “CRBSI” OR “CRBSIs” OR “CLA-BSI” OR “CLA-BSIs” OR “CLABSI” OR “CLABSIs”) 1,132
9 TS=(“art line*” OR “a line*” OR “IAC” OR “IACs”) 229,481
8 TS=((“arterial” OR “intraarterial” OR “artery” OR “arteries”) NEAR/3 (“line” OR “lines” OR access* OR “site” OR “sites” OR device*)) 8,270
7 TS=((“venous” OR “intravenous” OR vein* OR “vascular” OR “intravascular” OR “IV”) NEAR/3 (“line” OR “lines” OR access* OR “site” OR “sites” OR device* OR reservoir*)) 29,139
6 TS=(“peripheral” NEAR/3 (“line” OR “lines” OR access* OR “site” OR “sites” OR device*)) 6,962
5 TS=((“central” OR “subclavian” OR “jugular” OR “femoral”) NEAR/3 (“line” OR “lines” OR access* OR “site” OR “sites” OR device*)) 21,944
4 TS=(“central” NEAR/3 (“venous” OR “pressure”)) 25,227
3 TS=((“PIC” OR “CVP”) NEAR/3 (“line” OR “lines” OR access* OR “site” OR “sites” OR device*)) 210
2 TS=("CVC" OR "CVCs" OR "CVL" OR "CVLs" OR "PICC" OR "PICCs" OR "PIV" OR "PIVs" OR "PVC" OR "PVCs") 36,014
1 TS=(catheter* OR microcatheter* OR cannula* OR microcannula* OR canula* OR microcanula*) 188,516

A.5: Source: Conference Proceedings Citation Index- Science (CPCI-S)

Interface / URL: Web of Science
Database coverage dates: 1990-present. Last update 21/09/17
Search date: 22/09/17
Retrieved records: 309
Search strategy:

39 #25 OR #30 OR #37 Language Restriction: English 309
38 #25 OR #30 OR #37 316
37 #31 OR #32 OR #33 OR #34 OR #35 OR #36 18
36 TS=(“curos” OR “curosr” OR “curostm”) 2
35 TS=(“dual cap” OR "dualcap" OR “dual capr” OR "dualcapr" OR “dual captm” OR "dualcaptm") 1
34 TS=(“EffectIV” OR “EffectIVr” OR “EffectIVtm”) 11
33 TS=(“life shield*” OR lifeshield*) 3
32 TS=(“site scrub*” OR sitescrub*) 1
31 TS=(“swab cap*” OR swabcap*) 0
30 #26 OR #27 OR #28 OR #29 260
29 TS=(“passive” NEAR/5 disinfect*) 6

28 TS=((alcohol* OR ethanol* OR “chlorhexidine” OR isopropyl* OR impregn*) NEAR/3 (“cap” OR “caps”)) 5
27 TS=((catheter* OR “connector” OR “connectors” OR “hub” OR “hubs” OR “protector” OR “protectors” OR “protection” OR “protective” OR “barrier” OR antiinfect* OR anti-infect* OR antisep* OR anti-sep* OR antimicrob* OR anti-microb* OR antibacter* OR anti-bacter* OR disinfect* OR decontaminat* OR clean*) NEAR/1 (“cap” OR “caps”)) 118
26 TS=((“port” OR “ports” OR “hub” OR “hubs”) NEAR/3 protect*) 132
25 #16 AND #20 AND #24 43
24 #21 OR #22 OR #23 24,351
23 TS=("connector" OR "connectors") 5,744
22 TS=(“hub” OR “hubs”)5,503
21 TS=("cap" OR "caps") 13,159
20 #17 OR #18 OR #19 186,108
19 TS=(alcohol* OR ethanol* OR isopropyl* OR chlorhexidine*) 67,116
18 TS=(disinfect* OR decontaminat* OR clean* OR “barrier”) 106,544
17 TS=(antiinfect* OR anti-infect* OR antisep* OR anti-sep* OR antimicrob* OR anti-microb* OR antibacter* OR anti-bacter*) 15,049
16 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 110,967
15 TS=(“port a cath*” OR portacath* OR hickman* OR broviac* OR cook* OR seldinger* OR punktion* OR groshong* OR quinton*) 6,931
14 TS=(“IVD” OR “IVDs”)271
13 TS=(“CVA” OR “CVAD” OR “CVADs” OR “VAD” OR “VADs”) 2,088
12 TS=((“invasive” OR “percutaneous”) NEAR/3 device*) 747
11 TS=(access* NEAR/3 (device* OR “site” OR “sites” OR route*)) 5,545
10 TS=(“CA-BSI” OR “CA-BSIs” OR “CABSI” OR “CABSIs” OR “CR-BSI” OR “CR-BSIs” OR “CRBSI” OR “CRBSIs” OR “CLA-BSI” OR “CLA-BSIs” OR “CLABSI” OR “CLABSIs”) 75
9 TS=(“art line*” OR “a line*” OR “IAC” OR “IACs”) 61,815
8 TS=((“arterial” OR “intraarterial” OR “artery” OR “arteries”) NEAR/3 (“line” OR “lines” OR access* OR “site” OR “sites” OR device*)) 976
7 TS=((“venous” OR “intravenous” OR vein* OR “vascular” OR “intravascular” OR “IV”) NEAR/3 (“line” OR “lines” OR access* OR “site” OR “sites” OR device* OR reservoir*)) 3,188
6 TS=(“peripheral” NEAR/3 (“line” OR “lines” OR access* OR “site” OR “sites” OR device*)) 1,070
5 TS=((“central” OR “subclavian” OR “jugular” OR “femoral”) NEAR/3 (“line” OR “lines” OR access* OR “site” OR “sites” OR device*)) 3,051
4 TS=(“central” NEAR/3 (“venous” OR “pressure”)) 2,508
3 TS=((“PIC” OR “CVP”) NEAR/3 (“line” OR “lines” OR access* OR “site” OR “sites” OR device*)) 53
2 TS=("CVC" OR "CVCs" OR "CVL" OR "CVLs" OR "PICC" OR "PICCs" OR "PIV" OR "PIVs" OR "PVC" OR "PVCs") 8,750

1 TS=(catheter* OR microcatheter* OR cannula* OR microcannula* OR canula* OR microcanula*) 18,418

A.6: Source: CINAHL

Interface / URL: EBSCO
Database coverage dates: 1937 to current.
Search date: 21/09/17
Retrieved records: 281
Search strategy:

#	Query	Limiters/Expanders	Last Run Via	Results
S46	S31 OR S37 OR S44	Narrow by Language: - english		281
S45	S31 OR S37 OR S44			294
S44	S38 OR S39 OR S40 OR S41 OR S42 OR S43			16
S43	TI(curos OR curosr OR curostm) OR AB(curos OR curosr OR curostm)			4
S42	TI("dual cap*" OR dualcap*) OR AB("dual cap*" OR dualcap*)			9
S41	TI(EffectIV OR EffectIVr OR EffectIVtm) OR AB(EffectIV OR EffectIVr OR EffectIVtm)			0
S40	TI("life shield*" OR lifeshield*) OR AB("life shield*" OR lifeshield*)			0
S39	TI("site scrub*" OR sitescrub*) OR AB("site scrub*" OR sitescrub*)			2
S38	TI("swab cap*" OR swabcap*) OR AB("swab cap*" OR swabcap*)			1
S37	S32 OR S33 OR S34 OR S35 OR S36			119
S36	TI(passive N5 disinfect*) OR AB(passive N5 disinfect*)			9
S35	TI((alcohol* OR ethanol* OR chlorhexidine OR isopropyl* OR impregn*) N3 (cap OR caps)) OR AB((alcohol* OR ethanol* OR chlorhexidine OR isopropyl* OR impregn*) N3 (cap OR caps))			46
S34	AB((catheter* OR connector OR connectors OR hub OR hubs OR protector OR protectors OR protection OR protective OR barrier OR antiinfect* OR anti-infect* OR antisep* OR anti-sep* OR antimicrob* OR anti-microb* OR antibacter* OR anti-bacter* OR disinfect* OR decontaminat* OR clean*) N1 (cap OR caps))			38
S33	TI((catheter* OR connector OR connectors OR hub OR hubs OR protector OR protectors OR protection OR protective OR barrier OR antiinfect* OR anti-infect* OR antisep* OR anti-sep* OR antimicrob* OR anti-microb* OR antibacter* OR anti-bacter* OR disinfect* OR decontaminat* OR clean*) N1 (cap OR caps))			28
S32	TI((port OR ports OR hub OR hubs) N5 protect*) OR AB((port OR ports OR hub OR hubs) N5 protect*)			29
S31	S19 AND S26 AND S30			197
S30	S27 OR S28 OR S29			6,480
S29	TI(connector OR connectors) OR AB(connector OR connectors)			620
S28	TI(hub OR hubs) OR AB(hub OR hubs)			1,150
S27	TI(cap OR caps) OR AB(cap OR caps)			4,764
S26	S20 OR S21 OR S22 OR S23 OR S24 OR S25			265,203
S25	TI(alcohol* OR ethanol* OR isopropyl* OR chlorhexidine*) OR AB(alcohol* OR ethanol* OR isopropyl* OR chlorhexidine*)			65,175
S24	(MH "Alcohols+")			29,278

S23 TI(disinfect* OR decontaminat* OR clean* OR barrier) OR AB(disinfect* OR decontaminat* OR clean* OR barrier) 64,291
S22 TI(antiinfect* OR anti-infect* OR antisep* OR anti-sep* OR antimicrob* OR anti-microb* OR antibacter* OR anti-bacter*) OR AB(antiinfect* OR anti-infect* OR antisep* OR anti-sep* OR antimicrob* OR anti-microb* OR antibacter* OR anti-bacter*) 18,663
S21 (MH "Sterilization and Disinfection") 8,556
S20 (MH "Antiinfective Agents+") 111,505
S19 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 181,759
S18 TI("port a cath*" OR portacath* OR hickman* OR broviac* OR cook* OR seldinger* OR punktion* OR groshong* OR quinton*) OR AB("port a cath*" OR portacath* OR hickman* OR broviac* OR cook* OR seldinger* OR punktion* OR groshong* OR quinton*) 6,185
S17 TI(IVD OR IVDs) OR AB(IVD OR IVDs) 423
S16 TI(CVA OR CVAD OR CVADs OR VAD OR VADs) OR AB(CVA OR CVAD OR CVADs OR VAD OR VADs) 1,666
S15 TI((invasive OR percutaneous) N3 device*) OR AB((invasive OR percutaneous) N3 device*) 837
S14 TI(access* N3 (device* OR site OR sites OR route*)) OR AB(access* N3 (device* OR site OR sites OR route*)) 2,835
S13 TI(CA-BSI OR CA-BSIs OR CABSI OR CABSIs OR CR-BSI OR CR-BSIs OR CRBSI OR CRBSIs OR CLA-BSI OR CLA-BSIs OR CLABSI OR CLABSIs) OR AB(CA-BSI OR CA-BSIs OR CABSI OR CABSIs OR CR-BSI OR CR-BSIs OR CRBSI OR CRBSIs OR CLA-BSI OR CLA-BSIs OR CLABSI OR CLABSIs) 782
S12 TI("art line*"OR "a line*" OR IAC OR IACs) OR AB("art line*" OR "a line*" OR IAC OR IACs) 113,644
S11 TI((arterial OR intraarterial OR artery OR arteries) N3 (line OR lines OR access* OR site OR sites OR device*)) OR AB((arterial OR intraarterial OR artery OR arteries) N3 (line OR lines OR access* OR site OR sites OR device*)) 1,675
S10 TI((venous OR intravenous OR vein* OR vascular OR intravascular OR IV) N3 (line OR lines OR access* OR site OR sites OR device* OR reservoir*)) OR AB((venous OR intravenous OR vein* OR vascular OR intravascular OR IV) N3 (line OR lines OR access* OR site OR sites OR device* OR reservoir*)) 6,649
S9 TI(peripheral N3 (line OR lines OR access* OR site OR sites OR device*)) OR AB(peripheral N3 (line OR lines OR access* OR site OR sites OR device*)) 899
S8 TI((central OR subclavian OR jugular OR femoral) N3 (line OR lines OR access* OR site OR sites OR device*)) OR AB((central OR subclavian OR jugular OR femoral) N3 (line OR lines OR access* OR site OR sites OR device*)) 4,214
S7 TI(central N3 (venous OR pressure)) OR AB(central N3 (venous OR pressure)) 5,857
S6 TI((PIC OR CVP) N3 (line OR lines OR access* OR site OR sites OR device*)) OR AB((PIC OR CVP) N3 (line OR lines OR access* OR site OR sites OR device*))

S5 TI(CVC OR CVCs OR CVL OR CVLs OR PICC OR PICCs OR PIV OR PIVs OR PVC OR PVCs) OR AB(CVC OR CVCs OR CVL OR CVLs OR PICC OR PICCs OR PIV OR PIVs OR PVC OR PVCs) 2,573
S4 TI(catheter* OR microcatheter* OR cannula* OR microcannula* OR canula* OR microcanula*) OR AB(catheter* OR microcatheter* OR cannula* OR microcannula* OR canula* OR microcanula*) 35,965
S3 (MH "Catheter-Related Infections") OR (MH "Catheter-Related Bloodstream Infections") 4,730
S2 (MH "Catheters+") OR (MH "Vascular Access Devices") OR (MH "Catheter Care") OR (MH "Catheter Care, Vascular") 12,117
S1 (MH "Catheterization") OR (MH "Catheterization, Central Venous+") OR (MH "Catheterization, Peripheral+") OR (MH "Heart Catheterization+") 27,224

A.7: Source: Cochrane Database of Systematic Reviews (CDSR)

Interface / URL: Cochrane Library, Wiley
Database coverage dates: Issue 9 of 12, September 2017
Search date: 20/09/17
Retrieved records: 4
Search strategy:

Search Name: CUROS
Date Run: 20/09/17 13:38:58.812
Description:

ID Search Hits
#1 [mh ^Catheterization] 1631
#2 [mh ^"Catheterization, Central Venous"] 885
#3 [mh "Catheterization, Peripheral"] 867
#4 [mh ^"Cardiac Catheterization"] 1203
#5 [mh Catheters] 1516
#6 [mh ^"Catheter-Related Infections"] 287
#7 (catheter* or microcatheter* or cannula* or microcannula* or canula* or microcanula*):ti,ab,kw 21452
#8 (CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs):ti,ab,kw 1017
#9 ((PIC or CVP) near/3 (line or lines or access* or site or sites or device*)):ti,ab,kw 14
#10 (central near/3 (venous or pressure)):ti,ab,kw 3813
#11 ((central or subclavian or jugular or femoral) near/3 (line or lines or access* or site or sites or device*)):ti,ab,kw 1184
#12 (peripheral near/3 (line or lines or access* or site or sites or device*)):ti,ab,kw 344
#13 ((venous or intravenous or vein or veins or vascular or intravascular or IV) near/3 (line or lines or access* or site or sites or device* or reservoir*)):ti,ab,kw 2641

#14 ((arterial or intraarterial or artery or arteries) near/3 (line or lines or access* or site or sites or device*)):ti,ab,kw 961
#15 (art next line* or a next line* or IAC or IACs):ti,ab,kw 3151
#16 (CA-BSI or CA-BSIs or CABSI or CABSIs or CR-BSI or CR-BSIs or CRBSI or CRBSIs or CLA-BSI or CLA-BSIs or CLABSI or CLABSIs):ti,ab,kw 154
#17 (access* near/3 (device* or site or sites or route or routes)):ti,ab,kw 887
#18 ((invasive or percutaneous) near/3 device*):ti,ab,kw 298
#19 (CVA or CVAD or CVADs or VAD or VADs):ti,ab,kw 572
#20 (IVD or IVDs):ti,ab,kw 50
#21 (port next a next cath* or portacath* or hickman* or broviac* or cook* or seldinger* or punktion* or groshong* or quinton*):ti,ab,kw 1556
#22 {or #1-#21} 31648
#23 [mh "Anti-Infective Agents"] 27534
#24 [mh ^Disinfection] 340
#25 (antiinfect* or anti-infect* or antisep* or anti-sep* or antimicrob* or anti-microb* or antibacter* or anti-bacter*):ti,ab,kw 19786
#26 (disinfect* or decontaminat* or clean* or barrier):ti,ab,kw 10185
#27 [mh Alcohols] 32724
#28 [mh ^Chlorhexidine] 1577
#29 alcohol*:ti,ab,kw 18631
#30 ethanol*:ti,ab,kw 5557
#31 isopropyl*:ti,ab,kw 389
#32 chlorhexidine*:ti,ab,kw 2946
#33 {or #23-#32} 89495
#34 (cap or caps):ti,ab,kw 2151
#35 (hub or hubs):ti,ab,kw 221
#36 (connector or connectors):ti,ab,kw 140
#37 {or #34-#36} 2483
#38 #22 and #33 and #37 56
#39 ((port or ports or hub or hubs) near/5 protect*):ti,ab,kw 13
#40 ((catheter* or connector or connectors or hub or hubs or protector or protectors or protection or protective or barrier or antiinfect* or anti-infect* or antisep* or anti-sep* or antimicrob* or anti-microb* or antibacter* or anti-bacter* or disinfect* or decontaminat* or clean*) near/3 (cap or caps)):ti,ab,kw 28
#41 ((alcohol* or ethanol* or chlorhexidine or isopropyl* or impregn*) near/3 (cap or caps)):ti,ab,kw 10
#42 (passive near/5 disinfect*):ti,ab,kw 1
#43 {or #39-#42} 45
#44 (swab next cap* or swabcap*):ti,ab,kw 1
#45 (site next scrub* or sitescrub*):ti,ab,kw 2
#46 (life next shield* or lifeshield*):ti,ab,kw 0
#47 (EffectIV or EffectIVr or EffectIVtm):ti,ab,kw 2
#48 (dual next cap* or dualcap*):ti,ab,kw 1
#49 (curos or curosr or curostm):ti,ab,kw 1
#50 {or #44-#49} 7

#51 #38 or #43 or #50 93
#52 #51 in Cochrane Reviews (Reviews and Protocols) 4

A.8: Source: Cochrane Central Register of Controlled Trials (CENTRAL)

Interface / URL: Cochrane Library, Wiley
Database coverage dates: Issue 8 of 12, August 2017
Search date: 20/09/17
Retrieved records: 96
Search strategy:

Search Name: CUROS
Date Run: 20/09/17 12:58:46.94
Description:

ID Search Hits
#1 [mh ^Catheterization] 1631
#2 [mh ^"Catheterization, Central Venous"] 885
#3 [mh "Catheterization, Peripheral"] 867
#4 [mh ^"Cardiac Catheterization"] 1203
#5 [mh Catheters] 1516
#6 [mh ^"Catheter-Related Infections"] 287
#7 catheter* or microcatheter* or cannula* or microcannula* or canula* or microcanula* 23693
#8 CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs 1192
#9 (PIC or CVP) near/3 (line or lines or access* or site or sites or device*) 21
#10 central near/3 (venous or pressure) 4098
#11 (central or subclavian or jugular or femoral) near/3 (line or lines or access* or site or sites or device*) 1502
#12 peripheral near/3 (line or lines or access* or site or sites or device*) 423
#13 (venous or intravenous or vein or veins or vascular or intravascular or IV) near/3 (line or lines or access* or site or sites or device* or reservoir*) 3197
#14 (arterial or intraarterial or artery or arteries) near/3 (line or lines or access* or site or sites or device*) 1069
#15 art next line* or a next line* or IAC or IACs 3758
#16 CA-BSI or CA-BSIs or CABSI or CABSIs or CR-BSI or CR-BSIs or CRBSI or CRBSIs or CLA-BSI or CLA-BSIs or CLABSI or CLABSIs 199
#17 access* near/3 (device* or site or sites or route or routes) 1092
#18 (invasive or percutaneous) near/3 device* 350
#19 CVA or CVAD or CVADs or VAD or VADs 940
#20 IVD or IVDs 67
#21 port next a next cath* or portacath* or hickman* or broviac* or cook* or seldinger* or punktion* or groshong* or quinton* 6592

#22 {or #1-#21} 39910
#23 [mh "Anti-Infective Agents"] 27534
#24 [mh ^Disinfection] 340
#25 antiinfect* or anti-infect* or antisep* or anti-sep* or antimicrob* or anti-microb* or antibacter* or anti-bacter* 22911
#26 disinfect* or decontaminat* or clean* or barrier 11855
#27 [mh Alcohols] 32724
#28 [mh ^Chlorhexidine] 1577
#29 alcohol* 22737
#30 ethanol* 5809
#31 isopropyl* 444
#32 chlorhexidine* 3145
#33 {or #23-#32} 96606
#34 cap or caps 2895
#35 hub or hubs 350
#36 connector or connectors 171
#37 {or #34-#36} 3366
#38 #22 and #33 and #37 187
#39 (port or ports or hub or hubs) near/5 protect* 16
#40 (catheter* or connector or connectors or hub or hubs or protector or protectors or protection or protective or barrier or antiinfect* or anti-infect* or antisep* or anti-sep* or antimicrob* or anti-microb* or antibacter* or anti-bacter* or disinfect* or decontaminat* or clean*) near/3 (cap or caps) 45
#41 (alcohol* or ethanol* or chlorhexidine or isopropyl* or impregn*) near/3 (cap or caps) 14
#42 passive near/5 disinfect* 1
#43 {or #39-#42} 67
#44 swab next cap* or swabcap* 1
#45 site next scrub* or sitescrub* 2
#46 life next shield* or lifeshield* 2
#47 EffectIV or EffectIVr or EffectIVtm 38
#48 dual next cap* or dualcap* 1
#49 curos or curosr or curostm 6
#50 {or #44-#49} 50
#51 #38 or #43 or #50 278
#52 #51 in Trials 96

A.9: Source: Database of Abstracts of Reviews of Effect (DARE)

Interface / URL: Cochrane Library, Wiley
Database coverage dates: Issue 2 of 4, April 2015
Search date: 20/09/17
Retrieved records: 6
Search strategy:

Search Name: CUROS

Date Run: 20/09/17 13:03:47.636
Description:

ID	Search	Hits
#1	[mh ^Catheterization]	1631
#2	[mh ^"Catheterization, Central Venous"]	885
#3	[mh "Catheterization, Peripheral"]	867
#4	[mh ^"Cardiac Catheterization"]	1203
#5	[mh Catheters]	1516
#6	[mh ^"Catheter-Related Infections"]	287
#7	catheter* or microcatheter* or cannula* or microcannula* or canula* or microcanula*	23693
#8	CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs	1192
#9	(PIC or CVP) near/3 (line or lines or access* or site or sites or device*)	21
#10	central near/3 (venous or pressure)	4098
#11	(central or subclavian or jugular or femoral) near/3 (line or lines or access* or site or sites or device*)	1502
#12	peripheral near/3 (line or lines or access* or site or sites or device*)	423
#13	(venous or intravenous or vein or veins or vascular or intravascular or IV) near/3 (line or lines or access* or site or sites or device* or reservoir*)	3197
#14	(arterial or intraarterial or artery or arteries) near/3 (line or lines or access* or site or sites or device*)	1069
#15	art next line* or a next line* or IAC or IACs	3758
#16	CA-BSI or CA-BSIs or CABSI or CABSIs or CR-BSI or CR-BSIs or CRBSI or CRBSIs or CLA-BSI or CLA-BSIs or CLABSI or CLABSIs	199
#17	access* near/3 (device* or site or sites or route or routes)	1092
#18	(invasive or percutaneous) near/3 device*	350
#19	CVA or CVAD or CVADs or VAD or VADs	940
#20	IVD or IVDs	67
#21	port next a next cath* or portacath* or hickman* or broviac* or cook* or seldinger* or punktion* or groshong* or quinton*	6592
#22	{or #1-#21}	39910
#23	[mh "Anti-Infective Agents"]	27534
#24	[mh ^Disinfection]	340
#25	antiinfect* or anti-infect* or antisep* or anti-sep* or antimicrob* or anti-microb* or antibacter* or anti-bacter*	22911
#26	disinfect* or decontaminat* or clean* or barrier	11855
#27	[mh Alcohols]	32724
#28	[mh ^Chlorhexidine]	1577
#29	alcohol*	22737
#30	ethanol*	5809
#31	isopropyl*	444
#32	chlorhexidine*	3145
#33	{or #23-#32}	96606

#34 cap or caps 2895
#35 hub or hubs 350
#36 connector or connectors 171
#37 {or #34-#36} 3366
#38 #22 and #33 and #37 187
#39 (port or ports or hub or hubs) near/5 protect* 16
#40 (catheter* or connector or connectors or hub or hubs or protector or protectors or protection or protective or barrier or antiinfect* or anti-infect* or antisep* or anti-sep* or antimicrob* or anti-microb* or antibacter* or anti-bacter* or disinfect* or decontaminat* or clean*) near/3 (cap or caps) 45
#41 (alcohol* or ethanol* or chlorhexidine or isopropyl* or impregn*) near/3 (cap or caps) 14
#42 passive near/5 disinfect* 1
#43 {or #39-#42} 67
#44 swab next cap* or swabcap* 1
#45 site next scrub* or sitescrub* 2
#46 life next shield* or lifeshield* 2
#47 EffectIV or EffectIVr or EffectIVtm 38
#48 dual next cap* or dualcap* 1
#49 curos or curosr or curostm 6
#50 {or #44-#49} 50
#51 #38 or #43 or #50 278
#52 #51 in Other Reviews 6

A.10: Source: Health Technology Assessment (HTA) Database

Interface / URL: Cochrane Library, Wiley
Database coverage dates: Issue 4 of 4, October 2016
Search date: 20/09/17
Retrieved records: 7
Search strategy:

Search Name: CUROS
Date Run: 20/09/17 13:07:31.956
Description:

ID Search Hits
#1 [mh ^Catheterization] 1631
#2 [mh ^"Catheterization, Central Venous"] 885
#3 [mh "Catheterization, Peripheral"] 867
#4 [mh ^"Cardiac Catheterization"] 1203
#5 [mh Catheters] 1516
#6 [mh ^"Catheter-Related Infections"] 287
#7 catheter* or microcatheter* or cannula* or microcannula* or canula* or microcanula* 23693

#8 CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs 1192
#9 (PIC or CVP) near/3 (line or lines or access* or site or sites or device*) 21
#10 central near/3 (venous or pressure) 4098
#11 (central or subclavian or jugular or femoral) near/3 (line or lines or access* or site or sites or device*) 1502
#12 peripheral near/3 (line or lines or access* or site or sites or device*) 423
#13 (venous or intravenous or vein or veins or vascular or intravascular or IV) near/3 (line or lines or access* or site or sites or device* or reservoir*) 3197
#14 (arterial or intraarterial or artery or arteries) near/3 (line or lines or access* or site or sites or device*) 1069
#15 art next line* or a next line* or IAC or IACs 3758
#16 CA-BSI or CA-BSIs or CABSI or CABSIs or CR-BSI or CR-BSIs or CRBSI or CRBSIs or CLA-BSI or CLA-BSIs or CLABSI or CLABSIs 199
#17 access* near/3 (device* or site or sites or route or routes) 1092
#18 (invasive or percutaneous) near/3 device* 350
#19 CVA or CVAD or CVADs or VAD or VADs 940
#20 IVD or IVDs 67
#21 port next a next cath* or portacath* or hickman* or broviac* or cook* or seldinger* or punktion* or groshong* or quinton* 6592
#22 {or #1-#21} 39910
#23 [mh "Anti-Infective Agents"] 27534
#24 [mh ^Disinfection] 340
#25 antiinfect* or anti-infect* or antisep* or anti-sep* or antimicrob* or anti-microb* or antibacter* or anti-bacter* 22911
#26 disinfect* or decontaminat* or clean* or barrier 11855
#27 [mh Alcohols] 32724
#28 [mh ^Chlorhexidine] 1577
#29 alcohol* 22737
#30 ethanol* 5809
#31 isopropyl* 444
#32 chlorhexidine* 3145
#33 {or #23-#32} 96606
#34 cap or caps 2895
#35 hub or hubs 350
#36 connector or connectors 171
#37 {or #34-#36} 3366
#38 #22 and #33 and #37 187
#39 (port or ports or hub or hubs) near/5 protect* 16
#40 (catheter* or connector or connectors or hub or hubs or protector or protectors or protection or protective or barrier or antiinfect* or anti-infect* or antisep* or anti-sep* or antimicrob* or anti-microb* or antibacter* or anti-bacter* or disinfect* or decontaminat* or clean*) near/3 (cap or caps) 45
#41 (alcohol* or ethanol* or chlorhexidine or isopropyl* or impregn*) near/3 (cap or caps) 14

#42 passive near/5 disinfect* 1
#43 {or #39-#42} 67
#44 swab next cap* or swabcap* 1
#45 site next scrub* or sitescrub* 2
#46 life next shield* or lifeshield* 2
#47 EffectIV or EffectIVr or EffectIVtm 38
#48 dual next cap* or dualcap* 1
#49 curos or curosr or curostm 6
#50 {or #44-#49} 50
#51 #38 or #43 or #50 278
#52 #51 in Technology Assessments 7

A.11: Source: NHS Economic Evaluation Database (NHS EED)

Interface / URL: Cochrane Library, Wiley
Database coverage dates: Issue 2 of 4, April 2015
Search date: 20/09/17
Retrieved records: 11
Search strategy:

Search Name: CUROS
Date Run: 20/09/17 13:30:06.183
Description:

ID Search Hits
#1 [mh ^Catheterization] 1631
#2 [mh ^"Catheterization, Central Venous"] 885
#3 [mh "Catheterization, Peripheral"] 867
#4 [mh ^"Cardiac Catheterization"] 1203
#5 [mh Catheters] 1516
#6 [mh ^"Catheter-Related Infections"] 287
#7 catheter* or microcatheter* or cannula* or microcannula* or canula* or microcanula* 23693
#8 CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs 1192
#9 (PIC or CVP) near/3 (line or lines or access* or site or sites or device*) 21
#10 central near/3 (venous or pressure) 4098
#11 (central or subclavian or jugular or femoral) near/3 (line or lines or access* or site or sites or device*) 1502
#12 peripheral near/3 (line or lines or access* or site or sites or device*) 423
#13 (venous or intravenous or vein or veins or vascular or intravascular or IV) near/3 (line or lines or access* or site or sites or device* or reservoir*) 3197
#14 (arterial or intraarterial or artery or arteries) near/3 (line or lines or access* or site or sites or device*) 1069
#15 art next line* or a next line* or IAC or IACs 3758

#16 CA-BSI or CA-BSIs or CABSI or CABSIs or CR-BSI or CR-BSIs or CRBSI or CRBSIs or CLA-BSI or CLA-BSIs or CLABSI or CLABSIs 199
#17 access* near/3 (device* or site or sites or route or routes) 1092
#18 (invasive or percutaneous) near/3 device* 350
#19 CVA or CVAD or CVADs or VAD or VADs 940
#20 IVD or IVDs 67
#21 port next a next cath* or portacath* or hickman* or broviac* or cook* or seldinger* or punktion* or groshong* or quinton* 6592
#22 {or #1-#21} 39910
#23 [mh "Anti-Infective Agents"] 27534
#24 [mh ^Disinfection] 340
#25 antiinfect* or anti-infect* or antisep* or anti-sep* or antimicrob* or anti-microb* or antibacter* or anti-bacter* 22911
#26 disinfect* or decontaminat* or clean* or barrier 11855
#27 [mh Alcohols] 32724
#28 [mh ^Chlorhexidine] 1577
#29 alcohol* 22737
#30 ethanol* 5809
#31 isopropyl* 444
#32 chlorhexidine* 3145
#33 {or #23-#32} 96606
#34 cap or caps 2895
#35 hub or hubs 350
#36 connector or connectors 171
#37 {or #34-#36} 3366
#38 #22 and #33 and #37 187
#39 (port or ports or hub or hubs) near/5 protect* 16
#40 (catheter* or connector or connectors or hub or hubs or protector or protectors or protection or protective or barrier or antiinfect* or anti-infect* or antisep* or anti-sep* or antimicrob* or anti-microb* or antibacter* or anti-bacter* or disinfect* or decontaminat* or clean*) near/3 (cap or caps) 45
#41 (alcohol* or ethanol* or chlorhexidine or isopropyl* or impregn*) near/3 (cap or caps) 14
#42 passive near/5 disinfect* 1
#43 {or #39-#42} 67
#44 swab next cap* or swabcap* 1
#45 site next scrub* or sitescrub* 2
#46 life next shield* or lifeshield* 2
#47 EffectIV or EffectIVr or EffectIVtm 38
#48 dual next cap* or dualcap* 1
#49 curos or curosr or curostm 6
#50 {or #44-#49} 50
#51 #38 or #43 or #50 278
#52 #51 in Economic Evaluations 11

A.12: Source: ClinicalTrials.gov

Interface / URL: https://clinicaltrials.gov/ct2/home
Database coverage dates: Not provided
Search date: 22/09/17
Retrieved records: 311
Search strategy:

Search functionality is fairly limited preventing a straight translation of the MEDLINE strategy. The key terms/phrases (most likely to yield relevant records) were prioritised. Each combination listed below was searched separately and the results downloaded individually.

(catheter OR catheters OR catheterization OR catheterisation OR catheterize OR catheterise OR catheterized OR catheterised OR microcatheter OR microcatheters OR cannula OR cannulas OR cannulae OR cannulaes OR cannulize OR cannulise OR cannulized OR cannulised OR microcannula OR microcannulas OR canula OR canulas OR microcanula OR microcanulas OR CVC OR CVCs OR CVL OR CVLs OR PICC OR PICCs OR PIV OR PIVs OR PVC OR PVCs OR PIC OR CVP OR line OR lines OR IAC OR IACs OR CA-BSI OR CA-BSIs OR CABSI OR CABSIs OR CR-BSI OR CR-BSIs OR CRBSI OR CRBSIs OR CLA-BSI OR CLA-BSIs OR CLABSI OR CLABSIs OR CVA OR CVAD OR CVADs OR VAD OR VADs OR IVD OR IVDs OR "port a cath" OR portacath OR hickman OR broviac OR cook OR seldinger OR punktion OR groshong OR quinton) AND (alcohol OR alcohols OR ethanol OR isopropyl OR chlorhexidine OR disinfect OR disinfected OR disinfecting OR decontaminate OR decontaminated OR decontaminating OR clean OR cleaning OR cleaned OR cleanse OR cleansed OR cleansing OR barrier OR antiinfection OR anti-infection OR antiinfective OR anti-infective OR antiseptic OR anti-septic OR antimicrobial OR anti-microbial OR antibacteria OR anti-bacteria OR antibacterial OR anti-bacteria) AND (cap OR caps OR hub OR hubs OR connector OR connectors)
178 results

(venous OR intravenous OR vein OR veins OR vascular OR intravascular OR IV OR subclavian OR jugular OR femoral OR arterial OR intraarterial OR artery OR arteries) AND (access OR site OR sites OR device OR devices OR reservoir OR reservoirs) AND (alcohol OR alcohols OR ethanol OR isopropyl OR chlorhexidine OR disinfect OR disinfected OR disinfecting OR decontaminate OR decontaminated OR decontaminating OR clean OR cleaning OR cleaned OR cleanse OR cleansed OR cleansing OR barrier OR antiinfection OR anti-infection OR antiinfective OR anti-infective OR antiseptic

OR anti-septic OR antimicrobial OR anti-microbial OR antibacteria OR anti-bacteria OR antibacterial OR anti-bacteria) AND (cap OR caps OR hub OR hubs OR connector OR connectors)
125 results

"protective cap OR “protective caps” OR “port protector” OR “port protectors” OR “hub protector” OR “hub protectors” OR “connector protector” OR “connector protectors” OR “passive disinfection” OR “passive disinfecting” OR “swab cap” OR swabcap OR “site scrub” OR sitescrub OR “life shield” OR lifeshield OR “dual cap” OR dualcap OR curos OR effectIV
8 results

A.13: Source: WHO ITCRP

Interface / URL: http://apps.who.int/trialsearch/Default.aspx
Database coverage dates: Not provided
Search date: 21/09/17
Retrieved records: 83
Search strategy:

Search functionality is fairly limited preventing a straight translation of the MEDLINE strategy. The key terms/phrases (most likely to yield relevant records) were prioritised. Each combination listed below was searched separately and the results downloaded individually.

protective cap OR protective caps OR port protector* OR hub protector* OR connector protector* OR passiv* disinfecti* OR swab cap OR swabcap OR site scrub OR sitescrub OR life shield OR lifeshield OR dual cap OR dualcap OR curos OR effectIV = 5

catheter* AND cap OR catheter* AND caps OR catheter* AND hub OR catheter* AND hubs OR catheter* AND connector OR catheter* AND connectors = 23 (24 records for 23 trials)

antiinfect* AND cap OR antiinfect* AND caps OR antiinfect* AND hub OR antiinfect* AND hubs OR antiinfect* AND connector OR antiinfect* AND connector OR anti infect* AND cap OR anti infect* AND caps OR anti infect* AND hub OR anti infect* AND hubs OR anti infect* AND connector OR anti infect* AND connectors OR antisep* AND cap OR antisep* AND caps OR antisep* AND hub OR antisep* AND hubs OR antisep* AND connector OR antisep* AND connectors OR anti sep* AND cap OR anti sep* AND caps OR anti sep* AND hub OR anti sep* AND hubs OR anti sep* AND connector OR anti sep* AND connectors = 3

antimicrob* AND cap OR antimicrob* AND caps OR antimicrob* AND hub OR antimicrob* AND hubs OR antimicrob* AND connector OR antimicrob* AND

connectors OR anti microb* AND cap OR anti microb* AND caps OR anti microb* AND hub OR anti microb* AND hubs OR anti microb* AND connector OR anti microb* AND connectors OR antibacter* AND cap OR antibacter* AND caps OR antibacter* AND hub OR antibacter* AND hubs OR antibacter* AND connector OR antibacter* AND connectors OR anti bacter* AND cap OR anti bacter* AND caps OR anti bacter* AND hub OR anti bacter* AND hubs OR anti bacter* AND connector OR anti bacter* AND connectors = 4 (5 records for 4 trials)

disinfect* AND cap OR disinfect* AND caps OR disinfect* AND hub OR disinfect* AND hubs OR disinfect* AND connector OR disinfect* AND connectors OR decontaminat* AND cap OR decontaminat* AND caps OR decontaminat* AND hub OR decontaminat* AND hubs OR decontaminat* AND connector OR decontaminat* AND connectors OR clean* AND cap OR clean* AND caps OR clean* AND hub OR clean* AND hubs OR clean* AND connector OR clean* AND connectors OR barrier AND cap OR barrier AND caps OR barrier AND hub OR barrier AND hubs OR barrier AND connector OR barrier AND connectors = 16
(19 records for 16 trials)

alcohol* AND cap OR alcohol* AND caps OR alcohol* AND hub OR alcohol* AND hubs OR alcohol* AND connector OR alcohol* AND connectors OR ethanol* AND cap OR ethanol* AND caps OR ethanol* AND hub OR ethanol* AND hubs OR ethanol* AND connector OR ethanol* AND connectors OR isopropyl* AND cap OR isopropyl* AND caps OR isopropyl* AND hub OR isopropyl* AND hubs OR isopropyl* AND connector OR isopropyl* AND connectors OR chlorhexidine* AND cap OR chlorhexidine* AND caps OR chlorhexidine* AND hub OR chlorhexidine* AND hubs OR chlorhexidine* AND connector OR chlorhexidine* AND connectors = 32 (35 records for 32 trials)

A.14: Source: US Food and Drug Administration (FDA) Manufacturer and User Facility Device Experience (MAUDE) database

Interface / URL:
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm
Database coverage dates: MAUDE web search feature is limited to adverse event reports within the past 10 years. Last update 31/08/17
Search date: 20/09/17
Retrieved records: 45
Search strategy:

Search database for Brand Name: Curos
Date Report Received by FDA limited to 01/01/2007 to 09/20/2017
Start of date limit reflects that MAUDE web search only covers the last 10 years

No other options/fields selected

45 records retrieved and downloaded

A.15: Source: Medicines and Healthcare products Regulatory Agency (MHRA) webpages

Interface / URL: https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency
Database coverage dates: N/A
Search date: 20/09/17
Retrieved records: 0
Search strategy:

Results rapidly assessed by the information specialist. Obviously irrelevant results not selected and downloaded.

Site wide search of gov.uk for Curos – 5 results, all clearly irrelevant, 0 selected

Search of requests under the Freedom of Information Act https://www.gov.uk/government/publications/mhra-requests-under-the-freedom-of-information-act-foia The 4 listed PDFs were searched using the Ctrl F function for Curos.

MHRA FOIA request disclosure log 2 March 2017 – present (https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/616895/Disclosure_Log_1_June_2017.pdf) = 0 results

MHRA FOIA request disclosure log 22 November 2016 – 1 March 2017 (https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/595984/Disclosure_Log_1_March_2017.pdf) = 0 results

MHRA FOIA request disclosure log 17 April 2015 - 22 November 2016 (https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/574668/Disclosure_Log_December_2016.pdf) = 0 results

MHRA FOIA request disclosure log 18 January 2005 - 31 March 2015 (https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/595978/Disclosure_FOIA_requests_April_2015_-_Public.pdf). = 0 results

Search “Alerts and recalls for drugs and medical devices” https://www.gov.uk/drug-device-alerts for Curos 0 results

9.9.5 Details of any additional searches, such as searches of company or professional organisation databases (include a description of each database).

None.

9.9.6 The inclusion and exclusion criteria.

See Table B1, section 7.2.1.

9.9.7 The data abstraction strategy.

Data were extracted directly from the full text pulications or abstracts into Tables B3, B4,B6 and B9

9.10 Appendix 2: Search strategy for adverse events (section 7.7.1)

The following information should be provided.

9.10.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

See Section 10.1. The search strategies reported in Section 10.1 were not limited by outcome or study design. They would therefore identify any evidence reporting adverse events or safety outcomes related to the use of the eligible intervention. Separate searches of bibliographic databases (such as MEDLINE, Embase, and the Cochrane Library) to identify adverse event data were not required.

9.10.2 The date on which the search was conducted.

The searches were conducted between 19 and 22 September 2017.

9.10.3 The date span of the search.

The searches were not limited by date. The date coverage of each database searched is shown in Section 10.1.4.

9.10.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

See section 10.1.4.

9.10.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

None.

9.10.6 The inclusion and exclusion criteria.

See Table B1, section 7.2.1.

9.10.7 The data abstraction strategy.

Data were extracted directly from the MAUDE database into Tables B10 and Appendix 5

9.11 Appendix 3: Search strategy for economic evidence (section 8.1.1)

The following information should be provided.

9.11.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process

- EconLIT
- NHS EED.

See Section 10.1. The search strategies reported in Section 10.1 were not limited by outcome or study design. They would therefore identify any economic evidence related to the eligible intervention. Separate searches of bibliographic databases (such as MEDLINE, Embase, and the Cochrane Library databases) to identify economic evidence were not required. The strategy reported in Section 7.1 was additionally translated for the following resources specific to economic research:

- Econlit (Ovid);
- CEA Registry (http://healtheconomics.tuftsmedicalcenter.org/cear4/Home.aspx).

9.11.2 The date on which the search was conducted.

The searches were conducted between 20th and 21st September 2017.

9.11.3 The date span of the search.

The searches were not limited by date. The date coverage of each database searched is given below in Section 10.3.4.

9.11.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The searches are reported in section 10.1.4, and the following additional searches were undertaken just for economic studies.

A.16: Source: EconLit

Interface / URL: Ovid SP
Database coverage dates: 1886-August 2017
Search date: 20/09/17
Retrieved records: 21

Search strategy:

Database: Econlit <1886 to August 2017>
Search Strategy:
---
1 (catheter$ or microcatheter$ or cannula$ or microcannula$ or canula$ or microcanula$).ti,ab,kw. (39)
2 (CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs).ti,ab,kw. (62)
3 ((PIC or CVP) adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kw. (0)
4 (central adj3 (venous or pressure)).ti,ab,kw. (48)
5 ((central or subclavian or jugular or femoral) adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kw. (206)
6 (peripheral adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kw. (12)
7 ((venous or intravenous or vein$1 or vascular or intravascular or IV) adj3 (line$1 or access$ or site or sites or device$ or reservoir$)).ti,ab,kw. (22)
8 ((arterial or intraarterial or artery or arteries) adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kw. (4)
9 (art line$1 or a line$1 or IAC or IACs).ti,ab,kw. (343)
10 (CA-BSI or CA-BSIs or CABSI or CABSIs or CR-BSI or CR-BSIs or CRBSI or CRBSIs or CLA-BSI or CLA-BSIs or CLABSI or CLABSIs).ti,ab,kw. (0)
11 (access$ adj3 (device$ or site or sites or route$1)).ti,ab,kw. (93)
12 ((invasive or percutaneous) adj3 device$).ti,ab,kw. (1)
13 (CVA or CVAD or CVADs or VAD or VADs).ti,ab,kw. (99)
14 (IVD or IVDs).ti,ab,kw. (1)
15 (port a cath$1 or portacath$1 or hickman$1 or broviac$1 or cook$1 or seldinger$1 or punktion$1 or groshong$1 or quinton$1).ti,ab,kw. (366)
16 or/1-15 (1286)
17 (antiinfect$ or anti-infect$ or antisep$ or anti-sep$ or antimicrob$ or anti-microb$ or antibacter$ or anti-bacter$).ti,ab,kw. (73)
18 (disinfect$ or decontaminat$ or clean$ or barrier).ti,ab,kw. (6876)
19 alcohol$.ti,ab,kw. (1899)
20 ethanol$.ti,ab,kw. (831)
21 isopropyl$.ti,ab,kw. (0)
22 chlorhexidine$.ti,ab,kw. (1)
23 or/17-22 (9616)
24 (cap or caps).ti,ab,kw. (3818)
25 (hub or hubs).ti,ab,kw. (1306)
26 (connector or connectors).ti,ab,kw. (27)
27 or/24-26 (5145)
28 16 and 23 and 27 (1)
29 ((port or ports or hub or hubs) adj5 protect$).ti,ab,kw. (10)
30 ((catheter$ or connector or connectors or hub or hubs or protector or protectors or protection or protective or barrier or antiinfect$ or anti-infect$ or antisep$ or anti-

sep$ or antimicrob$ or anti-microb$ or antibacter$ or anti-bacter$ or disinfect$ or decontaminat$ or clean$) adj1 (cap or caps)).ti,ab,kw. (15)
31 ((alcohol$ or ethanol$ or chlorhexidine or isopropyl$ or impregn$) adj3 (cap or caps)).ti,ab,kw. (1)
32 (passive adj5 disinfect$).ti,ab,kw. (0)
33 or/29-32 (26)
34 (swab cap$2 or swabcap$2).ti,ab,kw. (0)
35 (site scrub$2 or sitescrub$2).ti,ab,kw. (0)
36 (life shield$2 or lifeshield$2).ti,ab,kw. (0)
37 (EffectIV or EffectIVr or EffectIVtm).ti,ab,kw. (0)
38 (dual cap$2 or dualcap$2).ti,ab,kw. (0)
39 curos$2.ti,ab,kw. (1)
40 or/34-39 (1)
41 28 or 33 or 40 (28)
42 limit 41 to english (21)

A.17: Source: CEA Registry

Interface / URL: http://healtheconomics.tuftsmedicalcenter.org/cear4/Home.aspx
Database coverage dates: Not provided
Search date: 21/09/17
Retrieved records: 0
Search strategy:

The freely available version of this resource has very basic functionality and only allows the use of single terms with no additional syntax supported. The translation of the MEDLINE strategy was therefore not possible. It was also not possible to search on a single concept only (e.g. cap or caps) as the volume of records returned was unacceptably high. We therefore searched for the named devices only – each term below was searched individually. Results were rapidly assessed by an information specialist and obviously irrelevant records were not downloaded.

EffectIV could not be searched for as the database automatically translated this as effective, returning over 5,000 results.

swab cap - 0
swabcap - 0
site scrub - 0
sitescrub - 0
life shield - 0
lifeshield - 0
dual cap - 0
dualcap - 0
curos – 1 records, obviously irrelevant, 0 selected.

9.11.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

None

9.12 Appendix 4: Resource identification, measurement and valuation (section 9.3.2)

The following information should be provided.

9.12.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

Database / information source	**Interface / URL**
Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)	OvidSP
Embase	OvidSP
Cochrane Database of Systematic Reviews (CDSR)	Cochrane Library / Wiley Interscience
Cochrane Central Register of Controlled Trials (CENTRAL)	Cochrane Library / Wiley Interscience
Health Technology Assessment Database (HTA)	Cochrane Library / Wiley Interscience
Database of Abstracts of Reviews of Effects (DARE)	Cochrane Library / Wiley Interscience
NHS Economic Evaluation Database (NHS EED)	Cochrane Library / Wiley Interscience
Econlit	OvidSP

9.12.2 The date on which the search was conducted.

The searches were conducted on 17/10/2017

9.12.3 The date span of the search.

Searches were restricted to studies published in English from 2012 to date. The choice of date restriction was informed by company knowledge, and

validated by nationally published sources from Health Protection Scotland [18] and Public Health Wales [19] which show reduced rates of CRBSI after 2011.

9.12.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

A4.1 Source: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Interface / URL: OvidSP
Search date: 17/10/17
Retrieved records: 514
Search strategy:

1 Catheter-Related Infections/ (3856)
2 (CA-BSI or CA-BSIs or CABSI or CABSIs or CR-BSI or CR-BSIs or CRBSI or CRBSIs or CLA-BSI or CLA-BSIs or CLABSI or CLABSIs).ti,ab,kf. (1369)
3 ((catheter$ or microcatheter$ or cannula$ or microcannula$ or canula$ or microcanula$) and (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or urosepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or candid?emi$ or parasit?emi$ or vir?emi$ or endotox?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ti. (5105)
4 ((catheter$ or microcatheter$ or cannula$ or microcannula$ or canula$ or microcanula$) adj3 (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or urosepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or candid?emi$ or parasit?emi$ or vir?emi$ or endotox?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ab,kf. (7863)
5 ((catheter$ or microcatheter$ or cannula$ or microcannula$ or canula$ or microcanula$) adj (related or associated)).ti,ab,kf. (9010)
6 ((CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs or CVA or CVAs or CVAD or CVADs or VAD or VADs or IVD or IVDs) and (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or urosepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or candid?emi$ or parasit?emi$ or vir?emi$ or endotox?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ti. (46)
7 ((CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs or CVA or CVAs or CVAD or CVADs or VAD or VADs or IVD or IVDs) adj3 (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or urosepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or candid?emi$ or parasit?emi$ or vir?emi$ or endotox?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ab,kf. (1031)
8 ((port a cath$2 or portacath$2 or hickman$2 or broviac$2 or cook$2 or seldinger$2 or punktion$2 or groshong$2 or quinton$2) and (infect$ or sepsis$ or septic$ or sepses

or postsepsis$ or urosepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or candid?emi$ or parasit?emi$ or vir?emi$ or endotox?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ti. (150)

9 ((port a cath$2 or portacath$2 or hickman$2 or broviac$2 or cook$2 or seldinger$2 or punktion$2 or groshong$2 or quinton$2) adj3 (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or urosepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or candid?emi$ or parasit?emi$ or vir?emi$ or endotox?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ab,kf. (141)

10 ((CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs or CVA or CVAs or CVAD or CVADs or VAD or VADs or IVD or IVDs) adj (related or associated)).ti,ab,kf. (851)

11 ((central line$1 or subclavian line$1 or jugular line$1 or femoral line$1 or venous line$1 or intravenous line$1 or vascular line$1 or intravascular line$1 or IV line$1 or peripheral line$1 or PIC line$1 or CVP line$1 or arterial line$1 or intraarterial line$1 or artery line$1 or arteries line$1 or art line$1 or a line$1 or IAC or IACs) and (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or urosepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or candid?emi$ or parasit?emi$ or vir?emi$ or endotox?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ti. (614)

12 ((central line$1 or subclavian line$1 or jugular line$1 or femoral line$1 or venous line$1 or intravenous line$1 or vascular line$1 or intravascular line$1 or IV line$1 or peripheral line$1 or PIC line$1 or CVP line$1 or arterial line$1 or intraarterial line$1 or artery line$1 or arteries line$1 or art line$1 or a line$1 or IAC or IACs) adj3 (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or urosepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or candid?emi$ or parasit?emi$ or vir?emi$ or endotox?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ab,kf. (1214)

13 ((line-associated or line-related) and (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or urosepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or candid?emi$ or parasit?emi$ or vir?emi$ or endotox?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ti. (465)

14 ((line-associated or line-related) adj3 (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or urosepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or candid?emi$ or parasit?emi$ or vir?emi$ or endotox?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ab,kf. (1016)

15 or/1-14 (16847)

16 exp Great Britain/ (362613)

17 (national health service* or nhs*).ti,ab,in. (158282)

18 (english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab. (92405)

19 (gb or "g.b." or britain* or (british* not "british columbia") or uk or "u.k." or united kingdom* or (england* not "new england") or northern ireland* or northern irish* or scotland* or scottish* or ((wales or "south wales") not "new south wales") or welsh*).ti,ab,jw,in. (1918225)

20 (bath or "bath's" or ((birmingham not alabama*) or ("birmingham's" not alabama*) or bradford or "bradford's" or brighton or "brighton's" or bristol or "bristol's" or carlisle* or "carlisle's" or (cambridge not (massachusetts* or boston* or harvard*)) or

("cambridge's" not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or ("canterbury's" not zealand*) or chelmsford or "chelmsford's" or chester or "chester's" or chichester or "chichester's" or coventry or "coventry's" or derby or "derby's" or (durham not (carolina* or nc)) or ("durham's" not (carolina* or nc)) or ely or "ely's" or exeter or "exeter's" or gloucester or "gloucester's" or hereford or "hereford's" or hull or "hull's" or lancaster or "lancaster's" or leeds* or leicester or "leicester's" or (lincoln not nebraska*) or ("lincoln's" not nebraska*) or (liverpool not (new south wales* or nsw)) or ("liverpool's" not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or ("london's" not (ontario* or ont or toronto*)) or manchester or "manchester's" or (newcastle not (new south wales* or nsw)) or ("newcastle's" not (new south wales* or nsw)) or norwich or "norwich's" or nottingham or "nottingham's" or oxford or "oxford's" or peterborough or "peterborough's" or plymouth or "plymouth's" or portsmouth or "portsmouth's" or preston or "preston's" or ripon or "ripon's" or salford or "salford's" or salisbury or "salisbury's" or sheffield or "sheffield's" or southampton or "southampton's" or st albans or stoke or "stoke's" or sunderland or "sunderland's" or truro or "truro's" or wakefield or "wakefield's" or wells or westminster or "westminster's" or winchester or "winchester's" or wolverhampton or "wolverhampton's" or (worcester not (massachusetts* or boston* or harvard*)) or ("worcester's" not (massachusetts* or boston* or harvard*)) or (york not ("new york*" or ny or ontario* or ont or toronto*)) or ("york's" not ("new york*" or ny or ontario* or ont or toronto*))))).ti,ab,in. (1267263)

21 (bangor or "bangor's" or cardiff or "cardiff's" or newport or "newport's" or st asaph or "st asaph's" or st davids or swansea or "swansea's").ti,ab,in. (47954)

22 (aberdeen or "aberdeen's" or dundee or "dundee's" or edinburgh or "edinburgh's" or glasgow or "glasgow's" or inverness or (perth not australia*) or ("perth's" not australia*) or stirling or "stirling's").ti,ab,in. (185382)

23 (armagh or "armagh's" or belfast or "belfast's" or lisburn or "lisburn's" or londonderry or "londonderry's" or derry or "derry's" or newry or "newry's").ti,ab,in. (22301)

24 or/16-23 (2453999)

25 (exp africa/ or exp americas/ or exp antarctic regions/ or exp arctic regions/ or exp asia/ or exp australia/ or exp oceania/) not (exp great britain/ or europe/) (2643960)

26 24 not 25 (2325120)

27 15 and 26 (1457)

28 exp animals/ not humans/ (4678300)

29 (news or comment or editorial or letter).pt. (1846283)

30 27 not (28 or 29) (1354)

31 limit 30 to (english language and yr="2012 -Current") (571)

32 remove duplicates from 31 (514)

A4.2: Source: Embase 1974 to 2017 October 16

Interface / URL: OvidSP

Search date: 17/10/17

Retrieved records: 978

Search strategy:

1 *catheter infection/ (5519)
2 (CA-BSI or CA-BSIs or CABSI or CABSIs or CR-BSI or CR-BSIs or CRBSI or CRBSIs or CLA-BSI or CLA-BSIs or CLABSI or CLABSIs).ti,ab,kw. (2527)
3 ((catheter$ or microcatheter$ or cannula$ or microcannula$ or canula$ or microcanula$) and (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or urosepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or candid?emi$ or parasit?emi$ or vir?emi$ or endotox?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ti. (6336)
4 ((catheter$ or microcatheter$ or cannula$ or microcannula$ or canula$ or microcanula$) adj3 (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or urosepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or candid?emi$ or parasit?emi$ or vir?emi$ or endotox?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ab,kw. (10854)
5 ((catheter$ or microcatheter$ or cannula$ or microcannula$ or canula$ or microcanula$) adj (related or associated)).ti,ab,kw. (12323)
6 ((CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs or CVA or CVAs or CVAD or CVADs or VAD or VADs or IVD or IVDs) and (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or urosepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or candid?emi$ or parasit?emi$ or vir?emi$ or endotox?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ti. (132)
7 ((CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs or CVA or CVAs or CVAD or CVADs or VAD or VADs or IVD or IVDs) adj3 (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or urosepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or candid?emi$ or parasit?emi$ or vir?emi$ or endotox?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ab,kw. (1728)
8 ((port a cath$2 or portacath$2 or hickman$2 or broviac$2 or cook$2 or seldinger$2 or punktion$2 or groshong$2 or quinton$2) and (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or urosepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or candid?emi$ or parasit?emi$ or vir?emi$ or endotox?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ti. (156)
9 ((port a cath$2 or portacath$2 or hickman$2 or broviac$2 or cook$2 or seldinger$2 or punktion$2 or groshong$2 or quinton$2) adj3 (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or urosepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or candid?emi$ or parasit?emi$ or vir?emi$ or endotox?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ab,kw. (182)
10 ((CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs or CVA or CVAs or CVAD or CVADs or VAD or VADs or IVD or IVDs) adj (related or associated)).ti,ab,kw. (1416)
11 ((central line$1 or subclavian line$1 or jugular line$1 or femoral line$1 or venous line$1 or intravenous line$1 or vascular line$1 or intravascular line$1 or IV line$1 or peripheral line$1 or PIC line$1 or CVP line$1 or arterial line$1 or intraarterial line$1 or artery line$1 or arteries line$1 or art line$1 or a line$1 or IAC or IACs) and (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or urosepsis$ or bacter?emi$ or

bacill?emi$ or fung?emi$ or candid?emi$ or parasit?emi$ or vir?emi$ or endotox?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ti. (948)
12 ((central line$1 or subclavian line$1 or jugular line$1 or femoral line$1 or venous line$1 or intravenous line$1 or vascular line$1 or intravascular line$1 or IV line$1 or peripheral line$1 or PIC line$1 or CVP line$1 or arterial line$1 or intraarterial line$1 or artery line$1 or arteries line$1 or art line$1 or a line$1 or IAC or IACs) adj3 (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or urosepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or candid?emi$ or parasit?emi$ or vir?emi$ or endotox?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ab,kw. (1835)
13 ((line-associated or line-related) and (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or urosepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or candid?emi$ or parasit?emi$ or vir?emi$ or endotox?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ti. (727)
14 ((line-associated or line-related) adj3 (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or urosepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or candid?emi$ or parasit?emi$ or vir?emi$ or endotox?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ab,kw. (1636)
15 or/1-14 (22539)
16 United Kingdom/ (387553)
17 (national health service* or nhs*).ti,ab,in,ad. (267640)
18 (english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab. (33609)
19 (gb or "g.b." or britain* or (british* not "british columbia") or uk or "u.k." or united kingdom* or (england* not "new england") or northern ireland* or northern irish* or scotland* or scottish* or ((wales or "south wales") not "new south wales") or welsh*).ti,ab,jw,in,ad. (2824442)
20 (bath or "bath's" or ((birmingham not alabama*) or ("birmingham's" not alabama*) or bradford or "bradford's" or brighton or "brighton's" or bristol or "bristol's" or carlisle* or "carlisle's" or (cambridge not (massachusetts* or boston* or harvard*)) or ("cambridge's" not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or ("canterbury's" not zealand*) or chelmsford or "chelmsford's" or chester or "chester's" or chichester or "chichester's" or coventry or "coventry's" or derby or "derby's" or (durham not (carolina* or nc)) or ("durham's" not (carolina* or nc)) or ely or "ely's" or exeter or "exeter's" or gloucester or "gloucester's" or hereford or "hereford's" or hull or "hull's" or lancaster or "lancaster's" or leeds* or leicester or "leicester's" or (lincoln not nebraska*) or ("lincoln's" not nebraska*) or (liverpool not (new south wales* or nsw)) or ("liverpool's" not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or ("london's" not (ontario* or ont or toronto*)) or manchester or "manchester's" or (newcastle not (new south wales* or nsw)) or ("newcastle's" not (new south wales* or nsw)) or norwich or "norwich's" or nottingham or "nottingham's" or oxford or "oxford's" or peterborough or "peterborough's" or plymouth or "plymouth's" or portsmouth or "portsmouth's" or preston or "preston's" or ripon or "ripon's" or salford or "salford's" or salisbury or "salisbury's" or sheffield or "sheffield's" or southampton or "southampton's" or st albans or stoke or "stoke's" or sunderland or "sunderland's" or truro or "truro's" or wakefield or "wakefield's" or wells

or westminster or "westminster's" or winchester or "winchester's" or wolverhampton or "wolverhampton's" or (worcester not (massachusetts* or boston* or harvard*)) or ("worcester's" not (massachusetts* or boston* or harvard*)) or (york not ("new york*" or ny or ontario* or ont or toronto*)) or ("york's" not ("new york*" or ny or ontario* or ont or toronto*))))).ti,ab,in,ad. (2104515)
21 (bangor or "bangor's" or cardiff or "cardiff's" or newport or "newport's" or st asaph or "st asaph's" or st davids or swansea or "swansea's").ti,ab,in,ad. (84987)
22 (aberdeen or "aberdeen's" or dundee or "dundee's" or edinburgh or "edinburgh's" or glasgow or "glasgow's" or inverness or (perth not australia*) or ("perth's" not australia*) or stirling or "stirling's").ti,ab,in,ad. (292559)
23 (armagh or "armagh's" or belfast or "belfast's" or lisburn or "lisburn's" or londonderry or "londonderry's" or derry or "derry's" or newry or "newry's").ti,ab,in,ad. (38165)
24 or/16-23 (3442897)
25 (exp "arctic and antarctic"/ or exp oceanic regions/ or exp western hemisphere/ or exp africa/ or exp asia/ or exp "australia and new zealand"/) not (united kingdom/ or europe/) (2738092)
26 24 not 25 (3267451)
27 15 and 26 (2557)
28 (animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/ (5808628)
29 (editorial or letter).pt. (1544446)
30 27 not (28 or 29) (2300)
31 limit 30 to (english language and yr="2012 -Current") (1013)
32 remove duplicates from 31 (978)

A4.3: Source: Cochrane Central Register of Controlled Trials: Issue 9 of 12, September 2017

Interface / URL: Cochrane Library / Wiley Interscience
Search date: 17/10/17
Retrieved records: 227
Search strategy:

#1 [mh ^"Catheter-Related Infections"] 290
#2 (CA-BSI or CA-BSIs or CABSI or CABSIs or CR-BSI or CR-BSIs or CRBSI or CRBSIs or CLA-BSI or CLA-BSIs or CLABSI or CLABSIs) 204
#3 ((catheter* or microcatheter* or cannula* or microcannula* or canula* or microcanula*) and (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti 734
#4 ((catheter* or microcatheter* or cannula* or microcannula* or canula* or microcanula*) near/3 (infect* or sepsis* or septic* or sepses or postsepsis* or

urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)) 1749

#5 ((catheter* or microcatheter* or cannula* or microcannula* or canula* or microcanula*) next (related or associated)) 1408

#6 ((CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs or CVA or CVAs or CVAD or CVADs or VAD or VADs or IVD or IVDs) and (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti 15

#7 ((CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs or CVA or CVAs or CVAD or CVADs or VAD or VADs or IVD or IVDs) near/3 (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)) 160

#8 ((port next a next cath* or portacath* or hickman* or broviac* or cook* or seldinger* or punktion* or groshong* or quinton*) and (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti 10

#9 ((port next a next cath* or portacath* or hickman* or broviac* or cook* or seldinger* or punktion* or groshong* or quinton*) near/3 (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)) 33

#10 ((CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs or CVA or CVAs or CVAD or CVADs or VAD or VADs or IVD or IVDs) next (related or associated)) 131

#11 ((central next line* or subclavian next line* or jugular next line* or femoral next line* or venous next line* or intravenous next line* or vascular next line* or intravascular next line* or IV next line* or peripheral next line* or PIC next line* or CVP next line* or arterial next line* or intraarterial next line* or artery next line* or arteries next line* or art next line* or a next line* or IAC or IACs) and (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti 47

#12 ((central next line* or subclavian next line* or jugular next line* or femoral next line* or venous next line* or intravenous next line* or vascular next line* or intravascular next line* or IV next line* or peripheral next line* or PIC next line* or CVP next line* or

arterial next line* or intraarterial next line* or artery next line* or arteries next line* or art next line* or a next line* or IAC or IACs) near/3 (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)) 118

#13 ((line-associated or line-related) and (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti 35

#14 ((line-associated or line-related) near/3 (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)) 103

#15 {or #1-#14} 2389

#16 [mh "Great Britain"] 6374

#17 (national next health next service* or nhs*) 29866

#18 (english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) near/5 english)) 39254

#19 (gb or "g.b." or britain* or british* or uk or "u.k." or united next kingdom* or england* or northern next ireland* or northern next irish* or scotland* or scottish* or wales or welsh*) 180416

#20 (bath* or birmingham* or bradford* or brighton* or bristol* or carlisle* or cambridge* or canterbury* or chelmsford* or chester* or chichester* or coventry* or derby* or durham* or ely* or exeter* or gloucester* or hereford* or hull* or lancaster* or leeds* or leicester* or lincoln* or liverpool* or london* or manchester* or newcastle* or norwich* or nottingham* or oxford* or peterborough* or plymouth* or portsmouth* or preston* or ripon* or salford* or salisbury* or sheffield* or southampton* or "st albans" or stoke* or sunderland* or truro* or wakefield* or wells or westminster* or winchester* or wolverhampton* or worcester* or york*) 135173

#21 (bangor* or cardiff* or newport* or st next asaph* or "st davids" or swansea*) 2032

#22 (aberdeen* or dundee* or edinburgh* or glasgow* or inverness or perth* or stirling*) 15464

#23 (armagh* or belfast* or lisburn* or londonderry* or derry* or newry*) 1436

#24 {or #16-#23} 287334

#25 ([mh africa] or [mh americas] or [mh "antarctic regions"] or [mh "arctic regions"] or [mh asia] or [mh australia] or [mh oceania]) not ([mh "great britain"] or [mh ^europe]) 50547

#26 #24 not #25 273385

#27 #15 and #26 754

#28 #27 Publication Year from 2012 to 2017 402

#29 #28 in Trials 227

A4.4: Source: Database of Abstracts of Reviews of Effect: Issue 2 of 4, April 2015

Interface / URL: Cochrane Library / Wiley Interscience
Search date: 17/10/17
Retrieved records: 44
Search strategy:

#1 [mh ^"Catheter-Related Infections"] 290
#2 (CA-BSI or CA-BSIs or CABSI or CABSIs or CR-BSI or CR-BSIs or CRBSI or CRBSIs or CLA-BSI or CLA-BSIs or CLABSI or CLABSIs) 204
#3 ((catheter* or microcatheter* or cannula* or microcannula* or canula* or microcanula*) and (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti 734
#4 ((catheter* or microcatheter* or cannula* or microcannula* or canula* or microcanula*) near/3 (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)) 1749
#5 ((catheter* or microcatheter* or cannula* or microcannula* or canula* or microcanula*) next (related or associated)) 1408
#6 ((CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs or CVA or CVAs or CVAD or CVADs or VAD or VADs or IVD or IVDs) and (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti 15
#7 ((CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs or CVA or CVAs or CVAD or CVADs or VAD or VADs or IVD or IVDs) near/3 (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)) 160
#8 ((port next a next cath* or portacath* or hickman* or broviac* or cook* or seldinger* or punktion* or groshong* or quinton*) and (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti 10

#9 ((port next a next cath* or portacath* or hickman* or broviac* or cook* or seldinger* or punktion* or groshong* or quinton*) near/3 (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)) 33

#10 ((CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs or CVA or CVAs or CVAD or CVADs or VAD or VADs or IVD or IVDs) next (related or associated)) 131

#11 ((central next line* or subclavian next line* or jugular next line* or femoral next line* or venous next line* or intravenous next line* or vascular next line* or intravascular next line* or IV next line* or peripheral next line* or PIC next line* or CVP next line* or arterial next line* or intraarterial next line* or artery next line* or arteries next line* or art next line* or a next line* or IAC or IACs) and (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti 47

#12 ((central next line* or subclavian next line* or jugular next line* or femoral next line* or venous next line* or intravenous next line* or vascular next line* or intravascular next line* or IV next line* or peripheral next line* or PIC next line* or CVP next line* or arterial next line* or intraarterial next line* or artery next line* or arteries next line* or art next line* or a next line* or IAC or IACs) near/3 (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)) 118

#13 ((line-associated or line-related) and (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti 35

#14 ((line-associated or line-related) near/3 (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)) 103

#15 {or #1-#14} 2389

#16 [mh "Great Britain"] 6374

#17 (national next health next service* or nhs*) 29866

#18 (english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) near/5 english)) 39254

#19 (gb or "g.b." or britain* or british* or uk or "u.k." or united next kingdom* or england* or northern next ireland* or northern next irish* or scotland* or scottish* or wales or welsh*) 180416

#20 (bath* or birmingham* or bradford* or brighton* or bristol* or carlisle* or cambridge* or canterbury* or chelmsford* or chester* or chichester* or coventry* or derby* or durham* or ely* or exeter* or gloucester* or hereford* or hull* or lancaster* or leeds* or leicester* or lincoln* or liverpool* or london* or manchester* or newcastle* or norwich* or nottingham* or oxford* or peterborough* or plymouth* or portsmouth* or preston* or ripon* or salford* or salisbury* or sheffield* or southampton* or "st albans" or stoke* or sunderland* or truro* or wakefield* or wells or westminster* or winchester* or wolverhampton* or worcester* or york*) 135173

#21 (bangor* or cardiff* or newport* or st next asaph* or "st davids" or swansea*) 2032

#22 (aberdeen* or dundee* or edinburgh* or glasgow* or inverness or perth* or stirling*) 15464

#23 (armagh* or belfast* or lisburn* or londonderry* or derry* or newry*) 1436

#24 {or #16-#23} 287334

#25 ([mh africa] or [mh americas] or [mh "antarctic regions"] or [mh "arctic regions"] or [mh asia] or [mh australia] or [mh oceania]) not ([mh "great britain"] or [mh ^europe]) 50547

#26 #24 not #25 273385

#27 #15 and #26 754

#28 #27 Publication Year from 2012 to 2017 402

#29 #15 Publication Year from 2012 to 2017 1051

#30 #29 in Other Reviews 44

A4.5: Source: Health Technology Assessment Database: Issue 4 of 4, October 2016

Interface / URL: Cochrane Library / Wiley Interscience

Search date: 17/10/17

Retrieved records: 23

Search strategy:

#1 [mh ^"Catheter-Related Infections"] 290

#2 (CA-BSI or CA-BSIs or CABSI or CABSIs or CR-BSI or CR-BSIs or CRBSI or CRBSIs or CLA-BSI or CLA-BSIs or CLABSI or CLABSIs) 204

#3 ((catheter* or microcatheter* or cannula* or microcannula* or canula* or microcanula*) and (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti 734

#4 ((catheter* or microcatheter* or cannula* or microcannula* or canula* or microcanula*) near/3 (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or

viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)) 1749
#5 ((catheter* or microcatheter* or cannula* or microcannula* or canula* or microcanula*) next (related or associated)) 1408
#6 ((CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs or CVA or CVAs or CVAD or CVADs or VAD or VADs or IVD or IVDs) and (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti 15
#7 ((CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs or CVA or CVAs or CVAD or CVADs or VAD or VADs or IVD or IVDs) near/3 (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)) 160
#8 ((port next a next cath* or portacath* or hickman* or broviac* or cook* or seldinger* or punktion* or groshong* or quinton*) and (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti 10
#9 ((port next a next cath* or portacath* or hickman* or broviac* or cook* or seldinger* or punktion* or groshong* or quinton*) near/3 (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)) 33
#10 ((CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs or CVA or CVAs or CVAD or CVADs or VAD or VADs or IVD or IVDs) next (related or associated)) 131
#11 ((central next line* or subclavian next line* or jugular next line* or femoral next line* or venous next line* or intravenous next line* or vascular next line* or intravascular next line* or IV next line* or peripheral next line* or PIC next line* or CVP next line* or arterial next line* or intraarterial next line* or artery next line* or arteries next line* or art next line* or a next line* or IAC or IACs) and (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti 47
#12 ((central next line* or subclavian next line* or jugular next line* or femoral next line* or venous next line* or intravenous next line* or vascular next line* or intravascular next line* or IV next line* or peripheral next line* or PIC next line* or CVP next line* or arterial next line* or intraarterial next line* or artery next line* or arteries next line* or art next line* or a next line* or IAC or IACs) near/3 (infect* or sepsis* or septic* or

sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)) 118

#13 ((line-associated or line-related) and (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti 35

#14 ((line-associated or line-related) near/3 (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)) 103

#15 {or #1-#14} 2389

#16 [mh "Great Britain"] 6374

#17 (national next health next service* or nhs*) 29866

#18 (english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) near/5 english)) 39254

#19 (gb or "g.b." or britain* or british* or uk or "u.k." or united next kingdom* or england* or northern next ireland* or northern next irish* or scotland* or scottish* or wales or welsh*) 180416

#20 (bath* or birmingham* or bradford* or brighton* or bristol* or carlisle* or cambridge* or canterbury* or chelmsford* or chester* or chichester* or coventry* or derby* or durham* or ely* or exeter* or gloucester* or hereford* or hull* or lancaster* or leeds* or leicester* or lincoln* or liverpool* or london* or manchester* or newcastle* or norwich* or nottingham* or oxford* or peterborough* or plymouth* or portsmouth* or preston* or ripon* or salford* or salisbury* or sheffield* or southampton* or "st albans" or stoke* or sunderland* or truro* or wakefield* or wells or westminster* or winchester* or wolverhampton* or worcester* or york*) 135173

#21 (bangor* or cardiff* or newport* or st next asaph* or "st davids" or swansea*) 2032

#22 (aberdeen* or dundee* or edinburgh* or glasgow* or inverness or perth* or stirling*) 15464

#23 (armagh* or belfast* or lisburn* or londonderry* or derry* or newry*) 1436

#24 {or #16-#23} 287334

#25 ([mh africa] or [mh americas] or [mh "antarctic regions"] or [mh "arctic regions"] or [mh asia] or [mh australia] or [mh oceania]) not ([mh "great britain"] or [mh ^europe]) 50547

#26 #24 not #25 273385

#27 #15 and #26 754

#28 #27 Publication Year from 2012 to 2017 402

#29 #15 Publication Year from 2012 to 2017 1051

#30 #29 in Other Reviews 44

#31 #29 in Technology Assessments 23

A4.6: Source: NHS Economic Evaluation Database: Issue 2 of 4, April 2015

Interface / URL: Cochrane Library / Wiley Interscience
Search date: 17/10/17
Retrieved records: 23
Search strategy:

#1 [mh ^"Catheter-Related Infections"] 290
#2 (CA-BSI or CA-BSIs or CABSI or CABSIs or CR-BSI or CR-BSIs or CRBSI or CRBSIs or CLA-BSI or CLA-BSIs or CLABSI or CLABSIs) 204
#3 ((catheter* or microcatheter* or cannula* or microcannula* or canula* or microcanula*) and (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti 734
#4 ((catheter* or microcatheter* or cannula* or microcannula* or canula* or microcanula*) near/3 (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)) 1749
#5 ((catheter* or microcatheter* or cannula* or microcannula* or canula* or microcanula*) next (related or associated)) 1408
#6 ((CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs or CVA or CVAs or CVAD or CVADs or VAD or VADs or IVD or IVDs) and (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti 15
#7 ((CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs or CVA or CVAs or CVAD or CVADs or VAD or VADs or IVD or IVDs) near/3 (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)) 160
#8 ((port next a next cath* or portacath* or hickman* or broviac* or cook* or seldinger* or punktion* or groshong* or quinton*) and (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or

candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti 10

#9 ((port next a next cath* or portacath* or hickman* or broviac* or cook* or seldinger* or punktion* or groshong* or quinton*) near/3 (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)) 33

#10 ((CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs or CVA or CVAs or CVAD or CVADs or VAD or VADs or IVD or IVDs) next (related or associated)) 131

#11 ((central next line* or subclavian next line* or jugular next line* or femoral next line* or venous next line* or intravenous next line* or vascular next line* or intravascular next line* or IV next line* or peripheral next line* or PIC next line* or CVP next line* or arterial next line* or intraarterial next line* or artery next line* or arteries next line* or art next line* or a next line* or IAC or IACs) and (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti 47

#12 ((central next line* or subclavian next line* or jugular next line* or femoral next line* or venous next line* or intravenous next line* or vascular next line* or intravascular next line* or IV next line* or peripheral next line* or PIC next line* or CVP next line* or arterial next line* or intraarterial next line* or artery next line* or arteries next line* or art next line* or a next line* or IAC or IACs) near/3 (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)) 118

#13 ((line-associated or line-related) and (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti 35

#14 ((line-associated or line-related) near/3 (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)) 103

#15 {or #1-#14} 2389

#16 [mh "Great Britain"] 6374
#17 (national next health next service* or nhs*) 29866
#18 (english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) near/5 english)) 39254
#19 (gb or "g.b." or britain* or british* or uk or "u.k." or united next kingdom* or england* or northern next ireland* or northern next irish* or scotland* or scottish* or wales or welsh*) 180416
#20 (bath* or birmingham* or bradford* or brighton* or bristol* or carlisle* or cambridge* or canterbury* or chelmsford* or chester* or chichester* or coventry* or derby* or durham* or ely* or exeter* or gloucester* or hereford* or hull* or lancaster* or leeds* or leicester* or lincoln* or liverpool* or london* or manchester* or newcastle* or norwich* or nottingham* or oxford* or peterborough* or plymouth* or portsmouth* or preston* or ripon* or salford* or salisbury* or sheffield* or southampton* or "st albans" or stoke* or sunderland* or truro* or wakefield* or wells or westminster* or winchester* or wolverhampton* or worcester* or york*) 135173
#21 (bangor* or cardiff* or newport* or st next asaph* or "st davids" or swansea*) 2032
#22 (aberdeen* or dundee* or edinburgh* or glasgow* or inverness or perth* or stirling*) 15464
#23 (armagh* or belfast* or lisburn* or londonderry* or derry* or newry*) 1436
#24 {or #16-#23} 287334
#25 ([mh africa] or [mh americas] or [mh "antarctic regions"] or [mh "arctic regions"] or [mh asia] or [mh australia] or [mh oceania]) not ([mh "great britain"] or [mh ^europe]) 50547
#26 #24 not #25 273385
#27 #15 and #26 754
#28 #27 Publication Year from 2012 to 2017 402
#29 #15 Publication Year from 2012 to 2017 1051
#30 #29 in Other Reviews 44
#31 #29 in Technology Assessments 23
#32 #29 in Economic Evaluations 23

A4.7: Source: Cochrane Database of Systematic Reviews: Issue 10 of 12, October 2017

Interface / URL: Cochrane Library / Wiley Interscience
Search date: 17/10/17
Retrieved records: 54
Search strategy:

#1 [mh ^"Catheter-Related Infections"] 290
#2 (CA-BSI or CA-BSIs or CABSI or CABSIs or CR-BSI or CR-BSIs or CRBSI or CRBSIs or CLA-BSI or CLA-BSIs or CLABSI or CLABSIs):ti,ab,kw 159

#3 ((catheter* or microcatheter* or cannula* or microcannula* or canula* or microcanula*) and (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti 734

#4 ((catheter* or microcatheter* or cannula* or microcannula* or canula* or microcanula*) near/3 (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti,ab,kw 1603

#5 ((catheter* or microcatheter* or cannula* or microcannula* or canula* or microcanula*) next (related or associated)):ti,ab,kw 1218

#6 ((CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs or CVA or CVAs or CVAD or CVADs or VAD or VADs or IVD or IVDs) and (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti 15

#7 ((CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs or CVA or CVAs or CVAD or CVADs or VAD or VADs or IVD or IVDs) near/3 (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti,ab,kw 127

#8 ((port next a next cath* or portacath* or hickman* or broviac* or cook* or seldinger* or punktion* or groshong* or quinton*) and (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti 10

#9 ((port next a next cath* or portacath* or hickman* or broviac* or cook* or seldinger* or punktion* or groshong* or quinton*) near/3 (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti,ab,kw 14

#10 ((CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs or CVA or CVAs or CVAD or CVADs or VAD or VADs or IVD or IVDs) next (related or associated)):ti,ab,kw 100

#11 ((central next line* or subclavian next line* or jugular next line* or femoral next line* or venous next line* or intravenous next line* or vascular next line* or intravascular next line* or IV next line* or peripheral next line* or PIC next line* or CVP next line* or arterial next line* or intraarterial next line* or artery next line* or arteries next line* or

art next line* or a next line* or IAC or IACs) and (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti 47

#12 ((central next line* or subclavian next line* or jugular next line* or femoral next line* or venous next line* or intravenous next line* or vascular next line* or intravascular next line* or IV next line* or peripheral next line* or PIC next line* or CVP next line* or arterial next line* or intraarterial next line* or artery next line* or arteries next line* or art next line* or a next line* or IAC or IACs) near/3 (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti,ab,kw 85

#13 ((line-associated or line-related) and (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti 35

#14 ((line-associated or line-related) near/3 (infect* or sepsis* or septic* or sepses or postsepsis* or urosepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or parasitemi* or parasitaemi* or viremi* or viraemi* or endotoxemi* or endotoxaemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti,ab,kw 79

#15 {or #1-#14} 2138

#16 [mh "Great Britain"] 6374

#17 (national next health next service* or nhs*) 29866

#18 (english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) near/5 english)) 39254

#19 (gb or "g.b." or britain* or british* or uk or "u.k." or united next kingdom* or england* or northern next ireland* or northern next irish* or scotland* or scottish* or wales or welsh*) 180416

#20 (bath* or birmingham* or bradford* or brighton* or bristol* or carlisle* or cambridge* or canterbury* or chelmsford* or chester* or chichester* or coventry* or derby* or durham* or ely* or exeter* or gloucester* or hereford* or hull* or lancaster* or leeds* or leicester* or lincoln* or liverpool* or london* or manchester* or newcastle* or norwich* or nottingham* or oxford* or peterborough* or plymouth* or portsmouth* or preston* or ripon* or salford* or salisbury* or sheffield* or southampton* or "st albans" or stoke* or sunderland* or truro* or wakefield* or wells or westminster* or winchester* or wolverhampton* or worcester* or york*) 135173

#21 (bangor* or cardiff* or newport* or st next asaph* or "st davids" or swansea*) 2032

#22 (aberdeen* or dundee* or edinburgh* or glasgow* or inverness or perth* or stirling*) 15464

#23 (armagh* or belfast* or lisburn* or londonderry* or derry* or newry*) 1436
#24 {or #16-#23} 287334
#25 ([mh africa] or [mh americas] or [mh "antarctic regions"] or [mh "arctic regions"] or [mh asia] or [mh australia] or [mh oceania]) not ([mh "great britain"] or [mh ^europe]) 50547
#26 #24 not #25 273385
#27 #15 and #26 584
#28 #27 Publication Year from 2012 to 2017 301
#29 #15 Publication Year from 2012 to 2017 930
#30 #29 in Cochrane Reviews (Reviews and Protocols) 54

A4.7: Source: Econlit 1886 to September 2017

Interface / URL: OvidSP
Search date: 17/10/17
Retrieved records: 3
Search strategy:

1 (CA-BSI or CA-BSIs or CABSI or CABSIs or CR-BSI or CR-BSIs or CRBSI or CRBSIs or CLA-BSI or CLA-BSIs or CLABSI or CLABSIs).af. (0)
2 ((catheter$ or microcatheter$ or cannula$ or microcannula$ or canula$ or microcanula$) and (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or urosepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or candid?emi$ or parasit?emi$ or vir?emi$ or endotox?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ti. (0)
3 ((catheter$ or microcatheter$ or cannula$ or microcannula$ or canula$ or microcanula$) adj3 (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or urosepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or candid?emi$ or parasit?emi$ or vir?emi$ or endotox?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).af. (2)
4 ((catheter$ or microcatheter$ or cannula$ or microcannula$ or canula$ or microcanula$) adj (related or associated)).af. (1)
5 ((CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs or CVA or CVAs or CVAD or CVADs or VAD or VADs or IVD or IVDs) and (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or urosepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or candid?emi$ or parasit?emi$ or vir?emi$ or endotox?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ti. (0)
6 ((CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs or CVA or CVAs or CVAD or CVADs or VAD or VADs or IVD or IVDs) adj3 (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or urosepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or candid?emi$ or parasit?emi$ or vir?emi$ or endotox?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).af. (0)
7 ((port a cath$2 or portacath$2 or hickman$2 or broviac$2 or cook$2 or seldinger$2 or punktion$2 or groshong$2 or quinton$2) and (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or urosepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or

candid?emi$ or parasit?emi$ or vir?emi$ or endotox?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ti. (0)
8 ((port a cath$2 or portacath$2 or hickman$2 or broviac$2 or cook$2 or seldinger$2 or punktion$2 or groshong$2 or quinton$2) adj3 (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or urosepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or candid?emi$ or parasit?emi$ or vir?emi$ or endotox?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).af. (0)
9 ((CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs or CVA or CVAs or CVAD or CVADs or VAD or VADs or IVD or IVDs) adj (related or associated)).af. (1)
10 ((central line$1 or subclavian line$1 or jugular line$1 or femoral line$1 or venous line$1 or intravenous line$1 or vascular line$1 or intravascular line$1 or IV line$1 or peripheral line$1 or PIC line$1 or CVP line$1 or arterial line$1 or intraarterial line$1 or artery line$1 or arteries line$1 or art line$1 or a line$1 or IAC or IACs) and (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or urosepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or candid?emi$ or parasit?emi$ or vir?emi$ or endotox?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ti. (0)
11 ((central line$1 or subclavian line$1 or jugular line$1 or femoral line$1 or venous line$1 or intravenous line$1 or vascular line$1 or intravascular line$1 or IV line$1 or peripheral line$1 or PIC line$1 or CVP line$1 or arterial line$1 or intraarterial line$1 or artery line$1 or arteries line$1 or art line$1 or a line$1 or IAC or IACs) adj3 (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or urosepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or candid?emi$ or parasit?emi$ or vir?emi$ or endotox?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).af. (0)
12 ((line-associated or line-related) and (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or urosepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or candid?emi$ or parasit?emi$ or vir?emi$ or endotox?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ti. (0)
13 ((line-associated or line-related) adj3 (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or urosepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or candid?emi$ or parasit?emi$ or vir?emi$ or endotox?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).af. (0)
14 or/1-13 (3)
15 limit 14 to (yr="2012 -Current" and english) (3)

9.12.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

In addition to the bibliographic database searches targeted searches of grey literature were performed. Nationwide CRBSI rates were identified for critically ill patients within the NHS for both Wales and Scotland in 2013 [18, 19].

9.12.6 The inclusion and exclusion criteria.

See Section 9.2.1

9.12.7 The data abstraction strategy.

See Section 9.2.1

9.13 Appendix 5: Maude database records of adverse events (n=39) (Section 7.7.3)

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
MW5070690	2017/05/24	Injury	3M Health Care	2017/06/27	LKB	3M's Curos disinfecting caps	Event description: concerns regarding the use of 3M's Curos disinfecting caps for needless connectors in neonates. Curos caps are imbedded with 70% isopropyl alcohol. It is used to reduce the incidence of infections. Background: in 1982 two groups of investigators. Gershanik in New Orleans and Brown in Portland concluded that "intravenous solutions of flush solutions containing 0.9% benzyl alcohol caused severe metabolic acidosis, encephalopathy, respiratory depression and gasping, and perhaps other abnormalities leading to death of a total of 16 infants. Blood and urine from several affected infants had high levels of both benzoic and hippuric acids, known metabolites of benzyl alcohol. Both group stated that no add'l cases occurred after solutions with benzyl alcohol preservative were banned from their nurseries." American Academy of Pediatrics, benzyl alcohol toxic agent in neonatal units. In 1983 the FDA, the CDC and the American Academy of Pediatrics recommended the elimination of benzyl alcohol as a preservative in IV solution and diluents used to reconstitute or dilute medications for infants. In 2000 Stremski reported that 70% isopropyl alcohol plasma concentration of >25 mg/dl is toxic for infants; in 2015 Sauron and colleagues examined the safety of the Swabcap, another disinfection cap (excelsior medical) also imbedded with 70% isopropyl alcohol. It is small bench study. The authors used the Swabcap to cap Smartsite and

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							Caresite connectors and found "the visual appearance of all smartsite valves and 67% of the Caresite valves was changed by Swabcap use. The mean isopropyl alcohol dosages were 52 mmol/l in the Smartsite and 8mmol/l in the Caresite at room temperature and 72 and 7 mmol/l, respectively, at 35 degrees C. No alcohol was found in the control circuit." the control circuit followed standard care, which consisted of disinfecting the luer access valve before injections using friction with an isopropyl alcohol pad for 15 seconds followed by a drying time of 15 seconds. The authors recommended that the Swabcap "should not be used for neonates without further research"; references: American Academy of Pediatrics, benzyl alcohol: toxic agent in neonatal units. Pediatrics, 1983, 72(3): p. 356-8. Stremski, E. And H. Hennes, accidental isopropanol ingestion in children. Pedtr Emerg Care, 2000. 16(4): p. 238-40. Sauron, C., P. Jouvet, G. Pinard, d. Goudreault, B. Martin, B. Rival and A. Moussa, using isopropyl alcohol impregnated disinfection caps in the neonatal intensive care unit can cause isopropyl alcohol toxicity. Acta pediatr, 2015. 104(11): p. E489-93. Vivier, P. M., W. J. Lewander, H. F. Martin and J. G. Linakis, isopropyl alcohol intoxication in a neonate through chronic dermal exposure a complication of a culturally-based umbilical care practice. Pediatr Emerg Care, 1994; 10(2): p. 91-3. Sivilotti, M.L.A., isopro;yl alcohol poisoning. Up to date, 2015. Version 12 (topic 334). Mydler T.T., G. S. Wasserman, W. A. Watson and

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							J. F. Knapp, two-week-old infant with isopropanol intoxication. Pediatr Emerg Care, 1993. 9(3): p. 146-8.
2110898-2017-00083	2017/05/01	Malfunction	3M health care	2017/06/06	LKB	3M Curos jet disinfecting cap for needleless connectors	Event description: customer reported Curos jet caps were placed on the needleless connectors of their IV tubing. The Curos jet caps were removed to connect IV fluids/medication. Two patients reportedly experienced leaking from the needleless connectors when the IV fluids/medication were infusing or being disconnected. Customer reported only a minimal amount of medication was lost and no patient harm occurred. Manufacturer narrative: on (b)(6) 2017; was used as the date of the event. No specific date of event was provided by reporter. No samples were available to 3M for evaluation. Customer reported samples were sent to Carefusion because they thought the issue was related to the needleless connectors.
2110898-2017-00066	2017/04/14	Malfunction	3M Health Care	2017/05/02	LKB	3M Curos tips disinfecting cap strip for male luers	Event description: customer reported the plastic film from cm5-200 Curos male tips was sporadically staying on the end of the male tip when removed from the strip. No known patient harm or injury has been associated with this report. Manufacturer narrative: pt information not provided by reporter. Customer reported a facility Medwatch report was sent to the FDA. On 5/2/2017, 3M has not received the facility Medwatch from the FDA yet.
2110898-2017-00062	2017/02/10	Malfunction	3M Health Care	2017/04/28	LKB	3M Curos jet disinfecting cap for	Event description: customer reported a patient had iv fluids infusing via an iv infusion pump. Curos jet caps were reportedly placed on the needleless connectors of the IV tubing. Customer stated the patient experienced leaking from the needleless

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
						needleless connectors	connector closest to the patient which reportedly had a Curos jet cap in place. The leak was noticed right away and the tubing was changed. No patient harm or consequence was reported. Manufacturer narrative: information not provided by reporter. On (b)(6) 2017- date 3M management made the internal decision to file an MDR report for this complaint. 3M completed a retrospective complaint review. This report is now being filed with the FDA due to similar reports where an injury occurred. There was no patient injury associated with this report.
6529588	2017/04/14	Malfunction	3M company, 3M Health Care	2017/04/28	LKB	Curos	Event description: when removing the Curos disinfecting cap from the strip for the male luers, the plastic strip that covers the tip in between the foil and tip remained on the Curos tip. So, when applied to the male connection on the line it can remain there. When injecting through the connection the plastic strip cam be forced into the I.V. line.
2110898-2017-00058	2017/01/23	Malfunction	3M Health Care	2017/04/27	LKB	3M Curos jet disinfecting cap for needleless connectors	Event description: customer reported an ICU patient was receiving levophed via an IV infusion pump. He reported a nurse discovered there was leaking from a needleless connector where a cfj5-250 Curos jet cap was in place. The iv tubing and Curos jet cap were reportedly replaced and no further leaks occurred. Customer reported no patient harm occurred. Manufacturer narrative: customer reported the event occurred between (b)(6) 2017 and (b)(6) 2017. Exact date was unknown. On (b)(6) 2017 was used for the event date in this report. On (b)(6) 2017 - date 3M

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							management made the internal decision to file an MDR report for this complaint. A 3M completed a retrospective complaint review. This report is now being filed with the FDA due to similar reports where an injury occurred. There was no patient injury associated with this report.
2110898-2017-00059	2017/02/09	Malfunction	3M Health Care	2017/04/27	LKB	3M Curos jet disinfecting cap for needleless connectors	Event description: customer reported Curos jet caps were placed on the iv tubing needleless connectors during a product evaluation. A nurse reported leaking from a connection between the needleless connector and the Curos jet cap when the IV tubing was accidentally left clamped. There was no patient injury or harm reported. Manufacturer narrative: on 04/21/2017- date 3M management made the internal decision to file an MDR report for this complaint. 3M completed a retrospective complaint review. This report is now being filed with the FDA due to similar reports where an injury occurred. There was no patient injury associated with this report. (b)(4) report received from the FDA.
2110898-2017-00060	2017/02/10	Malfunction	3M Health Care	2017/04/27	LKB	3M Curos jet disinfecting cap for needleless connectors	Event description: customer reported a patient was receiving an unspecified antibiotic via an IV infusion pump. Curos jet caps were reportedly placed on the IV tubing needleless connectors. Leaking was reported from the connection between the needleless connector and the Curos jet cap located in the mid portion of the IV tubing. The leak was reportedly noticed right away, the tubing was changed and new Curos jet caps were placed on the needleless connectors. No further leaking was reported. Customer reported there was no patient

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							harm or consequence as a result of the leaking. Manufacturer narrative: information not provided by reporter. On (b)(6) 2017- date 3M management made the internal decision to file an MDR report for this complaint. 3M completed a retrospective complaint review. This report is now being filed with the FDA due to similar reports where an injury occurred. There was no patient injury associated with this report.
2110898-2017-00061	2017/02/11	Malfunction	3M Health Care	2017/04/27	LKB	3M Curos jet disinfecting cap for needleless connectors	Event description: customer reported a patient had ATG (anti-thymocyte globulin) piggy backed into an IV tubing set with three needleless connectors. The infusion was running via an infusion pump. Curos jet caps were reportedly placed on the needleless connectors. Leaking was reported from one of the needleless connectors with a Curos jet cap in place. The leak was reportedly noticed right away, the tubing was changed and new Curos jet caps were placed on the needleless connectors. No further leaking was reported. Customer reported there was no patient harm or consequence as a result of the leaking. Manufacturer narrative: information not provided by reporter. Date 33M management made the internal decision to file an MDR report for this complaint. 3M completed a retrospective complaint review. This report is now being filed with the FDA due to similar reports where an injury occurred. There was no patient injury associated with this report.
2110898-2017-00055	2017/01/17	Malfunction	3M Health Care	2017/04/26	LKB	3M Curos jet disinfecting	Event description: customer reported Curos jet caps were placed on the iv tubing needleless connectors. Customer reported iv fluids were noted

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
						cap for needleless connectors	to be leaking from the needleless connector/ Curos jet cap connection located in the middle of the IV tubing. The Curos jet cap was removed and replaced with a Curos cap with foam. Iv fluids were reportedly infusing and no harm occurred to the patient. Manufacturer narrative: Pt information not provided by reporter report date 04/21/2017- date 3M management made the internal decision to file an MDR report for this complaint. 3M completed a retrospective complaint review. This report is now being filed with the FDA due to similar reports where an injury occurred. There was no patient injury associated with this report.
2110898-2017-00056	2017/01/01	Malfunction	3M Health Care	2017/04/26	LKB	3M Curos jet disinfecting cap for needleless connectors	Event description: customer reported Curos jet caps were placed on the IV tubing needleless connectors. Customer reported a nurse noted IV fluid leakage from the needleless connector / Curos jet cap located on the distal end of the IV tubing. The Curos jet cap was removed, replaced with a new Curos jet cap and no further leakage was noted. IV fluids were reportedly infusing and customer reported no patient harm occurred. Manufacturer narrative: customer reported the event occurred in early (b)(6), exact date was unknown. (b)(6) 2017 was used for the event date in this report. On (b)(6) 2017- date 3M management made the internal decision to file an MDR report for this complaint. 3M completed a retrospective complaint review. This report is now being filed with the FDA due to similar reports where an injury occurred. There was no patient injury associated with this report.

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
2110898-2017-00057	2017/01/16	Malfunction	3M Health Care	2017/04/26	LKB	3M Curos jet disinfecting cap for needleless connectors	Event description: customer reported they have been using cfj5-250 Curos jet caps for approximately two weeks and have had about six reports of leaking at the connection between the IV tubing needleless connector and the Curos jet cap. Customer reported no patient harm has occurred. Manufacturer narrative: customer reported the events occurred in the past week. Exact dates and details were unknown. The (b)(6) 2017 was used for the event date based on the report date of (b)(6) 2017. On (b)(6) 2017- date 3M management made the internal decision to file an MDR report for this complaint. 3M completed a retrospective complaint review. This report is now being filed with the FDA due to similar reports where an injury occurred. There was no patient injury associated with this report.
2110898-2017-00053	2017/01/01	Malfunction	3M Health Care	2017/04/25	LKB	3M Curos jet disinfecting cap for needleless connectors	Event description: customer reported Curos jet caps were placed on the iv tubing needleless connectors. A nurse clamped the iv tubing below the needleless connector and the infusion pump did not recognize a downstream occlusion because it was leaking under the Curos jet cap. During a routine assessment, the patient reported a few drops of fluid from the needleless connector/ Curos jet cap connection had dripped onto her pajamas. The Curos jet cap was removed and replaced with a new one. No further leaking was noted on that shift. Customer reported no harm occurred to the patient. Manufacturer narrative: information not provided by reporter. Customer reported the event occurred in early (b)(6) and did not have the exact

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							date of the event. On (b)(6) 2017 was used for date of event in this report. On 04/21/2017- date 3M management made the internal decision to file an mdr report for this complaint. 3M completed a retrospective complaint review. This report 2110898-2017-00053 is now being filed with the FDA due to similar reports where an injury occurred. There was no patient injury associated with this report.
2110898-2017-00050	2017/03/21	Injury	3M Health Care	2017/04/18	LKB	3M Curos disinfecting cap for needleless connectors	Event description: risk manager reported the mother of an (b)(6) old toddler alleged her son removed cff10-250 Curos disinfecting caps from his fluid line and put one in his mouth. The mother alleged her son was choking on one of the green caps and she removed it. Risk manager reported the toddler was evaluated following the reported event and his lungs were clear, O2 saturation was 100% and he had easy work of breathing. Manufacturer narrative: were not provided by reporter. There was no lot number provided for the product. Without lot number it is not possible to determine the expiration date or manufacture date. 3M received facility Medwatch report (b)(4) from the FDA and contacted the reporter to obtain additional information. Customer reported they have not had any other reports of children removing the Curos cap from the needleless connector. Packaging instructions for use contain the following caution statement: caution: potential choking hazard.
6493194	2017/03/15	Malfunction	3M company	2017/04/14	LKB	Curos	Event description: male end of tubing breaks off when Curos tips are applied.

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
6456187	2017/02/09	Malfunction	3M company	2017/04/04	LKB	Curos caps	Event description: a trial of 3M Curos jet alcohol caps started the first week of (b)(6) 2017. Approximately 1 week into the trial, a nurse reported fluid leaking from a baxter clearlink IV tubing access port with a Curos cap in place when the tubing was accidently left clamped. The event was reported to 3M to investigate the problem. Several weeks later, a second report was received of a Curos cap screwed on at an angle on a baxter clearlink IV access port causing fluid to leak from the port. The leaking stopped when a cap was placed on correctly. A third report was received of a damaged hospira microclave suspected by the nurse to be associated with the Curos jet cap. In a conference call with 3M representatives, we learned the 3M technical engineers were intermittently able to duplicate the leaking when the baxter clearlink tubing was put under pressure (the tubing was not pressurized above the maximum limit it is made to withstand) and a Curos jet cap was in place. They also said they could create a small leak without a jet cap in place. They said they had 5 other hospitals that experienced leaks when using the jet cap and baxter clearlink tubing. Manufacturer response for caps for iv tubing, Curos caps (per site reporter): date: February, 2017. Subject: reports of Baxter® clearlink IV access system leaking with use of 3M Curos jet disinfecting cap for needleless connectors. Dear valued healthcare partner, we have recently been made aware of reports that some Baxter® continu-flo solution sets with clearlink needleless connectors

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							may intermittently leak from their clearlink needleless connectors while under pressure when used in conjunction with 3M Curos jet disinfecting cap for needleless connectors. We have investigated the Curos jet lots in question and have found them to be within our design specifications. As your healthcare partner, 3M takes these reports very seriously and is vigorously investigating this issue. We have made Baxter® aware of the situation and are working with them to better understand the root cause of this issue. For questions and additional information related to 3M Curos disinfecting port protectors, please contact your local 3m sales representative, or the 3M health care customer helpline at (b)(4). Kindly, (b)(4).
6431666	2017/03/21	Malfunction	3M company, 3M Health Care	2017/03/24	LKB	Curos	Event description: the patient was found by his parent to have pulled the green Curos caps off of his fluid lines and tried to put them in his mouth. The parent stated that patient was choking on one of the caps and had been removed by parent. The patient's lung sounds clear, easy work of breathing and saturations are 100%.
2110898-2017-00026	2017/01/26	Injury	3M Health Care	2017/03/01	LKB	3M Curos jet disinfecting cap for needleless connectors	Event description: customer reported a patient had IV vancomycin infusing via an IV infusion pump. Curos jet caps were reportedly placed on the injection ports of the IV tubing. Customer reported the patient experienced leaking from the injection port closest to the patient. The injection port reportedly had a Curos jet cap in place. The leak was noticed right away so a limited amount of vancomycin was lost. The tubing was changed, the vancomycin levels were checked and reportedly

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							remained fine. No additional dosing was needed. Manufacturer narrative: no patient information was available for this report. Event date: (b)(6) 2017 was used for the date of event since the customer reported the event occurred approximately 3-4 weeks ago and did not have the exact date of occurrence. There was no given lot number for the product. Without lot number it is not possible to determine the expiration date or manufacture date. We received a delivery failure to our first EMDR submission which stated an "event type code" was required. We would like to be able to select "other" as we feel this report does not fit into death, serious injury or malfunction. As a result we selected "no information" with our first EMDR report and received the delivery failure. We feel the FDA should be aware of this reported event due to the nature of the intervention that was required. Serious injury was now selected as this section could not be left blank, however the patient did not suffer a serious injury as a result of this incident. The patient reportedly experienced leaking of medication. The patient required a blood level check to ensure a therapeutic level of the medication had been achieved. The patient had a therapeutic level and did not require any further intervention. Customer reported no sample or lot number was available for this report.
2110898-2017-00025	2017/02/02	Injury	3M Health Care	2017/02/28	LKB	3M Curos jet disinfecting cap for	Event description: customer reported a (b)(6) female patient had IV chemotherapy infusing via an IV pump. Curos jet caps were reportedly placed on the injection ports of the IV tubing. Customer

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
						needleless connectors	reported approximately 150 cc of the chemotherapy infusion was found to be leaking from the injection port closest to the patient which had a Curos jet cap in place. The patient required re-dosing and was given the estimated amount of chemotherapy that was lost due to leaking. Manufacturer narrative: date of event: (b)(6) 2017 was used for the date of event since the customer reported the event occurred approximately 1 1/2 weeks ago and did not have the exact date of occurrence. There was no given lot number for the product. Without lot number it is not possible to determine the expiration date or manufacture date. Customer reported no sample or lot number were available for this report.
2110898-2017-00020	2017/02/12	Injury	3M Health Care	2017/02/22	LKB	3M Curos jet disinfecting cap for needleless connectors	Event description: customer reported an ICU patient was receiving an epinephrine/neosynephrine drip via an IV infusion pump. The patient's blood pressure was reportedly dropping when the clinician discovered a puddle of fluid on the floor. Customer reported the IV fluids were leaking from an injection port where a (b)(4) Curos jet cap was in place. The Curos jet caps were discontinued and the tubing was reportedly replaced. No further leaks occurred and the customer reported the patient did not suffer and adverse consequences as a result of the reported incident. Manufacturer narrative: there was no given lot number for the product. Without lot number it is not possible to determine the expiration date or manufacture date. The product was not returned for evaluation as of the date of this report.

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
2110898-2017-00021	2017/01/25	Injury	3M Health Care	2017/02/22	LKB	3M Curos jet disinfecting cap for needleless connectors	Event description: customer reported they experienced periodic leaking from injection ports where cfj5-250 Curos jet disinfecting caps were used. In the past two weeks, there were two reports where patients had IV chemotherapy piggybacked into infusion tubing running via a pump (unknown brand). The leaking was reportedly discovered after only a few drops of leaking. There was reportedly no harm or consequence to the patient. The leaking reportedly stopped when the Curos jet cap was replaced or in some instances, when both the tubing and Curos jet caps were replaced. Manufacturer narrative: date of event: (b)(6) 2017 was used for the date of event since the customer reported the events occurred within the last two weeks and did not have the exact date of occurrence. There was no given lot number for the product. Without lot number it is not possible to determine the expiration date or manufacture date. The product was not returned for evaluation as of the date of this report.
2110898-2017-00012	2017/01/16	Injury	3M Health Care	2017/02/14	LKB	3M Curos disinfecting cap for needleless connectors	Event description: customer reported a CFF1 270r Curos cap was applied directly to the hub of a PICC catheter which resulted in separation of the sponge. Customer reported the PICC line was removed. No additional information was available. Customer reported this event was the result of user error and no fault with the device. The customer reported follow- up occurred on (b)(6) 2017 and training and support will be provided by the representative. Manufacturer narrative: patient information was not provided. There was no lot number or sample

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							provided for this report so full investigation could not be completed. Customer reported this event was the result of user error and no fault with the device. The customer reported follow- up occurred on (b)(6) 2017 and training and support will be provided by the representative. This compliant report involves product cff1-270r Curos disinfecting cap for needleless connectors which is sold outside the united states (OUS). Current OUS product packaging contains intended use information and states this product is intended for use on swabbable lure access valves as a disinfecting cleaner prior to line access. The cff1-270r Curos disinfecting cap for needleless connectors noted in this adverse event was reportedly not applied to a needleless luer valve. It was applied directly to the catheter hub. Manufacturer 3M markets a similar product in the US, cff1-270 Curos disinfecting cap for needleless connectors. The US product packaging was updated to include the following warning and cautionary statements: warning: to avoid potential injury - use only on needleless connectors. Caution: potential choking hazard. This warning and caution statement is scheduled to be added to the OUS packaging in March, 2017. In addition, 3M provides training materials (including graphics) instructing customers to apply Curos disinfecting cap for needleless connectors only to needleless connectors and not to apply the Curos disinfecting caps directly to a catheter hub. PDF of training materials are attached to this report. In summary, the packaging update clearly states via

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							warning that the product should only be used on needleless connectors.
2110898-2017-00013	2017/01/16	Injury	3M Health Care	2017/02/14	LKB	3M Curos disinfecting cap for needleless connectors	Event description: customer reported a CFF1 270r Curos cap was applied directly to the hub of a midline catheter which resulted in separation of the sponge. She reportedly witnessed the incident and was able to retrieve the sponge using a forceps. The midline catheter was reportedly removed following the incident due to infection risk. No additional information was available. Customer reported this event was the result of user error and no fault with the device. The customer reported follow- up occurred on (b)(6) 2017 and training and support will be provided by the representative. Manufacturer narrative: patient information was not provided. Date of event was not provided so report date was also used for date of event. There was no lot number or sample provided for this report so full investigation could not be completed. Customer reported this event was the result of user error and no fault with the device. The customer reported follow- up occurred on (b)(6) 2017 and training and support will be provided by the representative. This compliant report involves product CFF1-270r Curos disinfecting cap for needleless connectors which is sold outside the united states (OUS). Current OUS product packaging contains intended use information and states this product is intended for use on swabbable lure access valves as a disinfecting cleaner prior to line access.... · the CFF1-270r Curos disinfecting cap for needleless connectors noted in this adverse event was

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							reportedly not applied to a needleless luer valve. It was applied directly to the catheter hub. 3M markets a similar product in the US, CFF1-270 Curos disinfecting cap for needleless connectors. The us product packaging was updated to include the following warning and cautionary statements: warning: to avoid potential injury - use only on needleless connectors caution: potential choking hazard this warning and caution statement is scheduled to be added to the OUS packaging in March, 2017. The intended use and instructions for use packaging information is attached in the pdf. In addition, 3M provides training materials (including graphics) instructing customers to apply Curos disinfecting cap for needleless connectors only to needleless connectors and not to apply the Curos disinfecting caps directly to a catheter hub. PDF of training materials are attached to this report. In summary, the packaging update clearly states via warning that the product should only be used on needleless connectors.
2110898-2017-00014	2017/01/16	Malfunction	3M Health Care	2017/02/14	LKB	3M Curos disinfecting cap for needleless connectors	Event description: customer reported a CFF1 270r Curos cap was applied directly to the hub of a catheter (unspecified type) which resulted in separation of the sponge. At the time of the event, customer reported they did not know where the sponge was. The sponge was reportedly found several hours later in a bin. No additional information was available. Customer reported this event was the result of user error and no fault with the device. The customer reported follow- up occurred on (b)(6) 2017 and training and support

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							will be provided by the representative. Manufacturer narrative: patient information was not provided. Date of event was not provided so report date was also used for date of event. There was no lot number or sample provided for this report so full investigation could not be completed. Customer reported this event was the result of user error and no fault with the device. The customer reported follow- up occurred on (b)(6) 2017 and training and support will be provided by the representative. This compliant report involves product CFF1-270r Curos disinfecting cap for needleless connectors which is sold outside the united states (OUS). Current OUS product packaging contains intended use information and states this product is intended for use on swabbable lure access valves as a disinfecting cleaner prior to line access.... · the cff1-270r Curos disinfecting cap for needleless connectors noted in this adverse event was reportedly not applied to a needleless luer valve. It was applied directly to the catheter hub. 3M markets a similar product in the us, CFF1-270 Curos disinfecting cap for needleless connectors. The us product packaging was updated to include the following warning and cautionary statements: warning: to avoid potential injury - use only on needleless connectors caution: potential choking hazard. This warning and caution statement is scheduled to be added to the OUS packaging in March, 2017. The intended use and instructions for use packaging information is attached in the pdf. In addition, 3M provides training materials (including

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							graphics) instructing customers to apply Curos disinfecting cap for needleless connectors only to needleless connectors and not to apply the Curos disinfecting caps directly to a catheter hub. PDF of training materials are attached to this report. In summary, the packaging update clearly states via warning that the product should only be used on needleless connectors.
6325422	2017/01/31	Malfunction	3M company, 3M Health Care	2017/02/13	LKB	Curos	Event description: Curos cap broke in two while nurse was screwing the cap on a picc line.
6275607	2017/01/09	Malfunction	3M company	2017/01/25	LKB	3M, Curos disinfecting cap for Tego	Event description: internal ring of cap disconnected from the external cap.
2110898-2016-00041	2016/02/18	Death	3M Health Care	2016/03/22	LKB	3M Curos disinfecting cap for needleless connectors	Event description: customer reported a female patient with an abscess/bowel perforation was receiving antibiotics through an internal jugular, triple lumen central line catheter. A nursing student reportedly disconnected the IV setup (saline bag/antibiotic piggy back and needleless connector) down to the catheter hub. Customer reported the central line catheter lumen was not clamped when the IV was disconnected and a Curos cap was placed directly on the central line catheter hub. After disconnecting the IV, the patient was moved to a chair. Customer stated the patient then experienced headaches and respiratory issues which led to a respiratory arrest. Customer reported patient was in serious condition, diagnosed with a massive air embolic stroke and died sixteen days later. Manufacturer narrative: infusion nurses

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							society (INS) is a globally recognized authority for best practices related to infusion therapy. In the fifth edition of infusion nurses society (INS) policies and procedures, it states the following under key points related to air embolism: ensure the vascular access device (VAD) is securely clamped when disconnecting/reconnecting a new administration set, needleless connector, or any other add-on device. The central vascular access device was not clamped when the IV was disconnected. In addition, the Curos disinfecting port protector was not used as directed. Product packaging contains directions for use and intended use information. Intended use: the Curos is intended for use on swabbable luer access valves as a disinfecting cleaner prior to line access and to act as a physical barrier to contamination between line accesses.
2110898-2016-00022	2015/11/18	Injury	3M Health Care	2016/02/24	LKB	3M Curos disinfecting cap for needless connector	Event description: customer reported a patient had a right chest tube connected via a three-way stopcock to low wall suction. A green Curos cap had been placed over the three-way stopcock to cover the access port. The physician was concerned about blood clots so medication was ordered to be administered through the chest tube. After the medication was administered, the chest tube was clamped for 1 hour. When unclamped, the chest tube did not appear to be draining despite being hooked to low wall suction. The patient then reportedly started to medically decompensate and required a non-rebreather mask at 100% and multiple medications to manage his rising systolic blood pressure. A physician attempted to flush the

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							patient's chest tube and when he forcefully drew back on the access port leading to the patient's chest-tube stopcock, he noted a very small white ball at the very end of the access port. The physician was able to pull the small white ball out with his fingertips and noted it looked similar to the white portion of the Curos cap that is impregnated with alcohol. The original Curos cap had been discarded when the medication was administered so it was not available for inspection. Once the port was cleared of the small white ball, the chest tube began draining serosanguinous fluid and the patient recovered. Manufacturer narrative: the facility reported this event to the FDA ((b)(4)). 3M received the report from the FDA. In the facility report, the following information was noted: device usage problem. "the Curos cap product information notes that the Curos cap is intended for use on swabbable luer access valves prior to line access and to act as a physical barrier to contamination between line accesses. It should not be connected to a three-way stopcock. "the Curos passive disinfection device was used on a connector that it was not meant to be used on".
5406449	2015/11/18	Injury	3M	2016/02/03	LKB	Curos	Event description: the patient had a right-sided chest tube to low wall suction. In the morning, the interventional pulmonary physician ordered TPA (alteplase) and dornase to be administered via through the chest tube; the physician was concerned for blood clots and wanted to break them up. A green Curos cap had been placed over the three-way stopcock by the radiology physician

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							team to cover the access port. The administration was completed and the chest tube remained clamped for 1 hour. When is was unclamped an hour later, as directed by interventional pulm md, the chest tube did not appear to be draining. This failure to drain occurred despite the continuation of the low wall suction to the chest tubes. Concurrently, the patient started to medically decompensate and required a non-rebreather mask at 100% and multiple medications to manage his rising sbp (systolic blood pressure) to the 230s. Multiple providers were called to the bedside including medical mds and nursing specialists and supervisor. The interventional pulmonary physician returned to bedside and attempted to flush the patient's chest tube with 10cc ns in order to promote drainage. He remained concerned that a clot may have formed and blocked the tube. When he forcefully drew back on the access port leading to the patient's chest-tube stopcock, the physician noted a very small white ball appeared at the very end of the access port. The physician was able to pull small white ball out with his fingertips, commenting that it looked similar to white portion of the Curos cap that is impregnated with alcohol. The original cap had been discarded when the administration was provided one hour earlier, so it was not available for inspection. Once the tube was cleared of the small white ball, then the chest tube began draining serosanguinous drainage and the patient recovered.event description: the patient had a right-sided chest tube to low wall suction. In the

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							morning, the interventional pulmonary physician ordered TPA (alteplase)and dornase to be administered via through the chest tube; the physician was concerned for blood clots and wanted to break them up. A green Curos cap had been placed over the three-way stopcock by the radiology physician team to cover the access port. The administration was completed and the chest tube remained clamped for 1 hour. When is was unclamped an hour later, as directed by interventional Pulm MD, the chest tube did not appear to be draining. This failure to drain occurred despite the continuation of the low wall suction to the chest tubes. Concurrently, the patient started to medically decompensate and required a non-rebreather mask at 100% and multiple medications to manage his rising SBP (systolic blood pressure) to the 230s. Multiple providers were called to the bedside including medical MDs and nursing specialists and supervisor. The interventional pulmonary physician returned to bedside and attempted to flush the patient's chest tube with 10cc ns in order to promote drainage. He remained concerned that a clot may have formed and blocked the tube. When he forcefully drew back on the access port leading to the patient's chest-tube stopcock, the physician noted a very small white ball appeared at the very end of the access port. The physician was able to pull small white ball out with his fingertips, commenting that it looked similar to white portion of the Curos cap that is impregnated with alcohol. The original cap had

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							been discarded when the administration was provided one hour earlier, so it was not available for inspection. Once the tube was cleared of the small white ball, then the chest tube began draining serosanguinous drainage and the patient recovered.
4253141	2014/09/27	Malfunction	Ivera Medical	2014/10/01	FPA	Curos	Event description: RN unscrewed the Curos cap from the IV kine and the inside of the cap was still around the line. RN had to use a hemstat clamp to remove it.
3008142801-2014-00001	2014/07/11	Malfunction	Ivera Medical	2014/09/27	LKB	Curos disinfecting port protector	Event description: the Curos caps are breaking while patients are moving around in bed and also break apart as the nurse removes the cap. Manufacturer narrative: notification of the MDR was provided through a letter from the FDA dated on (b)(4) 2014. The letter was received at ivera on (b)(4) 2014. The reported device was not returned by the user facility nor was the lot number communicated. Without the device or lot number, ivera is not able to investigated the reported issue. Contact was made with the user facility, which they indicated that issues were minor and non-significant. There was no patient of safety related incident and they have not had any additional issues since the recent reports. Ivera did review verification requirements that are conducted in manufacturing of the product. Sampling is conducted on a continuous periodic basis, which tensile verification is part of inspection to confirm that a minimum retention force when engaged with a needleless luer activated valve (LAV). Manufacturing limits are established on the

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							manufacturing equipment, which is monitored real-time. If an excursion occurs outside the manufacturing limits, the manufacturing equipment will automatically segregate product produced at the time the excursion occurs.
3008142801-2014-00002	2014/08/03	Malfunction	Ivera Medical	2014/09/27	LKB	Curos disinfecting port protector	Event description: Curos cap broke apart. Little green ring stayed on the IV port when RN took the cap off. This apparently happened twice. Manufacturer narrative: MDR was observed when conducted a search of FDA 's Maude database on September 25, 2014. No other notification was provided by the user facility nor (b)(4)'s sale representatives. The reported device was not returned by the user facility nor was the lot number communicated. Without the device or lot number, (b)(4) is not able to investigated the reported issue. (b)(4) could not contact the user facility since contact information from the user facility was indicated in the reported information. (b)(4) did review verification requirements that are conducted in manufacturing of the product. Sampling is conducted on a continuous periodic basis, which tensile verification is part of inspection to confirm that a minimum retention force when engaged with a needleless luer activated valve (LAV). Manufacturing limits are established on the manufacturing equipment, which is monitored real-time. If an excursion occurs outside the manufacturing limits, the manufacturing equipment will automatically segregate product produced at the time the excursion occurs.

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
4253190	2014/09/09	Malfunction	Ivera Medical	2014/09/21	FPA	Curos	Event description: while trying to put a green Curos cap on a line, it broke and the nurse had to pry the broken piece off the port.
4023072	2014/08/03	Malfunction	Ivera Medical	2014/08/15	LKB	Curos	Event description: Curos cap broke apart. Little green ring stayed on the IV port when RN took the cap off. This apparently happened twice.
4023073	2014/07/11	Malfunction	Ivera Medical	2014/07/15	LKB	Curos	Event description: the Curos caps are breaking while patients are moving around in bed and also break apart as the nurse removes the cap.
2412604	2012/01/06	Malfunction	Ivera Medical Corporation	2012/01/09	LKB	Curos	Event description: the nurse put the Curos protector covers on the all the primary ports. She spiked the IV solution and primed the tubing. One of the Curos covers fell apart. The tubing was not attached to the patient at the time the cover broke.this is the first I have heard of this incident. Another Curos port protector was used from the same lot number.
MW5021324	2011/05/04	Injury	Ivera Medical Corporation	2011/07/11	LKB	Curos port protector	Event description: between (b)(6) 2011, we had (4) patients identified as having candida infections and all patients had lines placed during their admissions. The types of candida varied amongst patients and involved candida albicans, glabrata and parapsilosis. Prior to this time, line infections have been rare at our facility. We have done an extensive review to locate the source of these infections but have been unable to confirm the source. As a part of our review, it was identified that use of the Curos port protector caps on our lines were the only recent change. We first put the caps into use as a trial in our ICU on (b)(6) 2011. Since that time, we have begun to use them across the house. Although we have not identified the caps as a cause of the infection, it was recommended that

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							we report as a precaution. We were told by the manufacturer that they have not been informed of any similar types of issues with this product. Per the manufacturer, they do not have testing at this time that shows the efficacy of the Curos port protector in regards to candida (as it is not required). Dates of use: implemented (b)(6) 2011 pulled (b)(6) 2011. Reason for use: central line. Also see (b)(4).
MW5021325	2011/05/01	Injury	Ivera Medical Corporation	2011/07/11	LKB	Curos port protector	Event description: between (b)(6) 2011, we had (4) patients identified as having candida infections and all patients had lines placed during their admissions. The types of candida varied amongst patients and involved candida albicans, glabrata and parapsilosis. Prior to this time, line infections have been rare at our facility. We have done an extensive review to locate the source of these infections but have been unable to confirm the source. As a part of our review, it was identified that use of the Curos port protector caps on our lines were the only recent change. We first put the caps into use as a trial in our icu on (b)(6) 2011. Since that time, we have begun to use them across the house. Although we have not identified the caps as a cause of the infection, it was recommended that we report as a precaution. We were told by the manufacturer that they have not been informed of any similar types of issues with this product. Per the manufacturer, they do not have testing at this time that shows the efficacy of the Curos port protector in regards to candida (as it is not required). Dates of use: implemented (b)(6) 2011. Reason for use: central line. Also see (b)(4).

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
MW5021326	2011/05/01	Injury	Ivera Medical Corporation	2011/07/11	LKB	Curos port protector	Event description: between (b)(6) 2011 and (b)(6) 2011, we had (b)(6) patients identified as having candida infections and all patients had lines placed during their admissions. The types of candida varied amongst patients and involved candida albicans, glabrata and parapsilosis. Prior to this time, line infections have been rare at our facility. We have done an extensive review to locate the source of these infections, but have been unable to confirm the source. As a part of our review, it was identified that use of the Curos port protector caps on our lines were the only recent change. We first put the caps into use as a trial in our ICU on (b)(6) 2011. Since that time, we have begun to use them across the house. Although we have not identified the caps as a cause of the infection, it was recommended that we report as a precaution. We were told by the manufacturer that they have not been informed of any similar types of issues with this product. Per the manufacturer, they do not have testing at this time that shows the efficacy of the Curos port protector in regards to candida (as it is not required). Dates of use: implemented (b)(6) 2011 pulled (b)(6) 2011. Reason for use: central line. Also see MW5021324, MW5021325 and MW5021327.

10 Related procedures for evidence submission

10.1 Cost models

An electronic executable version of the cost model should be submitted to NICE with the full submission.

NICE accepts executable cost models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the External Assessment Centre, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the External Assessment Centre with temporary licences for the non-standard software for the duration of the assessment. NICE reserves the right to reject cost models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model programme and the written content of the evidence submission match.

NICE may distribute the executable version of the cost model to a consultee if they request it. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The consultee will be advised that the model is protected by intellectual property rights and can be used only for the purposes of commenting on the model's reliability and informing comments on the medical technology consultation document.

Sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. NICE may request additional information not submitted in the original submission of evidence. Any other information will be accepted at NICE's discretion.

When making a full submission, sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- a copy of the instructions for use, regulatory documentation and quality systems certificate have been submitted
- an executable electronic copy of the cost model has been submitted
- the checklist of confidential information provided by NICE has been completed and submitted.

- A PDF version of all studies (or other appropriate format for unpublished data, for example, a structured abstract) included in the submission have been submitted

10.2 Disclosure of information

To ensure that the assessment process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Medical Technologies Advisory Committee's decisions should be publicly available at the point of issuing the medical technology consultation document and medical technology guidance.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence').

When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

It is the responsibility of the sponsor to ensure that any confidential information in their evidence submission is clearly underlined and highlighted correctly. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Medical Technologies Advisory Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and highlight information that is submitted under 'commercial in confidence' in blue and information submitted under 'academic in confidence' in yellow.

NICE will ask sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the External Assessment Centre and the Medical Technologies Advisory Committee. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as 'commercial in confidence' may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any

information previously deemed ‘commercial in confidence’ before making any decision on disclosure.

10.3 Equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the evaluation of the technology, and to reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the evaluation, or if there is information that could be included in the evidence presented to the Medical Technologies Advisory Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE’s responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

References

Please use a recognised referencing style, such as Harvard or Vancouver.

1. Sweet MA, Cumpston A, Briggs F, Craig M, Hamadani M. Impact of alcohol-impregnated port protectors and needleless neutral pressure connectors on central line-associated bloodstream infections and contamination of blood cultures in an inpatient oncology unit. Am J Infect Control. 2012;40(10):931-4.

2. Ramirez C, Lee AM, Welch K. Central venous catheter protective connector caps reduce intraluminal catheter-related infection. JAVA - Journal of the Association for Vascular Access. 2012;17(4):210-13.
3. Merrill KC, Sumner S, Linford L, Taylor C, Macintosh C. Impact of universal disinfectant cap implementation on central line-associated bloodstream infections. Am J Infect Control. 2014;42(12):1274-7.
4. Cameron-Watson C. Port protectors in clinical practice: an audit. Br J Nurs. 2016;25(8):S25-31.
5. Martino A, Thompson L, Mitchell C, Trichel R, Chappell W, Miller J*, et al.* Efforts of a Unit Practice Council to implement practice change utilizing alcohol impregnated port protectors in a burn ICU. Burns. 2017;43(5):956-64.
6. Pong A, Salgado C, Speziale M, Grimm P, Abe C. Reduction of central line-associated bloodstream infection (CLABSI) in a neonatal intensive care unit with use of access site disinfection caps. In: ISDA Annual Meeting, Boston, MA; 21 October. 2011. P672
7. Danielson B, Willamson S, Kaur G, Brooks C, Scholl P, Baker A. Decreasing the incidence of central line-associated blood stream infections using alcohol-impregnated port protectors in a neonatal intensive care unit. Am J Infect Control. 2013;41(Suppl 6):S97-S98.
8. Sumner S, Merrill KC, Linford L, Taylor C. Decreasing CLABSI rates and cost following implementation of a disinfectant cap in a tertiary care hospital. Am J Infect Control. 2013;41(Suppl 6):S37.
9. Shiber J, Jolicoeur G, Crouchet T. Reducing central line-associated bloodstream infections through the addition of disinfecting port protector caps to the central line bundle. In: Ochsner Research Day, New Orleans, LA; 20 May. 2014. 8
10. Ventura R. Passive disinfection port protector: effect on the reduction of catheter related bloodstream infections. In: Gavacelt Conference 2015, Milan, Italy; 2015. 7
11. Rawlinson L. National IV Report Cleaning Survey Results. Swindon: Vygon UK; 2014. Available from: http://www.aim-at-zero.co.uk/wp-content/uploads/2016/04/PS304-EMAIL-National-Port-Cleaning-Survey-pages.pdf.
12. National Institute for Health and Care Excellence. Healthcare-associated infections: prevention and control in primary and community care (CG139). London: National Institute for Health and Care Excellence; 2012. Available from: https://www.nice.org.uk/guidance/cg139.
13. Loveday HP, Wilson JA, Pratt RJ, Golsorkhia M, Tingle A, Baka J*, et al.* epic3: National Evidence-Based Guidelines for Preventing Healthcare-Associated Infections in NHS Hospitals in England. J Hosp Infect. 2014;86(Suppl. 1):S1-S70.
14. Voor In 't Holt AF, Helder OK, Vos MC, Schafthuizen L, Sulz S, van den Hoogen A*, et al.* Antiseptic barrier cap effective in reducing central line-associated bloodstream infections: A systematic review and meta-analysis. Int J Nurs Stud. 2017;69:34-40.
15. Martino AL, Mitchell C, Fields JL, Martinez DM, Hatem AM, Bang S*, et al.* Successful outcomes associated with implementing the use of

alcohol impregnated port protectors in a burn unit. J Burn Care Res. 2014;35:S86.
16. Cooper K, Frampton G, Harris P, Jones J, Cooper T, Graves N*, et al.* Are educational interventions to prevent catheter-related bloodstream infections in intensive care unit cost-effective? J Hosp Infect. 2014;86(1):47-52.
17. National Institute for Health and Care Excellence (NICE). Medical technologies evaluation programme process guide. 2017.[cited 1st December 2017]. Available from: https://www.nice.org.uk/process/pmg34/chapter/introduction.
18. Health Protection Scotland. Surveillance of Healthcare Associated Infections in Scottish Intensive Care Units. Annual report of data from January - December 2013. 2014. Last updated August 2014 [cited 6th Jan 2015]. Available from: http://www.documents.hps.scot.nhs.uk/hai/sshaip/publications/icu-surveillance/icu-annual-report-2014.pdf.
19. Welsh Healthcare Associated Infection Programme. Central Venous Catheter (CVC) Infection and Ventilator Associated Pneumonia (VAP) in Critical Care - Annual Report. 2014. Last updated 25 July 2014 [cited 8th Jan 2015]. Available from: http://www2.nphs.wales.nhs.uk:8080/WHAIPDocs.nsf/($All)/28459C38515ACCAC80257D79005253C4/$File/Aneurin%20Bevan%20Critical%20Care%20CVC%20%26%20VAP%20Report%202013.pdf?OpenElement.
20. Bion J, Richardson A, Hibbert P, Beer J, Abrusci T, McCutcheon M*, et al.* 'Matching Michigan': a 2-year stepped interventional programme to minimise central venous catheter-blood stream infections in intensive care units in England. BMJ Qual Saf. 2013;22(2):110-23.
21. Ahmed SS, McCaskey MS, Bringman S, Eigen H. Catheter-associated bloodstream infection in the pediatric intensive care unit: a multidisciplinary approach (Provisional abstract). Pediatr Crit Care Med. 2012;13(2):e69-e72.
22. Aitken E, Iqbal K, Thomson P, Kasthuri R, Kingsmore D. Are early cannulation arteriovenous grafts (ecAVG) a viable alternative to tunnelled central venous catheters (TCVCs)? An observational "virtual study" and budget impact analysis. J. 2016;17(3):220-8.
23. Austin PD, Hand KS, Elia M. Impact of definition and procedures used for absent blood culture data on the rate of intravascular catheter infection during parenteral nutrition. J Hosp Infect. 2016;93(2):197-205.
24. Dixon JJ, Steele M, Makanjuola AD. Anti-microbial locks increase the prevalence of Staphylococcus aureus and antibiotic-resistant Enterobacter: observational retrospective cohort study. Nephrol Dial Transplant. 2012;27(9):3575-81.
25. Dyson JK, Thompson N, Northern Nutrition N. Adult parenteral nutrition in the North of England: a region-wide audit. BMJ Open. 2017;7(1):e012663.

26. Alexakis C, Malcolm L, Banks C. Central venous catheter associated sepsis in patients receiving parenteral nutrition: experience at a district general hospital. Clin Nutr ESPEN. 2015;10(5):e181-e82.
27. Hvas CL, Farrer K, Donaldson E, Blackett B, Lloyd H, Forde C*, et al.* Quality and safety impact on the provision of parenteral nutrition through introduction of a nutrition support team. Eur J Clin Nutr. 2014;68(12):1294-9.
28. Jackson A, Cooper S. Zero central-line infections in a 550-bedded district general hospital. Br J Nurs. 2012;21(14 SUPPL.):S24-S28.
29. Kanaa M, Wright MJ, Akbani H, Laboi P, Bhandari S, Sandoe JAT. Cathasept Line Lock and Microbial Colonization of Tunneled Hemodialysis Catheters: A Multicenter Randomized Controlled Trial. Am J Kidney Dis. 2015;66(6):1015-23.
30. Sammut D, Elliot CA, Kiely DG, Armstrong IJ, Martin L, Wilkinson J*, et al.* Central venous catheter-related blood stream infections in patients receiving intravenous iloprost for pulmonary hypertension. Eur J Clin Microbiol Infect Dis. 2013;32(7):883-9.
31. Youssouf S, Nache A, Wijesekara C, Middleton RJ, Lewis D, Shurrab AE*, et al.* Effect of a Quality Improvement Program to Improve Guideline Adherence and Attainment of Clinical Standards in Dialysis Care: Report of Outcomes in Year 1. Nephron. 2017;136(2):75-84.
32. Francis S, Cooper M, Jacob A, Jones H, MacWhannell A, Basu S. The impact of implementing matching michigan and EPIC3 recommendations to real life haemato-oncology patients: Results from a prospective uk based study. Haematologica. 2014;99:191.
33. Appleton ND, Corris A, Edwards C, Kenyon A, Walsh CJ. A dedicated peripherally inserted central catheter (PICC) line service: 2 year review. Int J Surg. 2013;11 (8):649.
34. Kilner M, Collins J, Price A, Richardson A, Samuel J, Straughan C*, et al.* Reducing central venous catheter infection rates amongst hematology patients: Real-life implementation of a 'Matching Michigan' approach in this patient population. Blood. Conference: 55th Annual Meeting of the American Society of Hematology, ASH. 2013;122(21)
35. Driver R, Mistry P, Swain D, Colinese E, Saich R. Timing of parenteral nutrition administration set changes: Impact on incidence of catheter associated infections. Gut. 2012;61:A100-A01.
36. Jenks M, Craig J, Green W, Hewitt N, Arber M, Sims A. Tegaderm CHG IV Securement Dressing for Central Venous and Arterial Catheter Insertion Sites: A NICE Medical Technology Guidance. Appl Health Econ Health Policy. 2016;14(2):135-49.
37. Thokala P, Arrowsmith M, Poku E, Martyn-St James M, Anderson J, Foster S*, et al.* Economic impact of Tegaderm chlorhexidine gluconate (CHG) dressing in critically ill patients. Journal of Infection Prevention. 2016;17(5):216-23.
38. Ahmadnia E, Hadley JS, Millar M, Hall D, Hewitt H. The effect of introduction of daily chlorhexidine bathing on healthcare-associated infections and acquisition of multi-drug resistant organisms. Intensive Care Medicine Experimental. Conference: 29th Annual Congress of

the European Society of Intensive Care Medicine, ESICM. 2016;4(no pagination)
39. Fuerstenberg F, Spencer C, Reay M, Mohankumar L, Raybould S. Audit and antimicrobiogram of isolates of central venous catheter blood stream infections in a nine bed critical care unit. Intensive Care Med. 2012;38:S273-S74.
40. National Institute for Health and Care Excellence. The 3M Tegaderm CHG IV securement dressing for central venous and arterial catheter insertion sites (MTG25). (MTG25). London: National Institute for Health and Care Excellence; 2015. Available from: https://www.nice.org.uk/guidance/mtg25.
41. Personal Social Services Research Unit (PSSRU). Unit Costs of Health & Social Care 2016. Canterbury: PSSRU; 2016. Available from: http://www.pssru.ac.uk/project-pages/unit-costs/2016/.
42. Casey AL, Karpanen TJ, Nightingale P, Chaganti S, Elliott TSJ. Microbiologic contamination of a positive- and a neutral- displacement needleless intravenous access device in clinical use. Am J Infect Control. 2016;44(12):1678-80.
43. Tan R, Knowles D, Streater C, Johnston A. The use of peripherally inserted central catheters in intensive care: should you pick the PICC? JICS. 2009;10(2)
44. Hockenhull JC, Dwan K, Boland A, Smith G, Bagust A, Dundar Y*, et al.* The clinical effectiveness and cost-effectiveness of central venous catheters treated with anti-infective agents in preventing bloodstream infections: a systematic review and economic evaluation. Health Technol Assess. 2008;12(12):iii-iv, xi-xii, 1-154.
45. National Institute for Health and Care Excellence. Rehabilitation after critical illness in adults (CG83). London: National Institute for Health and Care Excellence; 2009. Available from: https://www.nice.org.uk/guidance/cg83.
46. Information Services Division Scotland. Scottish Tariffs for Cross Boundary Flow Costing. In; 2013/14.
47. Department of Health. NHS Reference Costs 2015-16 [webpage]. London: 2016. Last updated 15 December 2016.[cited 30th June 2017]. Available from: https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016.
48. Granstedt EM, Petrov P, Knapp K, Cordero M, Patel V. Fast imaging diagnostics on the C-2U advanced beam-driven field-reversed configuration device. Rev Sci Instrum. 2016;87(11):11D416.
49. Heidari Zare H, Juhart V, Vass A, Franz G, Jocham D. Efficacy of silver/hydrophilic poly(p-xylylene) on preventing bacterial growth and biofilm formation in urinary catheters. Biointerphases. 2017;12(1):011001.

11 Appendices

11.1 Appendix 1: Search strategy for clinical evidence (section 7.1.1)

The following information should be provided:

11.1.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Database / information source	**Interface / URL**
MEDLINE, MEDLINE In-Process and MEDLINE(R) Daily Epub Ahead of Print	Ovid SP
PubMed	http://www.ncbi.nlm.nih.gov/pubmed
Embase	Ovid SP
Science Citation Index	Web of Science
Conference Proceedings Citation Index (Science)	Web of Science
CINAHL	EBSCO
Cochrane Database of Systematic Reviews (CDSR)	Cochrane Library
Cochrane Central Register of Controlled Trials (CENTRAL)	Cochrane Library
Database of Abstracts of Reviews of Effects (DARE)	Cochrane Library
Health Technology Assessment Database (HTA Database)	Cochrane Library
NHS Economic Evaluation Database (NHS EED)	Cochrane Library
ClinicalTrials.gov	https://clinicaltrials.gov./
WHO International Clinical Trials Registry Portal (ICTRP)	http://apps.who.int/trialsearch/
US Food and Drug Administration (FDA) Manufacturer and User Facility Device Experience (MAUDE) database	https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm
Medicines and Healthcare products Regulatory Agency (MHRA) webpages	https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency

11.1.2 The date on which the search was conducted.

The searches were conducted between 19 and 22 September 2017.

11.1.3 The date span of the search.

The searches were not limited by date. The date coverage of each database searched is shown below in Section 10.1.4.

11.1.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

A.1: Source: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Interface / URL: Ovid SP
Database coverage dates: 1946 to current. Updated daily.
Search date: 19/09/17
Retrieved records: 476
Search strategy:

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
---

1 Catheterization/ (50771)
2 Catheterization, Central Venous/ (14219)
3 exp Catheterization, Peripheral/ (10542)
4 Cardiac Catheterization/ (46864)
5 exp Catheters/ (25839)
6 Catheter-Related Infections/ (3731)
7 (catheter$ or microcatheter$ or cannula$ or microcannula$ or canula$ or microcanula$).ti,ab,kf. (230643)
8 (CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs).ti,ab,kf. (13811)
9 ((PIC or CVP) adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kf. (120)
10 (central adj3 (venous or pressure)).ti,ab,kf. (26654)
11 ((central or subclavian or jugular or femoral) adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kf. (16745)
12 (peripheral adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kf. (6784)

13 ((venous or intravenous or vein$1 or vascular or intravascular or IV) adj3 (line$1 or access$ or site or sites or device$ or reservoir$)).ti,ab,kf. (28701)
14 ((arterial or intraarterial or artery or arteries) adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kf. (8363)
15 (art line$1 or a line$1 or IAC or IACs).ti,ab,kf. (11320)
16 (CA-BSI or CA-BSIs or CABSI or CABSIs or CR-BSI or CR-BSIs or CRBSI or CRBSIs or CLA-BSI or CLA-BSIs or CLABSI or CLABSIs).ti,ab,kf. (1334)
17 (access$ adj3 (device$ or site or sites or route$1)).ti,ab,kf. (11997)
18 ((invasive or percutaneous) adj3 device$).ti,ab,kf. (3137)
19 (CVA or CVAD or CVADs or VAD or VADs).ti,ab,kf. (10084)
20 (IVD or IVDs).ti,ab,kf. (2176)
21 (port a cath$1 or portacath$1 or hickman$1 or broviac$1 or cook$1 or seldinger$1 or punktion$1 or groshong$1 or quinton$1).ti,ab,kf. (8686)
22 or/1-21 (384446)
23 exp Anti-Infective Agents/ (1520380)
24 Disinfection/ (13081)
25 (antiinfect$ or anti-infect$ or antisep$ or anti-sep$ or antimicrob$ or anti-microb$ or antibacter$ or anti-bacter$).ti,ab,kf. (196555)
26 (disinfect$ or decontaminat$ or clean$ or barrier).ti,ab,kf. (251828)
27 exp Alcohols/ (634010)
28 Chlorhexidine/ (7599)
29 alcohol$.ti,ab,kf. (302651)
30 ethanol$.ti,ab,kf. (123114)
31 isopropyl$.ti,ab,kf. (20518)
32 chlorhexidine$.ti,ab,kf. (9315)
33 or/23-32 (2588482)
34 (cap or caps).ti,ab,kf. (43615)
35 (hub or hubs).ti,ab,kf. (8875)
36 (connector or connectors).ti,ab,kf. (4030)
37 or/34-36 (56315)
38 22 and 33 and 37 (322)
39 ((port or ports or hub or hubs) adj5 protect$).ti,ab,kf. (82)
40 ((catheter$ or connector or connectors or hub or hubs or protector or protectors or protection or protective or barrier or antiinfect$ or anti-infect$ or antisep$ or anti-sep$ or antimicrob$ or anti-microb$ or antibacter$ or anti-bacter$ or disinfect$ or decontaminat$ or clean$) adj1 (cap or caps)).ti,ab,kf. (166)
41 ((alcohol$ or ethanol$ or chlorhexidine or isopropyl$ or impregn$) adj3 (cap or caps)).ti,ab,kf. (77)
42 (passive adj5 disinfect$).ti,ab,kf. (13)
43 or/39-42 (322)
44 (swab cap$2 or swabcap$2).ti,ab,kf. (3)
45 (site scrub$2 or sitescrub$2).ti,ab,kf. (3)
46 (life shield$2 or lifeshield$2).ti,ab,kf. (2)
47 (EffectIV or EffectIVr or EffectIVtm).ti,ab,kf. (6)
48 (dual cap$2 or dualcap$2).ti,ab,kf. (1)

49 curos$2.ti,ab,kf. (5)
50 or/44-49 (20)
51 38 or 43 or 50 (618)
52 exp animals/ not humans/ (4585070)
53 51 not 52 (546)
54 limit 53 to english language (498)
55 remove duplicates from 54 (476)

A.2: Source: PubMed

Interface / URL: http://www.ncbi.nlm.nih.gov/pubmed
Database coverage dates: 1940s to current. Updated daily.
Search date: 20/09/17
Retrieved records: 626
Search strategy:

Search Query Items found
#56 Search #53 NOT #54 Filters: English 626
#55 Search #53 NOT #54 643
#54 Search medline[sb] 24307328
#53 Search #51 not #52 3972
#52 Search animals[mh] NOT humans[mh:noexp] 4372391
#51 Search #38 or #43 or #50 4744
#50 Search #44 OR #45 OR #46 OR #47 OR #48 OR #49 15
#49 Search curos[tiab] OR curosr[tiab] OR curostm[tiab] 1
#48 Search dualcap[tiab] OR dualcapr[tiab] OR dualcaptm[tiab] OR dual cap[tiab] OR dual capr[tiab] OR dual captm[tiab] 2
#47 Search EffectIV[tiab] OR EffectIVr[tiab] OR EffectIVtm[tiab] 6
#46 Search lifeshield*[tiab] 1
#45 Search site scrub*[tiab] OR sitescrub*[tiab] 3
#44 Search swabcap*[tiab] 2
#43 Search #39 OR #40 OR #41 OR #42 4491
#42 Search passive[tiab] AND disinfect*[tiab] 93
#41 Search (alcohol*[tiab] OR ethanol*[tiab] OR chlorhexidine[tiab] OR isopropyl*[tiab] OR impregn*[tiab]) AND (cap[tiab] OR caps[tiab]) 583
#40 Search (catheter*[tiab] OR connector[tiab] OR connectors[tiab] OR hub[tiab] OR hubs[tiab] OR protector[tiab] OR protectors[tiab] OR protection[tiab] OR protective[tiab] OR barrier[tiab] OR antiinfect*[tiab] OR anti-infect*[tiab] OR antisep*[tiab] OR anti-sep*[tiab] OR antimicrob*[tiab] OR anti-microb*[tiab] OR antibacter*[tiab] OR anti-bacter*[tiab] OR disinfect*[tiab] OR decontaminat*[tiab] OR clean*[tiab]) AND (cap[tiab] OR caps[tiab]) 3110
#39 Search (port[tiab] OR ports[tiab] OR hub[tiab] OR hubs[tiab]) AND protect*[tiab] 824
#38 Search #22 AND #33 AND #37 408
#37 Search #34 OR #35 OR #36 53309
#36 Search connector[tiab] OR connectors[tiab] 3900

#35 Search hub[tiab] OR hubs[tiab] 8305
#34 Search cap[tiab] OR caps[tiab] 41302
#33 Search #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 1790680
#32 Search chlorhexidine*[tiab] 8914
#31 Search isopropyl*[tiab] 19083
#30 Search ethanol*[tiab] 118339
#29 Search alcohol*[tiab] 289728
#28 Search "Chlorhexidine"[mesh:noexp] 7252
#27 Search "Alcohols"[mesh] 605189
#26 Search disinfect*[tiab] OR decontaminat*[tiab] OR clean*[tiab] OR barrier[tiab] 241379
#25 Search antiinfect*[tiab] OR anti-infect*[tiab] OR antisep*[tiab] OR anti-sep*[tiab] OR antimicrob*[tiab] OR anti-microb*[tiab] OR antibacter*[tiab] OR anti-bacter*[tiab] 189196
#24 Search "Disinfection"[mesh:noexp] 12562
#23 Search "Anti-Infective Agents"[mesh] 614278
#22 Search #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 752724
#21 Search port a cath*[tiab] OR portacath*[tiab] OR hickman*[tiab] OR broviac*[tiab] OR cook*[tiab] OR seldinger*[tiab] OR punktion*[tiab] OR groshong*[tiab] OR quinton*[tiab] 27913
#20 Search IVD[tiab] OR IVDs[tiab] 2054
#19 Search CVA[tiab] OR CVAD[tiab] OR CVADs[tiab] OR VAD[tiab] OR VADs[tiab] 9815
#18 Search (invasive[tiab] OR percutaneous[tiab]) AND device*[tiab] 19671
#17 Search access*[tiab] AND (device*[tiab] OR site[tiab] OR sites[tiab] OR route*[tiab]) 62181
#16 Search CA-BSI[tiab] OR CA-BSIs[tiab] OR CABSI[tiab] OR CABSIs[tiab] OR CR-BSI[tiab] OR CR-BSIs[tiab] OR CRBSI[tiab] OR CRBSIs[tiab] OR CLA-BSI[tiab] OR CLA-BSIs[tiab] OR CLABSI[tiab] OR CLABSIs[tiab] 1269
#15 Search art line[tiab] OR a line*[tiab] OR IAC[tiab] OR IACs[tiab] 12673
#14 Search (arterial[tiab] OR intraarterial[tiab] OR artery[tiab] OR arteries[tiab]) AND (line[tiab] OR lines[tiab] OR access*[tiab] OR site[tiab] OR sites[tiab] OR device*[tiab]) 75341
#13 Search (venous[tiab] OR intravenous[tiab] OR vein*[tiab] OR vascular[tiab] OR intravascular[tiab] OR IV[tiab]) AND (line[tiab] OR lines[tiab] OR access*[tiab] OR site[tiab] OR sites[tiab] OR device*[tiab] OR reservoir*[tiab]) 169955
#12 Search peripheral[tiab] AND (line[tiab] OR lines[tiab] OR access*[tiab] OR site[tiab] OR sites[tiab] OR device*[tiab]) 69765
#11 Search (central[tiab] OR subclavian[tiab] OR jugular[tiab] OR femoral[tiab]) AND (line[tiab] OR lines[tiab] OR access*[tiab] OR site[tiab] OR sites[tiab] OR device*[tiab]) 129737
#10 Search central[tiab] AND (venous[tiab] OR pressure[tiab]) 59254

#9 Search (PIC[tiab] OR CVP[tiab]) AND (line[tiab] OR lines[tiab] OR access*[tiab] OR site[tiab] OR sites[tiab] OR device*[tiab])1253
#8 Search CVC[tiab] OR CVCs[tiab] OR CVL[tiab] OR CVLs[tiab] OR PICC[tiab] OR PICCs[tiab] OR PIV[tiab] OR PIVs[tiab] OR PVC[tiab] OR PVCs[tiab] 13108
#7 Search catheter*[tiab] OR microcatheter*[tiab] OR cannula*[tiab] OR microcannula*[tiab] OR canula*[tiab] OR microcanula*[tiab] 219373
#6 Search "Catheter-Related Infections"[mesh:noexp] 3530
#5 Search "Catheters"[mesh] 24443
#4 Search "Cardiac Catheterization"[mesh:noexp] 44434
#3 Search "Catheterization, Peripheral"[mesh] 10017
#2 Search "Catheterization, Central Venous"[mesh:noexp] 13549
#1 Search "Catheterization"[mesh:noexp] 48389

A.3: Source: Embase

Interface / URL: Ovid SP
Database coverage dates: 1974 to 19/09/17
Search date: 20/09/17
Retrieved records: 906
Search strategy:

Database: Embase <1974 to 2017 September 19>
Search Strategy:
---
1 catheterization/ or exp blood vessel catheterization/ or heart catheterization/ (122501)
2 exp catheter/ (148541)
3 catheter infection/ (14649)
4 vascular access/ (20727)
5 (catheter$ or microcatheter$ or cannula$ or microcannula$ or canula$ or microcanula$).ti,ab,kw. (316354)
6 (CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs).ti,ab,kw. (20604)
7 ((PIC or CVP) adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kw. (221)
8 (central adj3 (venous or pressure)).ti,ab,kw. (37150)
9 ((central or subclavian or jugular or femoral) adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kw. (24456)
10 (peripheral adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kw. (8606)
11 ((venous or intravenous or vein$1 or vascular or intravascular or IV) adj3 (line$1 or access$ or site or sites or device$ or reservoir$)).ti,ab,kw. (41338)
12 ((arterial or intraarterial or artery or arteries) adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kw. (12262)
13 (art line$1 or a line$1 or IAC or IACs).ti,ab,kw. (12601)
14 (CA-BSI or CA-BSIs or CABSI or CABSIs or CR-BSI or CR-BSIs or CRBSI or CRBSIs or CLA-BSI or CLA-BSIs or CLABSI or CLABSIs).ti,ab,kw. (2501)
15 (access$ adj3 (device$ or site or sites or route$1)).ti,ab,kw. (16431)

16 ((invasive or percutaneous) adj3 device$).ti,ab,kw. (4760)
17 (CVA or CVAD or CVADs or VAD or VADs).ti,ab,kw. (17140)
18 (IVD or IVDs).ti,ab,kw. (3540)
19 (port a cath$1 or portacath$1 or hickman$1 or broviac$1 or cook$1 or seldinger$1 or punktion$1 or groshong$1 or quinton$1).ti,ab,kw. (12289)
20 or/1-19 (541963)
21 exp antiinfective agent/ (2763330)
22 disinfection/ or disinfection system/ (22578)
23 (antiinfect$ or anti-infect$ or antisep$ or anti-sep$ or antimicrob$ or anti-microb$ or antibacter$ or anti-bacter$).ti,ab,kw. (255216)
24 (disinfect$ or decontaminat$ or clean$ or barrier).ti,ab,kw. (304745)
25 alcohol/ (229780)
26 exp alcohol derivative/ (420836)
27 Chlorhexidine/ (14866)
28 alcohol$.ti,ab,kw. (393352)
29 ethanol$.ti,ab,kw. (158573)
30 isopropyl$.ti,ab,kw. (23762)
31 chlorhexidine$.ti,ab,kw. (10376)
32 or/21-31 (3692178)
33 (cap or caps).ti,ab,kw. (56129)
34 (hub or hubs).ti,ab,kw. (11163)
35 (connector or connectors).ti,ab,kw. (4777)
36 or/33-35 (71715)
37 20 and 32 and 36 (691)
38 port protector/ (21)
39 ((port or ports or hub or hubs) adj5 protect$).ti,ab,kw. (146)
40 ((catheter$ or connector or connectors or hub or hubs or protector or protectors or protection or protective or barrier or antiinfect$ or anti-infect$ or antisep$ or anti-sep$ or antimicrob$ or anti-microb$ or antibacter$ or anti-bacter$ or disinfect$ or decontaminat$ or clean$) adj1 (cap or caps)).ti,ab,kw. (229)
41 ((alcohol$ or ethanol$ or chlorhexidine or isopropyl$ or impregn$) adj3 (cap or caps)).ti,ab,kw. (116)
42 (passive adj5 disinfect$).ti,ab,kw. (20)
43 or/38-42 (469)
44 (swab cap$2 or swabcap$2).ti,ab,kw,dv. (19)
45 (site scrub$2 or sitescrub$2).ti,ab,kw,dv. (6)
46 (life shield$2 or lifeshield$2).ti,ab,kw,dv. (10)
47 (EffectIV or EffectIVr or EffectIVtm).ti,ab,kw,dv. (36)
48 (dual cap$2 or dualcap$2).ti,ab,kw,dv. (3)
49 curos$2.ti,ab,kw,dv. (25)
50 or/44-49 (97)
51 37 or 43 or 50 (1118)
52 (animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/ (5766699)
53 51 not 52 (1013)

54 limit 53 to english language (925)
55 remove duplicates from 54 (906)

A.4: Source: Science Citation Index (SCI) Expanded

Interface / URL: Web of Science
Database coverage dates: 1900-present. Last update 21/09/17
Search date: 22/09/17
Retrieved records: 907
Search strategy:

39 #25 OR #30 OR #37 Language Restriction: English 907
38 #25 OR #30 OR #37 957
37 #31 OR #32 OR #33 OR #34 OR #35 OR #36 37
36 TS=(“curos” OR “curosr” OR “curostm”) 3
35 TS=(“dual cap” OR "dualcap" OR “dual capr” OR "dualcapr" OR “dual captm” OR "dualcaptm") 4
34 TS=(“EffectIV” OR “EffectIVr” OR “EffectIVtm”) 18
33 TS=(“life shield*” OR lifeshield*) 3
32 TS=(“site scrub*” OR sitescrub*) 4
31 TS=(“swab cap*” OR swabcap*) 5
30 #26 OR #27 OR #28 OR #29 679
29 TS=(“passive” NEAR/5 disinfect*) 15
28 TS=((alcohol* OR ethanol* OR “chlorhexidine” OR isopropyl* OR impregn*) NEAR/3 (“cap” OR “caps”)) 93
27 TS=((catheter* OR “connector” OR “connectors” OR “hub” OR “hubs” OR “protector” OR “protectors” OR “protection” OR “protective” OR “barrier” OR antiinfect* OR anti-infect* OR antisep* OR anti-sep* OR antimicrob* OR anti-microb* OR antibacter* OR anti-bacter* OR disinfect* OR decontaminat* OR clean*) NEAR/1 (“cap” OR “caps”)) 416
26 TS=((“port” OR “ports” OR “hub” OR “hubs”) NEAR/3 protect*) 172
25 #16 AND #20 AND #24 280
24 #21 OR #22 OR #23 99,701
23 TS=("connector" OR "connectors") 10,104
22 TS=(“hub” OR “hubs”)13,690
21 TS=("cap" OR "caps")76,165
20 #17 OR #18 OR #19 1,403,023
19 TS=(alcohol* OR ethanol* OR isopropyl* OR chlorhexidine*) 683,782
18 TS=(disinfect* OR decontaminat* OR clean* OR “barrier”) 505,153
17 TS=(antiinfect* OR anti-infect* OR antisep* OR anti-sep* OR antimicrob* OR anti-microb* OR antibacter* OR anti-bacter*) 250,882
16 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 585,838
15 TS=(“port a cath*” OR portacath* OR hickman* OR broviac* OR cook* OR seldinger* OR punktion* OR groshong* OR quinton*) 56,007
14 TS=(“IVD” OR “IVDs”)2,103

13 TS=(“CVA” OR “CVAD” OR “CVADs” OR “VAD” OR “VADs”) 10,257
12 TS=((“invasive” OR “percutaneous”) NEAR/3 device*) 3,513
11 TS=(access* NEAR/3 (device* OR “site” OR “sites” OR route*)) 17,426
10 TS=(“CA-BSI” OR “CA-BSIs” OR “CABSI” OR “CABSIs” OR “CR-BSI” OR “CR-BSIs” OR “CRBSI” OR “CRBSIs” OR “CLA-BSI” OR “CLA-BSIs” OR “CLABSI” OR “CLABSIs”) 1,132
9 TS=(“art line*” OR “a line*” OR “IAC” OR “IACs”) 229,481
8 TS=((“arterial” OR “intraarterial” OR “artery” OR “arteries”) NEAR/3 (“line” OR “lines” OR access* OR “site” OR “sites” OR device*)) 8,270
7 TS=((“venous” OR “intravenous” OR vein* OR “vascular” OR “intravascular” OR “IV”) NEAR/3 (“line” OR “lines” OR access* OR “site” OR “sites” OR device* OR reservoir*)) 29,139
6 TS=(“peripheral” NEAR/3 (“line” OR “lines” OR access* OR “site” OR “sites” OR device*)) 6,962
5 TS=((“central” OR “subclavian” OR “jugular” OR “femoral”) NEAR/3 (“line” OR “lines” OR access* OR “site” OR “sites” OR device*)) 21,944
4 TS=(“central” NEAR/3 (“venous” OR “pressure”)) 25,227
3 TS=((“PIC” OR “CVP”) NEAR/3 (“line” OR “lines” OR access* OR “site” OR “sites” OR device*)) 210
2 TS=("CVC" OR "CVCs" OR "CVL" OR "CVLs" OR "PICC" OR "PICCs" OR "PIV" OR "PIVs" OR "PVC" OR "PVCs") 36,014
1 TS=(catheter* OR microcatheter* OR cannula* OR microcannula* OR canula* OR microcanula*) 188,516

A.5: Source: Conference Proceedings Citation Index- Science (CPCI-S)

Interface / URL: Web of Science
Database coverage dates: 1990-present. Last update 21/09/17
Search date: 22/09/17
Retrieved records: 309
Search strategy:

39 #25 OR #30 OR #37 Language Restriction: English 309
38 #25 OR #30 OR #37 316
37 #31 OR #32 OR #33 OR #34 OR #35 OR #36 18
36 TS=(“curos” OR “curosr” OR “curostm”) 2
35 TS=(“dual cap” OR "dualcap" OR “dual capr” OR "dualcapr" OR “dual captm” OR "dualcaptm") 1
34 TS=(“EffectIV” OR “EffectIVr” OR “EffectIVtm”) 11
33 TS=(“life shield*” OR lifeshield*) 3
32 TS=(“site scrub*” OR sitescrub*) 1
31 TS=(“swab cap*” OR swabcap*) 0
30 #26 OR #27 OR #28 OR #29 260
29 TS=(“passive” NEAR/5 disinfect*) 6

28 TS=((alcohol* OR ethanol* OR “chlorhexidine” OR isopropyl* OR impregn*) NEAR/3 (“cap” OR “caps”)) 5
27 TS=((catheter* OR “connector” OR “connectors” OR “hub” OR “hubs” OR “protector” OR “protectors” OR “protection” OR “protective” OR “barrier” OR antiinfect* OR anti-infect* OR antisep* OR anti-sep* OR antimicrob* OR anti-microb* OR antibacter* OR anti-bacter* OR disinfect* OR decontaminat* OR clean*) NEAR/1 (“cap” OR “caps”)) 118
26 TS=((“port” OR “ports” OR “hub” OR “hubs”) NEAR/3 protect*) 132
25 #16 AND #20 AND #24 43
24 #21 OR #22 OR #23 24,351
23 TS=("connector" OR "connectors") 5,744
22 TS=(“hub” OR “hubs”)5,503
21 TS=("cap" OR "caps") 13,159
20 #17 OR #18 OR #19 186,108
19 TS=(alcohol* OR ethanol* OR isopropyl* OR chlorhexidine*) 67,116
18 TS=(disinfect* OR decontaminat* OR clean* OR “barrier”) 106,544
17 TS=(antiinfect* OR anti-infect* OR antisep* OR anti-sep* OR antimicrob* OR anti-microb* OR antibacter* OR anti-bacter*) 15,049
16 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 110,967
15 TS=(“port a cath*” OR portacath* OR hickman* OR broviac* OR cook* OR seldinger* OR punktion* OR groshong* OR quinton*) 6,931
14 TS=(“IVD” OR “IVDs”)271
13 TS=(“CVA” OR “CVAD” OR “CVADs” OR “VAD” OR “VADs”) 2,088
12 TS=((“invasive” OR “percutaneous”) NEAR/3 device*) 747
11 TS=(access* NEAR/3 (device* OR “site” OR “sites” OR route*)) 5,545
10 TS=(“CA-BSI” OR “CA-BSIs” OR “CABSI” OR “CABSIs” OR “CR-BSI” OR “CR-BSIs” OR “CRBSI” OR “CRBSIs” OR “CLA-BSI” OR “CLA-BSIs” OR “CLABSI” OR “CLABSIs”) 75
9 TS=(“art line*” OR “a line*” OR “IAC” OR “IACs”) 61,815
8 TS=((“arterial” OR “intraarterial” OR “artery” OR “arteries”) NEAR/3 (“line” OR “lines” OR access* OR “site” OR “sites” OR device*)) 976
7 TS=((“venous” OR “intravenous” OR vein* OR “vascular” OR “intravascular” OR “IV”) NEAR/3 (“line” OR “lines” OR access* OR “site” OR “sites” OR device* OR reservoir*)) 3,188
6 TS=(“peripheral” NEAR/3 (“line” OR “lines” OR access* OR “site” OR “sites” OR device*)) 1,070
5 TS=((“central” OR “subclavian” OR “jugular” OR “femoral”) NEAR/3 (“line” OR “lines” OR access* OR “site” OR “sites” OR device*)) 3,051
4 TS=(“central” NEAR/3 (“venous” OR “pressure”)) 2,508
3 TS=((“PIC” OR “CVP”) NEAR/3 (“line” OR “lines” OR access* OR “site” OR “sites” OR device*)) 53
2 TS=("CVC" OR "CVCs" OR "CVL" OR "CVLs" OR "PICC" OR "PICCs" OR "PIV" OR "PIVs" OR "PVC" OR "PVCs") 8,750

1 TS=(catheter* OR microcatheter* OR cannula* OR microcannula* OR canula* OR microcanula*) 18,418

A.6: Source: CINAHL

Interface / URL: EBSCO
Database coverage dates: 1937 to current.
Search date: 21/09/17
Retrieved records: 281
Search strategy:

#	Query	Limiters/Expanders	Last Run Via	Results
S46	S31 OR S37 OR S44	Narrow by Language: - english		281
S45	S31 OR S37 OR S44			294
S44	S38 OR S39 OR S40 OR S41 OR S42 OR S43			16
S43	TI(curos OR curosr OR curostm) OR AB(curos OR curosr OR curostm)			4
S42	TI("dual cap*" OR dualcap*) OR AB("dual cap*" OR dualcap*)			9
S41	TI(EffectIV OR EffectIVr OR EffectIVtm) OR AB(EffectIV OR EffectIVr OR EffectIVtm)			0
S40	TI("life shield*" OR lifeshield*) OR AB("life shield*" OR lifeshield*)			0
S39	TI("site scrub*" OR sitescrub*) OR AB("site scrub*" OR sitescrub*)			2
S38	TI("swab cap*" OR swabcap*) OR AB("swab cap*" OR swabcap*)			1
S37	S32 OR S33 OR S34 OR S35 OR S36			119
S36	TI(passive N5 disinfect*) OR AB(passive N5 disinfect*)			9
S35	TI((alcohol* OR ethanol* OR chlorhexidine OR isopropyl* OR impregn*) N3 (cap OR caps)) OR AB((alcohol* OR ethanol* OR chlorhexidine OR isopropyl* OR impregn*) N3 (cap OR caps))			46
S34	AB((catheter* OR connector OR connectors OR hub OR hubs OR protector OR protectors OR protection OR protective OR barrier OR antiinfect* OR anti-infect* OR antisep* OR anti-sep* OR antimicrob* OR anti-microb* OR antibacter* OR anti-bacter* OR disinfect* OR decontaminat* OR clean*) N1 (cap OR caps))			38
S33	TI((catheter* OR connector OR connectors OR hub OR hubs OR protector OR protectors OR protection OR protective OR barrier OR antiinfect* OR anti-infect* OR antisep* OR anti-sep* OR antimicrob* OR anti-microb* OR antibacter* OR anti-bacter* OR disinfect* OR decontaminat* OR clean*) N1 (cap OR caps))			28
S32	TI((port OR ports OR hub OR hubs) N5 protect*) OR AB((port OR ports OR hub OR hubs) N5 protect*)			29
S31	S19 AND S26 AND S30			197
S30	S27 OR S28 OR S29			6,480
S29	TI(connector OR connectors) OR AB(connector OR connectors)			620
S28	TI(hub OR hubs) OR AB(hub OR hubs)			1,150
S27	TI(cap OR caps) OR AB(cap OR caps)			4,764
S26	S20 OR S21 OR S22 OR S23 OR S24 OR S25			265,203
S25	TI(alcohol* OR ethanol* OR isopropyl* OR chlorhexidine*) OR AB(alcohol* OR ethanol* OR isopropyl* OR chlorhexidine*)			65,175
S24	(MH "Alcohols+")			29,278

S23 TI(disinfect* OR decontaminat* OR clean* OR barrier) OR AB(disinfect* OR decontaminat* OR clean* OR barrier) 64,291
S22 TI(antiinfect* OR anti-infect* OR antisep* OR anti-sep* OR antimicrob* OR anti-microb* OR antibacter* OR anti-bacter*) OR AB(antiinfect* OR anti-infect* OR antisep* OR anti-sep* OR antimicrob* OR anti-microb* OR antibacter* OR anti-bacter*) 18,663
S21 (MH "Sterilization and Disinfection") 8,556
S20 (MH "Antiinfective Agents+") 111,505
S19 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 181,759
S18 TI("port a cath*" OR portacath* OR hickman* OR broviac* OR cook* OR seldinger* OR punktion* OR groshong* OR quinton*) OR AB("port a cath*" OR portacath* OR hickman* OR broviac* OR cook* OR seldinger* OR punktion* OR groshong* OR quinton*) 6,185
S17 TI(IVD OR IVDs) OR AB(IVD OR IVDs) 423
S16 TI(CVA OR CVAD OR CVADs OR VAD OR VADs) OR AB(CVA OR CVAD OR CVADs OR VAD OR VADs) 1,666
S15 TI((invasive OR percutaneous) N3 device*) OR AB((invasive OR percutaneous) N3 device*) 837
S14 TI(access* N3 (device* OR site OR sites OR route*)) OR AB(access* N3 (device* OR site OR sites OR route*)) 2,835
S13 TI(CA-BSI OR CA-BSIs OR CABSI OR CABSIs OR CR-BSI OR CR-BSIs OR CRBSI OR CRBSIs OR CLA-BSI OR CLA-BSIs OR CLABSI OR CLABSIs) OR AB(CA-BSI OR CA-BSIs OR CABSI OR CABSIs OR CR-BSI OR CR-BSIs OR CRBSI OR CRBSIs OR CLA-BSI OR CLA-BSIs OR CLABSI OR CLABSIs) 782
S12 TI("art line*"OR "a line*" OR IAC OR IACs) OR AB("art line*" OR "a line*" OR IAC OR IACs) 113,644
S11 TI((arterial OR intraarterial OR artery OR arteries) N3 (line OR lines OR access* OR site OR sites OR device*)) OR AB((arterial OR intraarterial OR artery OR arteries) N3 (line OR lines OR access* OR site OR sites OR device*)) 1,675
S10 TI((venous OR intravenous OR vein* OR vascular OR intravascular OR IV) N3 (line OR lines OR access* OR site OR sites OR device* OR reservoir*)) OR AB((venous OR intravenous OR vein* OR vascular OR intravascular OR IV) N3 (line OR lines OR access* OR site OR sites OR device* OR reservoir*)) 6,649
S9 TI(peripheral N3 (line OR lines OR access* OR site OR sites OR device*)) OR AB(peripheral N3 (line OR lines OR access* OR site OR sites OR device*)) 899
S8 TI((central OR subclavian OR jugular OR femoral) N3 (line OR lines OR access* OR site OR sites OR device*)) OR AB((central OR subclavian OR jugular OR femoral) N3 (line OR lines OR access* OR site OR sites OR device*)) 4,214
S7 TI(central N3 (venous OR pressure)) OR AB(central N3 (venous OR pressure)) 5,857
S6 TI((PIC OR CVP) N3 (line OR lines OR access* OR site OR sites OR device*)) OR AB((PIC OR CVP) N3 (line OR lines OR access* OR site OR sites OR device*))

S5 TI(CVC OR CVCs OR CVL OR CVLs OR PICC OR PICCs OR PIV OR PIVs OR PVC OR PVCs) OR AB(CVC OR CVCs OR CVL OR CVLs OR PICC OR PICCs OR PIV OR PIVs OR PVC OR PVCs) 2,573
S4 TI(catheter* OR microcatheter* OR cannula* OR microcannula* OR canula* OR microcanula*) OR AB(catheter* OR microcatheter* OR cannula* OR microcannula* OR canula* OR microcanula*) 35,965
S3 (MH "Catheter-Related Infections") OR (MH "Catheter-Related Bloodstream Infections") 4,730
S2 (MH "Catheters+") OR (MH "Vascular Access Devices") OR (MH "Catheter Care") OR (MH "Catheter Care, Vascular") 12,117
S1 (MH "Catheterization") OR (MH "Catheterization, Central Venous+") OR (MH "Catheterization, Peripheral+") OR (MH "Heart Catheterization+") 27,224

A.7: Source: Cochrane Database of Systematic Reviews (CDSR)

Interface / URL: Cochrane Library, Wiley
Database coverage dates: Issue 9 of 12, September 2017
Search date: 20/09/17
Retrieved records: 4
Search strategy:

Search Name: CUROS
Date Run: 20/09/17 13:38:58.812
Description:

ID Search Hits
#1 [mh ^Catheterization] 1631
#2 [mh ^"Catheterization, Central Venous"] 885
#3 [mh "Catheterization, Peripheral"] 867
#4 [mh ^"Cardiac Catheterization"] 1203
#5 [mh Catheters] 1516
#6 [mh ^"Catheter-Related Infections"] 287
#7 (catheter* or microcatheter* or cannula* or microcannula* or canula* or microcanula*):ti,ab,kw 21452
#8 (CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs):ti,ab,kw 1017
#9 ((PIC or CVP) near/3 (line or lines or access* or site or sites or device*)):ti,ab,kw 14
#10 (central near/3 (venous or pressure)):ti,ab,kw 3813
#11 ((central or subclavian or jugular or femoral) near/3 (line or lines or access* or site or sites or device*)):ti,ab,kw 1184
#12 (peripheral near/3 (line or lines or access* or site or sites or device*)):ti,ab,kw 344
#13 ((venous or intravenous or vein or veins or vascular or intravascular or IV) near/3 (line or lines or access* or site or sites or device* or reservoir*)):ti,ab,kw 2641

#14 ((arterial or intraarterial or artery or arteries) near/3 (line or lines or access* or site or sites or device*)):ti,ab,kw 961
#15 (art next line* or a next line* or IAC or IACs):ti,ab,kw 3151
#16 (CA-BSI or CA-BSIs or CABSI or CABSIs or CR-BSI or CR-BSIs or CRBSI or CRBSIs or CLA-BSI or CLA-BSIs or CLABSI or CLABSIs):ti,ab,kw 154
#17 (access* near/3 (device* or site or sites or route or routes)):ti,ab,kw 887
#18 ((invasive or percutaneous) near/3 device*):ti,ab,kw 298
#19 (CVA or CVAD or CVADs or VAD or VADs):ti,ab,kw 572
#20 (IVD or IVDs):ti,ab,kw 50
#21 (port next a next cath* or portacath* or hickman* or broviac* or cook* or seldinger* or punktion* or groshong* or quinton*):ti,ab,kw 1556
#22 {or #1-#21} 31648
#23 [mh "Anti-Infective Agents"] 27534
#24 [mh ^Disinfection] 340
#25 (antiinfect* or anti-infect* or antisep* or anti-sep* or antimicrob* or anti-microb* or antibacter* or anti-bacter*):ti,ab,kw 19786
#26 (disinfect* or decontaminat* or clean* or barrier):ti,ab,kw 10185
#27 [mh Alcohols] 32724
#28 [mh ^Chlorhexidine] 1577
#29 alcohol*:ti,ab,kw 18631
#30 ethanol*:ti,ab,kw 5557
#31 isopropyl*:ti,ab,kw 389
#32 chlorhexidine*:ti,ab,kw 2946
#33 {or #23-#32} 89495
#34 (cap or caps):ti,ab,kw 2151
#35 (hub or hubs):ti,ab,kw 221
#36 (connector or connectors):ti,ab,kw 140
#37 {or #34-#36} 2483
#38 #22 and #33 and #37 56
#39 ((port or ports or hub or hubs) near/5 protect*):ti,ab,kw 13
#40 ((catheter* or connector or connectors or hub or hubs or protector or protectors or protection or protective or barrier or antiinfect* or anti-infect* or antisep* or anti-sep* or antimicrob* or anti-microb* or antibacter* or anti-bacter* or disinfect* or decontaminat* or clean*) near/3 (cap or caps)):ti,ab,kw 28
#41 ((alcohol* or ethanol* or chlorhexidine or isopropyl* or impregn*) near/3 (cap or caps)):ti,ab,kw 10
#42 (passive near/5 disinfect*):ti,ab,kw 1
#43 {or #39-#42} 45
#44 (swab next cap* or swabcap*):ti,ab,kw 1
#45 (site next scrub* or sitescrub*):ti,ab,kw 2
#46 (life next shield* or lifeshield*):ti,ab,kw 0
#47 (EffectIV or EffectIVr or EffectIVtm):ti,ab,kw 2
#48 (dual next cap* or dualcap*):ti,ab,kw 1
#49 (curos or curosr or curostm):ti,ab,kw 1
#50 {or #44-#49} 7

#51 #38 or #43 or #50 93
#52 #51 in Cochrane Reviews (Reviews and Protocols) 4

A.8: Source: Cochrane Central Register of Controlled Trials (CENTRAL)

Interface / URL: Cochrane Library, Wiley
Database coverage dates: Issue 8 of 12, August 2017
Search date: 20/09/17
Retrieved records: 96
Search strategy:

Search Name: CUROS
Date Run: 20/09/17 12:58:46.94
Description:

ID Search Hits
#1 [mh ^Catheterization] 1631
#2 [mh ^"Catheterization, Central Venous"] 885
#3 [mh "Catheterization, Peripheral"] 867
#4 [mh ^"Cardiac Catheterization"] 1203
#5 [mh Catheters] 1516
#6 [mh ^"Catheter-Related Infections"] 287
#7 catheter* or microcatheter* or cannula* or microcannula* or canula* or microcanula* 23693
#8 CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs 1192
#9 (PIC or CVP) near/3 (line or lines or access* or site or sites or device*) 21
#10 central near/3 (venous or pressure) 4098
#11 (central or subclavian or jugular or femoral) near/3 (line or lines or access* or site or sites or device*) 1502
#12 peripheral near/3 (line or lines or access* or site or sites or device*) 423
#13 (venous or intravenous or vein or veins or vascular or intravascular or IV) near/3 (line or lines or access* or site or sites or device* or reservoir*) 3197
#14 (arterial or intraarterial or artery or arteries) near/3 (line or lines or access* or site or sites or device*) 1069
#15 art next line* or a next line* or IAC or IACs 3758
#16 CA-BSI or CA-BSIs or CABSI or CABSIs or CR-BSI or CR-BSIs or CRBSI or CRBSIs or CLA-BSI or CLA-BSIs or CLABSI or CLABSIs 199
#17 access* near/3 (device* or site or sites or route or routes) 1092
#18 (invasive or percutaneous) near/3 device* 350
#19 CVA or CVAD or CVADs or VAD or VADs 940
#20 IVD or IVDs 67
#21 port next a next cath* or portacath* or hickman* or broviac* or cook* or seldinger* or punktion* or groshong* or quinton* 6592

#22 {or #1-#21} 39910
#23 [mh "Anti-Infective Agents"] 27534
#24 [mh ^Disinfection] 340
#25 antiinfect* or anti-infect* or antisep* or anti-sep* or antimicrob* or anti-microb* or antibacter* or anti-bacter* 22911
#26 disinfect* or decontaminat* or clean* or barrier 11855
#27 [mh Alcohols] 32724
#28 [mh ^Chlorhexidine] 1577
#29 alcohol* 22737
#30 ethanol* 5809
#31 isopropyl* 444
#32 chlorhexidine* 3145
#33 {or #23-#32} 96606
#34 cap or caps 2895
#35 hub or hubs 350
#36 connector or connectors 171
#37 {or #34-#36} 3366
#38 #22 and #33 and #37 187
#39 (port or ports or hub or hubs) near/5 protect* 16
#40 (catheter* or connector or connectors or hub or hubs or protector or protectors or protection or protective or barrier or antiinfect* or anti-infect* or antisep* or anti-sep* or antimicrob* or anti-microb* or antibacter* or anti-bacter* or disinfect* or decontaminat* or clean*) near/3 (cap or caps) 45
#41 (alcohol* or ethanol* or chlorhexidine or isopropyl* or impregn*) near/3 (cap or caps) 14
#42 passive near/5 disinfect* 1
#43 {or #39-#42} 67
#44 swab next cap* or swabcap* 1
#45 site next scrub* or sitescrub* 2
#46 life next shield* or lifeshield* 2
#47 EffectIV or EffectIVr or EffectIVtm 38
#48 dual next cap* or dualcap* 1
#49 curos or curosr or curostm 6
#50 {or #44-#49} 50
#51 #38 or #43 or #50 278
#52 #51 in Trials 96

A.9: Source: Database of Abstracts of Reviews of Effect (DARE)

Interface / URL: Cochrane Library, Wiley
Database coverage dates: Issue 2 of 4, April 2015
Search date: 20/09/17
Retrieved records: 6
Search strategy:

Search Name: CUROS

Date Run: 20/09/17 13:03:47.636
Description:

ID	Search	Hits
#1	[mh ^Catheterization]	1631
#2	[mh ^"Catheterization, Central Venous"]	885
#3	[mh "Catheterization, Peripheral"]	867
#4	[mh ^"Cardiac Catheterization"]	1203
#5	[mh Catheters]	1516
#6	[mh ^"Catheter-Related Infections"]	287
#7	catheter* or microcatheter* or cannula* or microcannula* or canula* or microcanula*	23693
#8	CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs	1192
#9	(PIC or CVP) near/3 (line or lines or access* or site or sites or device*)	21
#10	central near/3 (venous or pressure)	4098
#11	(central or subclavian or jugular or femoral) near/3 (line or lines or access* or site or sites or device*)	1502
#12	peripheral near/3 (line or lines or access* or site or sites or device*)	423
#13	(venous or intravenous or vein or veins or vascular or intravascular or IV) near/3 (line or lines or access* or site or sites or device* or reservoir*)	3197
#14	(arterial or intraarterial or artery or arteries) near/3 (line or lines or access* or site or sites or device*)	1069
#15	art next line* or a next line* or IAC or IACs	3758
#16	CA-BSI or CA-BSIs or CABSI or CABSIs or CR-BSI or CR-BSIs or CRBSI or CRBSIs or CLA-BSI or CLA-BSIs or CLABSI or CLABSIs	199
#17	access* near/3 (device* or site or sites or route or routes)	1092
#18	(invasive or percutaneous) near/3 device*	350
#19	CVA or CVAD or CVADs or VAD or VADs	940
#20	IVD or IVDs	67
#21	port next a next cath* or portacath* or hickman* or broviac* or cook* or seldinger* or punktion* or groshong* or quinton*	6592
#22	{or #1-#21}	39910
#23	[mh "Anti-Infective Agents"]	27534
#24	[mh ^Disinfection]	340
#25	antiinfect* or anti-infect* or antisep* or anti-sep* or antimicrob* or anti-microb* or antibacter* or anti-bacter*	22911
#26	disinfect* or decontaminat* or clean* or barrier	11855
#27	[mh Alcohols]	32724
#28	[mh ^Chlorhexidine]	1577
#29	alcohol*	22737
#30	ethanol*	5809
#31	isopropyl*	444
#32	chlorhexidine*	3145
#33	{or #23-#32}	96606

#34 cap or caps 2895
#35 hub or hubs 350
#36 connector or connectors 171
#37 {or #34-#36} 3366
#38 #22 and #33 and #37 187
#39 (port or ports or hub or hubs) near/5 protect* 16
#40 (catheter* or connector or connectors or hub or hubs or protector or protectors or protection or protective or barrier or antiinfect* or anti-infect* or antisep* or anti-sep* or antimicrob* or anti-microb* or antibacter* or anti-bacter* or disinfect* or decontaminat* or clean*) near/3 (cap or caps) 45
#41 (alcohol* or ethanol* or chlorhexidine or isopropyl* or impregn*) near/3 (cap or caps) 14
#42 passive near/5 disinfect* 1
#43 {or #39-#42} 67
#44 swab next cap* or swabcap* 1
#45 site next scrub* or sitescrub* 2
#46 life next shield* or lifeshield* 2
#47 EffectIV or EffectIVr or EffectIVtm 38
#48 dual next cap* or dualcap* 1
#49 curos or curosr or curostm 6
#50 {or #44-#49} 50
#51 #38 or #43 or #50 278
#52 #51 in Other Reviews 6

A.10: Source: Health Technology Assessment (HTA) Database

Interface / URL: Cochrane Library, Wiley
Database coverage dates: Issue 4 of 4, October 2016
Search date: 20/09/17
Retrieved records: 7
Search strategy:

Search Name: CUROS
Date Run: 20/09/17 13:07:31.956
Description:

ID Search Hits
#1 [mh ^Catheterization] 1631
#2 [mh ^"Catheterization, Central Venous"] 885
#3 [mh "Catheterization, Peripheral"] 867
#4 [mh ^"Cardiac Catheterization"] 1203
#5 [mh Catheters] 1516
#6 [mh ^"Catheter-Related Infections"] 287
#7 catheter* or microcatheter* or cannula* or microcannula* or canula* or microcanula* 23693

#8 CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs 1192
#9 (PIC or CVP) near/3 (line or lines or access* or site or sites or device*) 21
#10 central near/3 (venous or pressure) 4098
#11 (central or subclavian or jugular or femoral) near/3 (line or lines or access* or site or sites or device*) 1502
#12 peripheral near/3 (line or lines or access* or site or sites or device*) 423
#13 (venous or intravenous or vein or veins or vascular or intravascular or IV) near/3 (line or lines or access* or site or sites or device* or reservoir*) 3197
#14 (arterial or intraarterial or artery or arteries) near/3 (line or lines or access* or site or sites or device*) 1069
#15 art next line* or a next line* or IAC or IACs 3758
#16 CA-BSI or CA-BSIs or CABSI or CABSIs or CR-BSI or CR-BSIs or CRBSI or CRBSIs or CLA-BSI or CLA-BSIs or CLABSI or CLABSIs 199
#17 access* near/3 (device* or site or sites or route or routes) 1092
#18 (invasive or percutaneous) near/3 device* 350
#19 CVA or CVAD or CVADs or VAD or VADs 940
#20 IVD or IVDs 67
#21 port next a next cath* or portacath* or hickman* or broviac* or cook* or seldinger* or punktion* or groshong* or quinton* 6592
#22 {or #1-#21} 39910
#23 [mh "Anti-Infective Agents"] 27534
#24 [mh ^Disinfection] 340
#25 antiinfect* or anti-infect* or antisep* or anti-sep* or antimicrob* or anti-microb* or antibacter* or anti-bacter* 22911
#26 disinfect* or decontaminat* or clean* or barrier 11855
#27 [mh Alcohols] 32724
#28 [mh ^Chlorhexidine] 1577
#29 alcohol* 22737
#30 ethanol* 5809
#31 isopropyl* 444
#32 chlorhexidine* 3145
#33 {or #23-#32} 96606
#34 cap or caps 2895
#35 hub or hubs 350
#36 connector or connectors 171
#37 {or #34-#36} 3366
#38 #22 and #33 and #37 187
#39 (port or ports or hub or hubs) near/5 protect* 16
#40 (catheter* or connector or connectors or hub or hubs or protector or protectors or protection or protective or barrier or antiinfect* or anti-infect* or antisep* or anti-sep* or antimicrob* or anti-microb* or antibacter* or anti-bacter* or disinfect* or decontaminat* or clean*) near/3 (cap or caps) 45
#41 (alcohol* or ethanol* or chlorhexidine or isopropyl* or impregn*) near/3 (cap or caps) 14

#42 passive near/5 disinfect* 1
#43 {or #39-#42} 67
#44 swab next cap* or swabcap* 1
#45 site next scrub* or sitescrub* 2
#46 life next shield* or lifeshield* 2
#47 EffectIV or EffectIVr or EffectIVtm 38
#48 dual next cap* or dualcap* 1
#49 curos or curosr or curostm 6
#50 {or #44-#49} 50
#51 #38 or #43 or #50 278
#52 #51 in Technology Assessments 7

A.11: Source: NHS Economic Evaluation Database (NHS EED)

Interface / URL: Cochrane Library, Wiley
Database coverage dates: Issue 2 of 4, April 2015
Search date: 20/09/17
Retrieved records: 11
Search strategy:

Search Name: CUROS
Date Run: 20/09/17 13:30:06.183
Description:

ID Search Hits
#1 [mh ^Catheterization] 1631
#2 [mh ^"Catheterization, Central Venous"] 885
#3 [mh "Catheterization, Peripheral"] 867
#4 [mh ^"Cardiac Catheterization"] 1203
#5 [mh Catheters] 1516
#6 [mh ^"Catheter-Related Infections"] 287
#7 catheter* or microcatheter* or cannula* or microcannula* or canula* or microcanula* 23693
#8 CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs 1192
#9 (PIC or CVP) near/3 (line or lines or access* or site or sites or device*) 21
#10 central near/3 (venous or pressure) 4098
#11 (central or subclavian or jugular or femoral) near/3 (line or lines or access* or site or sites or device*) 1502
#12 peripheral near/3 (line or lines or access* or site or sites or device*) 423
#13 (venous or intravenous or vein or veins or vascular or intravascular or IV) near/3 (line or lines or access* or site or sites or device* or reservoir*) 3197
#14 (arterial or intraarterial or artery or arteries) near/3 (line or lines or access* or site or sites or device*) 1069
#15 art next line* or a next line* or IAC or IACs 3758

#16 CA-BSI or CA-BSIs or CABSI or CABSIs or CR-BSI or CR-BSIs or CRBSI or CRBSIs or CLA-BSI or CLA-BSIs or CLABSI or CLABSIs 199
#17 access* near/3 (device* or site or sites or route or routes) 1092
#18 (invasive or percutaneous) near/3 device* 350
#19 CVA or CVAD or CVADs or VAD or VADs 940
#20 IVD or IVDs 67
#21 port next a next cath* or portacath* or hickman* or broviac* or cook* or seldinger* or punktion* or groshong* or quinton* 6592
#22 {or #1-#21} 39910
#23 [mh "Anti-Infective Agents"] 27534
#24 [mh ^Disinfection] 340
#25 antiinfect* or anti-infect* or antisep* or anti-sep* or antimicrob* or anti-microb* or antibacter* or anti-bacter* 22911
#26 disinfect* or decontaminat* or clean* or barrier 11855
#27 [mh Alcohols] 32724
#28 [mh ^Chlorhexidine] 1577
#29 alcohol* 22737
#30 ethanol* 5809
#31 isopropyl* 444
#32 chlorhexidine* 3145
#33 {or #23-#32} 96606
#34 cap or caps 2895
#35 hub or hubs 350
#36 connector or connectors 171
#37 {or #34-#36} 3366
#38 #22 and #33 and #37 187
#39 (port or ports or hub or hubs) near/5 protect* 16
#40 (catheter* or connector or connectors or hub or hubs or protector or protectors or protection or protective or barrier or antiinfect* or anti-infect* or antisep* or anti-sep* or antimicrob* or anti-microb* or antibacter* or anti-bacter* or disinfect* or decontaminat* or clean*) near/3 (cap or caps) 45
#41 (alcohol* or ethanol* or chlorhexidine or isopropyl* or impregn*) near/3 (cap or caps) 14
#42 passive near/5 disinfect* 1
#43 {or #39-#42} 67
#44 swab next cap* or swabcap* 1
#45 site next scrub* or sitescrub* 2
#46 life next shield* or lifeshield* 2
#47 EffectIV or EffectIVr or EffectIVtm 38
#48 dual next cap* or dualcap* 1
#49 curos or curosr or curostm 6
#50 {or #44-#49} 50
#51 #38 or #43 or #50 278
#52 #51 in Economic Evaluations 11

A.12: Source: ClinicalTrials.gov

Interface / URL: https://clinicaltrials.gov/ct2/home
Database coverage dates: Not provided
Search date: 22/09/17
Retrieved records: 311
Search strategy:

Search functionality is fairly limited preventing a straight translation of the MEDLINE strategy. The key terms/phrases (most likely to yield relevant records) were prioritised. Each combination listed below was searched separately and the results downloaded individually.

(catheter OR catheters OR catheterization OR catheterisation OR catheterize OR catheterise OR catheterized OR catheterised OR microcatheter OR microcatheters OR cannula OR cannulas OR cannulae OR cannulaes OR cannulize OR cannulise OR cannulized OR cannulised OR microcannula OR microcannulas OR canula OR canulas OR microcanula OR microcanulas OR CVC OR CVCs OR CVL OR CVLs OR PICC OR PICCs OR PIV OR PIVs OR PVC OR PVCs OR PIC OR CVP OR line OR lines OR IAC OR IACs OR CA-BSI OR CA-BSIs OR CABSI OR CABSIs OR CR-BSI OR CR-BSIs OR CRBSI OR CRBSIs OR CLA-BSI OR CLA-BSIs OR CLABSI OR CLABSIs OR CVA OR CVAD OR CVADs OR VAD OR VADs OR IVD OR IVDs OR "port a cath" OR portacath OR hickman OR broviac OR cook OR seldinger OR punktion OR groshong OR quinton) AND (alcohol OR alcohols OR ethanol OR isopropyl OR chlorhexidine OR disinfect OR disinfected OR disinfecting OR decontaminate OR decontaminated OR decontaminating OR clean OR cleaning OR cleaned OR cleanse OR cleansed OR cleansing OR barrier OR antiinfection OR anti-infection OR antiinfective OR anti-infective OR antiseptic OR anti-septic OR antimicrobial OR anti-microbial OR antibacteria OR anti-bacteria OR antibacterial OR anti-bacteria) AND (cap OR caps OR hub OR hubs OR connector OR connectors)
178 results

(venous OR intravenous OR vein OR veins OR vascular OR intravascular OR IV OR subclavian OR jugular OR femoral OR arterial OR intraarterial OR artery OR arteries) AND (access OR site OR sites OR device OR devices OR reservoir OR reservoirs) AND (alcohol OR alcohols OR ethanol OR isopropyl OR chlorhexidine OR disinfect OR disinfected OR disinfecting OR decontaminate OR decontaminated OR decontaminating OR clean OR cleaning OR cleaned OR cleanse OR cleansed OR cleansing OR barrier OR antiinfection OR anti-infection OR antiinfective OR anti-infective OR antiseptic

OR anti-septic OR antimicrobial OR anti-microbial OR antibacteria OR anti-bacteria OR antibacterial OR anti-bacteria) AND (cap OR caps OR hub OR hubs OR connector OR connectors)
125 results

"protective cap OR “protective caps” OR “port protector” OR “port protectors” OR “hub protector” OR “hub protectors” OR “connector protector” OR “connector protectors” OR “passive disinfection” OR “passive disinfecting” OR “swab cap” OR swabcap OR “site scrub” OR sitescrub OR “life shield” OR lifeshield OR “dual cap” OR dualcap OR curos OR effectIV
8 results

A.13: Source: WHO ITCRP

Interface / URL: http://apps.who.int/trialsearch/Default.aspx
Database coverage dates: Not provided
Search date: 21/09/17
Retrieved records: 83
Search strategy:

Search functionality is fairly limited preventing a straight translation of the MEDLINE strategy. The key terms/phrases (most likely to yield relevant records) were prioritised. Each combination listed below was searched separately and the results downloaded individually.

protective cap OR protective caps OR port protector* OR hub protector* OR connector protector* OR passiv* disinfecti* OR swab cap OR swabcap OR site scrub OR sitescrub OR life shield OR lifeshield OR dual cap OR dualcap OR curos OR effectIV = 5

catheter* AND cap OR catheter* AND caps OR catheter* AND hub OR catheter* AND hubs OR catheter* AND connector OR catheter* AND connectors = 23 (24 records for 23 trials)

antiinfect* AND cap OR antiinfect* AND caps OR antiinfect* AND hub OR antiinfect* AND hubs OR antiinfect* AND connector OR antiinfect* AND connector OR anti infect* AND cap OR anti infect* AND caps OR anti infect* AND hub OR anti infect* AND hubs OR anti infect* AND connector OR anti infect* AND connectors OR antisep* AND cap OR antisep* AND caps OR antisep* AND hub OR antisep* AND hubs OR antisep* AND connector OR antisep* AND connectors OR anti sep* AND cap OR anti sep* AND caps OR anti sep* AND hub OR anti sep* AND hubs OR anti sep* AND connector OR anti sep* AND connectors = 3

antimicrob* AND cap OR antimicrob* AND caps OR antimicrob* AND hub OR antimicrob* AND hubs OR antimicrob* AND connector OR antimicrob* AND

connectors OR anti microb* AND cap OR anti microb* AND caps OR anti microb* AND hub OR anti microb* AND hubs OR anti microb* AND connector OR anti microb* AND connectors OR antibacter* AND cap OR antibacter* AND caps OR antibacter* AND hub OR antibacter* AND hubs OR antibacter* AND connector OR antibacter* AND connectors OR anti bacter* AND cap OR anti bacter* AND caps OR anti bacter* AND hub OR anti bacter* AND hubs OR anti bacter* AND connector OR anti bacter* AND connectors = 4 (5 records for 4 trials)

disinfect* AND cap OR disinfect* AND caps OR disinfect* AND hub OR disinfect* AND hubs OR disinfect* AND connector OR disinfect* AND connectors OR decontaminat* AND cap OR decontaminat* AND caps OR decontaminat* AND hub OR decontaminat* AND hubs OR decontaminat* AND connector OR decontaminat* AND connectors OR clean* AND cap OR clean* AND caps OR clean* AND hub OR clean* AND hubs OR clean* AND connector OR clean* AND connectors OR barrier AND cap OR barrier AND caps OR barrier AND hub OR barrier AND hubs OR barrier AND connector OR barrier AND connectors = 16
(19 records for 16 trials)

alcohol* AND cap OR alcohol* AND caps OR alcohol* AND hub OR alcohol* AND hubs OR alcohol* AND connector OR alcohol* AND connectors OR ethanol* AND cap OR ethanol* AND caps OR ethanol* AND hub OR ethanol* AND hubs OR ethanol* AND connector OR ethanol* AND connectors OR isopropyl* AND cap OR isopropyl* AND caps OR isopropyl* AND hub OR isopropyl* AND hubs OR isopropyl* AND connector OR isopropyl* AND connectors OR chlorhexidine* AND cap OR chlorhexidine* AND caps OR chlorhexidine* AND hub OR chlorhexidine* AND hubs OR chlorhexidine* AND connector OR chlorhexidine* AND connectors = 32 (35 records for 32 trials)

A.14: Source: US Food and Drug Administration (FDA) Manufacturer and User Facility Device Experience (MAUDE) database

Interface / URL:
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm
Database coverage dates: MAUDE web search feature is limited to adverse event reports within the past 10 years. Last update 31/08/17
Search date: 20/09/17
Retrieved records: 45
Search strategy:

Search database for Brand Name: Curos
Date Report Received by FDA limited to 01/01/2007 to 09/20/2017
Start of date limit reflects that MAUDE web search only covers the last 10 years

No other options/fields selected

45 records retrieved and downloaded

A.15: Source: Medicines and Healthcare products Regulatory Agency (MHRA) webpages

Interface / URL: https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency
Database coverage dates: N/A
Search date: 20/09/17
Retrieved records: 0
Search strategy:

Results rapidly assessed by the information specialist. Obviously irrelevant results not selected and downloaded.

Site wide search of gov.uk for Curos – 5 results, all clearly irrelevant, 0 selected

Search of requests under the Freedom of Information Act https://www.gov.uk/government/publications/mhra-requests-under-the-freedom-of-information-act-foia The 4 listed PDFs were searched using the Ctrl F function for Curos.

MHRA FOIA request disclosure log 2 March 2017 – present (https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/616895/Disclosure_Log_1_June_2017.pdf) = 0 results

MHRA FOIA request disclosure log 22 November 2016 – 1 March 2017 (https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/595984/Disclosure_Log_1_March_2017.pdf) = 0 results

MHRA FOIA request disclosure log 17 April 2015 - 22 November 2016 (https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/574668/Disclosure_Log_December_2016.pdf) = 0 results

MHRA FOIA request disclosure log 18 January 2005 - 31 March 2015 (https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/595978/Disclosure_FOIA_requests_April_2015_-_Public.pdf). = 0 results

Search “Alerts and recalls for drugs and medical devices” https://www.gov.uk/drug-device-alerts for Curos 0 results

11.1.5 Details of any additional searches, such as searches of company or professional organisation databases (include a description of each database).

None.

11.1.6 The inclusion and exclusion criteria.

See Table B1, section 7.2.1.

11.1.7 The data abstraction strategy.

Data were extracted directly from the full text pulications or abstracts into Tables B3, B4,B6 and B9

11.2 Appendix 2: Search strategy for adverse events (section 7.7.1)

The following information should be provided.

11.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

See Section 10.1. The search strategies reported in Section 10.1 were not limited by outcome or study design. They would therefore identify any evidence reporting adverse events or safety outcomes related to the use of the eligible intervention. Separate searches of bibliographic databases (such as MEDLINE, Embase, and the Cochrane Library) to identify adverse event data were not required.

11.2.2 The date on which the search was conducted.

The searches were conducted between 19 and 22 September 2017.

11.2.3 The date span of the search.

The searches were not limited by date. The date coverage of each database searched is shown in Section 10.1.4.

11.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

See section 10.1.4.

11.2.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

None.

11.2.6 The inclusion and exclusion criteria.

See Table B1, section 7.2.1.

11.2.7 The data abstraction strategy.

Data were extracted directly from the MAUDE database into Tables B10 and Appendix 5

11.3 Appendix 5: Maude database records of adverse events (n=39) (Section 7.7.3)

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
MW5070690	2017/05/24	Injury	3M Health Care	2017/06/27	LKB	3M's Curos disinfecting caps	Event description: concerns regarding the use of 3M's Curos disinfecting caps for needless connectors in neonates. Curos caps are imbedded with 70% isopropyl alcohol. It is used to reduce

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							the incidence of infections. Background: in 1982 two groups of investigators. Gershanik in New Orleans and Brown in Portland concluded that "intravenous solutions of flush solutions containing 0.9% benzyl alcohol caused severe metabolic acidosis, encephalopathy, respiratory depression and gasping, and perhaps other abnormalities leading to death of a total of 16 infants. Blood and urine from several affected infants had high levels of both benzoic and hippuric acids, known metabolites of benzyl alcohol. Both group stated that no add'l cases occurred after solutions with benzyl alcohol preservative were banned from their nurseries." American Academy of Pediatrics, benzyl alcohol toxic agent in neonatal units. In 1983 the FDA, the CDC and the American Academy of Pediatrics recommended the elimination of benzyl alcohol as a preservative in IV solution and diluents used to reconstitute or dilute medications for infants. In 2000 Stremski reported that 70% isopropyl alcohol plasma concentration of >25 mg/dl is toxic for infants; in 2015 Sauron and colleagues examined the safety of the Swabcap, another disinfection cap (excelsior medical) also imbedded with 70% isopropyl alcohol. It is small bench study. The authors used the Swabcap to cap Smartsite and Caresite connectors and found "the visual appearance of all smartsite valves and 67% of the Caresite valves was changed by Swabcap use. The mean isopropyl alcohol

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							dosages were 52 mmol/l in the Smartsite and 8mmol/l in the Caresite at room temperature and 72 and 7 mmol/l, respectively, at 35 degrees C. No alcohol was found in the control circuit." the control circuit followed standard care, which consisted of disinfecting the luer access valve before injections using friction with an isopropyl alcohol pad for 15 seconds followed by a drying time of 15 seconds. The authors recommended that the Swabcap "should not be used for neonates without further research"; references: American Academy of Pediatrics, benzyl alcohol: toxic agent in neonatal units. Pediatrics, 1983, 72(3): p. 356-8. Stremski, E. And H. Hennes, accidental isopropanol ingestion in children. Pedtr Emerg Care, 2000. 16(4): p. 238-40. Sauron, C., P. Jouvet, G. Pinard, d. Goudreault, B. Martin, B. Rival and A. Moussa, using isopropyl alcohol impregnated disinfection caps in the neonatal intensive care unit can cause isopropyl alcohol toxicity. Acta pediatr, 2015. 104(11): p. E489-93. Vivier, P. M., W. J. Lewander, H. F. Martin and J. G. Linakis, isopropyl alcohol intoxication in a neonate through chronic dermal exposure a complication of a culturally-based umbilical care practice. Pediatr Emerg Care, 1994; 10(2): p. 91-3. Sivilotti, M.L.A., isopro;yl alcohol poisoning. Up to date, 2015. Version 12 (topic 334). Mydler T.T., G. S. Wasserman, W. A. Watson and J. F. Knapp, two-week-old infant with isopropanol

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							intoxication. Pediatr Emerg Care, 1993. 9(3): p. 146-8.
2110898-2017-00083	2017/05/01	Malfunction	3M health care	2017/06/06	LKB	3M Curos jet disinfecting cap for needleless connectors	Event description: customer reported Curos jet caps were placed on the needleless connectors of their IV tubing. The Curos jet caps were removed to connect IV fluids/medication. Two patients reportedly experienced leaking from the needleless connectors when the IV fluids/medication were infusing or being disconnected. Customer reported only a minimal amount of medication was lost and no patient harm occurred. Manufacturer narrative: on (b)(6) 2017; was used as the date of the event. No specific date of event was provided by reporter. No samples were available to 3M for evaluation. Customer reported samples were sent to Carefusion because they thought the issue was related to the needleless connectors.
2110898-2017-00066	2017/04/14	Malfunction	3M Health Care	2017/05/02	LKB	3M Curos tips disinfecting cap strip for male luers	Event description: customer reported the plastic film from cm5-200 Curos male tips was sporadically staying on the end of the male tip when removed from the strip. No known patient harm or injury has been associated with this report. Manufacturer narrative: pt information not provided by reporter. Customer reported a facility Medwatch report was sent to the FDA. On 5/2/2017, 3M has not received the facility Medwatch from the FDA yet.
2110898-2017-00062	2017/02/10	Malfunction	3M Health Care	2017/04/28	LKB	3M Curos jet disinfecting cap for needleless	Event description: customer reported a patient had iv fluids infusing via an iv infusion pump. Curos jet caps were reportedly placed on the needleless connectors of the IV tubing. Customer stated the patient experienced leaking from the needleless

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
						connectors	connector closest to the patient which reportedly had a Curos jet cap in place. The leak was noticed right away and the tubing was changed. No patient harm or consequence was reported. Manufacturer narrative: information not provided by reporter. On (b)(6) 2017- date 3M management made the internal decision to file an MDR report for this complaint. 3M completed a retrospective complaint review. This report is now being filed with the FDA due to similar reports where an injury occurred. There was no patient injury associated with this report.
6529588	2017/04/14	Malfunction	3M company, 3M Health Care	2017/04/28	LKB	Curos	Event description: when removing the Curos disinfecting cap from the strip for the male luers, the plastic strip that covers the tip in between the foil and tip remained on the Curos tip. So, when applied to the male connection on the line it can remain there. When injecting through the connection the plastic strip cam be forced into the I.V. line.
2110898-2017-00058	2017/01/23	Malfunction	3M Health Care	2017/04/27	LKB	3M Curos jet disinfecting cap for needleless connectors	Event description: customer reported an ICU patient was receiving levophed via an IV infusion pump. He reported a nurse discovered there was leaking from a needleless connector where a cfj5-250 Curos jet cap was in place. The iv tubing and Curos jet cap were reportedly replaced and no further leaks occurred. Customer reported no patient harm occurred. Manufacturer narrative: customer reported the event occurred between (b)(6) 2017 and (b)(6) 2017. Exact date was unknown. On (b)(6) 2017 was used for the event date in this report. On (b)(6) 2017 -

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							date 3M management made the internal decision to file an MDR report for this complaint. A 3M completed a retrospective complaint review. This report is now being filed with the FDA due to similar reports where an injury occurred. There was no patient injury associated with this report.
2110898-2017-00059	2017/02/09	Malfunction	3M Health Care	2017/04/27	LKB	3M Curos jet disinfecting cap for needleless connectors	Event description: customer reported Curos jet caps were placed on the iv tubing needleless connectors during a product evaluation. A nurse reported leaking from a connection between the needleless connector and the Curos jet cap when the IV tubing was accidentally left clamped. There was no patient injury or harm reported. Manufacturer narrative: on 04/21/2017- date 3M management made the internal decision to file an MDR report for this complaint. 3M completed a retrospective complaint review. This report is now being filed with the FDA due to similar reports where an injury occurred. There was no patient injury associated with this report. (b)(4) report received from the FDA.
2110898-2017-00060	2017/02/10	Malfunction	3M Health Care	2017/04/27	LKB	3M Curos jet disinfecting cap for needleless connectors	Event description: customer reported a patient was receiving an unspecified antibiotic via an IV infusion pump. Curos jet caps were reportedly placed on the IV tubing needleless connectors. Leaking was reported from the connection between the needleless connector and the Curos jet cap located in the mid portion of the IV tubing. The leak was reportedly noticed right away, the tubing was changed and new Curos jet caps were placed on the needleless connectors. No

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							further leaking was reported. Customer reported there was no patient harm or consequence as a result of the leaking. Manufacturer narrative: information not provided by reporter. On (b)(6) 2017- date 3M management made the internal decision to file an MDR report for this complaint. 3M completed a retrospective complaint review. This report is now being filed with the FDA due to similar reports where an injury occurred. There was no patient injury associated with this report.
2110898-2017-00061	2017/02/11	Malfunction	3M Health Care	2017/04/27	LKB	3M Curos jet disinfecting cap for needleless connectors	Event description: customer reported a patient had ATG (anti-thymocyte globulin) piggy backed into an IV tubing set with three needleless connectors. The infusion was running via an infusion pump. Curos jet caps were reportedly placed on the needleless connectors. Leaking was reported from one of the needleless connectors with a Curos jet cap in place. The leak was reportedly noticed right away, the tubing was changed and new Curos jet caps were placed on the needleless connectors. No further leaking was reported. Customer reported there was no patient harm or consequence as a result of the leaking. Manufacturer narrative: information not provided by reporter. Date 33M management made the internal decision to file an MDR report for this complaint. 3M completed a retrospective complaint review. This report is now being filed with the FDA due to similar reports where an injury occurred. There was no

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							patient injury associated with this report.
2110898-2017-00055	2017/01/17	Malfunction	3M Health Care	2017/04/26	LKB	3M Curos jet disinfecting cap for needleless connectors	Event description: customer reported Curos jet caps were placed on the iv tubing needleless connectors. Customer reported iv fluids were noted to be leaking from the needleless connector/ Curos jet cap connection located in the middle of the IV tubing. The Curos jet cap was removed and replaced with a Curos cap with foam. Iv fluids were reportedly infusing and no harm occurred to the patient. Manufacturer narrative: Pt information not provided by reporter report date 04/21/2017- date 3M management made the internal decision to file an MDR report for this complaint. 3M completed a retrospective complaint review. This report is now being filed with the FDA due to similar reports where an injury occurred. There was no patient injury associated with this report.
2110898-2017-00056	2017/01/01	Malfunction	3M Health Care	2017/04/26	LKB	3M Curos jet disinfecting cap for needleless connectors	Event description: customer reported Curos jet caps were placed on the IV tubing needleless connectors. Customer reported a nurse noted IV fluid leakage from the needleless connector / Curos jet cap located on the distal end of the IV tubing. The Curos jet cap was removed, replaced with a new Curos jet cap and no further leakage was noted. IV fluids were reportedly infusing and customer reported no patient harm occurred. Manufacturer narrative: customer reported the event occurred in early (b)(6), exact date was unknown. (b)(6) 2017 was used for the event date in this report. On (b)(6) 2017- date 3M management

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							made the internal decision to file an MDR report for this complaint. 3M completed a retrospective complaint review. This report is now being filed with the FDA due to similar reports where an injury occurred. There was no patient injury associated with this report.
2110898-2017-00057	2017/01/16	Malfunction	3M Health Care	2017/04/26	LKB	3M Curos jet disinfecting cap for needleless connectors	Event description: customer reported they have been using cfj5-250 Curos jet caps for approximately two weeks and have had about six reports of leaking at the connection between the IV tubing needleless connector and the Curos jet cap. Customer reported no patient harm has occurred. Manufacturer narrative: customer reported the events occurred in the past week. Exact dates and details were unknown. The (b)(6) 2017 was used for the event date based on the report date of (b)(6) 2017. On (b)(6) 2017-date 3M management made the internal decision to file an MDR report for this complaint. 3M completed a retrospective complaint review. This report is now being filed with the FDA due to similar reports where an injury occurred. There was no patient injury associated with this report.
2110898-2017-00053	2017/01/01	Malfunction	3M Health Care	2017/04/25	LKB	3M Curos jet disinfecting cap for needleless connectors	Event description: customer reported Curos jet caps were placed on the iv tubing needleless connectors. A nurse clamped the iv tubing below the needleless connector and the infusion pump did not recognize a downstream occlusion because it was leaking under the Curos jet cap. During a routine assessment, the patient reported a few drops of fluid from the needleless

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							connector/ Curos jet cap connection had dripped onto her pajamas. The Curos jet cap was removed and replaced with a new one. No further leaking was noted on that shift. Customer reported no harm occurred to the patient. Manufacturer narrative: information not provided by reporter. Customer reported the event occurred in early (b)(6) and did not have the exact date of the event. On (b)(6) 2017 was used for date of event in this report. On 04/21/2017-date 3M management made the internal decision to file an mdr report for this complaint. 3M completed a retrospective complaint review. This report 2110898-2017-00053 is now being filed with the FDA due to similar reports where an injury occurred. There was no patient injury associated with this report.
2110898-2017-00050	2017/03/21	Injury	3M Health Care	2017/04/18	LKB	3M Curos disinfecting cap for needleless connectors	Event description: risk manager reported the mother of an (b)(6) old toddler alleged her son removed cff10-250 Curos disinfecting caps from his fluid line and put one in his mouth. The mother alleged her son was choking on one of the green caps and she removed it. Risk manager reported the toddler was evaluated following the reported event and his lungs were clear, O2 saturation was 100% and he had easy work of breathing. Manufacturer narrative: were not provided by reporter. There was no lot number provided for the product. Without lot number it is not possible to determine the expiration date or manufacture date. 3M received facility Medwatch report (b)(4) from the FDA

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							and contacted the reporter to obtain additional information. Customer reported they have not had any other reports of children removing the Curos cap from the needleless connector. Packaging instructions for use contain the following caution statement: caution: potential choking hazard.
6493194	2017/03/15	Malfunction	3M company	2017/04/14	LKB	Curos	Event description: male end of tubing breaks off when Curos tips are applied.
6456187	2017/02/09	Malfunction	3M company	2017/04/04	LKB	Curos caps	Event description: a trial of 3M Curos jet alcohol caps started the first week of (b)(6) 2017. Approximately 1 week into the trial, a nurse reported fluid leaking from a baxter clearlink IV tubing access port with a Curos cap in place when the tubing was accidently left clamped. The event was reported to 3M to investigate the problem. Several weeks later, a second report was received of a Curos cap screwed on at an angle on a baxter clearlink IV access port causing fluid to leak from the port. The leaking stopped when a cap was placed on correctly. A third report was received of a damaged hospira microclave suspected by the nurse to be associated with the Curos jet cap. In a conference call with 3M representatives, we learned the 3M technical engineers were intermittently able to duplicate the leaking when the baxter clearlink tubing was put under pressure (the tubing was not pressurized above the maximum limit it is made to withstand) and a Curos jet cap was in place. They also said they could create a small leak without a jet cap in place. They said they had 5

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							other hospitals that experienced leaks when using the jet cap and baxter clearlink tubing. Manufacturer response for caps for iv tubing, Curos caps (per site reporter): date: February, 2017. Subject: reports of Baxter® clearlink IV access system leaking with use of 3M Curos jet disinfecting cap for needleless connectors. Dear valued healthcare partner, we have recently been made aware of reports that some Baxter® continu-flo solution sets with clearlink needleless connectors may intermittently leak from their clearlink needleless connectors while under pressure when used in conjunction with 3M Curos jet disinfecting cap for needleless connectors. We have investigated the Curos jet lots in question and have found them to be within our design specifications. As your healthcare partner, 3M takes these reports very seriously and is vigorously investigating this issue. We have made Baxter® aware of the situation and are working with them to better understand the root cause of this issue. For questions and additional information related to 3M Curos disinfecting port protectors, please contact your local 3m sales representative, or the 3M health care customer helpline at (b)(4). Kindly, (b)(4).
6431666	2017/03/21	Malfunction	3M company, 3M Health Care	2017/03/24	LKB	Curos	Event description: the patient was found by his parent to have pulled the green Curos caps off of his fluid lines and tried to put them in his mouth. The parent stated that patient was choking on one of the caps and had been removed by parent. The patient's lung

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							sounds clear, easy work of breathing and saturations are 100%.
2110898-2017-00026	2017/01/26	Injury	3M Health Care	2017/03/01	LKB	3M Curos jet disinfecting cap for needleless connectors	Event description: customer reported a patient had IV vancomycin infusing via an IV infusion pump. Curos jet caps were reportedly placed on the injection ports of the IV tubing. Customer reported the patient experienced leaking from the injection port closest to the patient. The injection port reportedly had a Curos jet cap in place. The leak was noticed right away so a limited amount of vancomycin was lost. The tubing was changed, the vancomycin levels were checked and reportedly remained fine. No additional dosing was needed. Manufacturer narrative: no patient information was available for this report. Event date: (b)(6) 2017 was used for the date of event since the customer reported the event occurred approximately 3-4 weeks ago and did not have the exact date of occurrence. There was no given lot number for the product. Without lot number it is not possible to determine the expiration date or manufacture date. We received a delivery failure to our first EMDR submission which stated an "event type code" was required. We would like to be able to select "other" as we feel this report does not fit into death, serious injury or malfunction. As a result we selected "no information" with our first EMDR report and received the delivery failure. We feel the FDA should be aware of this reported event due to the nature of the intervention that was required. Serious injury

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							was now selected as this section could not be left blank, however the patient did not suffer a serious injury as a result of this incident. The patient reportedly experienced leaking of medication. The patient required a blood level check to ensure a therapeutic level of the medication had been achieved. The patient had a therapeutic level and did not require any further intervention. Customer reported no sample or lot number was available for this report.
2110898-2017-00025	2017/02/02	Injury	3M Health Care	2017/02/28	LKB	3M Curos jet disinfecting cap for needleless connectors	Event description: customer reported a (b)(6) female patient had IV chemotherapy infusing via an IV pump. Curos jet caps were reportedly placed on the injection ports of the IV tubing. Customer reported approximately 150 cc of the chemotherapy infusion was found to be leaking from the injection port closest to the patient which had a Curos jet cap in place. The patient required re-dosing and was given the estimated amount of chemotherapy that was lost due to leaking. Manufacturer narrative: date of event: (b)(6) 2017 was used for the date of event since the customer reported the event occurred approximately 1 1/2 weeks ago and did not have the exact date of occurrence. There was no given lot number for the product. Without lot number it is not possible to determine the expiration date or manufacture date. Customer reported no sample or lot number were available for this report.

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
2110898-2017-00020	2017/02/12	Injury	3M Health Care	2017/02/22	LKB	3M Curos jet disinfecting cap for needleless connectors	Event description: customer reported an ICU patient was receiving an epinephrine/neosynephrine drip via an IV infusion pump. The patient's blood pressure was reportedly dropping when the clinician discovered a puddle of fluid on the floor. Customer reported the IV fluids were leaking from an injection port where a (b)(4) Curos jet cap was in place. The Curos jet caps were discontinued and the tubing was reportedly replaced. No further leaks occurred and the customer reported the patient did not suffer and adverse consequences as a result of the reported incident. Manufacturer narrative: there was no given lot number for the product. Without lot number it is not possible to determine the expiration date or manufacture date. The product was not returned for evaluation as of the date of this report.
2110898-2017-00021	2017/01/25	Injury	3M Health Care	2017/02/22	LKB	3M Curos jet disinfecting cap for needleless connectors	Event description: customer reported they experienced periodic leaking from injection ports where cfj5-250 Curos jet disinfecting caps were used. In the past two weeks, there were two reports where patients had IV chemotherapy piggybacked into infusion tubing running via a pump (unknown brand). The leaking was reportedly discovered after only a few drops of leaking. There was reportedly no harm or consequence to the patient. The leaking reportedly stopped when the Curos jet cap was replaced or in some instances, when both the tubing and Curos jet caps were replaced. Manufacturer narrative: date of event: (b)(6) 2017 was used for the date of

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							event since the customer reported the events occurred within the last two weeks and did not have the exact date of occurrence. There was no given lot number for the product. Without lot number it is not possible to determine the expiration date or manufacture date. The product was not returned for evaluation as of the date of this report.
2110898-2017-00012	2017/01/16	Injury	3M Health Care	2017/02/14	LKB	3M Curos disinfecting cap for needleless connectors	Event description: customer reported a CFF1 270r Curos cap was applied directly to the hub of a PICC catheter which resulted in separation of the sponge. Customer reported the PICC line was removed. No additional information was available. Customer reported this event was the result of user error and no fault with the device. The customer reported follow- up occurred on (b)(6) 2017 and training and support will be provided by the representative. Manufacturer narrative: patient information was not provided. There was no lot number or sample provided for this report so full investigation could not be completed. Customer reported this event was the result of user error and no fault with the device. The customer reported follow- up occurred on (b)(6) 2017 and training and support will be provided by the representative. This compliant report involves product cff1-270r Curos disinfecting cap for needleless connectors which is sold outside the united states (OUS). Current OUS product packaging contains intended use information and states this product is intended

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							for use on swabbable lure access valves as a disinfecting cleaner prior to line access. The cff1-270r Curos disinfecting cap for needleless connectors noted in this adverse event was reportedly not applied to a needleless luer valve. It was applied directly to the catheter hub. Manufacturer 3M markets a similar product in the US, cff1-270 Curos disinfecting cap for needleless connectors. The US product packaging was updated to include the following warning and cautionary statements: warning: to avoid potential injury - use only on needleless connectors. Caution: potential choking hazard. This warning and caution statement is scheduled to be added to the OUS packaging in March, 2017. In addition, 3M provides training materials (including graphics) instructing customers to apply Curos disinfecting cap for needleless connectors only to needleless connectors and not to apply the Curos disinfecting caps directly to a catheter hub. PDF of training materials are attached to this report. In summary, the packaging update clearly states via warning that the product should only be used on needleless connectors.
2110898-2017-00013	2017/01/16	Injury	3M Health Care	2017/02/14	LKB	3M Curos disinfecting cap for needleless connectors	Event description: customer reported a CFF1 270r Curos cap was applied directly to the hub of a midline catheter which resulted in separation of the sponge. She reportedly witnessed the incident and was able to retrieve the sponge using a forceps. The midline catheter was reportedly removed following

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							the incident due to infection risk. No additional information was available. Customer reported this event was the result of user error and no fault with the device. The customer reported follow- up occurred on (b)(6) 2017 and training and support will be provided by the representative. Manufacturer narrative: patient information was not provided. Date of event was not provided so report date was also used for date of event. There was no lot number or sample provided for this report so full investigation could not be completed. Customer reported this event was the result of user error and no fault with the device. The customer reported follow- up occurred on (b)(6) 2017 and training and support will be provided by the representative. This compliant report involves product CFF1-270r Curos disinfecting cap for needleless connectors which is sold outside the united states (OUS). Current OUS product packaging contains intended use information and states this product is intended for use on swabbable lure access valves as a disinfecting cleaner prior to line access.... · the CFF1-270r Curos disinfecting cap for needleless connectors noted in this adverse event was reportedly not applied to a needleless luer valve. It was applied directly to the catheter hub. 3M markets a similar product in the US, CFF1-270 Curos disinfecting cap for needleless connectors. The us product packaging was updated to include the following warning

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							and cautionary statements: warning: to avoid potential injury - use only on needleless connectors caution: potential choking hazard this warning and caution statement is scheduled to be added to the OUS packaging in March, 2017. The intended use and instructions for use packaging information is attached in the pdf. In addition, 3M provides training materials (including graphics) instructing customers to apply Curos disinfecting cap for needleless connectors only to needleless connectors and not to apply the Curos disinfecting caps directly to a catheter hub. PDF of training materials are attached to this report. In summary, the packaging update clearly states via warning that the product should only be used on needleless connectors.
2110898-2017-00014	2017/01/16	Malfunction	3M Health Care	2017/02/14	LKB	3M Curos disinfecting cap for needleless connectors	Event description: customer reported a CFF1 270r Curos cap was applied directly to the hub of a catheter (unspecified type) which resulted in separation of the sponge. At the time of the event, customer reported they did not know where the sponge was. The sponge was reportedly found several hours later in a bin. No additional information was available. Customer reported this event was the result of user error and no fault with the device. The customer reported follow- up occurred on (b)(6) 2017 and training and support will be provided by the representative. Manufacturer narrative: patient information was not provided. Date of event was not provided so report date was also used for date of

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							event. There was no lot number or sample provided for this report so full investigation could not be completed. Customer reported this event was the result of user error and no fault with the device. The customer reported follow- up occurred on (b)(6) 2017 and training and support will be provided by the representative. This compliant report involves product CFF1-270r Curos disinfecting cap for needleless connectors which is sold outside the united states (OUS). Current OUS product packaging contains intended use information and states this product is intended for use on swabbable lure access valves as a disinfecting cleaner prior to line access.... · the cff1-270r Curos disinfecting cap for needleless connectors noted in this adverse event was reportedly not applied to a needleless luer valve. It was applied directly to the catheter hub. 3M markets a similar product in the us, CFF1-270 Curos disinfecting cap for needleless connectors. The us product packaging was updated to include the following warning and cautionary statements: warning: to avoid potential injury - use only on needleless connectors caution: potential choking hazard. This warning and caution statement is scheduled to be added to the OUS packaging in March, 2017. The intended use and instructions for use packaging information is attached in the pdf. In addition, 3M provides training materials (including graphics) instructing

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							customers to apply Curos disinfecting cap for needleless connectors only to needleless connectors and not to apply the Curos disinfecting caps directly to a catheter hub. PDF of training materials are attached to this report. In summary, the packaging update clearly states via warning that the product should only be used on needleless connectors.
6325422	2017/01/31	Malfunction	3M company, 3M Health Care	2017/02/13	LKB	Curos	Event description: Curos cap broke in two while nurse was screwing the cap on a picc line.
6275607	2017/01/09	Malfunction	3M company	2017/01/25	LKB	3M, Curos disinfecting cap for Tego	Event description: internal ring of cap disconnected from the external cap.
2110898-2016-00041	2016/02/18	Death	3M Health Care	2016/03/22	LKB	3M Curos disinfecting cap for needleless connectors	Event description: customer reported a female patient with an abscess/bowel perforation was receiving antibiotics through an internal jugular, triple lumen central line catheter. A nursing student reportedly disconnected the IV setup (saline bag/antibiotic piggy back and needleless connector) down to the catheter hub. Customer reported the central line catheter lumen was not clamped when the IV was disconnected and a Curos cap was placed directly on the central line catheter hub. After disconnecting the IV, the patient was moved to a chair. Customer stated the patient then experienced headaches and respiratory issues which led to a respiratory arrest. Customer reported patient was in serious condition, diagnosed with a massive air embolic stroke and died sixteen days

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							later. Manufacturer narrative: infusion nurses society (INS) is a globally recognized authority for best practices related to infusion therapy. In the fifth edition of infusion nurses society (INS) policies and procedures, it states the following under key points related to air embolism: ensure the vascular access device (VAD) is securely clamped when disconnecting/reconnecting a new administration set, needleless connector, or any other add-on device. The central vascular access device was not clamped when the IV was disconnected. In addition, the Curos disinfecting port protector was not used as directed. Product packaging contains directions for use and intended use information. Intended use: the Curos is intended for use on swabbable luer access valves as a disinfecting cleaner prior to line access and to act as a physical barrier to contamination between line accesses.
2110898-2016-00022	2015/11/18	Injury	3M Health Care	2016/02/24	LKB	3M Curos disinfecting cap for needless connector	Event description: customer reported a patient had a right chest tube connected via a three-way stopcock to low wall suction. A green Curos cap had been placed over the three-way stopcock to cover the access port. The physician was concerned about blood clots so medication was ordered to be administered through the chest tube. After the medication was administered, the chest tube was clamped for 1 hour. When unclamped, the chest tube did not appear to be draining despite being hooked to low wall suction. The patient then reportedly

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							started to medically decompensate and required a non-rebreather mask at 100% and multiple medications to manage his rising systolic blood pressure. A physician attempted to flush the patient's chest tube and when he forcefully drew back on the access port leading to the patient's chest-tube stopcock, he noted a very small white ball at the very end of the access port. The physician was able to pull the small white ball out with his fingertips and noted it looked similar to the white portion of the Curos cap that is impregnated with alcohol. The original Curos cap had been discarded when the medication was administered so it was not available for inspection. Once the port was cleared of the small white ball, the chest tube began draining serosanguinous fluid and the patient recovered. Manufacturer narrative: the facility reported this event to the FDA ((b)(4)). 3M received the report from the FDA. In the facility report, the following information was noted: device usage problem. "the Curos cap product information notes that the Curos cap is intended for use on swabbable luer access valves prior to line access and to act as a physical barrier to contamination between line accesses. It should not be connected to a three-way stopcock. "the Curos passive disinfection device was used on a connector that it was not meant to be used on".
5406449	2015/11/18	Injury	3M	2016/02/03	LKB	Curos	Event description: the patient had a right-sided chest tube to low wall suction. In the morning, the interventional

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							pulmonary physician ordered TPA (alteplase) and dornase to be administered via through the chest tube; the physician was concerned for blood clots and wanted to break them up. A green Curos cap had been placed over the three-way stopcock by the radiology physician team to cover the access port. The administration was completed and the chest tube remained clamped for 1 hour. When is was unclamped an hour later, as directed by interventional pulm md, the chest tube did not appear to be draining. This failure to drain occurred despite the continuation of the low wall suction to the chest tubes. Concurrently, the patient started to medically decompensate and required a non-rebreather mask at 100% and multiple medications to manage his rising sbp (systolic blood pressure) to the 230s. Multiple providers were called to the bedside including medical mds and nursing specialists and supervisor. The interventional pulmonary physician returned to bedside and attempted to flush the patient's chest tube with 10cc ns in order to promote drainage. He remained concerned that a clot may have formed and blocked the tube. When he forcefully drew back on the access port leading to the patient's chest-tube stopcock, the physician noted a very small white ball appeared at the very end of the access port. The physician was able to pull small white ball out with his fingertips, commenting that it looked similar to white portion of the Curos cap that is

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							impregnated with alcohol. The original cap had been discarded when the administration was provided one hour earlier, so it was not available for inspection. Once the tube was cleared of the small white ball, then the chest tube began draining serosanguinous drainage and the patient recovered.event description: the patient had a right-sided chest tube to low wall suction. In the morning, the interventional pulmonary physician ordered TPA (alteplase)and dornase to be administered via through the chest tube; the physician was concerned for blood clots and wanted to break them up. A green Curos cap had been placed over the three-way stopcock by the radiology physician team to cover the access port. The administration was completed and the chest tube remained clamped for 1 hour. When is was unclamped an hour later, as directed by interventional Pulm MD, the chest tube did not appear to be draining. This failure to drain occurred despite the continuation of the low wall suction to the chest tubes. Concurrently, the patient started to medically decompensate and required a non-rebreather mask at 100% and multiple medications to manage his rising SBP (systolic blood pressure) to the 230s. Multiple providers were called to the bedside including medical MDs and nursing specialists and supervisor. The interventional pulmonary physician returned to bedside and attempted to flush the patient's chest tube with 10cc ns in order to promote drainage. He remained

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							concerned that a clot may have formed and blocked the tube. When he forcefully drew back on the access port leading to the patient's chest-tube stopcock, the physician noted a very small white ball appeared at the very end of the access port. The physician was able to pull small white ball out with his fingertips, commenting that it looked similar to white portion of the Curos cap that is impregnated with alcohol. The original cap had been discarded when the administration was provided one hour earlier, so it was not available for inspection. Once the tube was cleared of the small white ball, then the chest tube began draining serosanguinous drainage and the patient recovered.
4253141	2014/09/27	Malfunction	Ivera Medical	2014/10/01	FPA	Curos	Event description: RN unscrewed the Curos cap from the IV kine and the inside of the cap was still around the line. RN had to use a hemstat clamp to remove it.
3008142801-2014-00001	2014/07/11	Malfunction	Ivera Medical	2014/09/27	LKB	Curos disinfecting port protector	Event description: the Curos caps are breaking while patients are moving around in bed and also break apart as the nurse removes the cap. Manufacturer narrative: notification of the MDR was provided through a letter from the FDA dated on (b)(4) 2014. The letter was received at ivera on (b)(4) 2014. The reported device was not returned by the user facility nor was the lot number communicated. Without the device or lot number, ivera is not able to investigated the reported issue. Contact was made with the user facility, which they indicated that issues were minor and non-significant. There was no

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							patient of safety related incident and they have not had any additional issues since the recent reports. Ivera did review verification requirements that are conducted in manufacturing of the product. Sampling is conducted on a continuous periodic basis, which tensile verification is part of inspection to confirm that a minimum retention force when engaged with a needleless luer activated valve (LAV). Manufacturing limits are established on the manufacturing equipment, which is monitored real-time. If an excursion occurs outside the manufacturing limits, the manufacturing equipment will automatically segregate product produced at the time the excursion occurs.
3008142801-2014-00002	2014/08/03	Malfunction	Ivera Medical	2014/09/27	LKB	Curos disinfecting port protector	Event description: Curos cap broke apart. Little green ring stayed on the IV port when RN took the cap off. This apparently happened twice. Manufacturer narrative: MDR was observed when conducted a search of FDA 's Maude database on September 25, 2014. No other notification was provided by the user facility nor (b)(4)'s sale representatives. The reported device was not returned by the user facility nor was the lot number communicated. Without the device or lot number, (b)(4) is not able to investigated the reported issue. (b)(4) could not contact the user facility since contact information from the user facility was indicated in the reported information. (b)(4) did review verification requirements that are conducted in manufacturing of the product. Sampling is

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							conducted on a continuous periodic basis, which tensile verification is part of inspection to confirm that a minimum retention force when engaged with a needleless luer activated valve (LAV). Manufacturing limits are established on the manufacturing equipment, which is monitored real-time. If an excursion occurs outside the manufacturing limits, the manufacturing equipment will automatically segregate product produced at the time the excursion occurs.
4253190	2014/09/09	Malfunction	Ivera Medical	2014/09/21	FPA	Curos	Event description: while trying to put a green Curos cap on a line, it broke and the nurse had to pry the broken piece off the port.
4023072	2014/08/03	Malfunction	Ivera Medical	2014/08/15	LKB	Curos	Event description: Curos cap broke apart. Little green ring stayed on the IV port when RN took the cap off. This apparently happened twice.
4023073	2014/07/11	Malfunction	Ivera Medical	2014/07/15	LKB	Curos	Event description: the Curos caps are breaking while patients are moving around in bed and also break apart as the nurse removes the cap.
2412604	2012/01/06	Malfunction	Ivera Medical Corporation	2012/01/09	LKB	Curos	Event description: the nurse put the Curos protector covers on the all the primary ports. She spiked the IV solution and primed the tubing. One of the Curos covers fell apart. The tubing was not attached to the patient at the time the cover broke.this is the first I have heard of this incident. Another Curos port protector was used from the same lot number.
MW5021324	2011/05/04	Injury	Ivera Medical Corporation	2011/07/11	LKB	Curos port protector	Event description: between (b)(6) 2011, we had (4) patients identified as having candida infections and all patients had lines placed during their admissions. The types of candida varied amongst patients and

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							involved candida albicans, glabrata and parapsilosis. Prior to this time, line infections have been rare at our facility. We have done an extensive review to locate the source of these infections but have been unable to confirm the source. As a part of our review, it was identified that use of the Curos port protector caps on our lines were the only recent change. We first put the caps into use as a trial in our ICU on (b)(6) 2011. Since that time, we have begun to use them across the house. Although we have not identified the caps as a cause of the infection, it was recommended that we report as a precaution. We were told by the manufacturer that they have not been informed of any similar types of issues with this product. Per the manufacturer, they do not have testing at this time that shows the efficacy of the Curos port protector in regards to candida (as it is not required). Dates of use: implemented (b)(6) 2011 pulled (b)(6) 2011. Reason for use: central line. Also see (b)(4).
MW5021325	2011/05/01	Injury	Ivera Medical Corporation	2011/07/11	LKB	Curos port protector	Event description: between (b)(6) 2011, we had (4) patients identified as having candida infections and all patients had lines placed during their admissions. The types of candida varied amongst patients and involved candida albicans, glabrata and parapsilosis. Prior to this time, line infections have been rare at our facility. We have done an extensive review to locate the source of these infections but have been unable to confirm the source. As a part of our

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							review, it was identified that use of the Curos port protector caps on our lines were the only recent change. We first put the caps into use as a trial in our icu on (b)(6) 2011. Since that time, we have begun to use them across the house. Although we have not identified the caps as a cause of the infection, it was recommended that we report as a precaution. We were told by the manufacturer that they have not been informed of any similar types of issues with this product. Per the manufacturer, they do not have testing at this time that shows the efficacy of the Curos port protector in regards to candida (as it is not required). Dates of use: implemented (b)(6) 2011. Reason for use: central line. Also see (b)(4).
MW5021326	2011/05/01	Injury	Ivera Medical Corporation	2011/07/11	LKB	Curos port protector	Event description: between (b)(6) 2011 and (b)(6) 2011, we had (b)(6) patients identified as having candida infections and all patients had lines placed during their admissions. The types of candida varied amongst patients and involved candida albicans, glabrata and parapsilosis. Prior to this time, line infections have been rare at our facility. We have done an extensive review to locate the source of these infections, but have been unable to confirm the source. As a part of our review, it was identified that use of the Curos port protector caps on our lines were the only recent change. We first put the caps into use as a trial in our ICU on (b)(6) 2011. Since that time, we have begun to use them across the house. Although

Report Number	Event Date	Event type	Manufacturer	Date Received	Product Code	Brand name	Event text
							we have not identified the caps as a cause of the infection, it was recommended that we report as a precaution. We were told by the manufacturer that they have not been informed of any similar types of issues with this product. Per the manufacturer, they do not have testing at this time that shows the efficacy of the Curos port protector in regards to candida (as it is not required). Dates of use: implemented (b)(6) 2011 pulled (b)(6) 2011. Reason for use: central line. Also see MW5021324, MW5021325 and MW5021327.

National Institute for Health and Care Excellence

Medtech Innovation Briefing

Collated comments table

Expert contact details and declarations of interest:

Expert #1	Dr Elizabeth Pilling, Consultant neonatologist, Royal Hallamshire Hospital
	DOI: Yes The study undertaken was supported by Vygon on a “buy 1 get 1 free” basis, with refund of all costs if there was not a reduction in infection rates by 1/3. Since this reduction did not occur, the cost of all port protectors used was refunded. No member of the team received any financial payment at any point.
Expert #2	Ms Catherine Plowright, Acute Care Consultant Nurse, Urgent Care & Long Term Conditions Division, East Kent Hospitals University NHS Foundation Trust
	DOI: None
Expert #3	Ms Corinne Cameron-Watson, Infection Control Nurse, North East London NHS Treatment Centre, Care UK
	DOI: Yes Have undertaken consultancy work with 3M speaking at vascular access workshops. 2016 Published paper in British Journal of Nursing: Port protectors in clinical practice: an audit
Expert #4	Roy Ventura, Lead Vascular Access Clinical Nurse Specialist, Anaesthetics, University Hospital Coventry & Warwickshire
	DOI: None
Expert #5	Ms Doreen Crawford, Critical Care Nurse, Representing RCN
	DOI: None
Expert #6	Ms Jan Hitchcock, General Manager (Interim) Infection Prevention & Control, Imperial College Healthcare NHS Trust
Expert #7	Dr Alag Raajkumar Consultant Anaesthetist, NHS Worcestershire Acute Hospitals,
	DOI: None

1	Please describe your level of experience with the technology, for example: − Are you familiar with the technology? − Have you used it? − Are you currently using it? − Have you been involved in any research or development on this technology? − Do you know how widely used this technology is in the NHS?	Expert #1: I coordinated a service evaluation (paper in preparation, poster published see below) with this technology, using the port protector device for 8 months with before, during and after analysis of infection rates in a tertiary neonatal unit. Budhiraja S, Clargo H, McLellan E, et al G573(P) Impact of passive disinfection device on the rate of catheter related blood stream infections in neonates: A quality improvement initiative Archives of Disease in Childhood 2016;101:A341. As a result of this project we discontinued use of the port protector device as it did not result in a decrease in infection rates within our neonatal unit therefore was not cost effective. There was actually a non-significant trend to increase in infection rate with the device which reverted to baseline after discontinuing usage. The compliance in our study was high and the device was widely accepted by the nursing staff. The company supporting the study sent an independent observer to attend the neonatal unit during the active phase to observe practice in view of interim results of no effect, but no variation in practice/reason for the lack of effect could be found. I am aware that some hospitals do use this technology and that a further evaluation in the neonatal population was underway, however it is not currently standard practice in neonatal units.
		Expert #2 I have not used this product I am not familiar with this product I have not been involved in any research regarding this product I have worked in two Trusts in the last 16 years and neither of them has used this product. I have not seen it advertised at any conferences I have attended in recent years

		Expert #3 I led a study into the technology which was published in 2016.
		Expert #4 I have an extensive experience with the technology. I have used the device for over 3 years, since 2014. I have in fact implemented the device use trust-wide, for the use on central venous access devices and some peripheral IV access. I am very familiar with how the technology works. Currently, in my new job (NHS hospital) I am using for some select patients. I am in the process of implementing the product trust-wide as part of the CVAD care bundle. I have been involved in analysing the impact of the technology on the reduction of CRBSIs. I have a published abstract presented in the World Congress of Vascular Access in Portugal on 2016. There are few trust in the NHS that are using the technology. The trust which have an dedicated IV team and a proactive Infection Prevention & Control teams are normally the trust that use it.
		Expert #5 Have not used them, They are however logical in concept and if they could reduce long line sepsis it would be very welcome addition to preventing harm to patients. Have not been involved in any research, development or clinical trials in this technology. Have not seen it used in NNU's, adult ITU's or CYP ITU's during my inspection roles with CQC. Do not think it is widely used.
		Expert #6 I am familiar with this product and use if in our organisation for selected patients based on a risk assessment. I have not been involved in any research or it its development to date. I believe it is increasingly being used in the NHS.
		Expert #7 I am familiar with the technology .But I am not currently using it and have not been involved in research or development of this technology.
2		Expert #1:

	Has the technology been superseded or replaced?	Not that I am aware of
		Expert #2 I do not think so
		Expert #3 No
		Expert# 4 This technology has not been superseded. It is a new and unique product.
		Expert #5 No comment to offer, if adopted it could augment standard lines currently in use providing it is system compatible.
		Expert #6 No
		Expert #7 Not to my knowledge

Current management

3	How innovative is this technology, compared to the current standard of care? Is it a minor variation or a novel concept/design?	Expert #1: It is a novel concept
		Expert #2 We know that staff at times can barley clean the hubs so this product design is ideal. Looks easy to use
		Expert #3 I consider it very innovative compared to use of wipes
		Expert #4

		The current standard of care requires meticulous use and consumes time. The degree of variance in practice poses risk in the current standards. Compared to the new technology, it promotes the ease of use, saving of time and standardised practice. The technology is a novel design.
		Expert #5 If it were to reduce catheter infections, was straightforward and cost effective it would be very welcome
		Expert #6 It is not a novel concept in that Needle free connectors need decontamination, the novelty of it is that it has a continuous affect whilst insitu
		Expert #7 It is a good concept and should decrease infection and save staff time.
4	Are you aware of any other competing or alternative technologies available to the NHS which have a similar function/mode of action to the notified technology? If so, how do these products differ from the technology described in the briefing?	Expert #1: Not that I am aware of. I had been aware of the use of this product in the USA, prior to it becoming available to the UK market.
		Expert #2 I am not aware of any
		Expert #3 No
		Expert #4 Yes, there are similar products to this technology. The concept of function and use are the same. The only difference is that is manufactured by a different industry.
		Expert #5 Not aware of other systems
		Expert #6 No
		Expert #7

		I am not aware of alternative technologies with similar functions.

Potential patient benefits

5	What do you consider to be the potential benefits to patients from using this technology?	Expert #1: If the product reduces infection rates, this is of patient benefit. If it has no impact on infection rates, there is no patient benefit.
		Expert #2 Reduction inline infections
		Expert #3 Reduced risk of infection through Vascular Access Devices (VAD)
		Expert #4 The use of this technology has numerous potential benefits to patients. One main benefit is the prevention of an infection/CRBSI, when used on a patient's vascular access device. The cost of treating a CRBSI is obvious, but the other impact of the preventable problem is not normally accounted for. The loss of life, trauma, etc. as impact of CRBSI to patients need to be highlighted. The technology gives patients confidence. Despite having an invasive device, they are re-assured that they are properly protected from contamination. It also provides them reassurance that the health care system is investing on them, to prevent them from further complication. The technology can potentially give a patient more independence and freedom too; knowing that they and their device are protected from infection.
		Expert #5 Data on central line infections are collected it would be easy to see a reduction in incidence between units who adopt the connections and those who do not. Patients who acquire central line sepsis, have delayed recovery, prolonged hospital stay, higher morbidity and mortality rates. Central line sepsis is costly to the NHS and the individual
		Expert #6 Improving patient safety by helping to prevent catheter associated blood stream infections (CRBSI)

		Expert #7 Decrease in VAD associated infections
6	Are there any groups of people who would particularly benefit from this technology?	Expert #1: Assuming the above, patients with higher risk of catheter related infection eg immunosuppressed, those with central lines, those requiring catheters for a long period of time, the neonatal population (as they fulfil all of the above) would benefit the most.
		Expert #2 High risk patients e.g. those in critical care units and those with venous access in place for extended periods of time
		Expert #3 Patients in the Intensive Care Setting and Haematology/Oncology patients both in the inpatient and outpatient settings
		Expert #4 The clinical staff managing a patient with vascular access device (VAD) can benefit from the use of the technology. These staff include medical and nursing staff. The technology can save them time and effort in managing a VAD The Trust can benefit from this too. It can save a hefty amount of money by preventing expensive treatment of CRBSI. The cost of litigations can be minimized too, by the prevention of complications. Our scientists will benefit from this technology too, I believe. We are in an era where current antibiotics are no longer sufficient to treat virulent infections. There is a massive drive in terms of antibiotic stewardship because of inappropriate or over-usage of antibiotics. Prevention is better than cure. The technology will prevent complications which will lead to the use or over-use of drugs to treat infections. The patient's family or care givers will benefit too, in terms of saving them from going through the trauma of dealing with a patient who's acquired an infection. Although these are indirect benefits, I still believe they matter.
		Expert #5 Neonates with umbilical lines are particularly susceptible to sepsis. Can these connectors be used in these lines as well?

		Expert #6 Yes
		Expert #7 Elderly patients with decreased immunity, HDU and ITU patients, vascular patients, patients needing longer duration of antibiotics , in theatres and in ward setting.
7	Does this technology have the potential to change the current pathway or clinical outcomes? Could it lead, for example, to improved outcomes, fewer hospital visits or less invasive treatment?	Expert #1: Yes- (assuming reduced infection rates). A central line infection may result in admission to hospital/increased length of stay/clinical deterioration including intensive care admission, further intravenous access, removal/replacement of the central line, additional blood tests, courses of antibiotics with risks associated with this. Very severe infections may result in death. For the neonatal population, there can be long term neurodevelopmental sequelae as infection can damage the developing brain. Any intervention that reduces infection rates, therefore reduces all of the above.
		Expert #2 Has potential to lead to shorter length if stays if CRBSI do not occur
		Expert #3 The technology could improve patient outcomes by preventing VAD infections which could progress to catheter related bloodstream infections (CRBSI) in a hospital setting. By preventing CRBSI's patients have better outcomes and hospitals make better use of beds
		Expert #4 The technology will change the current outcomes. It will lead to a much-improved result. Patients hospital length of stay is shortened because of the avoidance of complications. It can lead to shorter morbidity, fewer hospital visits and less unnecessary invasive treatment. This all can be related to the prevention of complications and improved longevity of the VAD.
		Expert #5 Yes overlap with 5
		Expert #6

		Improved outcomes in patients more susceptible to infection and in particular catheter related infections.
		Expert #7 If the antibacterial effects are as pronounced as claimed, it should lead to easier care of VAD from nursing point of view saving man- hours. Also leading to decreased bacteraemia and line associated infections and sepsis shortening hospital stays. There is a possibility of potential benefits even in the community, as well on patients needing long term intravenous antibiotics.

Potential system impact

8	What do you consider to be the potential benefits to the health or care system from using this technology?	Expert #1: Assuming reduced infection rates, all of the patient benefits are also system benefits as a central line infection has significant resource implications both cost and staff time. The cost of bed days/intensive care, equipment (central lines), theatre time (some are inserted in the operating theatre), drugs. Staff time implications include - diagnosing/treating infection, replacing lines
		Expert #2 Shorter length of stay Cost savings
		Expert #3 By preventing CRBSI's patients have better outcomes and hospitals make better use of beds.
		Expert #4 The number one potential benefit of the technology to the health care system is financial gain from the savings reaped from the prevention of catheter related infections and complications. This financial gain can then be better invested in other health care projects. The technology will indirectly give the HCS a sense of pride by giving a patient the best care possible. It will also give them a sense of security; free of complaints, law suits, etc., by the prevention of device and hospital related complications.
		Expert #5 Providing it is effective, easy to use the potential benefits to patients are clear.

		Expert #6 Preventing an CRBSI at any point could improve the flow of patients as additional treatment and extended length of stay will impede patient flow.
		Expert #7 Saving man-hours and decreasing infections.
9	Considering the care pathway as a whole, including initial capital and possible future costs avoided, is the technology likely to cost more or less than current standard care, or about the same?	Expert #1: The equipment costs more than the current standard of practice- ie a single port protector costs more than an alcohol impregnated wipe, even accounting for a slight time saving-20 seconds to “scrub the hub” with the wipe versus a few seconds to apply the port protector. Any cost saving depends of the efficacy of the product within the population it is applied to (eg intensive care, paediatric etc)
		Expert #2 It will cost more but that needs to be outweighed with the cost to an organisation of treating a patient with a CRBSI
		Expert #3 Although the initial cost is more expensive than a disinfection wipe the potential longer term costs could be less than the current standard if VAD infections are reduced due reduction in antibiotic therapy and reduced length of stay.
		Expert #4 The technology is no doubt less expensive that the current standard of care, if all matters are considered i.e. possible future costs avoided, etc.
		Expert #5 If the costs of sepsis are all factored in the adoption should be cost benefit / neutral
		Expert #6 This technology has the potential to save considerable resources and have a positive impact on finances, if used wisely.
		Expert #7

		Considering the hospital costs involved in care of line associated infections and minimal cost of the proposed device the technology seems to give a positive cost benefit on the investment. But due to the volume of the patients in a hospital there is a possibility of marginal increase in the overall cost.
10	What do you consider to be the resource impact from adopting this technology? Could it, for example, change the number or type of staff needed, the need for other equipment, or effect a shift in the care setting such as from inpatient to outpatient, or secondary to primary care?	Expert #1: If the device reduces infection rates, there will be a cost saving. For those with very long term central access at home, it may reduce admission rates, however this is a small number of patinets. For the majority of patients the reduction in central line infection rate will result in a reduced length of stay and reduced need for further intervention (replacement of line, antibiotics, investigations).
		Expert #2 Main resource is a change in attitude and culture for staff particularly nurses
		Expert #3 If the technology is adopted nursing time per each patient would be freed up for other duties.
		Expert #4 There are many benefits in terms of resource from adopting this technology. One is the nursing time saved. The cost savings from nursing time saved can be re-invested in employing another member of staff, or valuable equipment. There is really no direct impact on the number or type of staff. It is more an effect on the human factors and the economic value. There will be an indirect shift in the care setting, where in patients are managed in an outpatient settings more. This can be attributed the avoidance of complications, which can lead to a prolonged inpatient stay.
		Expert#5 Overlaps with 9 Not aware of the exact unit cost as yet. Briefing paper seemed to suggest 26p and 32p certainly when compared to med wipes and the like more expensive but if more effective (sepsis prevention) and in place for 7 days the cost per line manipulation reduces. Not likely to impact on number of staff as 2 members of staff would continue to be used to check and change central lines especially when double pumping inotropes.
		Expert #6 Financial

		Expert #7 The care of VAD could be taught to HCA's (and other allied health professionals) thereby saving time for nurses to do other jobs. The shift of care could be done on an outpatient and community basis which should potentially save more bed space availability in acute hospital settings.
11	Are any changes to facilities or infrastructure, or any specific training needed in order to use the technology?	Expert #1: Minimal training is required to use this product
		Expert #2 Minimal training.
		Expert #3 No changes to facilities or infrastructure. Minimal training is required prior to implementing the technology.
		Expert #4 There is no change required to facilities or infrastructure. Training is required in order to use the technology. It will be a minimal training. The technology is user friendly and very easy to use.
		Expert #5 Not anticipated
		Expert #6 Education on the use of the device would be required. This should be able to be provided within existing structures in the majority of organisations
		Expert #7 I don't expect any major change in the infrastructure .But training could be delivered by groups or online (e-learning) to increase familiarity of the device and connecting intravenous drugs.
12	Are you aware of any safety concerns or regulatory issues surrounding this technology?	Expert #1: Yes- within the young paediatric population there was concern regarding the port protectors acting as a choking hazard- if they dislodged/were removed.

		Expert #2 I am not aware of any
		Expert #3 No
		Expert #4 I am not aware of any regulatory issues. There are some concerns though, in terms of the use of the technology in the clinical setting, where by the technology is being mistaken for another. One concrete example is that the cap is being utilised as an obturator for the ends of the vascular access device. The technology does not offer this provision, to create a closed system on the vascular access device. This error can pose complications when not addressed immediately. It is not the technologies' fault, rather a user error. However, this error can easily be avoided with provision of proper training on the use of the technology.
		Expert #5 Not aware would like to see it risk assessed for cracking, spillage and potential skin damage especially in neonatal and CYP care.
		Expert #6 Caution in paediatrics as a very small device that is a choking risk when removed, it would be easy for a child to self remove
		Expert #7 Delivery of blood products, parental nutrition and specific chemotherapy drugs compatibility with the device need to be clarified. Is it licensed to be used in paediatrics?

General advice

13	Please add any further comments on your particular experiences or knowledge of the technology, or	Expert #1: As already mentioned above, although readily accepted by the neonatal unit staff, this product did not result in a reduction of infection rates. There was a suggestion that this may have been due to incompatible needleless

	experiences within your organisation.	connectors, although this had been reviewed prior to the study and the company's data suggested the protectors were compatible with all devices, including those used locally. I would be concerned about this device becoming standard practice in neonatal units without further data on its efficacy- none appears to have been submitted to date.
		Expert #2 I am not able to add anything as I have no knowledge of this product in my everyday clinical practice
		Expert #3 It is important that if only implemented in certain areas within an organisation that the patients pathway is mapped to ensure that staff for instance in interventional radiology are aware of the new technology and that they have been trained in replacing and have stocks or the technology goes with the patient.
		Expert #4 In addition to the benefits mentioned above, the technology and the use of it is auditable. Compliance on the use of it is auditable. It has help me and my organisation benchmark and assess our practice in terms of infection prevention and the management of vascular access device. The technology offered satisfaction to patients and staff too.
		Expert #5 Use in neonatal units?
		Expert #6 Our experience is that we use on high risk patients , eg patients with a long term PICC or tunnelled catheter being cared for in the outpatient setting, eg chemotherapy . We use for patients that have a PICC or tunnelled catheter who also have a stoma. We risk assess other in patients , eg MRSA or CPE colonisation that have long term VAD The curos alone will not prevent CRBSI, rather a bundle approach of which this could be one aspect, hand hygiene at the point of care is the key. The studies in the brief all have limitations so there is no hard conclusive evidence the Curos alone made the difference in rates os CRBSI
		Expert #7 It is important to dispose removed caps and not to leave on the bed of vulnerable patients , which may cause skin damage .

Other considerations

14	Approximately how many people each year would be eligible for intervention with this technology, either as an estimated number, or a proportion of the target population?	Expert #1: I can't give an exact number. If the aim is for every patient with an intravenous line to have a port protector applied, I would suggest this would be almost every admission to an acute hospital. If the proposed usage is more selective- ie those with central lines, the number of eligible patients will be fewer and the device more cost effective as the majority of significant catheter related infections are in those with central lines.
		Expert #2 Every patient who has a vascular access device Some of these devices have more than one port so more than one cap will be required. The caps have to be discarded after each use. And for some patients that will be many times per day Unable to give any figures
		Expert #3 More than an estimated 250000 are inserted annually in UK Vascular Access - A Bodenham - 2017 ScienceDirect https://www.sciencedirect.com/science/article/pii/S0716864017301244
		Expert #4 In my previous organisation (750 bed capacity hospital), there were about 6000 patients per year that have benefited from the use of the technology. 43 (number of CRBSIs in the Trust per year) of these patients were saved from having a catheter related blood stream infections.
		Expert #5 Do not have that data
		Expert #6

		I am unclear on this aspect.
		Expert #7 Depends on the size of the hospital and specialist services delivered.
15	Would this technology replace or be an addition to the current standard of care?	Expert #1: This would replace “scrub the hub” advice
		Expert #2 In an ideal world it should replace but in reality I expect it to be in additional and probably used in areas were there are high risk patients
		Expert #3 It would replace
		Expert #4 This technology can either be a replacement or an addition.
		Expert #5 Addition
		Expert #6 If used effectively it has the possibility of replacing the need to decontaminate the Needle free connector
		Expert #7 Addition to the current standard of care.
16	Are there any issues with the usability or practical aspects of the technology?	Expert #1: As described above- possible compatibility issues with alternative needleless connectors
		Expert #2 I do not think so
		Expert #3

		No
		Expert#4 I have not encountered any issue in terms of usability or practical aspect.
		Expert #5 Would like to see how easy it is to attach to a line and where – when using octopus lines when it would go. How heavy is it would it drag the line down?
		Expert #6 No
		Expert #7 The fixing and removal of caps if used, should be easy and straightforward.
17	Are you aware of any issues which would prevent (or have prevented) this technology being adopted in your organisation or across the wider NHS?	Expert #1: As described above- this device was not found to result in reduction in infection rates within the neonatal unit therefore use was discontinued since the driver to implement it was to reduce infection rates.
		Expert #2 No
		Expert #3 The two main issues preventing adoption are: The epic 3 recommendation that a single-use application of 2% chlorhexidine gluconate in 70% isopropyl alcohol (or povidone iodine in alcohol for patients with sensitivity to chlorhexidine) be used. The cost:- organisations see the initial cost to there budgets and stop there very few look into the wider issue of spend to save which this technology has the potential to achieve across the healthcare establishment. As with other innovative technologies which initially are more expensive the more organisations who bring it on board the cheaper it may become.
		Expert #4 The issue that I see in regards to the adoption of the technology across the wider NHS is that it will be seen as a cost pressure. The technology will be seen as an expensive alternative to the current standard of care. Not many organisations in the NHS measure the amount of catheter related blood stream infections and other

		complication relating to it and so there will be a struggle to measure the outcome and benefits of the use of the technology. Apart from that, there are no other issues that I can think of.
		Expert #5 No
		Expert #6 The studies all have limitations so the implementation cost would be a barrier in the current economic climate as the evidence is not that strong to support implementation.
		Expert #7 No
18	Are you aware of any further evidence for the technology that is not included in this briefing?	Expert #1: I am aware that a further study was being undertaken within the neonatal population, supported by Vygon, however I am not aware of the results, and cannot find them with a literature search.
		Expert #2 No
		Expert #3 No
		Expert #4 Yes. There is numerous evidence for the technology that are out there. These are few examples. http://www.ajicjournal.org/article/S0196-6553(13)00479-3/abstract http://www.ajicjournal.org/article/S0196-6553(12)01023-1/abstract https://www.cambridge.org/core/journals/infection-control-and-hospital-epidemiology/article/use-of-disinfection-cap-to-reduce-centrallineassociated-bloodstream-infection-and-blood-culture-contamination-among-hematologyoncology-patients/DAF151CAF642875365D67E05AFB3D8E0
		Expert #5 No comment

		Expert #6 No
		Expert #7 No
19	Are you aware of any further ongoing research or locally collected data (e.g. audit) on this technology? Please indicate if you would be able/willing to share this data with NICE. Any information you provide will be considered in confidence within the NICE process and will not be shared or published.	Expert #1: I am willing to share my data with NICE.
		Expert #2 No
		Expert #3 No
		Expert #4 I am not aware of any further ongoing research.
		Expert #5 Not aware
		Expert #6 No
		Expert #7 No
20	Is there any research that you feel would be needed to address uncertainties in the evidence base?	Expert #1: Data on the use in specific situations- home central line use, paediatric, neonatal. Also whether use in all patients is beneficial or if targeted usage is as efficacious ie just those in intensive/high dependency care, or with central lines, or high risk?
		Expert #2 More UK based research and audits around this product could be of use

		Expert #3 No
		Expert #4 The research that I am keen to see is a comparison between the technology and a similar which contains alcohol and chlorhexidine. However, I am not sure if there is already a technology that is out there in the market like that.
		Expert #5 Always good to have more evidence especially when hoping for a NICE endorsement/recommendation.
		Expert #6 A large scale randomised controlled trial is required
		Expert #7 No
21	How useful would NICE guidance on this particular technology be to you or other NHS colleagues?	Expert #1: This device is relatively expensive if it is to be used on all patients with intravenous cannulas and I do not feel there is currently enough data to support widespread usage, therefore guidance may be of use to help either guide research in this area or support departments in not using this product.
		Expert #2 It would/could be useful
		Expert #3 Very helpful when putting forward the case for implementation. Organisations and specialists look to both NICE and EPIC recommendations when implementing new technologies however EPIC 3 was published in 2014 and currently it is not known if there will be another EPIC review so as healthcare professionals we should always be looking to the future technologies to improve and safeguard our patients experience this is why NICE guidance is so important.
		Expert #4

		A NICE guidance on this particular technology will be utterly valuable. An economic value recommendation from NICE will clear uncertainties on the use of the technology. This in particular pertains to the impact in the reduction of blood stream infections.
		Expert #5 NICE guidance helps to support adoption
		Expert #6 It is useful in that if confirms what we already know and what areas we need to focus our research in.
		Expert #7 Very useful

National Institute for Health and Care Excellence

External Assessment Centre correspondence table

MT396 Curos Disinfectant Caps for needleless connectors

The purpose of this table is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the sponsors' original submission. This is normally where the External Assessment Centre:

a) become aware of additional relevant evidence not submitted by the sponsor
b) need to check "real world" assumptions with NICE's expert advisers, or
c) need to ask the sponsor for additional information or data not included in the original submission, or
d) need to correspond with an organisation or individual outside of NICE

These events are recorded in the table to ensure that all information relevant to the assessment of the topic is made available to MTAC. The table is presented to MTAC in the Assessment Report Overview, and is made available at public consultation.

Submission section #	Question / Request	Response	Action / Impact / Other comments
Teleconference with NICE/Manufacturers 20/09/2011			
General question re: Curos	*Is it possible to replace the used cap by mistake?*	The process reduces this risk. If clinical staff are using the strip correctly they will need to remove the sterile foil on the unit before applying. Staff are trained to use Curos in line with the IFU. There is nothing about the physical design which prevents re-use	
	How can you record how long the cap is on for?	Part of the training. IFU – for use up to 7 days (aligned to the use of a needle-free connector which is also for up to 7 days) Should be recorded in the patient notes too. Many places have specific IV notes – the manufacturer will go through this as bespoke training with the trust.	
	Training videos (out of date). Some say 3 minutes, others 1 minute for disinfection. When did this change and why?	Early 2017 – commissioned microbiology test lab, confirmed 1 min kill using several microorganisms. Made sure met the minimum standard of a 4 log reduction (to achieve disinfection).	
	How long devices would typically be in place?	Patient condition and usage dependent. As a rough guide: • Peripheral intravascular: 6-12 hours, to as long as indicated • Mid-line catheters: 2-6 weeks • PICCs: 6-24 months • Temp CVC: 5-7 days • Tunnelled CVC: - up to several years • Implantable port: – could be in place for up to 5 years	
	How often is access required?	IV antibiotics administered 4-6 times per day in standard ward. In high dependency units eg critical care, would access 10-15 times per day for various medications. Very variable.	
	Sequential access protocols?	In practice should be no requirement to wipe in between procedures. All of the medication should have been prepared under aseptic technique. So the only time a wiping of the device would be required would be if that ANTT(?) protocol was broken.	
	How often do patients go home with these in community?	Unit sales in the year to date Jan-Aug. Sold >182,000 units in community setting (for homecare, but coming via the NHS).	
	Protocol for homecare. Patients given training if left >7 days?	Yes they would receive training via their local OPAT service (Outpatient antibiotic training).	

	Studies – excluded studies list and reasons were requested.	Have been provided by the manufacturer by e-mail to Kimberley Carter which has been forwarded to the EAC (e-mail dated 20/09/2018).	In an e-mail (20/09/2018) the manufacturer states: 1. There is an error in the PRISMA diagram for the clinical evidence. The PRISMA for the economic evidence was included instead. Response: The correct diagram was attached to the e-mail and will be included in the EAC report as an appendix. 2. Retrospective studies were excluded as they used a systematic review (Voor et al) as the basis from which to update the evidence and as there were prospective studies, they did not feel it was worth looking for retrospective evidence. 3. Outcomes relating to resource use were included in the economic model but not the clinical review 4. All studies pre 2015 were excluded as these were judged to have been considered by Voor et al.
Questions re: Economic Submission	*Query about the reference to something being send under separate email cover as part of notification? (Section 4.5 of the manufacturers submission)*	Data relating to the use of Curos in the UK (a list of NHS trusts using Curos) were sent to Tara Chernick in a separate e-mail. Kim has that but the EAC hasn't had it yet. Anna Tims to re-send this information marked as 'Commercial In Confidence' where appropriate. Data to be sent to Kim in the first instance.	If you are sending as commercial in confidence or academic in confidence you need to declare it in the checklist and highlight it (as

			NICE instruct with yellow/blue/turquoise) so we are aware it is confidential.
	Is the model going to be in Excel or other software?	Excel	
	Are you hoping to focus it on hospital or will it consider community settings?	The model will just focus on hospital. To add in community data we would have to go back to the beginning, so it will need to be just hospital. (Important for EAC to be aware of this).	
Scope	*NICE wanted to look at community settings as well as in hospital. Why did the company only submit data from hospitals. Is that because there wasn't any evidence from the community?*	No, this was due to the short timeframe to submit. We prepared searches in advance of the scope from NICE, and focused on hospital use. Manufacturer admits they should have flagged the discrepancy in the scope and queried whether it is possible to go back and adjust that? NICE Response: "No. The EAC when reviewing will point that out. They may turn up additional studies in their search." Can easily be sorted out as the evaluation goes on.	Instructions for EAC: If there is any evidence in community settings then NICE "would like to" see it (but not essential).
	Competitor cap comparator. Other caps are commercially available globally.	NICE isn't interested in comparisons with other caps as it isn't standard care in the NHS. Generally the focus is on Curos, the committee won't make recommendations about other caps. We would primarily be looking at standard care comparator. Studies with other competitor products could be left in (eg to back up other evidence), but we wouldn't be looking at it in the same way as we would the standard care comparator.	
Ongoing Studies	Two trials which would provide relevant data were identified on clinicaltrials.gov 1. NCT02351258: Community Central Line Infection Prevention Trial (CCLIP)	1. Response received from the PI indicates that results will not be available before mid-2019 and they are not prepared to share any interim results at this time.	1. No further action

	The study is a community based study which is of particular interest as it is likely the only evidence in this setting. The study is due to complete in October, e-mail sent to request estimation of publication timelines 2. NCT03486093: Port Protectors for Prevention of CLABSIs in Respiratory Semi-intensive Care Unit The trial completed in 2014 according to clinicaltrials.gov Email to PI to determine whether the results have been published/are available		
E-MAIL to Dr Elizabeth Pilling			
Unpublished Literature	The EAC asked whether there were any plans to publish the full study results		
	Asked for more information about the study	Our study was essentially cohort. I have been looking at our central line infection data for a number of years within the neonatal unit. As a background, I work on a regional NICU with 18 ICU, 8HDU and 18 SCBU cots. We trialled the Curos as a study supported by Vygon (on a buy 1 get 1 free basis, with our money back if our infection rate did not fall by 1/3). We used the product for 8 months and monitored our infection rate. The study was lengthened with Vygon support, initially planned as 6 months, due to lack of effect. We used the port protector for all babies in ICU/HDU (irrespective of whether they had a central line or not). Our compliance (as audited frequently) was good (95%, quoted requirement was 80-85%). We saw no statistical improvement in infection rate (in fact there was a non-statistically significant increase, which fell back to baseline once we reverted to previous practice of "scrub the hub"- active disinfection with 2%alcohol wipes for 2 mins).	

		During the study, Vygon paid for someone to come and "inspect" to see why our infection rate was not falling- they could not come up with a solution.	
	Is it possible that the type of needleless connector makes a difference	Prior to the study, I had seen data suggesting that there was effect of Curos irrespective of the needleless connector type, however after the study, there was a suggestion that as you highlight, there may be a difference with the needleless connector. We used "smart sites". (by carefusion I think). These were not neutral pressure, but exerted negative pressure.	
	General comments provided	*My comments for the MIB were as that I understand there is adult data that suggests that Curos do reduce line infections so I can't say they don't work for all patients however there is no data to support their use in neonates. Why they don't seem to work I'm not sure. I suspect (but I am a neonatologist so can't be certain), that we use central lines for longer, and I know that our patients have a higher central line infection rate (at least 8/1000 central line days if not higher so more that in adult literature)- partly as a result of mostly being preterm infants with a lower immunity, and also having more procedures/episodes of skin breaks. However this should mean even a small improvement in port asepsis should lead to a bigger reduction in infection rate.* *I do worry about their use in toddlers, but that is more the potential choking hazard of the cap rather than the efficacy.*	
	The EAC asked whether there was any information on the waste/environmental impact of Curos	*I am not aware of there being any specific impact on waste management. I would assume it may have balanced out as there would be waste from the Curos but not from the alcohol wipes that we otherwise used to "scrub the hub".*	
Model Inputs	*On average, how long would it take a nurse to replace a Curos cap?*	*15seconds*	
	On average, how long would a nurse typically spend on manual disinfection?	*20seconds to "scrub the hub" plus the time to get the equipment required*	
	On average, how many ports/hubs would a patient in each of the following settings have:	*ITU-4-6* *Ward- 1-2*	

	(i) A critically ill patient in ICU? *(ii) A patient in hospital (on any ward)?*		
	On average, how many times per day per port would replacement of a Curos cap be required? *(i) A critically ill patient in ICU?* *(ii) A patient in hospital (on any ward)?*	*ITU-for every blood gas (up to 6/day)* *-for each drug (2-10)* *Ward patient-probably 2-3/day*	
	On average, how many times per day per port would manual disinfection occur?	*Same as curos replacement*	
	What grade (or grades) of nurse would typically carry out replacement of a Curos cap or manual disinfection: *(i) In ICU?* *On a general hospital ward?*	*Band 5/6/7 for both*	
	The literature that we have identified suggests that patients are in ICU with a catheter for between 5 and 9.4 days. Does this range seem reasonable based on your experience? What would you consider to be the average duration?	*Neonatal intensive care will be longer- can be a month or more of central lines especially for those with surgical issues who may have them for even longer. Average difficult to specify as there is a big range. The minimum for an extreme preterm infant is 6 days.*	
	The literature that we have identified suggests that patients are in hospital with a catheter for between 7 and 244 days. Does this range seem reasonable based on your experience? What would you consider to be the average duration?	*Infants with central lines are in ITU or HDU within the neonatal setting.*	
	Would you expect CRBSI rates to be lower or higher in a non-ICU setting compared with an ICU setting?	*Lower in non-ICU as lower risk infants with fewer central line day and less accessing of lines*	

	We have assumed that manual disinfection is carried out using a 70% alcohol and 2% chlorhexidine gluconate wipe. Does this seem reasonable?	*yes*	
	Would ports typically be manually disinfected when the catheter is first inserted?	*Ports disinfected prior to accessing/infusions being attached*	
E-mail to Catherine Plowright			
Model Inputs	*On average, how long would it take a nurse to replace a Curos cap?*	*Less than one minute*	
	On average, how long would a nurse typically spend on manual disinfection?	*Less than one minute*	
	On average, how many ports/hubs would a patient in each of the following settings have: *(iii) A critically ill patient in ICU?* *(iv) A patient in hospital (on any ward)?*	*Difficult to say* *1) Often may ports* *Usually one 1 or 2*	
	On average, how many times per day per port would replacement of a Curos cap be required? *(i) A critically ill patient in ICU?* *(ii) A patient in hospital (on any ward)?*	*Difficult to say*	
	On average, how many times per day per port would manual disinfection occur?	*Difficult to say*	
	What grade (or grades) of nurse would typically carry out replacement of a Curos cap or manual disinfection: *(j) In ICU?* *On a general hospital ward?*	*All should be a minimum of Band 5 as they are giving IV drugs*	

	The literature that we have identified suggests that patients are in ICU with a catheter for between 5 and 9.4 days. Does this range seem reasonable based on your experience? What would you consider to be the average duration?	*Yes*	
	The literature that we have identified suggests that patients are in hospital with a catheter for between 7 and 244 days. Does this range seem reasonable based on your experience? What would you consider to be the average duration?	*Yes As some patient are in for a long time*	
	Would you expect CRBSI rates to be lower or higher in a non-ICU setting compared with an ICU setting?	*Lower hopefully*	
	We have assumed that manual disinfection is carried out using a 70% alcohol and 2% chlorhexidine gluconate wipe. Does this seem reasonable?	*yes*	
	Would ports typically be manually disinfected when the catheter is first inserted?	*I do not think so as at insertion all is sterile*	
Email to Jan Hitchcock			
	On average, how long would it take a nurse to replace a Curos cap?	*A second or two*	
	On average, how long would a nurse typically spend on manual disinfection?	*We advocate 30 seconds to clean and 30 seconds to dry*	
	On average, how many ports/hubs would a patient in each of the following settings have:	*ICU – can have up to 10-15 portals if a Quinn lumen CVC is used with triple extension set.* *Ward patient , dependent by be a single cannula with two lumen extension set or multiple cannula+ or – a medium term VAD such as a*	

	(v) A critically ill patient in ICU? *(vi) A patient in hospital (on any ward)?*	*PICC or Midline or even a CVC ,most commonly four lumens, no extension sets*	
	On average, how many times per day per port would replacement of a Curos cap be required? *(i) A critically ill patient in ICU?* *(ii) A patient in hospital (on any ward)?*	*ICU – difficult to say as the patient may have multiple infusions some of which are continuous, ie a Curos would not be required .* *Ward - once again difficult to say, they may be on OD IV drugs but equally TDS regimes, +/- continuous infusions.*	
	On average, how many times per day per port would manual disinfection occur?	*Every time the catheter is accessed*	
	What grade (or grades) of nurse would typically carry out replacement of a Curos cap or manual disinfection: *(k) In ICU?* *On a general hospital ward?*	*Any registered nurse that is IV competency irrespective of grade would replace the Curos, but mostly B5-7.* *Doctors who take bloods via the Long ter. CVADs would also disinfect the cap and replace the Curos*	
	The literature that we have identified suggests that patients are in ICU with a catheter for between 5 and 9.4 days. Does this range seem reasonable based on your experience? What would you consider to be the average duration?	*This does seem a reasonable time frame, however in one of my ITU's this figure would exceed this.* *I would need some time to interrogate our local data.*	
	The literature that we have identified suggests that patients are in hospital with a catheter for between 7 and 244 days. Does this range seem reasonable based on your experience? What would you consider to be the average duration?	*This does seem reasonable, if supported by the literature*	
	Would you expect CRBSI rates to be lower or higher in a non-ICU setting compared with an ICU setting?	*It depends on the speciality and complexity of patients, they should be lower in most non ICU areas*	

	We have assumed that manual disinfection is carried out using a 70% alcohol and 2% chlorhexidine gluconate wipe. Does this seem reasonable?	*We use this in our practise.*	
	Would ports typically be manually disinfected when the catheter is first inserted?	*No, as this is part if the insertion process and they will be sterile, however they would be used prior to any use.*	
E-mail requesting information about parenteral nutrition lines			
	Is there any reason why the risk of infection in patients with parenteral nutrition ports would be different from a general central line population? Is there anything specifically I should be aware of if I were using infection rates in this population to represent the baseline risk for patients with central lines?	*Response from Catherine Plowright* Over the years there have been a number of papers showing that infection rates can be higher in patents receiving parental nutrition and lots of places now use dedicated lines that are tunnelled to give this sort of nutrition. A quick google search has come up with the following. But I am sure you can find more up to date information and literature https://www.nursingtimes.net/infection-rates-and-parenteral-nutrition/262784.article http://ajcc.aacnjournals.org/content/12/4/326.short https://www.sciencedirect.com/science/article/pii/S0195670111003410 http://www.actamedicamediterranea.com/archive/2015/medica-6/the-association-between-total-parenteral-nutrition-and-central-line-associated-bloodstream-infection/pdf https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3564563/ I was taught many years ago that parental nutrition because of what it contained was a good breeding ground for bugs	
		Response from Jan Hitchcock The formulation of parenteral nutrition is a rich medium for bacteria unlike other intravenous fluids so those with a CVAD insitu and have PN are if you like doubly at risk of a potential infection. We record	

		infection rates in patients receiving PN by the number of days they receive PN not the number of CVAD days which we record as per 100 catheter days, so we don't even report a similar number so very difficult to compare this.	
Teleconference with Manufacturers on economic submission			
	1. Time horizon stated <1 year. What exactly is it?	The time horizon is the average time the patient is at risk (assumed to be the period of hospitalization) plus the time to resolve an episode of infection (assumed 6-10 days; pg. 9, s9.1.8). So in total the time horizon is around 10-20 days. The reason it's stated as <1 year is to explain why no discounting was done. Also according to the literature (and supported by a clinical expert) patients could be on a general ward with a catheter inserted for up to 244 days. These patients will be outliers though and on average the time horizon will be 10-20 days.	
	2. Why was mortality excluded?	Mortality was not reported in the clinical studies for Curos. Mortality could have been included as a proportion of the people who had CRBSIs with the assumption that this proportion remained the same with the introduction of Curos which would have enhanced the benefits of Curos. So excluding mortality is conservative	
	3. Why exclude children only studies? This was not an exclusion in the scope	This was a pragmatic decision, Children only studies were excluded for the baseline rate of CLABSI pragmatic search because we did not want to develop two separate models (children and adults). This decision was made in order to find a representative incidence of CLABSI for the model so children only studies were excluded as this would not be generalizable to general NHS population and would not be well matched with clinical studies as those all included adult patients.	
	4. What number was used for the number of ports per patient as this question was	The clinical expert, Roy Ventura indicated 1-2 ports for general ward and 10-15 in ICU (pg. 22 Table C4e.)	The EAC meant to ask this question in relation to the number of manual disinfections. Further information from the

	not answered by the clinical specialist.		teleconference was provided by the manufacturers and followed up in an e-mail to NICE and the EAC. *The question which was not answered by Roy Ventura was "How many times per day per port would manual disinfection occur?". The reason he couldn't answer this one is because manual disinfection refers to what nurses are doing in normal clinical practice, which is likely to differ between hospitals.* *In the economic model we assumed disinfection each time the port was accessed (5-10 per day in ICU and 3 per day in other wards). This is as per recommendation IVAD30 in the Epic3 guidelines which says that "the hub should be cleaned for a minimum of 15s and allowed to dry before accessing the system".*
	5. Do all patients with CLABSI/CRBSI move to ICU from general wards? Similarly if a patient starts in ICU will they always have general hospital days associated with	Not necessarily although it would be very unusual to see someone on a general ward with a central line in situ. However there would be movement between ICU and high dependency wards and step down wards which is where the majority of central lines would be in situ. However patients may move from general wards to ICU/High dependency wards from general wards if they get a general Vascular Access Device Bacteraemia leading to Sepsis etc. The clinical experts told us that the treatment would typically involve 2-3 days in ICU	

	the CLABSI	followed by 4-7 days in a general ward (pg. 28. However, the costing is based on an assumed representative treatment pattern (1.5 followed by 5.13). It does not assume that all patients have exactly the same clinical pathway, but rather that taken overall this will be an average.	
	I'm not clear what is meant on page 13 in relation to the ICU comparative study exclusions.	for studies conducted within an ICU we only considered those studies reporting on rates of CRBSI/CLABSI in the ICU setting generally. Those studies that compared new experimental interventions to reduce CRBSI infections were not not included as these would not reflect practice across the NHS more widely. In the ICU setting we already had good baseline data from Bion et al. (2012) and were therefore able to be a bit more focused and only look for studies that were an improvement on Bion (e.g. just as generalisable, but perhaps more recent). On the general ward we didn't have this luxury, so we included studies comparing an intervention to a comparator, recognising that neither will fully reflect practice across the NHS which will likely comprise a mixture of interventions for reducing rates of CLABSI/CRBSI.	
	6. Are there different costs for CLABSI/CRBSI? Specific lab tests?	A standard CRBSI/CLABSI will cost circa £9,900. There are more robust microbiology tests required to determine a CRBSI aligned to culture and sensitivity testing which would incur additional Laboratory costs such as Tip Cultures. However blood samples are sent to the laboratory for both tests. Because we used an overall episode cost, the costs of individual tests would not be relevant because these costs would be included in the overall episode cost. Michelle.	
	7. Auditing the use of Curos – how do you monitor whether caps have been changed within 7 days if they are on ports not regularly used?	The Needle Free device is changed every 7 days, therefore the Curos cap and the needle free device both have a maximum 7 day wear time. When the needle free device is changed the cap would also be changed therefore ensuring that no cap is left on for more than 7 days.	
E-mail sent to author of included study – Dr Michael Sweet			
	In the tables included in the publication it says that there were 836 patients pre-intervention and 436 patients during the	No, It is total patient encounters versus total unique patients	

	intervention but the text in the results section says there were 472 patients and 282 patients. Could you clarify why these might be different, is it because some patients are excluded based on blood culture results		
	The results section talks about 472 patients for 911 admissions and 6851 line days – can I just clarify that there may be more than one admission per patient contributing to the line days? If this is the case, do any of these patients leave hospital still with a line in place?	Yes Data point was not specifically collected, but most probable since approximately 30% of the lines were implanted ports.	
	Similarly in the blood culture section of the results we are a little unclear as to where the denominator data has come from when it talks about 1 of 692 and 1 of 470 – does the denominator relate to the number of blood cultures rather than patient/admission numbers?.	Yes	
E-mail to Company regarding meta-analysis			
	Can you give me a bit of a rundown of how the script is using the rate ratios from the Merrill study given that the study doesn't include the infections and catheter day information and you have used the rate ratio and confidence intervals from the paper? I assume it's just a	The data was given in different formats. Sweet and Merrill reported incidence risk ratios with 95% CI, and they were read in by the R code (lines 27 – 44 of the code). Ramirez and Martino did not report incidence risk ratios with 95% CIs, and they were calculated from the pre-intervention and post-intervention data (lines 54 - 61 of the code). All the risk ratios and 95% CIs (those which were read in and those which were calculated) were then processed by the meta-analysis	

	straightforward script that adds the rate ratios from each study to the forest plot but if you could give me a bit more of the technical detail I would appreciate it.	(remaining lines of the code). This way the data from four studies could be used.	
	In addition, we were wondering whether you could possibly add the data from the Cameron-Watson study to the meta-analysis if it wasn't too much trouble at this stage? I understand the reasons that it was excluded but we are interested to see how that data impacts the results given that it is the only UK study.	The view here is that Cameron-Watson does not report enough data and cannot be added to the meta-analysis. They do not report catheter days, nor do they report risk ratios with 95% CI and it is for this reason that they are not able to be included.	

NICE National Institute for Health and Care Excellence

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

External Assessment Centre Report factual check

Curos disinfecting cap for needleless connectors

Please find enclosed the assessment report prepared for this assessment by the External Assessment Centre (EAC).

You are asked to check the assessment report from Cedar to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 12pm, **13th November 2018** using the below proforma comments table. All your comments on factual inaccuracies will receive a response from the EAC and when appropriate, will be amended in the EAC report. This table, including EAC responses will be presented to the Medical Technologies Advisory Committee and will subsequently be published on the NICE website with the Assessment report.

8th November 2018

Issue 1

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 9, **Section 2.1 Overview and critique of company's description of clinical context:** CLABSI is defined as **catheter** line associated bloodstream infections	It should say **central** line associated bloodstream infections	clarity	This change has been made

Issue 2

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 42, **Resource identification, measurement and valuation (and throughout the economic report):** The EAC accepts that manual disinfection may take 45 seconds given a 30 second drying time however the EAC considers that the nurse would utilise the drying time to carry out associated tasks such as preparing the syringe or writing in the notes and this can therefore not be considered time saved when using Curos. This is incorrect. The nurse would <u>not</u> be able to do anything else during the 30 seconds drying time as they need to hold the needle free connector whilst it is drying. If they let it go to carry out other duties the needle free connector will once again become contaminated and the "scrub the hub" process would have to be started from the beginning again. The drying time is essential because it is during this period that the micro-organisms are killed.	Re-run the economic model with the assumption that the 30 seconds drying time is a period when the nurse <u>cannot</u> carry out associated tasks.	This assumption is false and has a significant bearing on the economic case for Curos.	The EAC does not agree that the assumption made on nurse time is false rather it represents a situation where disinfection protocols which include either manual disinfection or Curos caps may take equal amounts of nurse time. The EAC highlights that none of the clinical experts contacted indicated that the drying time involves holding the needlefree connector. The EAC considers that in reality, the amount of time it takes to carry out disinfection procedures will vary depending on local protocols and the decision on nurse time should be made with clinical expert input and discussion.

Issue 3

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 28, **Section 2.6**: There are variations in the way that bloodstream infections are reported with the term CLABSI and CRBSI being used interchangeable throughout the literature and in practice. The only way to know definitively whether a bloodstream infection is related to the catheter port is to carry out specific laboratory tests. This is partially true but there are definitions of CLABSI and CRBSI which may be worth clarifying.	A CLABSI as defined by CDC, is a primary (i.e., no apparent infection at another site) BSI in a patient that had a central line within the 48-hour period before the development of the BSI. BSI is defined using either laboratory confirmed bloodstream infection (LCBI) or clinical sepsis (CSEP) definitions. There is no minimum period of time that the central line must be in place in order for the BSI to be considered central line–associated. The culture of the catheter tip is not a criterion for CLABSI. CRBSI Is a more rigorous clinical definition, defined by precise laboratory findings that identify the CVC as the source of the BSI and, used to determine diagnosis, treatment, and possibly epidemiology of BSI in patients with a CVC. Using the CRBSI definition requires more resources than use of the CLABSI definition as hospitals must have the capacity to correctly collect and label blood culture sets drawn from the CVC and a peripheral phlebotomy as well as culturing the CVC segment/ tips. Typically this rigorous approach requires a research study and staff. Therefore the base rate for CRBSI will always be lower than that of CLABSI due to the tighter testing criterion.	Clarification of CRBSI vs CLABSI will have a bearing on base rates for infection	The EAC has edited this section to include these definitions and has added some clarity.