NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology consultation: GID-MT561 ClearGuard HD Antimicrobial Barrier Cap for preventing haemodialysis catheter-related bloodstream infections

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. **Scope of evaluation** – the framework for assessing the technology, taking into account how it works, its comparator(s), the relevant patient population(s), and its effect on clinical and system outcomes. The scope is based on the sponsor's case for adoption.
4. **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.
5. **Sponsor submission of evidence** – the evidence submitted to NICE by the notifying company.
6. **Expert questionnaires** – expert commentary gathered by the NICE team on the technology.
7. **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.
8. **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.

Document cover sheet

Assessment report: ClearGuard

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

GID-MT561 - ClearGuard HD Antimicrobial Barrier Cap for preventing haemodialysis catheter-related bloodstream infections

External Assessment Centre report

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Purpose of the assessment report

The purpose of this External Assessment Centre (EAC) report is to review and critically evaluate the company's clinical and economic evidence presented in the submission to support their case for adoption in the NHS. The report may also include additional analysis of the submitted evidence or new clinical and/or economic evidence. NICE has commissioned this work and provided the template for the report. The report forms part of the papers considered by the Medical Technologies Advisory Committee when it is making decisions about the guidance.

Declared interests of the authors

Description of any declared interests with related companies, and the matter under consideration. See NICE's Policy on managing interests for board members and employees.

None.

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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.

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Abbreviations

Term	Definition
ARBSI	Access Related Blood Stream Infection
BSI	Blood Stream Infection
CI	Confidence interval
CLABSI	Central line-associated bloodstream infection
CRBSI	Catheter-Related BloodStream Infection
CVC	Central Venous Catheters
DHSC	Department of Health and Social Care
EAC	External Assessment Centre
FY	Financial Year
HD	Haemodialysis
IQR	Interquartile range
IRR	Incidence Rate Ratio
IV	Intravenous
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
PBC	Positive Blood Cultures
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

Executive summary

The company included 7 studies in their submission; 3 studies were full texts and 4 were abstracts. The EAC excluded 1 of the submitted abstracts but included the other studies and did not identify any other relevant studies. Overall, the EAC believes the clinical evidence base is of moderate quality.

Two RCTs are reported in the literature (Brunelli et al. 2018 and Hymes et al. 2017). Both were large, open-label, cluster-randomised trials from the US. The EAC considers these studies to be the strongest evidence available, with the comparator in Hymes et al. 2017 (standard CVC caps) being more relevant to the decision problem than that in Brunelli et al. 2017 (Tego connectors with Curos caps). These studies are at some risk of bias due to the lack of blinding and unbalanced groups in several patient characteristics. The remaining study reported in full text was Weiss et al. 2021, which was a large, retrospective analysis, however this study is methodologically weak. The remaining abstracts are limited in detail and do not add much more to the decision problem. The studies had largely homogeneous populations with mean ages varying from 61.1 years to 62.8 years (although 1 abstract, Glennon et al. 2020, reported a paediatric population) and the percentage of men from 51-53%. All of the studies were conducted in the US, which may not be easily generalisable to the UK setting.

Rates of bloodstream infection were consistently reported to be lower in ClearGuard groups compared with various comparator groups. Hospital admissions were also found to be lower in several studies (Brunelli, Hymes and Sibbell) although not always significantly. There was limited information on rates of mortality and length of stay, and no information on IV antibiotics use or staff time reported in the clinical evidence. Furthermore, no evidence was found of ClearGuard being used in the home setting. No meta-analysis was conducted by the company or EAC due to the heterogeneity in the comparators and outcomes reported in the literature.

An economic search identified 1 relevant abstract, which was also included in the clinical evidence review (Glennon et al. 2020). This paper reported a reduction in total annual costs when using ClearGuard in a paediatric population (£18,050 vs £7,078 per patient. The applicability of this result to an adult population is unclear.

A de novo model was submitted by the company comparing ClearGuard with 4 comparators. The clinical parameters used were generally acceptable, but the EAC provided additional results in the ClearGuard arm. This was based on discussions with clincal experts, who suggested that they may still use disinfection protocols, even when using ClearGuard. The final results showed that Clearguard is cost saving when compared to all the four comparators.

The EAC found through additional sensitivity analysis that with the baseline incidence rate of infection associated with the comparator, the IRR associated with ClearGuard and average cost of treating CBRSI had the largest impact on cost results in most cases and broadly smiliar to the company's sensitivity analysis. The most major uncertainty is the applicability of the US evidence to the UK setting.

1 Decision problem

The company did not suggest any variations to the scope.

2 Overview of the technology

ClearGuard HD Antimicrobial Barrier Caps (ICU Medical) are designed to cap off ports of central venous catheters (CVCs) used in haemodialysis. CVCs are used as intravenous (IV) access to the blood stream during haemodialysis. A cap refers to a device that screws on to and occludes the catheter hub. The catheter hub refers to the end of the CVC that connects to the blood line or cap. ClearGuard HD caps are supplied and stored in pairs in foil pouches.

The mechanical design of the ClearGuard HD cap (hereafter referred to as ClearGuard) contains a rod that extends into the catheter hub. The rod and cap threads contain a dry coating of chlorhexidine acetate, a broad-spectrum antimicrobial agent. Chlorhexidine acetate is intended to reduce the presence of pathogenic organisms in the CVC lock to reduce the risk of catheter-related bloodstream infections (CRBSI). When the ClearGuard HD cap is inserted into the liquid-filled catheter, the chlorhexidine acetate coating dissolves. The antimicrobial agent is held inside the catheter hub in between treatments using the existing catheter clamp. ClearGuard HD caps are intended to replace standard caps and need to be replaced every dialysis session. The recommended maximum use time for the cap is 3 days.

The innovative aspect of the ClearGuard HD cap is the coating of chlorhexidine acetate. This mechanism proposes to reduce CRBSI through the releasing of antimicrobial agents within the catheter hub and may reduce the need to clean the connector port with 2% chlorhexidine in 70% alcohol and wait for it to airdry.

ClearGuard HD Antimicrobial Barrier Cap is a CE-marked class IIb medical device. It received its CE mark in 2019.

3 Clinical context

End stage kidney disease (ESKD) is an irreversible and progressive deterioration in kidney function. Haemodialysis is a type of renal replacement therapy (RRT) used for ESKD. This is a way of filtering blood outside of the

body using a dialysis machine. Haemodiafiltration is also a form of haemodialysis with additional convection (Gilbert et al. 2018). Hereafter, the term haemodialysis will be used to refer to all rates of convection, as clincal experts stated that the function of CVC caps is the same. According to the 22nd annual report by the UK Renal Registry (on 31st December 2018), 36.8% (24,366 adults) of the adult UK RRT (dialysis and transplant) population received haemodialysis in hospital or specialist renal units for ESKD. A further 11.4% (107) of children and young people with ESKD receive haemodialysis as their treatment option.

IV access is required for haemodialysis to allow blood to flow in or out of the body. This access also enables the administration of drugs and fluids directly into the bloodstream. This access may be required to remain in place for days to years. Types of IV access for haemodialysis may occur in the form of a CVC and arteriovenous fistulae (AVF). CVCs do not require vascular surgery. A non-cuffed CVC is used for emergency, acute and shorter-term dialysis. More routinely, tunnelled (cuffed) CVCs are used for haemodialysis. A cuff and the catheter are placed under the skin. The cuff keeps the catheter in position, forms a seal, helps prevent the migration of microorganisms and attempts to minimise CRBSI. AVF is used as a longer-term dialysis access point. The access point is created by a vascular surgical procedure in which an artery and a vein are joined. For certain patient groups, such as those who have had previous surgieries CVC maybe more appropriate than AVF if the access will be shorter term, or if the surgical procedure is not possible or available, especially in light of the coronavirus pandemic. Older people tend to have higher catheter use than others.

It is considered that the rate of bloodstream infections (BSIs) is higher in more temporary access approaches. Each time treatments are administered through an access point there is a risk of introducing microorganisms that can cause blood stream infections. The access points should only be used for dialysis treatment, unless it is a life threatening emergency. CRBSIs are associated with CVC access. This type of infection causes fever, red skin and soreness around the access site. Complications arising from CRBSI may

include additional line changes, prolonged antibiotic treatment, prolonged hospital stays, increased risk of morbidity and mortality. As a result CRBSI are associated with a higher healthcare costs.

CVCs are considered to be a closed-loop. In order to reduce CRBSIs, each time access is required via the CVC, a strict infection control protocol will need to be adhered to in order to prevent CRBSI. NICE clinical guideline CG139 for healthcare-associated infections: prevention and control in primary and community care recommends decontaminating the vascular access device catheter hub before and after accessing the system. This consists of scrubbing the connector hub of the CVC before and after each access to the catheter with 2% chlorhexidine gluconate in 70% alcohol wipes and allowing the hub to air dry, for a minimum of 15 seconds (NICE, 2017). Experts commented that this practice can also remove blood clots and debris from the catheter hub. A fresh cap should be used after each time the CVC has been accessed, or if the closed-loop has been broken.

There are several types of cap systems on the market. Standard cap systems are sterile caps that screw on to catheter hubs. Cap systems with passive disinfectant are impregnated with alcohol. Cap and connector systems (such as Tego connectors used with Curos caps) consist of a connector and a cap, where the cap is replaced after each access and the connector less frequently. Antimicrobial locking (AML) solutions are also used to reduce rates of CRBSI. These solutions are left in the distal lumen of the catheter for between 12 to 24 hours, before being withdrawn and replaced.

Haemodialysis can take place in a clinical or a home setting. Haemodialysis in clinic routinely takes place three times a week, for 3-5 hours. Haemodialysis in a home setting may take place more frequently for a shorter length of time, depending on the patient's lifestyle. NICE Guideline for renal replacement therapy promotes the choice of dialysis mode and location to be discussed with the individual and family encompassing clinical considerations and individual preference. The UK Renal Register (31/12/2018) reported the majority of haemodialysis to take place in a hospital or community clinic setting with only 4% of the haemodialysis being carried out in the home

setting. The coronavirus pandemic has highlighted the benefits of home dialysis and although statistics are not yet available experts are expecting an increasing uptake in home dialysis in the future.

It should be noted that there are several terms for catheter-related blood stream infections. CRBSI is often used interchangeably with CLABSI (central line–associated bloodstream infection), although they do not mean the same thing. CRBSI is considered to be a clinical definition used when diagnosing and treating patients and requires lab testing to confirm the catheter as the source of the infection. A CLABSI, however, is defined as "either… (1) a recognized pathogen and not related to an infection at another site, or (2) a common commensal from two blood draws, not related to an infection at another site, and patient has at least one of: fever, chills, or hypotension" (CDC, 2017).

Further, ARBSI (Access-related bloodstream infection) is defined by the CDC as a "Positive blood culture with the suspected source reported as the vascular access or uncertain" (CDC, 2018).

Special considerations, including issues related to equality
People from lower socio-economic groups are more likely to suffer from kidney disease. People of Black and Asian family origin are more likely to progress faster towards kidney failure and are less likely to receive a transplant. Men are more likely to start dialysis than women. There are high-rates of severe mental illness in people on dialysis.

Family origin, sex and disability are protected characteristics under the Equality Act 2010.

4 Clinical evidence selection

4.1 *Evidence search strategy and study selection*

The search strategies submitted by the company included invalid Medical Subject Headings (MeSH) and Emtree headings (more details in Appendix). The EAC revised this search following PRISMA-Search and Peer-Review of Search Strategies (PRESS) guidance and re-ran the searches on 2nd June 2021.

The new search followed the agreed scope from NICE and found 112 results. After removing 32 duplicates, the EAC screened 80 results and identified 10 relevant records (3 journal articles, 5 conference abstracts, and 2 clinical trial registry records – both excluded for being related to published journal papers). Compared to records listed in the company's submission, we added one new conference abstract (Brunelli et al. 2017) to the list of included studies. Two EAC members screened the remaining 8 records and included 6 reports: 3 full journal articles (Brunelli et al. 2018, Hymes et al. 2017, and Weiss et al. 2021) and 3 abstracts (Glennon et al. 2020, Li et al. 2019, Sibbel et al. 2020), excluding Brunelli et al. 2017 (which was superseded by the full text published in 2018) and Nitz et al. 2021, which was considered to be out of scope.

4.2 *Included and excluded studies*

Table 1: Studies selected by the EAC as the evidence base

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Brunelli et al. 2018 Cluster-Randomized Trial of Devices to Prevent Catheter-Related Bloodstream Infection The US Multicentre (40 sites) Funded by Pursuit Medical Published as a full text. 🟡 **Amber**	Prospective, Multi-centre, Open-label luster RCT ClearGuardHD vs Tego connectors + Curos disinfecting caps 🟢 **Green**	1911 participants undergoing dialysis with CVC were randomised (951 ClearGuard vs 960 Tego connector + Curos) across 40 dialysis facilities. Upon randomisation there was an initial 3-month run-in phase to assess whether BSI rates were equivalent between arms prior to implementation of study interventions. 1671 completed the 13-month intervention phase. Male: 51%; average age, yrs. 62.8 (SD 14.9) Curos was replaced each session and Tego was replaced once a week. The ClearGuard caps were replaced at each session. 🟡 **Amber**	**PBC** 0.28 PBCs per 1000 CVC days in the ClearGuard group and 0.75 per 1000 CVC days in the Tego + Curos group. PBCs were experienced in 21 and 63 unique patients, in the ClearGuard and Tego + Curos group respectively. IRR was 0.37 (p=0.001) favouring ClearGuard. **CRBSI** The IRR was 0.37 (p=0.003), favouring ClearGuard. **CLABSI** The IRR was 0.35 (p=0.003), favouring ClearGuard. **ARBSI** The IRR was 0.31 (p<0.001), favouring ClearGuard. For ARSBI comprising of Gram negative organisms only the IRR was 0.19 (p =	Baseline characteristics were generally similar, with the exception of race: 35% black in the ClearGuard group vs 46% black in the Tego + Curos group (p = 0.02) and diabetes: 55% vs. 64%, respectively; (p<0.001), however the groups were imbalanced for age during the intervention phase (p=0.02). Dialysis facilities were pair matched by BSI rate, number of patients using CVCs, and geographic location and then cluster randomised 1:1. No information was reported on a power calculation. Open-label. Patients treated with a CVC for <21 days were excluded from analysis.

			0.001), favouring ClearGuard. For ARSBI comprising of Gram positive organisms only the IRR was 0.4 (p=0.001), favouring ClearGuard. Analysis performed to investigate if there was a decrease in IV antibiotic starts within 3 days of a PBC, the IRR was 0.37 (p<0.001), favouring ClearGuard. **Hospital admissions** Rate of admissions in the ClearGuard vs Tego+Curos: 0.06 vs 0.11 per 1000 CVC days respectively (IRR = 0.55; p= 0.5) **Green**	

Hymes et al. 2017 Dialysis Catheter–Related Bloodstream Infections: A Cluster-Randomized Trial of the ClearGuard HD Antimicrobial Barrier Cap The US. Company supported – Pursuit Vascular, Inc. (ICU medical) Published as a full text.	Prospective, multi-centre, open-label, cluster RCT ClearGuard HD vs standard CVC caps. 🟢**Green**	20 dialysis facilities (1,245 participants) were randomised to ClearGuard vs 20 dialysis facilities (1,225 participants) to standard CVC caps. 2,912 participants with CVC caps at all participating facilities were dialysed. Of these, 2,470 participants with CVCs dialysed for longer than 21-day were included. Mean age: 61.1 ± 15.5, male: 51% 12-month follow-up period 🟢**Green**	**PBC** 0.26/1000 days in the ClearGuard group vs 0.59/1,000 days in the standard caps CVC group; IRR=0.44 (p=0.01) **Hospital admissions for BSI** 0.28/1,000 days in the ClearGuard group vs 0.47/1,000 days in the standard CVC caps group; IRR=0.60 (p=0.04) **Hospitalisation-days for BSI** 3.24/1,000 days in the ClearGuard group vs 4.68/1,000 days in the CVC group; IRR=0.69 (p=0.2) **Number of IV antibiotic starts** 1.68/1,000 days in the ClearGuard group vs 1.78/1,000 days in the CVC group; IRR=0.94 (p=0.6) 🟢**Green**	Baseline characteristics were similar in the ClearGuard and standard CVC cap groups, p-values not reported Sites were paired by PBC rate and number of patients with CVCs anjd then randomised 1:1 using Computer-generated randomisation. Open-label Three authors are employed by the company – Pursuit Vascular, Inc. (ICU medical)
Weiss et al. 2021 The US	Retrospective, multi-centre, observational study	Health records of 5934 participants from 13 dialysis centres were analysed.	**CLABSI** 0.03/1,000 days in the chlorhexidine group vs 0.70/1,000 days in the standard CVC caps group (p	Almost all patients were switched to the chlorhexidine-coated caps during the second study period.

Company funded – ICU medical Published as a full text.	ClearGuard HD vs Tego connectors and standard caps. ● **Green**	Male: 53%; Mean age, 61.3 yrs. ClearGuard (4,614 patients) vs standard CVC caps (1,320 patients) Two study periods, first study period was 5 months (n=2011) and the second study period spanned 9 months (n=3923). Outpatient dialysis clinics ● **Green**	< 0.0001) for the first 5-month study period 0.09/1,000 days in the chlorhexidine group vs 0.63/1,000 days in the standard CVC caps group (p<0.0001) for the two study periods combined. ● **Green**	Limited patient characteristics data reported.
Glennon et al. 2020 Cost-effective and prophylactic use of ClearGuard Caps for a sustained reduced catheter associated blood stream infection rate The US Published as an abstract Funding not reported	Retrospective observational study ClearGuard HD caps with and without antimicrobial locking. ● **Amber**	ClearGuard caps vs. antimicrobial locks in paediatric dialysis population. Standard caps + antimicrobial locks were used in the first year while ClearGuard was used in the second year. ● **Amber**	**CA-BSI** 1.82 per 100 patient months in the first year (FY18) in high-risk patients 0.26 per 100 patient months in the second year (FY19) in high-risk and non-high risk patients. ● **Green**	Results reported as a poster (Butaud et al.) and abstract. Number of participants included is not reported. Definition of high risk patients is not reported Information on patient characteristics is not reported. Abstract only, limited information.

Li et al. 2019 The US Dialysis-Related Bloodstream Infections: A Pre- and Post-ClearGuard HD Cap Conception Study Published as an abstract Funding not reported	Retrospective observational, single-arm study ClearGuard HD No comparator Funding not reported **Amber**	150 patients receiving dialysis over a 4-year period, ClearGuard caps Pre-intervention (ClearGuard) follow-up, mean (range): 1.75 (0.02 – 4.26) yrs. Post-intervention (ClearGuard) follow-up, mean (range): 0.19 (0.08 – 0.21) yrs. Outpatient centre **Amber**	**Bacteremia infection rates** 9.7 (95% CI 6.7 -14.1) events per 100 person-years for pre-intervention (ClearGuard) vs. post-intervention (ClearGuard) 0 (95% CI 0.0 – infinity); p = 0.318 **Amber**	The study lacked statistical power. Those receiving ClearGuard had a shorter follow-up period compared with those pre-ClearGuard adoption. No comparator group Abstract only, limited information
Sibbel et al. 2020 Association Between Antimicrobial Barrier Cap Use and Outcomes Among Haeomdialysis Patients Using A Central Venous CatheterThe US Published as an abstract Funding not reported	Retrospective observational, single-arm study ClearGuard HD Comparator unclear. Funding not reported **Amber**	Study data was derived from medical records 3 months pre- and post- antimicrobial cap (ClearGuard) adoption; 37,642 patients were included in the pre-period and 40,498 patients were included in the post-period. Outpatient centre **Amber**	**BSI rate** 0.54/100 CVC days in pre-period to 0.36/100 CVC days in the post-period **Hospital admissions** 0.22 fewer hospital admissions per patient-year in the post-period **Green**	No comparator Unclear if the same patients were included in the pre- and post-antimicrobial cap adoption Abstract only, limited information
Acronyms: ARBSI, Access Related Bloodstream Infection; BSI, bloodstream infection; CA-BSI, catheter associated bloodstream infection; CI, confidence interval; CLABSI, central line-associated bloodstream infection; CVC, central venous catheters; EAC, external assessment centre; FY, financial year; IRR, incidence rate ratio; PBC, positive blood cultures; US, United States; yrs., years.				

Table 2: Studies included by company and excluded by the EAC

Study name and location	Design and intervention(s)	Participants	Outcomes	EAC comments
Nitz et al. 2021 Prevention of central line associated blood stream infections in a pediatric dialysis unit. USA	Prospective case series study Implementation of five infection prevention actions: 1. Video audits of clinical staff while preforming hand hygiene and patient care 2. Implementation of a standardised protocol for catheter connection/disconnection and exit care 3. Reinforcement of patient restrictions relating to showers and water exposure 4. Standard use of ClearGuard caps and	28 patients 11 women, 17 men Mean (range) age, 11.7 (0.4 – 21) yrs. Paediatric hospital dialysis unit	**Compliance** 88 – 97% patients complied with the established protocols. ● **Red** **CLABSI** There were no outpatient CLABSIs experienced by the patient cohort over a period of 1,115 consecutive days. ● **Green**	**Included by the company, excluded by the EAC** The intervention and one of the outcomes do not match the scope and do not contribute to the decision problem.

	StatLock stabilisers 5. Patient and staff participation in education activities Funding not reported No comparator 🔴 **Red**			
Acronyms: CLABSI, central line-associated bloodstream infection; EAC, external assessment centre; US, United States; yrs., years.				

5 Clinical evidence review

5.1 *Overview of methodologies of all included studies*

The EAC included 6 studies; 3 studies were reported as full texts (Brunelli et al. 2018, Hymes et al. 2017 and Weiss et al. 2021) while the remaining 3 were reported as abstracts and a poster (Glennon et al. 2020, Li et al. 2019 and Sibbel et al. 2020). The full text studies included a total of 10,757 participants (approximately 775,000 CVC days) and the abstracts included a total of 78,290 participants (not including Glennon et al. 2020, which did not report the number of participants included) totalling at least 89,047 participants. All of the studies were supported by the company or did not report funding sources.

The company included 1 further study that was excluded by the EAC (Nitz et al. 2021) due to the intervention and outcomes not fully matching the scope. This study included ClearGuard alongside 4 other quality improvement measures and only reported CLABSI rate in a population which had all 5 measures implemented. The effect of ClearGuard in absence of the other measures was not possible to determine from the paper, so the EAC felt that this did not add much to the decision problem.

Two of the full text papers are prospective, multi-centre, open-label, cluster RCTs (Brunelli et al. 2018 and Hymes et al. 2017). These studies included 40 sites each, which were pair matched for BSI rate (Brunelli) or PBC rate (Hymes), number of patients with CVCs and geographic location and then randomised 1:1. The remaining studies are all retrospective analyses; Weiss et al. 2021 is a multi-centre study, while the 2 abstracts reported single-centre studies. All of the studies were undertaken in the US.

Comparators varied between the studies. Brunelli et al. 2018 is unique in comparing ClearGuard to Tego Connectors used with Curos disinfecting caps. This may be a less relevant comparator to the NHS setting, according to clinical experts. Hymes et al. 2017 compares ClearGuard to standard CVC

caps, while Weiss et al. 2021 uses Tego needlefree connectors with standard caps as a comparator. Glennon et al. 2020 compared a period of using ClearGuard alongside antimicrobial locks to a period of using ClearGuard alone. The final 2 abstracts reported non-comparative studies. Outcomes also varied between the studies, with various measures of BSI being reported. PBC rate was also reported as a primary outcome in both RCTs. Other important outcomes included hospital admissions, hospital stays and mortality.

In the full text studies, the mean age of participants varied from 61.1 years to 62.8 years and the percentage of men varied from 51-53%. This suggests that the studies have very comparable populations, perhaps unsurprising given the large numbers of participants in the same setting. Diabetes rates in the 2 RCTs was 59-60%. Baseline characteristics appeared to be generally well balanced; however, the ClearGuard group was significantly older (p=0.02) in Brunelli et al. 2018 and Hymes et al. 2017 did not report p-values. Although large populations were included in both studies, no power calculations were reported. However, the EAC performed independent power calculations for the studies and found that they were adequately powered. Both RCTs were unable to blind either the investigators or participants, most likely due to the difference in appearance of the caps.

5.2 *Critical appraisal of studies and review of company's critical appraisal*

The 2 RCTs reported in the literature are large, cluster randomised trials and are overall considered to be of moderate quality, with some potential for bias. Hymes et al. 2017 compared ClearGuard to standard CVC caps and so could be considered more relevant to the decision problem. Neither study incorporated any blinding, which could generate bias, although blinding of the medical device is pragmatically difficult. Clinicians may have been more careful when using the experimental caps compared to the standard, for example when changing them and scrubbing the hub. Some patient characteristics were also imbalanced in Brunelli et al. 2018 (race, age and

diabetes). The ClearGuard group were less likely to have diabetes and had a higher proportion of white participants which may bias results in favour of ClearGuard. However, the ClearGuard group was also significantly older, which may bias results in favour of Tego + Curos.

Weiss et al. 2021 is a large, comparative, multi-centre study but is also retrospective. It compared ClearGuard with Tego needlefree connectors used alongside standard CVC caps in 13 US dialysis centres. There were 2 study periods; the 1st period lasted 5 months and included roughly equal numbers of participants using the intervention and comparator, while the latter 13 month period had almost all participants using the intervention. The paper reported results for the initial period and both periods combined. This makes it difficult to draw conclusions from the results of both periods combined, as they are imbalanced. There was no direct comparison of outcomes as it was not possible to match data from the 2 groups due to the limited availability of patient characteristics and medical histories.

The 3 studies reported as abstracts do not add much more to the decision problem. Glennon et al. 2020, however, was the only study which compared standard caps with the use of antimicrobial locking to ClearGuard alone. This study found that the CA-BSI rate was 1.82 per 100 patient months in the group employing anti-microbial locking versus only 0.26 in the ClearGuard alone group. It should be noted, however, that this is a retrospective analysis reported as an abstract and poster. Further, the antimicrobial locking group only included high-risk patients, while the ClearGuard group included non-high risk patients as well, limiting the utility of this result.

Sibbel et al. 2020 includes a very large number of participants in a retrospective before-and-after analysis. However, it is unclear if the same participants are included in the before and after cohorts.

5.3 *Results from the evidence base*

Study	PBC	CRBSI	CLABSI	CA-BSI	BSI rate	ARBSI	Bacteraemia infection rates	IV antibiotic starts	Hospital admissions	Hospitalisation days
Brunelli et al. 2018.	0.28 PBCs per 1000 CVC days in ClearGuard vs 0.75 per 1000 CVC days in the Tego + Curos group. PBCs were experienced in 21 and 63 unique patients, in the ClearGuard and Tego + Curos group respectively IRR was 0.37 (p=0.001) favouring ClearGuard.	IRR: 0.37 (p=0.003), favouring ClearGuard.	IRR: 0.35 (p=0.003), favouring ClearGuard.	NR	NR	IRR: 0.31 (p<0.001), favouring ClearGuard. Comprising of Gram negative organisms only the IRR was 0.19 (p = 0.001), favouring ClearGuard. Comprising of Gram positive organisms only the IRR was 0.4 (p=0.001), favouring ClearGuard.	NR	IV antibiotic starts within 3 days of a PBC analysis IRR: 0.37 (p<0.001), favouring ClearGuard	Rate of admissions in the ClearGuard vs Tego+Curos: 0.06 vs 0.11 per 1000 CVC days respectively (IRR = 0.55; p= 0.5)	

Study	PBC	CRBSI	CLABSI	CA-BSI	BSI rate	ARBSI	Bacteraemia infection rates	IV antibiotic starts	Hospital admissions	Hospitalisation days
Glennon et al. 2020.	NR	NR	NR	1.82 per 100 patient months in the first year (FY18) in high-risk patients 0.26 per 100 patient months in the second year (FY19) in high-risk and non-high risk patients.	NR	NR	NR	NR	NR	NR

Study	PBC	CRBSI	CLABSI	CA-BSI	BSI rate	ARBSI	Bacteraemia infection rates	IV antibiotic starts	Hospital admissions	Hospitalisation days
Hymes et al. 2017.	0.26/1000 days in the ClearGuard vs 0.59/1,000 days in the standard caps CVC group; IRR=0.44 (p=0.01)	NR	NR	NR	NR	NR	NR	1.68/1,000 days in the ClearGuard vs 1.78/1,000 days in the CVC group; IRR=0.94 (p=0.6)	0.28/1,000 days in the ClearGuard vs 0.47/1,000 days in the standard CVC caps group; IRR=0.60 (p=0.04)	3.24/1,000 days in the ClearGuard vs 4.68/1,000 days in the CVC group; IRR=0.69 (p=0.2)
Li et al. 2019.	NR	NR	NR	NR	NR	NR	9.7 (95% CI 6.7 -14.1) events per 100 person-years for pre-intervention (ClearGuard) vs. post-intervention (ClearGuard) 0 (95% CI 0.0 – infinity); p = 0.318	NR	NR	NR

Study	PBC	CRBSI	CLABSI	CA-BSI	BSI rate	ARBSI	Bacteraemia infection rates	IV antibiotic starts	Hospital admissions	Hospitalisation days
Sibbel et al. 2020.	NR	NR	NR	NR	0.54/1000 CVC days in pre-period to 0.36/1000 CVC days in the post-period of AmBC	NR	NR	NR	IRR: 0.22 fewer hospital admissions per patient-year in the post-period of AmBC	NR

Study	PBC	CRBSI	CLABSI	CA-BSI	BSI rate	ARBSI	Bacteraemia infection rates	IV antibiotic starts	Hospital admissions	Hospitalisation days
Weiss et al. 2021.	NR	NR	0.03/1,000 days in the chlorhexidine group vs 0.70/1,000 days in the Tego connector group ($p < 0.0001$) for the first 5-month study period 0.09/1,000 days in the chlorhexidine group vs 0.63/1,000 days in the Tego connector group ($p<0.0001$) for the two study periods combined.	NR	NR	NR	NR	NR	NR	NR

Acronyms: AmBC, antimicrobial cap; ARBSI, access related blood stream infection; BSI, blood stream infection; CLABSI, central line associated blood stream infection; CA-BSI, CVC, central venous catheter; FY, financial year; IRR, incidence rate ratio IV, intravenous; NR, not reported; PBC, positive blood cultures.

6 Adverse events

The EAC searched the MHRA and FDA database on the 10th of June using the terms “Clear Guard”, “ClearGuard” and “PEH”. Nine records were found on the FDA Manufacturer and User Facility Device Experience (MAUDE) database.

The first two entries (30/01/2019) were the same report on two separate events. The reports were relating to the ClearGuard caps “coming off” for a single patient on two separate occasion. No patient was injured. The third and fourth entries (30/01/2019) were reports relating to the ClearGuard cap becoming detached from the catheter hub whilst a patient was asleep. No patient was injured. The fifth entry (30/01/2019) was relating to the rod of the ClearGuard cap breaking loose into the catheter. No patient was injured, and the manufacturer was not able to replicate the reported issue despite testing the same lot exceeding the clinically recommended force. The sixth (06/08/2019), seventh (14/08/2019), eighth (25/03/2019) and ninth (25/03/2019) entries were reporting a similar issue as the third and fourth entry. No patient was injured due to these events.

No adverse events were reported in Brunelli et al. 2018, Hymes et al 2017 or Weiss et al. 2021.

7 Evidence synthesis and meta-analysis

The company did not perform a meta-analysis or evidence synthesis, due to the small number of full text studies with differing comparators. The EAC also believed that a meta-analysis was not practical due to these factors.

8 Interpretation of the clinical evidence

The evidence base is entirely comprised of studies performed outside the UK (all in the US/North America), meaning it may not be generaliable to the NHS. One major potential discrepancy in practice is the use of high-concentrate citrate in the UK but not in the US, where it is not authorised by the FDA. The

experts believed that use of high-concentrate citrate may lead to lower baseline rates of BSI in the UK than the US.

All of the studies report positive outcomes for ClearGuard, compared to several different comparators and covering several different measures of infection rate and hospital time.

Brunelli et al 2018 and Hymes et al. 2017 employ different comparators, and are considered by the EAC to be the 2 pivotal studies. It is notable that both RCTs report a similar PBC rate in the ClearGuard groups (0.28 PBCs per 1000 CVC days and 0.26 PBCs per 1000 CVC days, respectively). In fact, Hymes et al. 2017 reported a lower PBC rate in the standard CVC cap group than Brunelli et al. 2018 reported in the Tego + Curos group (0.59 PBCs per 1000 CVC days and 0.75 PBCs per 1000 CVC days, respectively). In both cases, significantly lower PBC rates were reported for ClearGuard (Hymes: IRR = 0.44; p = 0.01 and Brunelli: IRR = 0.37; p = 0.001) than the comparators. It should be noted again that the comparator in Hymes et al. 2017 is considered to be more relevant to the NHS setting.

BSI rates were widely reported, although terminology was not always consistent. Brunelli et al. 2018 reported CRBSI, CLABSI and ARBSI vs Tego + Curos and found that lower rates of all 3 in the ClearGuard group (IRR= 0.37; p = 0.001, IRR = 0.35; p = 0.003 and IRR = 0.31; p <0.001, respectively). Further, the paper reported an IRR of 0.19 and p = 0.001 for ARBSI comprising only of Gram negative organisms, again favouring ClearGuard and an IRR of 0.40, p = 0.001 for Gram positive organisms only in ClearGuard's favour. Weiss et al. 2021 reported a significantly reduced rate of CLABSI in the ClearGuard group compared with Tego needle-free connectors. This was a retrospective study with 2 study periods and reported a CLABSI of 0.03 per 1,000 days vs 0.70 per 1,000 days (p < 0.0001) in the first 5 month period and 0.09 per 1,000 days vs 0.63 per 1,000 days (p<0.0001) in the latter 9 month period. The initial study period included roughly equal numbers of participants in each group (967 vs 1044 in the ClearGuard and comparator groups, respectively), while the second period included mainly ClearGuard caps. The total number of participants in each

group was 4614 in the ClearGuard group and 1320 in the comparator group. Glennon et al. 2020 was another retrospective analysis and reported a CA-BSI rate of 1.82 per 100 patients months in paediatric participants using standard caps with antimicrobial locking and 0.26 per 100 patient months using ClearGuard alone. This result may be misleading, however, as only high-risk patients were included in the first group, while non-high risk patients were included in the ClearGuard alone group. Sibbel et al. 2020 reported a BSI rate of 0.54 per 1000 CVC days in a study period prior to the adoption of ClearGuard and 0.36 per 1000 CVC days after adoption of ClearGuard. However, the groups were unbalanced, and it is not clear what caps and strategies were being employed prior to ClearGuard.

Brunelli et al. 2018, Hymes et al. 2017 and Sibbel et al. 2020 all reported data on hospital admissions and stays. Brunelli et al. 2018 found that the rate of admissions in the ClearGuard group was lower (but not significantly) than the Tego + Curos group (0.06 vs 0.11 per 1000 CVC days respectively, IRR = 0.55; p= 0.5). Hymes et al. 2017 found that hospital admissions were significantly lower in the ClearGuard group compared with the standard CVC cap group (0.28/1,000 days vs 0.47/1,000 days; IRR=0.60, p=0.04). Sibbel et al. 2020 reported 0.22 fewer hospital admissions per patient-year after ClearGuard was implemented.

Using ClearGuard may reduce the required time for clinicians (or home dialysis patients) to change caps, as there is no need to scrub the hub with alcohol wipes, or to dip caps in alcohol and wait for them to air dry. However, none of the papers included reported information on clinician time or resource use. Furthermore, experts felt that, even when using ClearGuard, they would continue to use practices like scrubbing the hub.

Li et al. 2019 reported rates of bacteremia infection (which experts report is a type of BSI) and found that there were 9.7 (95% CI 6.7 -14.1) events per 100 person-years in the pre-intervention group vs 0 (95% CI 0.0 – infinity); p = 0.318, in the ClearGuard group.

Baseline patient characteristics were reasonably similar where reported, although this wasn't consistently well reported. This is unlikely to have a major effect on results but may have a slight effect in favour of ClearGuard. All of the studies are in part or fully funded/sponsored by the company, or do not report funding, which could impart some bias to the results.

8.1 *Integration into the NHS*

None of the included studies were performed in the UK.

The EAC do not believe that implementing ClearGuard caps will require any significant changes to the current care pathway. They are likely to directly replace standard CVC caps that are currently in use. No additional training would be required to use ClearGuard caps compared to standard caps. Clinical experts felt that their practice would be unlikely to change and that they would continue with practices like scrubbing the hub with alcohol wipes, even if using ClearGuard.

Although experts felt that although the home dialysis population is currently small, it is reported to be growing and ClearGuard caps may be used in this setting. Patients or their carers may be able to use ClearGuard caps with minimal training. There was no evidence identified on the use of ClearGuard in the home setting.

8.2 *Ongoing studies*

The company did not identify any ongoing studies. The EAC did not identify any ongoing studies.

9 Economic evidence

9.1 *Published economic evidence*

Search strategy and selection

A search for economic evidence was carried out by the company on MEDLINE(R), Embase, NHS EED, DARE, HTA via CRD Database, CEA registry via Centre for the Evaluation of Value and Risk in Health. The EAC reviewed the search strategy used by the company (Appendix A of company submission) and found it to be appropriate. The search resulted in the inclusion of 1 abstract. The EAC conducted its own search (see section 4.1 and Appendix A) to confirm no relevant papers had been missed. The EAC included the following databases in its search; Embase, MEDLINE, PubMed, ClinicalTrials, WHO ICTR, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, INAHTA Database, and EconLit. Following the application of cost and economic filters, the EAC confirmed that no economic evidence in addition to the studies submitted by the company was available. Since no other papers were available, the abstract has been considered as part of the economic evidence by the EAC.

Specific inclusion and exclusion criteria were applied for study selection. The inclusion criteria were patients undergoing HD using CVCs; interventions included ClearGuard to minimize the risk of CRBSIs amongst patients undergoing HD using CVCs; comparators included current standard care, which includes the use of alcohol wipes and alcohol containing solution of chlorhexidine gluconate (2% chlorhexidine gluconate in 70% alcohol), as well as alternative barrier caps; outcomes included Life-years gained Quality-adjusted life-years (QALYs) gained, Incremental cost-effectiveness ratios (ICERs), Clinical effectiveness (e.g., survival rates, healing rates, etc.),details of the results of sensitivity analyses; study design included Cost-effectiveness analyses (CEA),Cost-utility analyses (CUA),Cost-benefit analyses (CBA),Cost-minimization analyses (CMA),Cost-consequence studies, Budget impact models, and Cost studies. Language restrictions included English language only. There was no restriction on search dates and country. Exclusion criteria included animal studies, surveys, database analyses,

editorials; commentary,device name not reported as intervention or comparator, incorrect population, and incorrect outcomes. The EAC accepted the inclusion and exclusion criteria used by the company.

Published economic evidence review

The search identified one economic study, which was an abstract (Glennon et al., 2020). The objective of the study was to compare the catheter associated blood stream infection (CA-BSI) rates and cost associated with antimicrobial locks (AMLs) versus ClearGuard caps in the paediatric dialysis setting. The population of interest was haemodialysis patients with a central venous catheter (CVC) in a paediatric setting in the United States. No further details of population characteristics were given. There was no loss to follow up or withdrawal of patients from the study reported. Methodological data pertaining to the total number of patients, catheter months and number of infections was obtained from the Eectronic Medical Record while information relating to the cost of AMLs, and ClearGuard caps was obtained from the pharmacy department. In terms of results, the study revealed that CA-BSI rate for the financial year 2018 (FY18) was 1.82 per 100 patient months with cost of prophylactic AML usage in 4 high risk patients amounting to $25,896 (£18,050). In the financial year 2019 (FY19), AML usage was discontinued and ClearGuard caps were used for all haemodialysis patients with CVC (including high risk and non-high-risk patients). This resulted in a total annual cost of $10,140(£7,078) and the CA-BSI rate dropped to 0.26 per 100 patient months. While the study indicates a lower CA-BSI rate and lower cost-per-year for ClearGuard caps versus AMLs, the study also reports a cost for 4 high risk patients totalling $25,896. The abstract does not report costs for the remaining patients and compares the figure for the high-risk patients to the total cost for ClearGuard caps for all patients (including high and non-high-risk patients). Moreover, the unit cost used for reporting the analysis is not mentioned. There was no sensitivity analysis performed to ascertain the robustness of the low cost and CA-BSI rate claimed in the study.

Results from the economic evidence

The results from the included abstract shows low CA-BSI rate and low cost per year for ClearGuard caps versus AMLs usage. The EAC notes that this is in a paediatric setting, and its applicability to adult setting is uncertain.

9.2 *Company de novo cost analysis*

Economic model structure

With no published economic evidence available except for one abstract, the company has submitted a de novo cost model for the technology. The model structure included a decision tree that looked at the cost-savings of the intervention compared to all relevant comparators. The model was developed to simulate a hypothetical cohort of HD patients, with a tunnelled CVC, undergoing dialysis and receiving one of five interventions: (1) ClearGuard HD Antimicrobial Barrier Caps, (2) Standard CVC caps, combined with the use of alcohol wipes for disinfection, (3) Standard CVC caps, combined with the use of an antimicrobial lock solution and alcohol wipes for disinfection, (4) Tego haemodialysis connectors used with Curos disinfecting caps (Tego + Curos), or (5) Tego haemodialysis connectors on their own, with manual decontamination of the catheter hub with alcohol wipes, in the hospital setting. The EAC thinks the population, intervention, and comparators are reasonable to be included for this assessment, and in line with the scope. The EAC notes that only one comparator - Tego haemodialysis connectors alone - is not appropriate, since it is a connector, not an alternative cap and is therefore out of scope. However, as it provides extra information for the committee, the EAC did not exclude this from their analysis.

The model was developed from the perspective of the NHS and Personal Social Services (PSS) in England. Costs and health outcomes were assessed over the short-term (1-year time horizon). The aim of the analysis was to assess the costs and outcomes associated with introduction of ClearGuard HD, with benefits assessed in terms of reduction in infection rates (and their associated costs) and subsequent mortality. The model structure (Fig 1) is simple, as introduction of ClearGuard is a straightforward replacement of one barrier cap method for another, with minimal impact on the existing patient

pathway. The model structure begins with all HD patients receiving 1 of the alternative methods being compared, i.e., intervention or comparator(s). Following this, patients may either experience a catheter-related bloodstream infection (CRBSI) or they may be infection-free. Where patients experience a CRBSI they may ultimately recover from the infection, or they may die. The EAC thinks the model structure, time horizon, and perspective are appropriate.

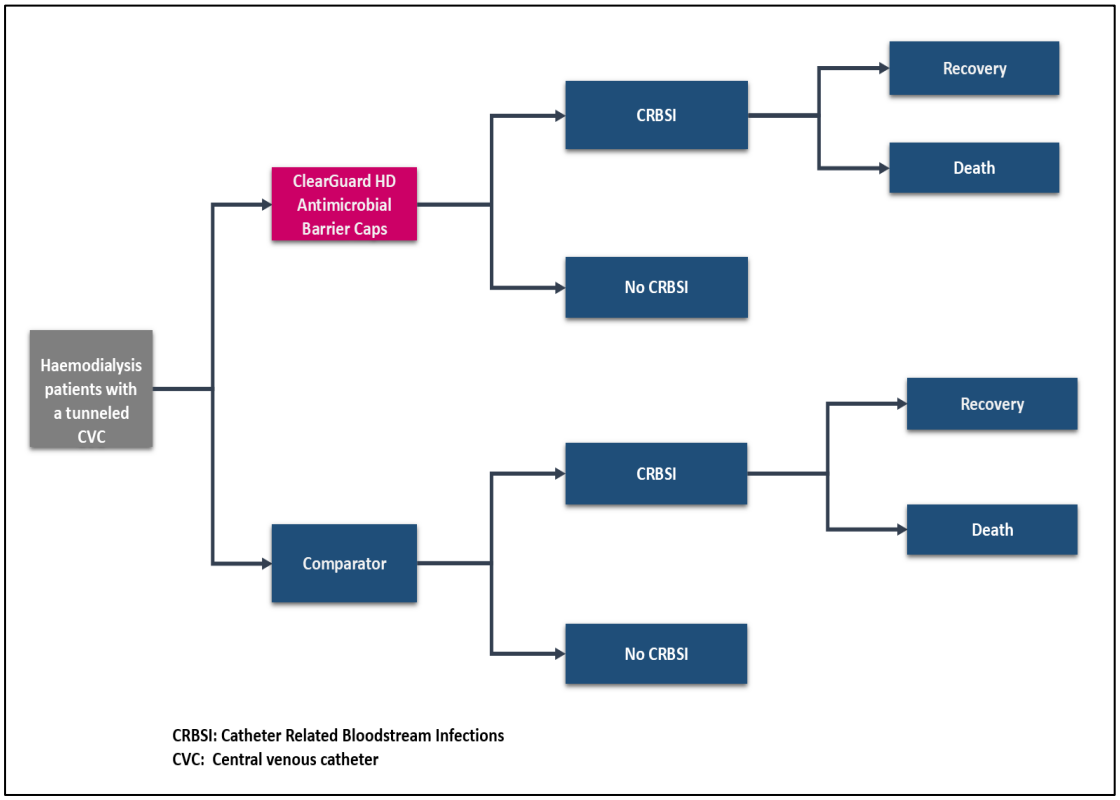


Fig 1 : Company model structure.

In addition, the model makes the following assumptions.

- Though the model structure shows CRBSI as the relevant infection outcome, some of the data used in the analysis may be based on CLABSI, CABSI or PBC data rather than CRBSI data. The terms are often used interchangeably in the literature. This assumption is acceptable to the EAC and has been discussed in the clinical sections of the report. The sensitivity in the values due to the interchangeability is further explored in the sensitivity analysis performed by the EAC.

- Due to the lack of relevant data to support an analysis of the intervention in the community setting, the model assumes that all patients are receiving haemodialysis, and the intervention, in the hospital setting. This is acceptable to the EAC.

- No costs associated with training health care staff on the use of the device are included in the model. This assumption is based on input from the company, that minimal, if any, training would be required on use of the device, which is reasonable to the EAC. The EAC would like to note that the company has assumed 15s of band 5 nurse time will be saved, as the opportunity cost of staff time on disinfecting the cap . The EAC highlights a recommendation from MTG44 Curos which might be relevant for this assessment. “4.7The committee agreed with the EAC that the reliability of the cost modelling was limited because of the uncertainty in the clinical evidence. Clinical expert advice was mixed: although some experts agreed that Curos may save time compared with manual disinfection, others noted that compliance with manual disinfection protocols is very low in practice and using Curos would be unlikely to free up any staff time. The committee accepted the EAC's revisions to the cost model but concluded that further evidence is needed to show if using Curos releases staff resources or not.”

- No adverse events that would have an effect on patients were identified in the review of clinical evidence, or in the specific search for information on device-related adverse events, and hence these have not been included in the model. The EAC thinks this is the case based on its own clinical review.

- The model considers the occurrence of CRBSI/CLABSI/CABSI/PBC only, and impact of the intervention on CRBSI/CLABSI/CABSI/PBC rates and the subsequent impact on hospital stay and mortality. Therefore, additional catheter-associated outcomes (such as catheter colonisation leading to local infection or hypersensitivity reactions) are not considered. This is reasonable to the EAC.

- Evidence from the literature (Goto et al. 2013) highlights the increased mortality risk associated with infection, and has been included as an outcome in the model, which the EAC thinks is reasonable. However, the EAC notes that Goto et al. 2013 reports mortality rate associated with overall bloodstream infections in North America and Europe, rather than catheter associated bloodstream infection. Though there is an increased risk of mortality with those having BSI, the inclusion of mortality in the model is redundant, because the cost of caps and treating infection is assigned to patients who die. The current model is good enough as a model without mortality included.

- For the purpose of the costing exercise, compliance with the intervention and comparator(s) is not explicitly considered. This assumption was made on the basis of a lack of available evidence associated with compliance to appropriate practices related to use of the device(s). Therefore, 100% compliance was assumed in the analysis, and is consistent with that made in NICE MTG44 (NICE 2019). Clincal experts also opined that this compliance level was reasonable.

- The cost savings associated with ClearGuard HD were estimated based on its potential for certain common practices (such as the manual disinfection of the catheter hub) to be replaced by using this innovative cap. However, clinical evidence on the effectiveness of the cap used in the model may be derived from studies which did not remove existing practices following introduction of the intervention, i.e., practices outside of use of the intervention remained the same in both arms of the clinical study. This assumption is valid according to the EAC, since it can't be known for certain that all the usual practices like scrubbing the hub were removed when using ClearGuard. It was confirmed by clinical experts that such practices would likely continue even if ClearGuard was implemented. However, it is to be noted that for the ClearGuard arm in the model, scrubbing was not included but for other comparator arms it was included. Since the practice of manual

disinfecting is mixed, the EAC has provided additional results adding manual disinfecting to the ClearGuard arm in the model

In summary, the EAC thinks the model structure, time horizon, outcomes and assumptions used by the company are appropriate for this assessment.

Economic model parameters

Clinical parameters and variables

- The age of the cohort is not defined in the model. While the average age of the patients undergoing hemodialysis is 60-65, one of the incidence rate ratios reported (see below) is for a paediatric population.
- The company reports an incidence rate of CRBSI per 1,000 CVC-days using standard CVC caps of 0.7. This was based on NICE MTG44, and the EAC notes that the value was not specific to CVCs and HD population. In the absence of other evidence, the EAC finds this value acceptable based on the NICE MTG44 report but recommends based on clinical studies (Kanaa et al, 2015, Aitken et al, 2016, Crowley et al, 2017, Youssouf et al, 2017, Hymes et al, 2017) that a wider range of values is incorporated in the sensitivity analysis.
- The company reports an incidence rate of CRBSI per 1,000 CVC-days using antimicrobial lock solution with standard CVC caps of 0.61. The value is identified from a published abstract by Glennon et al. 2020 with the outcome of CABSI (not CRBSI). The EAC believes that this estimate was derived by converting 1.82 for 100 patient months into days, 100/12*365=3042 days. If 1,000 days is 32.8767%, then applying it to the estimate in Glennon et al. 2020 of 1.82, 1.82*0.328767=0.598. The company clarified that the difference is because the company assumed 360 days/year for its calculation, and the EAC used 365/year, which is more precise. The EAC broadly accepts this value of 0.61, however recommends

it be changed to 0.598. In the absence of other data available, the EAC notes that while the population was undergoing haemodyalysis, it was in a paediatric setting. Based on clinical expert opinion, the incidence rate may be higher for the average population undergoing haemodyalysis (60-65 years) who are likely to be on the haemodyalysis for longer than the paediatric population. The EAC suggests that broader ranges of this value are incorporated into sensitivity analysis.

- The company reports an incidence rate of CRBSI per 1,000 CVC-days using Tego + Curos of 0.75 based on the study by Brunelli et al. 2018. The EAC accepts this estimate, but recommends based on Merrill et al. 2014, that a CRBSI estimate for Curos of 0.577 (95% CI: 0.393-0.842) is used to account for this range in the sensitivity analysis.
- The company reports an incidence rate of CRBSI per 1,000 CVC-days using Tego alone of 0.63 based on Weiss et al. 2021. The EAC accepts the statistical validity of this value with a recommendation that a wider range of values is explored in the sensitivity analysis in the absence of further clinical evidence for incidence rate of CBRSI for Tego alone and in view of comments in section 9.2.
- The company reports an IRR of CRBSI using ClearGuard caps compared to standard CVC caps of 0.44 based on the study by Hymes et al. 2017. The EAC accepts the statistical validity of this value.
- The company reports an incidence rate reduction (IRR) of CRBSI using ClearGuard caps compared to using antimicrobial lock solution with standard CVC caps of 0.14 based on the abstract published by Glennon et al. 2020. The EAC accepts this estimate.
- The company reports an IRR of CRBSI using ClearGuard caps compared to Tego + Curos caps of 0.37 based on the study by Brunelli et al. 2018. The EAC accepts this value, however,

recommends based on a subgroup analysis for IRR of Curos alone (Voor In't Holt et al. 2017) of 0.48 (95% CI: 0.24 - 0.95) to incorporate this range in the sensitivity analysis.

- The company reports an IRR of CRBSI using ClearGuard caps compared to Tego alone of 0.14 based on the study by Weiss et al. 2021. The EAC accepts the statistical validity of this value with a recommendation that a wider range of values is explored in the sensitivity analysis based on an explanatory analysis presented in Brunelli et al. 2018.
- The company reports a probability of death following CRBSI of 0.15 based on the study by Goto et al. 2013. This study refers to mortality rate for overall bloodstream infection in the North American and European populations. The EAC accepts this value, noting that MTG44 and the MTG25 (3M Tegaderm CHG IV securement dressing for central venous and arterial catheter insertion sites) confirmed that there is no relevant, reliable mortality rate related to CRBSI in the UK. The EAC recommends to expand the range of values in the sensitivity analysis based on clinical experts opinion.
- The company reports the average number of CVC days per patient per year of 132 based on 3 published studies. The EAC considers this value to be appropriate.
- The company reports the total number of HD patient-years (CVC) at risk of 7,026 from Crowley et al. 2017 based on UK Renal Registry report.This report includes key data associated with dialysis patients, including the number of infectious episodes reported to Public Health England in that year, and the number of infections per individual dialysis centre. This study also reports the total number of patient years at risk (7,026) associated with central venous catheters amongst HD patients in that year. They estimate this value based on the distribution of access type using data from all centres in England which provided access data in that year. They then use this distribution, in combination with the total number of patients on HD in that year, to assign an estimated number of patient years at risk associated with CVCs amongst this population

in that year.In the model, the company simply use this figure on number of patient years at risk in one year (7,026) to calculate the number of patients at risk in one year in England (7,026/132 (132 being the average number of CVC days that HD patients undergo in a year)). This total number of patients at risk each year in England is used to estimate total costs associated with the different comparators in the model This value is acceptable to the EAC.

Table 3: Clinical parameters used in the company's model and any changes made by the EAC

Variable	Company value	Source	EAC value	EAC comment
Incidence rate of CRBSI per 1,000 CVC-days using standard CVC caps	0.70	NICE MTG44	0.70	EAC recommends 50% SA range (0.53; 0.88)
Incidence rate of CRBSI per 1,000 CVC-days using antimicrobial lock solution with standard CVC caps	0.61	Glennon et al, 2020	0.598	Slight change based on calculations from Glennon et al, 2020. EAC recommends 50% SA range (0.45; 0.75)
Incidence rate of CRBSI per 1,000 CVC-days using Tego + Curos	0.75	Brunelli et al, 2018	0.75	EAC recommends 50% SA range (0.56; 0.94)
Incidence rate of CRBSI per 1,000 CVC-days using Tego alone	0.63	Weiss et al, 2017	0.63	EAC recommends 50% SA range (0.47; 0.79)
IRR of CRBSI using ClearGuard Caps compared to standard CVC caps	0.44	Hymes et al, 2017	0.44	EAC recommends 50% SA range (0.23; 0.83)
IRR of CRBSI using ClearGuard Caps compared to using antimicrobial lock solution with standard CVC caps	0.14	Glennon et al, 2020	0.14	EAC recommends 50% SA range (0.11; 0.18)
IRR of CRBSI using ClearGuard Caps	0.37	Brunelli et al, 2018	0.37	EAC recommends 50% SA range (0.2; 0.68)

compared to Tego + Curos caps				
IRR of CRBSI using ClearGuard Caps compared to Tego alone	0.14	Weiss et al, 2017	0.14	EAC recommends 50% SA range(0.11; 0.18)
Probability of death following CRBSI	0.15	Goto et al, 2013	0.15	EAC recommends 50% SA range (12%; 32%)
Average number of CVC days per patient per year	132	Kwak et al, 2012 Crowley et al, 2017 Hymes et al, 2017	132	EAC recommends 50% SA range (123; 141)
Total number of HD patient-years (CVC) at risk	7,026	Crowley et al, 2017	7,026	Unchanged

Resource identification, measurement and valuation

Costs were presented in 4 broad categories; technologies, additional materials, complications, and hospital stay. The company included unit costs of ClearGuard caps, three alternative comparator caps, and one connector alone, including costs of associated solutions and alcohol wipes. The model assumes that all patients are receiving 3 haemodialysis sessions per week, in the hospital setting. The EAC agrees that this is an appropriate assumption for the population. The EAC notes that the company used CRBSI (catheter-related bloodstream infections) as the relevant infection outcome. However, there were differing infection outcome descriptions across studies that reported outcomes in terms of CLABSI (central-line-associated bloodstream infections), CABSI (catheter-associated bloodstream infections) or PBC (positive blood culture) data**.** The EAC clarified with the company and confirmed that while CRBSI, CLABSI, CABSI, PBC have different formal definitions, these terms were used interchangeably. The company stated that since the data used to inform impact on infection rates is based on differing definitions of infection, the results are similar and the model did not account for any cost difference in the types of infection. The EAC considers this to be an appropriate assumption, though the EAC notes that CDC doesn't consider these to be interchangeable. To mitigate any effects, the EAC has used extreme values of 50% variation in their sensitivity analysis.

- The first comparator is the standard CVC caps used with alcohol wipes for catheter hub disinfection. The company referenced the price per cap in the range of £0.30-£0.40 from NICE MIB234 (2020) and selected the mid-point £0.35 for their model, which the EAC considers appropriate. Two standard CVC caps are used for each dialysis session. Two alcohol wipes are also used per dialysis session for disinfecting the standard CVC caps. Typically, these alcohol wipes contain 2% chlorhexidine and 70% alcohol, according to NICE Clinical Guideline CG139 (2017). The average unit cost per alcohol wipe at £0.02 was referenced from NICE MTG44 (2018). The EAC notes that in MIB234, which was published in 2020, the unit cost of an alcohol wipe for CVC cap disinfection is similarly at £0.02, hence concludes that this cost is reasonable. The unit nurse time that is required for manually disinfecting one catheter hub, or 'scrub the hub', is 15 seconds, followed by 30 seconds drying time, according to MTG44. The company model costed 15 seconds disinfection time at the Band 5 nurse hourly rate, as it is suggested in MTG44 that the 30 second drying time would be utilised for alternative tasks. From the referenced PSSRU, Curtis & Burns (2020), the cost of Band 5 nurse hourly rate was £40 and manual disinfection time was 0.25 minutes. The company calculated the cost of a Band 5 nurse allocated for 'scrub the hub' procedure to be £40 ÷ 60 x 0.25 = £0.17 per dialysis session; the EAC accepts this estimate. Since the model assumes 3 dialysis sessions per week, the EAC calculated that the total weekly cost of this comparator is then (£0.35 + £0.02 + £0.17) x 2 x 3 = £3.24.
- The second comparator is standard CVC caps and alcohol wipes, in combination with an antimicrobial lock solution. Considered an addition to the standard solutions (such as citrate 4%, heparinized saline or heparin), the model assumed TauroLock is the antimicrobial lock solution. The cost includes the twice-a-week use of Hep 500 at £2.50 per vial, and once-a-week use of TauroLock

urokinase at £25 per vial. Since there are 3 dialysis sessions per week, the presented unit cost of TauroLock is then ((£2.5 x 2) + £25) ÷ 3 = £10 per dialysis (Valiant Medical website), which is acceptable to the EAC. This addition to the standard solution is used in both the technology and intervention arms, hence the EAC notes that its associated costs are not formally considered as part of the economic analysis.

- The third comparator is the Tego haemodialysis connectors with Curos disinfecting caps (Tego + Curos). The use of Tego connectors and Curos caps does not require manual disinfection of the catheter hub with alcohol wipe. The cost of Tego was derived from Science Equipment providers, where a standard 100-pack costs £228.65, and 1 dialysis session requires 2 Tego needleless connectors. Hence, the Tego connector's unit cost is presented at £2.29 (£228.65 ÷ 100). The cost of Curos caps was derived from MTG44 at £0.35, inflated to 2019/20 values. The submission notes it to be based on PSSRU inflation rates, but on query the company clarified that they have used the online EPPI converter. The EAC considers the PSSRU inflation rates to be more appropriate to the UK context and amended the cost to £0.33. In MTG44, the cost of Curos caps is £0.32 at 2018 value, using the 2.21% value from PSSRU inflation indices (2020), the EAC generated the new cost to be £0.32 + ((£0.32 x 2.21 ÷ 100) x 2) = £0.33. Two Tego connectors are used and need to be replaced once per week, while 2 Curos caps are used and replaced per dialysis (3 times per week). The company calculated the total unit cost of Tego + Curos caps per week at £6.68. The EAC replaced this formula with the new cost of Curos cap adjusted for inflation and arrived at a weekly cost of (£2.29 x 2) + ((£0.33 x 2) x 3) = £6.56.
- The fourth comparator is the Tego haemodialysis connector alone. As calculated above, the unit cost of 1 Tego needleless connector is £2.29. Manual disinfection of the catheter hub with an alcohol wipe is required in this intervention. Since the usage of 2 Tego

connectors only requires replacement once per week, the EAC calculated that the weekly cost of this comparator is (£2.29 x 2) + (((£0.02 + £0.17) x 2) x 3) = £5.72.

- The cost of CRBSI is estimated as £11,071, including diagnosis, treatment, and additional length of stay associated with infection. This value was derived from NICE MTG44 (2018), which was in turn sourced from MTG25 (2015). In MTG44, it was calculated using a bottom-up costing approach based on resource usage information from expert advisors. While cost of CRBSI is assumed to consist of separate resource components, the company reported the cost of CRBSI in an aggregated form. The EAC reviewed the various sources on cost of CRBSI and inflation of the data in MTG25 (2015) with the figures used in the company model. In MTG25, the cost of CRBSI was £9,990 in 2015, the EAC amended the cost, also using the 2.21% PSSRU, Curtis & Burns (2020) rate, to: £9,990 + ((£9,990 x 2.21 ÷ 100) x 5) = £11,094, but the discrepancies between estimates by the company and the EAC were small at £23. This difference is due to the alternative inflation calculator used by the company . Furthermore, the EAC recommends performing sensitivity analysis on this value over the range of +/- 50% (£5,547 – £16,641) instead of 25% to explore its impact on the overall results.
- The company model also included the average length of stay associated with a CRBSI event in the general ward and ICU settings. In NICE MTG44 (2018), clinical experts estimated the average length of stay for a CRBSI patient to vary between 6 days (first 2 days in ICU and 4 days a general ward) and 10 days (first 3 days in ICU and 7 days in a general ward). Hence, the EAC considers the mid-point values of 2.5 ICU days and 5.5 general ward days in the company model to be appropriate. However, it was noted that the estimated cost of CRBSI already captured costs associated with increased length of stay, to avoid double-counting,

this model does not consider the separate costs of these outcome measures.

- The unit cost of ClearGuard caps is given as £4 per pair in the listed price provided by the company. As the model assumes haemodialysis is conducted 3 times per week, where each dialysis session uses and discards 2 caps, the weekly cost of ClearGuard is £4 x 3 = £12. No additional cost is associated with the use of ClearGuard because manual disinfection of the catheter hub is not required. As the company estimates the average number of days that HD patients would need a CVC in a year is 132 days (Kwak et al., 2012, Crowley et al., 2017, and Hymes et al., 2017). This leads to a total cost of £12 x (132/7) = £226 per patient per year using ClearGuard caps. The EAC considers these costs to be reasonable. However, since the practice of manual disinfecting is mixed, the EAC has provided additional results adding manual disinfecting time to the ClearGuard arm in the model.
- No costs associated with training health care staff on use of the device are included in the model.

Table 4: Cost parameters used in the company's model and changes made by the EAC

Parameter	Company value	Source	EAC value	EAC comment
ClearGuard HD caps (price per pair of caps)	4.00	ICU Medical, Inc. (company listed price)	4.00	EAC recommends 50% SA range 2 - 6
Standard CVC caps (price per cap)	0.35	NICE MIB234 (2020)	0.35	EAC recommends 50% SA range: 0.175-0.525
Curos caps (price per unit)	0.35	NICE MTG44 (2018)	0.33	EAC amended cost inflation and recommends 50% SA

				range: 0.165-0.495
Cost of Tego (price per unit)	2.29	Science Equip (company listed price)	2.29	EAC recommends 50% SA range: 1.145-3.435
Cost of antimicrobial lock solution (TauroLock) per dialysis session	10	Valiant Medical (company listed price)	10	EAC recommends 50% SA range: 5–15
Average cost of alcohol wipes	0.02	NICE MTG44 (2018)	0.02	EAC recommends 50% SA range: 0.01-0.03
Hourly cost of a Band 5 nurse	40.00	Curtis & Burns (2020)	40.00	Unchanged
Nurse time for manual disinfection (minutes)	0.25	NICE MTG44 (2018)	0.25	EAC recommends 50% SA range: 0.125-0.375
Cost of nurse time for disinfection	0.17	Company calculation	0.17	EAC recommends 50% SA range: 0.085-0.255
Average cost of treating CRBSI	11,071	NICE MTG44 (2018)	11,094	EAC amended cost inflation and recommends 50% SA range: 5,547-16,641
ICU length of stay due to CRBSI (days)	2.5	NICE MTG44 (2018)	2.5	EAC recommends 50% SA range: 1.25-3.75
General hospital ward length of stay due to CRBSI (days)	5.5	NICE MTG44 (2018)	5.5	EAC recommends 50% SA range: 2.75 – 8.25

Sensitivity analysis

The company presents one-way sensitivity analyses, varying all model parameters by 25% or by a range available from the evidence. These

analyses investigate the impact on the incremental cost of the intervention, representing a comparison between ClearGuard and one of the 4 comparators. A probabilistic sensitivity analysis assigning distributions to the parameters has also been performed. The EAC checked the sensitivity analysis and is of the opinion that they have been well performed. As most parameters are derived from the US-based studies and given the uncertainty surrounding the transferability of findings to the UK, EAC recommends that all parameters lacking clinical data validation are varied by +/-50% in the sensitivity analyses, apart from the unit cost of ClearGuard caps.

The company also conducted 5 scenario analyses. In the first scenario analysis A, an alternative value was assigned to TauroLock (antimicrobial lock solution) to account for varying practices in the UK. A value of £7.50 per week was applied, as opposed to the base-case value of £30, to account for the fact that many practices would use TauroLock with 3, £2.50 vials of Hep 500 per week rather than utilising the '2+1' protocol, including the use of urokinase as well as two vials of Hep 500 per week. The EAC finds this scenario analysis satisfactory.

Scenario	Base-case values	Variation
Scenario B	Incidence rate of CRBSI with standard CVC caps = 0.70; IRR with ClearGuard = 0.44	Incidence rate of CRBSI with standard CVC caps = 0.53; IRR with ClearGuard = 0.83
Scenario C	Incidence rate of CRBSI with standard CVC caps and antimicrobial lock solution = 0.61; IRR with ClearGuard = 0.14	Incidence rate of CRBSI with standard CVC caps and antimicrobial lock solution = 0.46; IRR with ClearGuard = 0.18
Scenario D	Incidence rate of CRBSI with Tego + Curos = 0.75; IRR with ClearGuard = 0.37	Incidence rate of CRBSI with Tego + Curos = 0.56; IRR with ClearGuard = 0.68
Scenario E	Incidence rate of CRBSI with Tego alone = 0.63; IRR with ClearGuard = 0.14	Incidence rate of CRBSI with Tego alone = 0.47; IRR with ClearGuard = 0.18

A series of 'worst case' scenario analyses (B – E) were conducted in which the base-case baseline infection rate associated with each of the 4 comparators was based on the lower-end of the value range, and the IRR of CRBSI with ClearGuard was based on the upper-end of the value range. For

these scenarios, based on clinical expert opinion and a variability of clinical estimates from published studies, the EAC recommends that the parameters are varied by +/-50% or by a different range suggested below rather than +/-25%. In scenario B, an incidence rate of CRBSI with standard CVC caps of 0.7 is used. Kanaa et al. 2015, Aitken et al. 2016, Crowley et al. 2017, Youssouf et al. 2017 and Hymes et al. 2017 provide a broad range of 0.24 - 2.65 that falls outside the values captured in this scenario. The EAC recommends accounting for this range. Scenario C uses a baseline incidence rate of CRBSI with standard CVC caps and antimicrobial lock solution of 0.61. The EAC believes, based on clinical expert opinion, that the rate may differ for the typical population undergoing haemodialysis, as they are likely to remain on haemodialysis for a longer period of time than the paediatric population. Furthermore, an explanatory analysis presented in Brunelli et al. 2018 suggests that IRR may vary in the range (0.18 - 0.37). Hence, it is possible that this incidence rate varies by more than +/-25% captured in the company analysis and the EAC recommends that these values are accounted for in the scenario analysis. In scenario D, the incidence rate of CRBSI with Tego + Curos is 0.75. The EAC believes based on the study by Merrill et al. 2014, which reported an IRR of 0.577 for Curos (95% CI: 0.393-0.842), that the estimate may be lower than the value of 0.56 used as the bottom range in the company scenario analysis. Furthermore, for scenario D, where an IRR with ClearGuard of 0.37 is used, the EAC believes based on the meta-analysis by Voor In't Holt et al. 2017 reporting IRR for Curos of 0.48 (95% CI: 0.24 - 0.95) that a wider range of values needs to be captured in this scenario analysis. The EAC recommends that these values are accounted for in the scenario analysis. In the absence of further clinical evidence for incidence rate of CBRSI for Tego alone and in view of comments in section 9.2 regarding this comparator being a connector without a cap, the EAC recommends varying the parameters for both values +/-50% in scenario E.

9.3 *Results from the economic modelling*

Base case results

Table 5: Summary of base case results

Cost per patient/Cost savings(company)

	Clear guard (£)	Standard caps + alcohol wipes (£)	Standard caps + AML solution + alcohol wipes (£)	Tego + Curos (£)	Tego only + alcohol wipes (£)	Technology vs Standard caps + alcohol wipes (£)	Technology vs Standard caps + AML solution + alcohol wipes (£)	Technology vs Tego + Curos (£)*	Technology vs Tego only + alcohol wipes (£)
Device cost per year (costs associated with procedure/caps/process only (excluding CRBSI costs))	226	61	626	126	107	+ 165	- 400	+ 100	+ 119
Adverse events per year (CRBSI)	450	1,023	891	1,096	921	- 573	- 441	- 646	- 471
Total	**676**	**1,084**	**1,518**	**1,222**	**1,028**	**- 408**	**- 841**	**- 546**	**- 352**
			* Negative values indicate a cost saving.						

The above table provided by the company reports the cost savings of ClearGuard against the comparators. However, in the submission the cost of ClearGuard per patient is £676, when compared to standard caps + alcohol wipes. The above table has used this cost to differentiate the per patient cost (ClearGuard) for other comparators as well, which is erroneous. For each comparator, the per patient cost of ClearGuard is different, since the baseline rates differ. The electronic model shows the correct figures. The EAC has reported the correct company results in Table 6 – 9).

Table 6: Cost savings compared to Standard caps + alcohol wipes

	Company's results			**EAC results**		
	Technology	**Comparator**	**Cost saving per patient**	**Technology**	**Comparator**	**Cost saving per patient**
Cost of caps	£ 226	£ 61	+ £165	£226	£61	+£165

Cost of treating CRBSI	£ 450	£ 1,023	−£ 573	£451	£1,025	-£574
Total	**£ 676**	**£1,084**	**-£ 408**	**£677**	**£1,086**	**-£408**

Table 7: Cost savings compared to Standard caps + AML solution + alcohol wipes

	Company's results			**EAC results**		
	Technology	**Comparator**	**Cost saving per patient**	**Technology**	**Comparator**	**Cost saving per patient**
Cost of caps	£ 226	£ 626	- £400	£226	£626	-£400
Cost of treating CRBSI	£ 125	£ 891	−£ 766	£123	£876	-£753
Total	**£ 351**	**£ 1,518**	**-£ 1,167**	**£349**	**£1,502**	**-£1,153**

Table 8: Cost savings compared to Tego +Curos

	Company's results			**EAC results**		
	Technology	**Comparator**	**Cost saving per patient**	**Technology**	**Comparator**	**Cost saving per patient**
Cost of caps	£ 226	£ 126	+ £100	£226	£124	£103
Cost of treating CRBSI	£ 406	£ 1,096	−£ 690	£406	£1,098	-£692
Total	**£ 632**	**£ 1,222**	**-£ 590**	**£633**	**£1,222**	**£589**

The Curos &Tego scenario does not include manual disinfection costs because the Curos caps themselves are for the purpose of disinfection. However, for the assumption that clinicians perform 'scub the hub' with all comparators, the costs of manual disinfection were added to the Tego+Curos arm for consideration. Observing the average cost per HD patient per year,

there was no change in the resulting incremental cost differences between the Curos Tego arm against Clearguard HD caps and disinfection. This is due to the fact that adding the manual disinfection cost only changed the total cost of this arm ever so slightly, hence when divided by the patient population, the average cost stays the same.

Table 9: Cost savings compared to Tego only + alcohol wipes

	Company's results			**EAC results**		
	Technology	**Comparator**	**Cost saving per patient**	**Technology**	**Comparator**	**Cost saving per patient**
Cost of caps	£ 226	£ 107	+ £119	£226	£107	£119
Cost of treating CRBSI	£ 129	£ 921	−£ 792	£129	£923	-£793
Total	**£ 355**	**£ 1,028**	**-£ 673**	**£355**	**£1,030**	**-£675**

The below tables(10-13) provides cost savings results when cost of disinfecting is added to the ClearGuard arm.

Table 10: Cost savings compared to Standard caps + alcohol wipes

	Company's results			**EAC results**		
	Technology	**Comparator**	**Cost saving per patient**	**Technology**	**Comparator**	**Cost saving per patient**
Cost of caps	£ 226	£ 61	+ £165	£247	£61	+£187
Cost of treating CRBSI	£ 450	£ 1,023	−£ 573	£451	£1,025	-£574
Total	**£ 676**	**£1,084**	**-£ 408**	**£698**	**£1,086**	**-£387**

Table 11: Cost savings compared to Standard caps + AML solution + alcohol wipes

	Company's results			**EAC results**		
	Technology	**Comparator**	**Cost saving per patient**	**Technology**	**Comparator**	**Cost saving per patient**
Cost of caps	£ 226	£ 626	- £400	£247	£626	-£379
Cost of treating CRBSI	£ 125	£ 891	−£ 766	£123	£876	-£753
Total	**£ 351**	**£ 1,518**	**-£ 1,167**	**£370**	**£1,502**	**-£1,132**

Table 12: Cost savings compared to Tego +Curos

	Company's results			**EAC results**		
	Technology	**Comparator**	**Cost saving per patient**	**Technology**	**Comparator**	**Cost saving per patient**
Cost of caps	£ 226	£ 126	+ £100	£247	£124	£123
Cost of treating CRBSI	£ 406	£ 1,096	−£ 690	£406	£1,098	-£692
Total	**£ 632**	**£ 1,222**	**-£ 590**	**£654**	**£1,222**	**-£568**

Table 13: Cost savings compared to Tego only + alcohol wipes

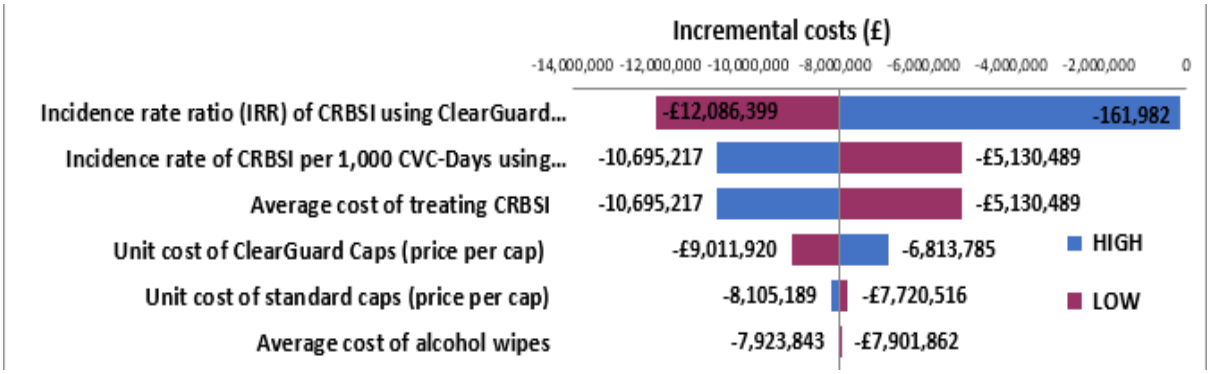
	Company's results			**EAC results**		
	Technology	**Comparator**	**Cost saving per patient**	**Technology**	**Comparator**	**Cost saving per patient**

Cost of caps	£ 226	£ 107	+ £119	£247	£107	£140
Cost of treating CRBSI	£ 129	£ 921	−£ 792	£129	£923	-£793
Total	**£ 355**	**£ 1,028**	**-£ 673**	**£377**	**£1,030**	**-£653**

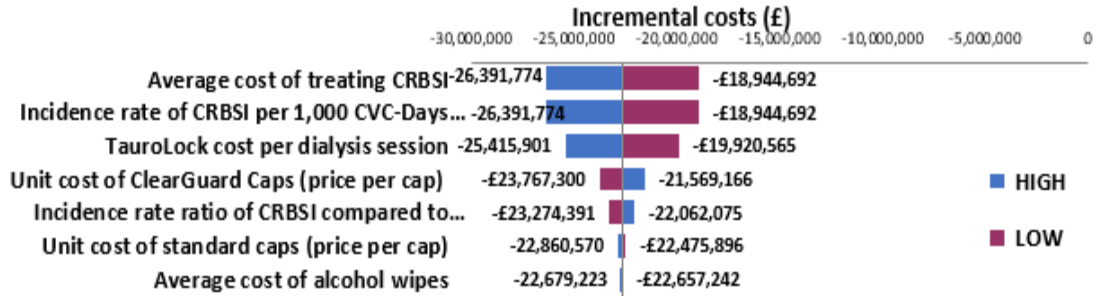
Sensitivity analysis results

In the majority of cases, the results show that the parameters which have the largest impact on cost results are the baseline incidence rate of infection associated with the comparator, and the IRR associated with ClearGuard. When the baseline incidence rate associated with the comparator is increased, cost savings associated with the introduction of the intervention increase as well. Conversely, when the IRR of ClearGuard is increased, i.e., it has less of an impact on the occurrence of CRBSIs, cost savings are reduced. These 2 parameters have a large impact in all comparisons.

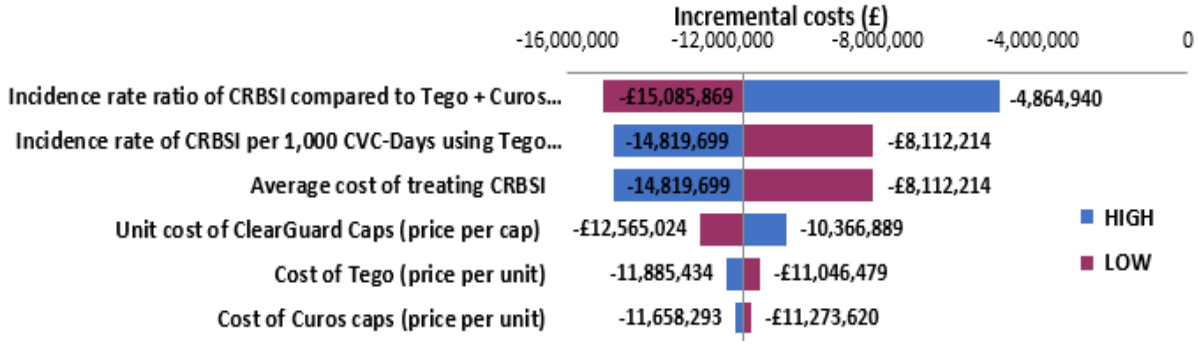
Comparison 1 with standard CVC caps



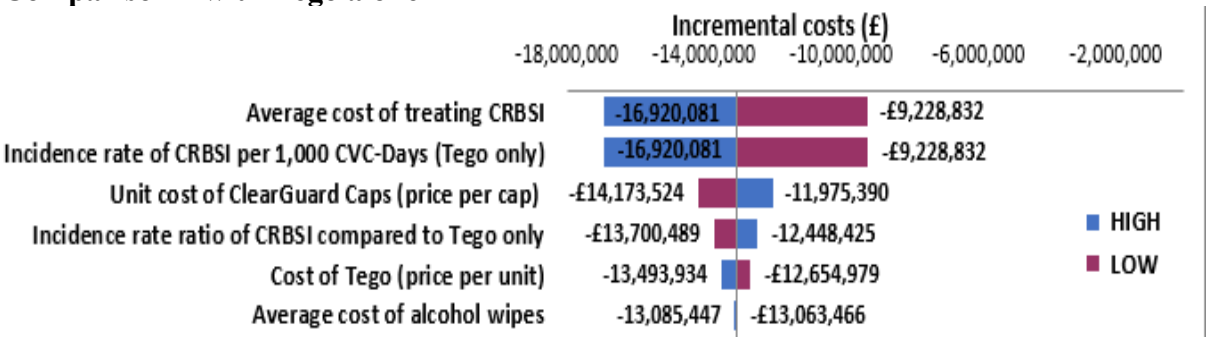
Comparison 2 with standard CVC caps combined with antimicrobial lock solution



Comparison 3 with Tego + Curos



Comparison 4 with Tego alone



The company predicts, based on the sensitivity analyses, that ClearGuard is a cost-saving intervention across the 4 comparators.

In Scenario A, despite the reduction in the cost of antimicrobial locks, the intervention remains cost saving (-£418). In scenarios B-E, where the base-case baseline infection rate with each of the comparators has been reduced, and the base-case IRR of CRBSI with the intervention has been increased, ClearGuard remains cost saving.

Table 10 : Scenario analysis results

	Mean discounted cost per patient using the technology (£)	Mean discounted cost per patient using the comparator (£)	Difference in cost per patient (£)*

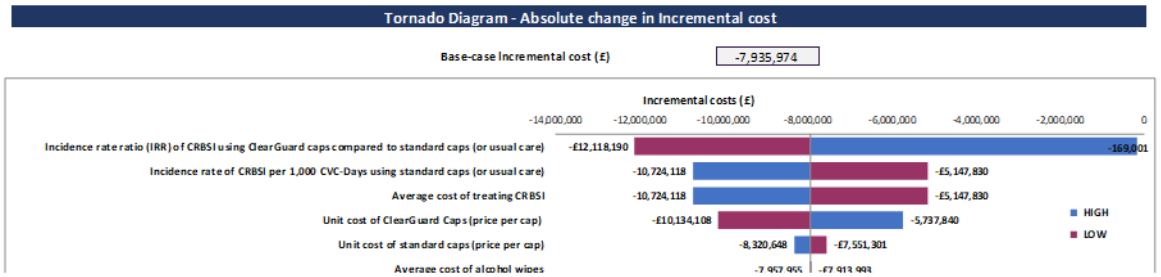
Scenario A (total costs)	676 (as in the base-case analysis)	1,094 (reduction from £1,518 in the base-case analysis)	-418
Scenario B (total costs)	676 (as in the base-case analysis)	835 (reduction from £1,084 in the base-case analysis)	-159
Scenario C (total costs)	676 (as in the base-case analysis)	1,299 (reduction from £1,518 in the base-case analysis)	-623
Scenario D (total costs)	676 (as in the base-case analysis)	944 (reduction from £1,222 in the base-case analysis)	-268
Scenario E (total costs)	676 (as in the base-case analysis)	794 (reduction from £1,028 in the base-case analysis)	-118

EAC sensitivity analysis

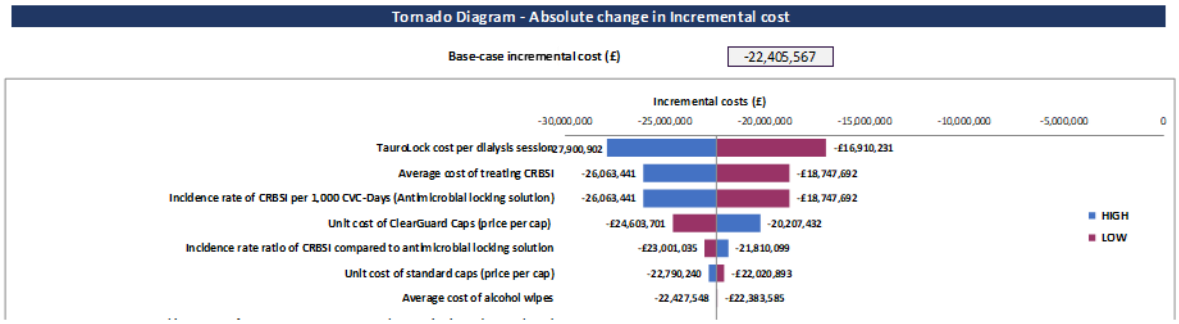
EAC performed two sensitivity analyses omitting and incorporating disinfection costs and by varying the parameters by the range of +/-50%. The tornado plots based on these analyses are presented below.

Updated Model (no disinfection costs)

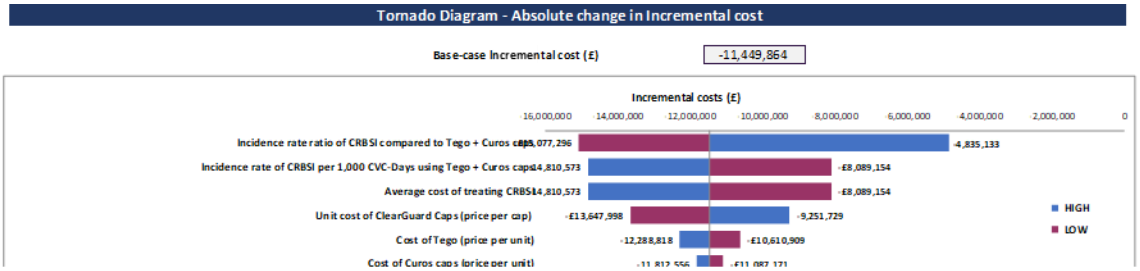
Comparison 1 with standard CVC caps



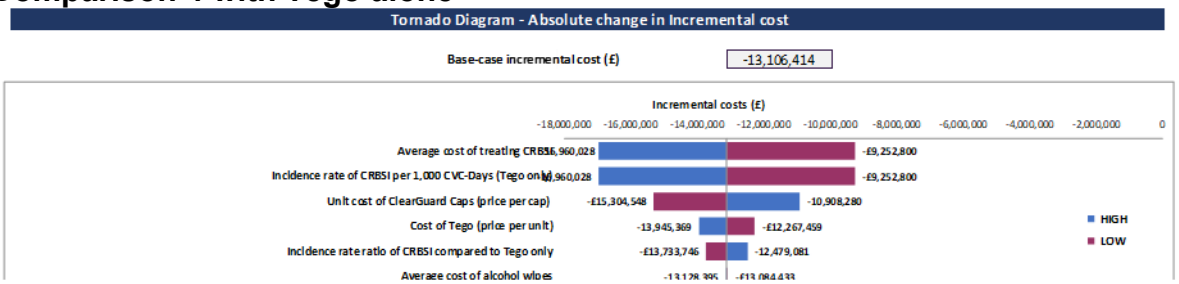
Comparison 2 with standard CVC caps combined with antimicrobial lock solution



Comparison 3 with Tego + Curos

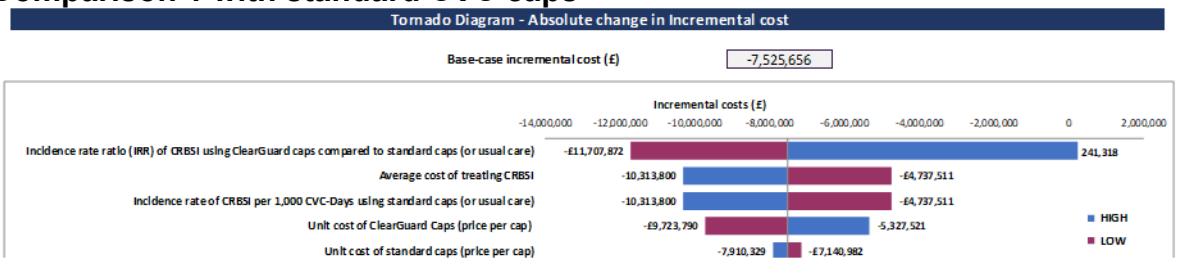


Comparison 4 with Tego alone

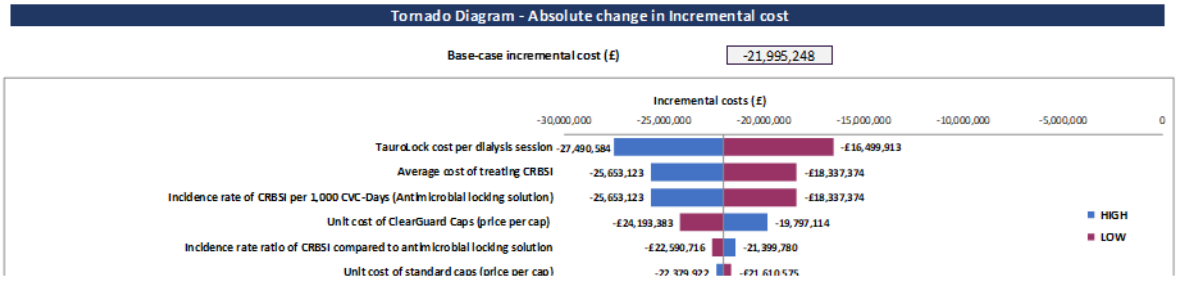


Updated Model (including disinfection costs)

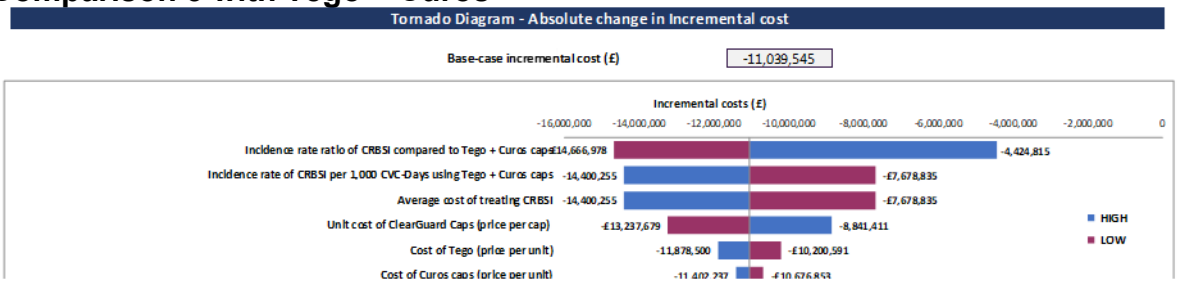
Comparison 1 with standard CVC caps



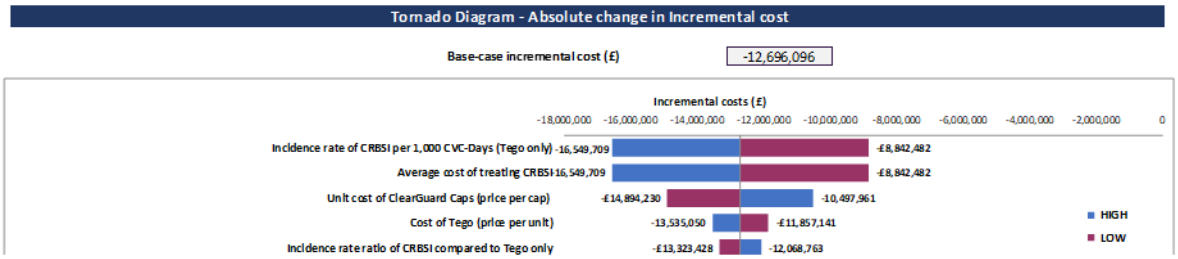
Comparison 2 with standard CVC caps combined with antimicrobial lock solution



Comparison 3 with Tego + Curos



Comparison 4 with Tego alone



EAC results have not changed the conclusions significantly with the baseline incidence rate of infection associated with the comparator, the IRR associated with **ClearGuard** and average cost of treating CBRSI having the largest impact on cost results in most cases.

The EAC results regarding the main cost drivers differ from those reported by the company for Comparator 2 (standard CVC caps with antimicrobial lock solution). In both models (with and without disinfection costs), the largest impact on costs is Taurlock cost per dialysis session in the EAC model, while in the company model it was the third driver of costs.

9.4 *The EAC's interpretation of the economic evidence*

The decision model includes all HD patients receiving 1 of the alternative methods being compared, i.e., intervention or comparator(s). The hypothetical cohort of HD patients, with a tunnelled CVC, undergoing dialysis receives one of five interventions: (1) ClearGuard HD Antimicrobial Barrier Caps, (2) Standard CVC caps, combined with the use of alcohol wipes for disinfection, (3) Standard CVC caps, combined with the use of an antimicrobial lock solution and alcohol wipes for disinfection, (4) Tego haemodialysis connectors used with Curos disinfecting caps (Tego + Curos), or (5) Tego haemodialysis connectors on their own, with manual decontamination of the catheter hub with alcohol wipes, in the hospital setting .Following this, patients may either experience a catheter-related bloodstream infection (CRBSI) or they may be infection-free. The model uses incidence rate of CRBSI per 1,000 CVC-days for each of the four comparators and applies incidence rate reduction of CRBSI for ClearGuard to model the outcomes. Though mortality following CRBSI is included, they do not affect the cost savings , because costs of

caps and treating infections are assigned to patients who die too. The clinical parameters are predominantly from US based studies, and due to the lack of UK based evidence, the EAC thinks the clinical parameters are agreeable to be included in the model. The EAC only made a minor revision to the incidence rate of CRBSI per 1,000 CVC-days using antimicrobial lock solution with standard CVC caps, due to calculation errors. The main costs included are the cost of caps and cost of treating CRBSI derived from NICE MTG44. These costs were agreeable to the EAC, but revised for the cost of curos cap and cost of treating CRBSI, due to the variation in inflation methods used.

The major issue the EAC had with the company model is that it assumed that there is no disinfecting involved the ClearGuard caps. However, since the practice of manual disinfecting is mixed, the EAC has provided additional results adding manual disinfecting time to the ClearGuard arm in the model.

To check for robustness to extreme values, the EAC, omitted and incorporated disinfection costs and varied the parameters by the range of +/- 50% for each. Similar to the results of the sensitivity analyses reported by the company, EAC found that the baseline incidence rate of infection associated with the comparator, the IRR associated with ClearGuard and average cost of treating CBRSI had the largest impact on cost results in most cases. There was one noticeable difference for comparator 2 (standard CVC caps and antimicrobial lock solution) with Taurlock cost per dialysis session being the main driver of costs in the EAC sensitivity analyses as opposed to it being a third main contributor to costs in the company model.

The resulting cost savings in both scenarios show that ClearGuard is cost saving compared to all the four comparators, and support the case of adoption, if the committee accepts the clinical parameters which are predominatly US based, and might not be generalisable to UK context.

10 Conclusions

10.1 *Conclusions from the clinical evidence*

The company included 7 studies in their submission; 3 studies were full texts and 4 were abstracts. The EAC excluded 1 of the submitted abstracts (Nitz et al. 2021) but included the other studies and did not identify any other relevant studies. Overall, the EAC believes the clinical evidence base is of moderate quality.

Two large cluster-randomised RCTs are reported in the literature (Brunelli et al. 2018 and Hymes et al. 2017). These studies are the strongest evidence available and are considered pivotal by the EAC. The comparator in Hymes et al. 2017 (standard CVC caps) is considered more relevant to the NHS setting than the comparator in Brunelli et al. 2018 (Tego connectors with Curos caps). The RCTs are at risk of some bias – in ClearGuard's favour – due to being unblinded (Hymes 2017 and Bruneli 2018) and unbalanced (Brunelli 2018). This effect may be slight, due to the large size of the studies and the use of laboratory tests to confirm BSI. All included studies were performed in the US and may not be easily generalizable to the UK setting, where baseline rates of infection may be lower due to the use of high-concentration citrate.

The literature consistently shows lower infection rates (CRBSI, CLABSI, ARBSI, PBC, bacteremia) when using ClearGuard than various comparators. Rates of hospital admission were also found to be lower from 3 studies (Brunelli et al. 2018, Hymes et al. 2017 and Sibbel et al. 2020), although not always significantly (Brunelli et al. 2018, vs Tego + Curos). There is limited reported information on length of hospital stay and rates of mortality in the literature, and no data on use of IV antibiotics or staff time.

It is likely that ClearGuard reduces BSI rates compared with standard caps, but it is difficult to conclude to what degree this effect would be present in the UK setting.

10.2 *Conclusions from the economic evidence*

The economic evidence included an abstract (Glennon et al 2020). The study revealed that CA-BSI rate for the financial year 2018 (FY18), the cost of prophylactic AML usage in 4 high risk patients amounts to $25,896 (£18,050). In the financial year 2019 (FY19), AML usage was discontinued and ClearGuard caps was used for all haemodialysis patients with CVC (including high risk and non-high-risk patients). This resulted in a total annual cost of $10,140 (£7,078). The EAC notes that this is in a paediatric setting, and its applicability to adult setting is uncertain.

Following this a de novo cost model comparing Clearguard with 4 comparators was submitted. The population, comparators, model structure, and time horizon was in line with the scope. The clinical parameters, which were predominantly US based studies and the cost parameters were generally agreeable to the EAC. According to clinical experts, the practice of disinfecting Clearguard caps were mixed in the UK. Since the company claimed that there would be no disinfection involved with Clearguard and the evidence was mixed, the EAC provided additional results including the cost of disinfection to the Clearguard arm.

The final cost savings results showed Clearguard is cost saving when compared to all the four comparators. In the additional sensitivity analysis performed, the EAC found that with the baseline incidence rate of infection associated with the comparator, the IRR associated with ClearGuard and average cost of treating CBRSI had the largest impact on cost results in most cases and broadly smiliar to the company's sensitivity analysis.

In conclusion, the economic evidence is in line with the scope, and supports the case if the committee accepts US based evidence used to parameterize the model.

11 Summary of the combined clinical and economic sections

The evidence reported in the literature consistently shows reduced rates of BSI in groups using ClearGuard vs standard caps and vs Curos + Tego. There is also limited evidence to suggest that using ClearGuard reduces hospital admissions, length of stay and mortality, but this evidence is weak. The generalisability of the evidence to the UK setting is unclear and this is the most major uncertainty in the decision problem.

The economic model provided by the company is broadly acceptable to the EAC and suggests that ClearGuard is cost saving when compared with 4 different comparators. However, the clinical parameters that are used in the model are all taken from US-based studies meaning that this conclusion is not certain, as baseline rates of BSI may differ in the UK. Baseline CRBSI was taken from MTG44 (Curos) and is likely to be a reasonable estimate. Company and EAC sensitivity analyses showed similar results, with baseline incidence rate, IRR and cost of treating CRBSI having the most impact on results.

12 Implications for research

Given the uncertainty in the applicabaility of US evidence to the UK population, a UK-based study would be recommended. This could be an RCT, similar to the cluster-randomised trials included in the evidence review, but could also be other observational designs. Ideally, downstream clinical utlility outcomes, like mortality, length of hospital stay, use of intravenous antibiotics and staff time would be collected. Finally, given the increasing prevalence of home dialysis, investigating the utility of ClearGuard caps in this setting would be very valuable.

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14 Appendices

Appendix A

Search strategy.

Search date: 2 June 2021

List of searches sources:

- MEDLINE via Ovid SP
- Embase via Ovid SP
- Cochrane Database of Systematic Reviews via Cochrane Library
- Cochrane Central Register of Controlled Trials via Cochrane Library
- ClinicalTrials.Gov
- WHO International Clinical Trial Registry Platform Search Portal (ICTRP)
- INAHTA International HTA Database

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to June 01, 2021>
1 Dialysis/ or Hemodialysis Units, Hospital/ or Hemodialysis, Home/ or Renal Dialysis/ or (Dialy* or H?emodialy*).ti,ab. (194873) 2 Catheterization/ or Catheters/ or Catheters, Indwelling/ or Vascular Access Devices/ or Catheterization, Central Venous/ or Catheter-Related Infections/ or (Arterial?Line? or Can?ula* or Catheter* or Intra?Arterial Line? or Microcan?ula* or Microcatheter* or Port?A?Cath or "Vascular Access" or Venous Reservoir*).ti,ab. (291825) 3 (Cap or Caps or CGHD or Clear?Guard* or Curos* or SwabCab*).ti,ab. (51806) 4 1 and 2 and 3 (22)
Embase <1974 to 2021 Week 21> via Ovid SP
1 Dialysis/ or exp Hemodialysis/ or Hemodialysis Patient/ or (Dialy* or H?emodialy*).ti,ab. (274562) 2 Antimicrobial Catheter/ or Catheter/ or Catheter Care/ or Catheter Infection/ or exp Central Venous Catheter/ or exp Dialysis Catheter/ or Indwelling Catheter/ or Intravenous Catheter/ or Vascular Access/ or (Arterial?Line? or Can?ula* or Catheter* or Intra?Arterial Line? or Microcan?ula* or Microcatheter* or Port?A?Cath or "Vascular Access" or Venous Reservoir*).ti,ab. (427492) 3 Catheter Disinfecting Cap/ or (Cap or Caps or CGHD or Clear?Guard* or Curos* or SwabCab*).ti,ab. (71816) 4 1 and 2 and 3 (71)
Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL) via Cochrane Library
Date Run: 03/06/2021 02:15:42 ([mh ^Dialysis] or [mh "Hemodialysis Units, Hospital"] or [mh "Hemodialysis, Home"] or [mh ^"Renal Dialysis"] or (Dialy* OR H?emodialy*):ti,ab) AND ([mh ^Catheterization] or [mh ^Catheters] or [mh "Catheters, Indwelling"] or

[mh ^"Vascular Access Devices"] or [mh "Catheterization, Central Venous"] or [mh "Catheter-Related Infections"] or (Arterial?Line? or Can?ula* or Catheter* or Intra?Arterial Line? or Microcan?ula* or Microcatheter* or Port?A?Cath or "Vascular Access" or Venous Reservoir*):ti,ab) AND ((Cap or Caps or CGHD or Clear?Guard* or Curos* or SwabCab*):ti,ab) 15
ClinicalTrials.gov
Other terms: ClearGuard 2 Studies found for: ClearGuard
WHO ICTRP
ClearGuard 2 records for 2 trials found for: ClearGuard
INAHTA International HTA Database
ClearGuard Search Results [0 Hits] Selected Records [0 Hits]

Critique of company strategy.

The information specialist checked search strategies submitted by the company against PRISMA-Search and Peer-Review of Search Strategies (PRESS) guidance.

- The strategies included invalid Medical Subject Headings (MeSH) and Emtree headings such as Clear Guard/, CGHD/, Pursuit Vascular/, Antiseptic cap/, Antimicrobial barrier cap/, and Antiseptic lock/ with zero number of results.

- Some of the MeSH terms were missing: Dialysis/, Hemodialysis Units, Hospital/, Hemodialysis, Home/, Renal Dialysis/, Catheterization/, Catheters/, Vascular Access Devices/, and Catheterization, Central Venous/.

- One of the MeSH terms was entered in the non-inverted format: central venous catheters/.

- In the Embase strategy, Hemodialysis/ and Central Venous Catheter/ were not exploded to cover the narrower topics.

- Some Emtree terms were missing: Antimicrobial Catheter/, Catheter Care/, exp Dialysis Catheter/, and Intravenous Catheter/.

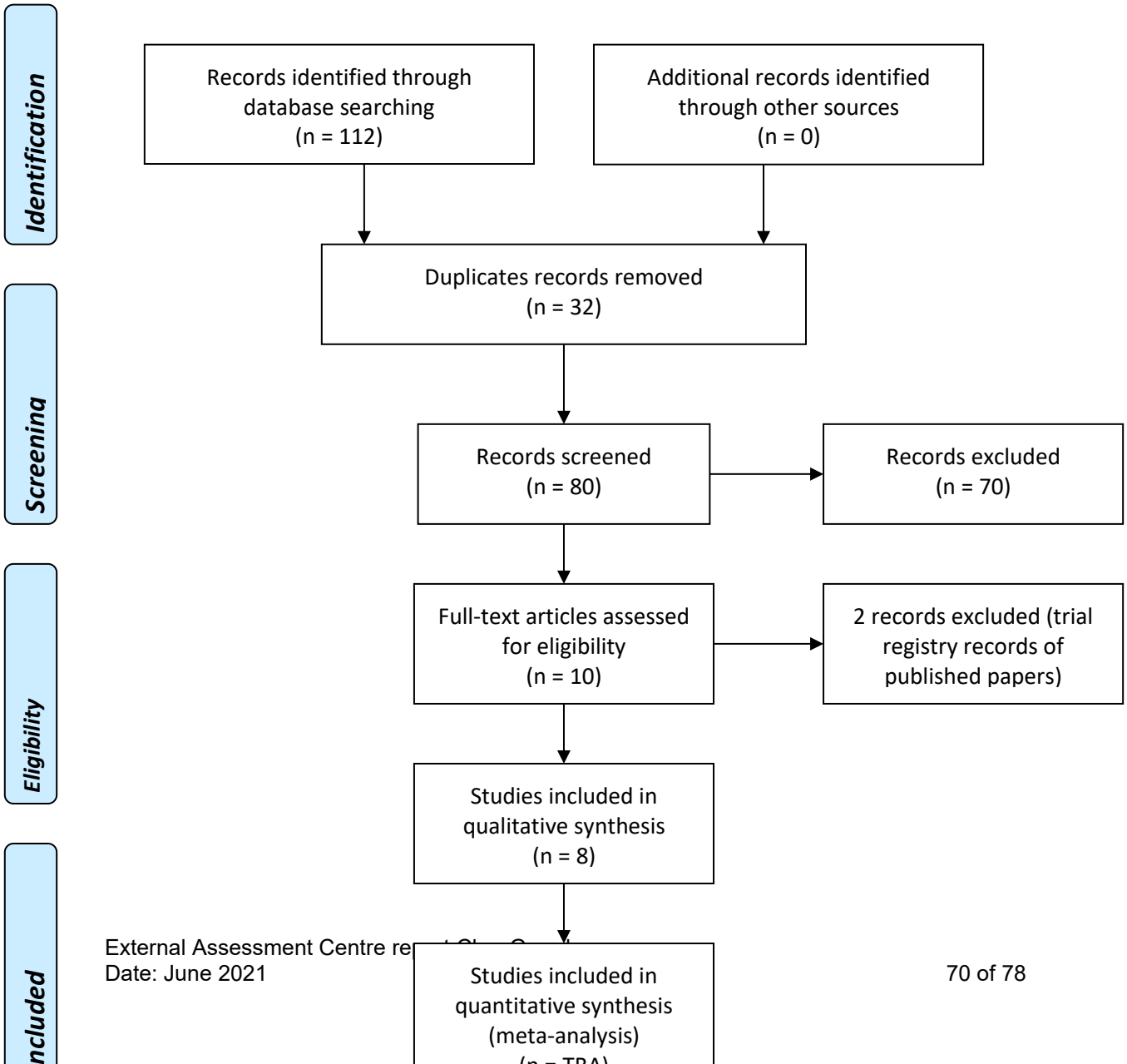
- Emtree term "Catheters, indwelling/" was in the inverted format.

- The only Emtree term relevant to catheter caps was missing from the search: Catheter Disinfecting Cap/.

- The Cochrane Library search was not a translation of Embase/MEDLINE search and was missing all MeSH terms.

The EAC information specialist used some of the terms from the company's searches, revised, and re-ran the searches on 2nd June 2021.

PRISMA diagram.



Appendix B

Cochrane Risk of Bias 2:

Unique ID		**Study ID**	Brunelli 2018	**Assessor**	
Ref or Label		**Aim**			
Experimental	ClearGuard	**Comparator**	Tego + Curos	**Source**	Journal article
Outcome		**Results**		**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	PY	Cluster randomisation; methods of randomisation not reported.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PY	Baseline characteristics were generally similar but there was a statistically significant difference in race, diabetes and age.
	Risk of bias judgement	**Some concerns**	
Bias due to deviations	2.1 Were participants aware of their assigned intervention during the trial?	Y	Open label trial. Due to the labelling and appearance of the caps it is not

from intended interventions	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	possible to blind patients and carers/health care professionals.
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	NA	
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	NA	
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	NA	
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	**Some concerns**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PN	231/1911 (12%) Patients were excluded if they had <21 CVC days.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	Sensitivity analysis was conducted in which all patients with CVCs were considered from their study start.
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	N	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	N	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	

	4.3 Were outcome assessors aware of the intervention received by study participants?	Y	Open label
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	N	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	N	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	Pre-specified analysis plan not reported.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PY	
	5.3 ... multiple eligible analyses of the data?	NI	
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID		**Study ID**	Hymes 2017	**Assessor**	
Ref or Label		**Aim**			

Experimental	ClearGuard	**Comparator**	Standard central venous catheter	**Source**	Journal article
Outcome		**Results**		**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	Cluster randomised; randomly assigned using a computer-generated random number
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	N	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Y	Baseline characteristics were similar in the ClearGuard and standard CVC group.
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	Y	Open label trial. Due to the labelling and appearance of the caps it is not possible to blind patients and carers/health care professionals.
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	NA	
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	N	
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	NA	

	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	**Some concerns**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PN	442 patients were excluded if they had <21 CVC days.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	PN	Patients excluded were not included in the final analysis.
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	PN	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NI	
	Risk of bias judgement	**Some concerns**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	Y	Open label study
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	N	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	N	
	Risk of bias judgement	**Low**	

Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	
	5.3 ... multiple eligible analyses of the data?	PN	
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Table 10: Summary of the strengths and weaknesses of the trial incorporating internal and external validity

Weiss et al. 2021

	Strengths	Weaknesses
Study design	Multi-centre comparative study	Retrospective
Patient selection	Appears to reflect eligible population	Might not reflect UK population
Randomisation	None	Non-randomised
Blinding	NA	No blinding
Patient attrition	None	Retrospective (no attrition)
Reporting of outcomes	Monthly CLABSI rates were recorded	Direct comparison of outcomes was not possible as it was not possible to match data from the two groups due to limited patient demographics and medical history
Statistical analysis	NA	Power calculation not reported
Study company	NA	Company funded by ICU medical

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

Assessment report overview

ClearGuard HD Antimicrobial Barrier Cap for preventing haemodialysis catheter-related bloodstream infections

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 does not contain any confidential information. The overview contains:

- Appendix A: Sources of evidence
- Appendix B: Comments from professional bodies
- Appendix C: Comments from patient organisations
- Appendix D: Decision problem

1 The technology

ClearGuard HD Antimicrobial Barrier Cap (ICU Medical) is for use with central venous catheters (CVC) in haemodialysis. The cap includes a rod that extends into the CVC hub. The innovative aspect of the ClearGuard HD caps is the coating on the rod and cap threads of chlorhexidine acetate, a broad-spectrum antimicrobial agent. This proposes to release chlorhexidine acetate into the catheter lock solution, which remains inside the catheter hub in between treatments with an aim to reduce the presence of pathogenic organisms and the risk of catheter-related bloodstream infections (CRBSI). This may reduce the need to clean the connector port with 2% chlorhexidine in 70% alcohol and then have to wait for it to air dry.

ClearGuard HD caps are proposed to be used in place of a standard cap or cap and connector and need to be replaced during every dialysis session, it cannot be reused once removed. The recommended maximum use time for the cap is 3 days. ClearGuard HD Antimicrobial Barrier Cap is a CE-marked class IIb medical device. It received its CE mark in 2019.

2 Proposed use of the technology

2.1 Disease or condition

The ClearGuard HD antimicrobial cap is intended for use on central venous catheters to reduce the risk of catheter related bloodstream infections (CRBSI) in the management of haemodialysis for end stage kidney disease (ESKD).

CRBSI causes fever, red skin and soreness around the access site and is associated with the need for additional treatment that may include line changes, prolonged antibiotic treatment, prolonged hospital stays, increased risk of morbidity, mortality and resultant healthcare costs.

2.2 Patient group

End stage kidney disease is an irreversible and progressive deterioration in kidney function. Haemodialysis is a type of renal replacement therapy (RRT) used to treat ESKD. Haemodialysis is a way of filtering blood outside of the body using a dialysis machine. Haemodiafiltration is also a form of haemodialysis with additional convection. Hereafter, the term haemodialysis will be used to refer to all rates of convection, as clinical experts stated that the function of CVC caps remains the same. According to the 22nd annual report by the UK Renal Registry (on 31st December 2018), 36.8% (24,366 adults) of the adult dialysis and transplant population received haemodialysis in hospital or specialist renal units for ESKD. And a further 11.4% (107) children and young people receiving haemodialysis as their treatment option for ESKD.

Types of haemodialysis access involve IV access, most commonly using central venous catheters or arteriovenous fistula (AVF). Arteriovenous fistula require vascular surgery and are used as a longer term dialysis access point. For shorter term, more urgent IV access CVCs are commonly used as well as if the surgical procedure is not available (such as during the pandemic). Each time treatments are administered through an access point there is a risk of introducing microorganisms that can cause blood stream infections. It is considered that the rate of bloodstream infections (BSIs) is higher in more temporary access approaches.

It should be noted that people from lower socio-economic groups are more likely to suffer from kidney disease. People of Black and Asian family origin are more likely to progress faster towards kidney failure and are less likely to receive a transplant. Men are more likely to start dialysis than women. There are high rates of severe mental illness in people on dialysis. Family origin, sex and disability are protected characteristics under the Equality Act 2010.

2.3 Current management

NICE Guideline for renal replacement therapy promotes the choice of dialysis mode and location be discussed with the individual and family encompassing clinical considerations and individual preference. The UK Renal register (31/12/2018) reported most haemodialysis takes place in hospital or community clinic setting with only 4% of the haemodialysis being carried out in the home setting. Haemodialysis in clinic routinely takes place three times a week or on alternate days, for 3-5 hours, but duration and frequency can vary in the home setting. Haemodialysis in a home setting may take place more frequently for a shorter length of time, depending on the patient's lifestyle. The coronavirus pandemic has highlighted the benefits of home dialysis and although statistics are not yet available, experts reported to expect an increase in uptake in home dialysis in the future.

When managing haemodialysis using central venous catheters (CVC) NICE clinical guideline for healthcare-associated infections: prevention and control in primary and community care recommends decontaminating the vascular access device catheter hub before and after accessing the system. This consists of scrubbing the connector hub of the CVC before and after each access to the catheter with 2% chlorhexidine gluconate in 70% alcohol wipes and allow the hub to air dry, for a minimum of 15 seconds (NICE, 2017). This method requires the CVC cap to dry before it can be used which takes at least 15 seconds. A fresh cap should be used after each time the CVC has been accessed, or if the closed loop has been broken.

There are several types of cap systems on the market. Standard cap systems are sterile caps that screw on to catheter hubs. Cap systems with passive disinfectant are impregnated with alcohol. Cap and connector systems (such as Tego connectors used with Curos caps) consist of a connector and a cap, where the cap is replaced after each access and the connector less frequently. Antimicrobial locking (AML) solutions are also used to reduce rates of CRBSI. These solutions are left in the distal lumen of the catheter for between 12 to 24 hours, before being withdrawn and replaced. Experts

reported that high concentrate citrate is commonly used as an antimicrobial lock solution in UK practice, with some variability in concentrate used across Trusts (30% and 46.7%). Citrate is not used as a line lock solution in paediatric standard practice.

The ClearGuard HD antimicrobial cap was recently assessed by Health Technology Wales with guidance published in May 2021 to support the routine adoption of ClearGuard HD antimicrobial barrier caps for use with haemodialysis catheter hubs. Health Technology Wales recommends the collection of real-world audit data around the use of ClearGuard HD caps in Wales.

2.4 Proposed management with new technology

ClearGuard HD caps are proposed to replace current use of standard caps on CVC lines during haemodialysis. The caps are not currently in use within the NHS. The EAC and experts do not believe that implementing the ClearGuard HD caps would alter the current pathway and report that minimal training is required.

3 Company claimed benefits and the decision problem

The decision problem is described in the scope (Appendix D). The company did not propose any changes to the decision problem.

The company claims the benefits to patients with the use of ClearGuard HD caps are:

- Reduced risk of catheter related bloodstream infections (CRBSI)
- Reduced hospital attendances and length of stay due to CRBSI
- Reduced mortality as a result of reduced risk of CRBSI
- Improved patient experience through the prevention of avoidable infections and reduced length of inpatient stay.

The benefits to the healthcare system claimed by the company are:

- Reduced length of stay and reduced intensive care bed days for treatment of CRBSI
- Reduced readmissions due to CRBSI
- Cost savings due to reduced need for antibiotic use, replacement of CVC and critical care cost for treatment of CRBSI
- Reduced mortality as a result of reduced risk of CRBSI

4 The evidence

4.1 Summary of evidence of clinical benefit

The company submitted 7 studies from its literature search, including 3 full texts (Brunelli et al. 2018, Hymes et al. 2017 and Weiss et al. 2021) and 4 abstracts (Glennon et al. 2020, Li et al. 2019 and Sibbel et al. 2020, Nitz et al, 2021). The EAC carried out their own literature search after reporting search strategies submitted by the company included invalid medical subject headings (MeSH) and Emtree headings (details in the assessment report Appendix A). A revised search was carried out and is a reported upon in section 4.1 of the Assessment Report.

The EAC agreed with the inclusion of 6 of these 7 studies; 3 full texts (Brunelli et al. 2018, Hymes et al. 2017 and Weiss et al. 2021) and 3 abstracts (Glennon et al. 2020, Li et al. 2019 and Sibbel et al. 2020). One additional study submitted by the company (Nitz et al, 2021) was excluded by the EAC as the intervention and outcomes did not match the scope and it was felt it did not add to the decision problem.

Table 1. summary of included studies

Studies included by both EAC and company	
Publication and study design	• 2 RCTs have been included by both the company and the EAC (Brunelli et al, 2018, Hymes et al, 2017). • 1 observational study (Weiss et al, 2021) • 3 abstracts (Glennon et al, 2020, Li et al, 2019, Sibbel et al, 2020).

Studies in submission excluded by EAC	
Publication and study design	• 1 case series (Nitz et al, 2021) excluded by the EAC as the intervention and one of the outcomes are out of scope and it was deemed did not contribute to the decision problem.
***Abbreviations**: RCT randomised controlled trial. EAC external assessment centre*	

The clinical evidence base for ClearGuard HD caps is entirely comprised of studies performed outside the UK (in US and North America). The 3 full text studies included in this evidence base totalled 10,757 participants. The EAC considered the two most pivotal studies to the decision problem to be Brunelli et al 2018, Hymes et al, 2017, as prospective multi centre open label cluster RCTs, which included 40 sites each. The remaining full text article (Weiss et al, 2021) was a large retrospective analysis, however this study is considered methodologically weak. The abstracts (Glennon et al, 2020., Li et al, 2019, Sibbel at al, 2020) are all retrospective analyses with limited detail and do not add much more to the decision problem. The studies had largely homogenous populations with percentage of men ranging from 51-53% and mean ages varying from 61.1years to 62.8 years (except for Glennon et al, 2020 which reported on a paediatric population).

Across the studies, comparators varied with Brunelli et al (2018) comparing Clearguard HD caps to Tego (connectors) with Curos (caps), which on discussion with clinical experts may be a less relevant comparator for the NHS setting than Hymes et al study (2017), which compares Clearguard HD caps to standard CVC caps. Outcomes varied between the studies with various measures of BSI being reported. Positive blood culture (PBC) was the primary outcome in both pivotal RCTs. Other important outcomes included hospital admissions and mortality. Key outcomes can be seen in Table 2.

It should be noted that there are several terms reported for catheter-related blood stream infections outcomes (PBC, CRBSI, CLABSI, ARBSI). CRBSI is often used interchangeably with CLABSI (central line-associated bloodstream infection), although experts highlight that CRBSI is a clinical definition which

requires laboratory testing to confirm the catheter as the source of infection (CDC, 2017). Similarly, ARBSI (Access-related bloodstream infection) is defined by the CDC as a “Positive blood culture with the suspected source reported as the vascular access or uncertain” (CDC, 2018). Full details of these outcomes across all studies can be found in section 5.3 of the assessment report.

Table 2 Summary of key studies:

Study and design	Participants/ population	Intervention & comparator	Outcome measures and follow up	Results	Funding	Comments
Brunelli et al. 2018 **Design:** Cluster-Randomised Trial **Location**: US, Multicentre (40 sites)	**Participants:** 1,911 participants undergoing dialysis with CVC were randomised **Intervention** n=951 **Comparator** n=960 **Excluded** n= 231 (12%) for patients who had <21 CVC days **Patient demographics:** 51% male, average age 62.8years (SD 14.9)	**Intervention:** ClearGuard HD caps replaced at each session. **Comparator**: Tego (replaced once a week) and Curos (replaced each session).	**Primary** • PBC **Secondary:** • CRBSI • CLABSI • ARBSI	**PBC:** 0.28 PBCs per 1000 CVC days (ClearGuard HD caps) and 0.75 per 1000 CVC days (Tego + Curos). **IRR:** 0.37 (p=0.001) favouring ClearGuardv HD caps. **CRBSI:** IRR was 0.37 (p=0.003), favouring ClearGuard HD caps. **CLABSI:** IRR was 0.35 (p=0.003), favouring ClearGuard HD caps. **ARBSI:** The IRR was 0.31 (p<0.001), favouring ClearGuard HD caps.	Company funded– Pursuit Vascular, Inc. (ICU Medical)	The study was assessed to be of moderate quality, with low risk of bias in the design of the study. The study was pair matched for BSI rate. Baseline characteristics were similar with the exception of age which was significantly older (0=0.02) in the ClearGuard HD caps group. As well as race and diabetes: 35% and 46% of people identified as black; and 55% and 64% had diabetes in the intervention and comparators arms. The study was open label due to practicalities of cap usage, which may introduce bias. No information was reported on a power calculation. The EAC carried out separate analysis,

						which demonstrated it to be adequately powered.
Hymes et al. 2017 **Design:** A Cluster-Randomised Trial **Location:** The US.	**Participants:** 2,912 participants undergoing dialysis with CVC **Intervention** n=1245 **Comparator** n=1225 **Excluded** n=442 (as they dialysed for <21 days) **Patient demographics:** **5**1% male, average age 61.1years (SD 15.5)	**Intervention:** ClearGuard HD caps **Comparator**: standard CVC caps	**Primary** • PBC **Secondary:** Hospital admissions for BSI Hospitalisation days for BSI Number of IV antibiotic starts	**PBC:** IRR=0.44 (p=0.01). 0.26/1000 days vs 0.59/1000 days ClearGuard HD caps to comparator respectively. **Hospital admissions for BSI:** IRR 0.69 (p=0.2). 0.28/1000 days vs 0.47/1000 in ClearGuard HD caps to comparator respectively. **Hospitalisation days for BSI:** IRR=0.69 (p=0.2) 3.24/1000 days vs 4.68/1000 days Clearguard HD caps to comparator respectively **Number of IV antibiotic starts:** IRR=0.94 (p=0.6). 1.68/1000 days to 1.78/1000 days in ClearGuard HD caps to comparator respectively.	Three authors are employee of company Pusuit Vascular, Inc (ICU Medical).	The study was assessed to be of moderate quality, with low risk of bias in the design and implementation of the study. Sites were paired by PBC rate and number of patients with CVCs and then randomised 1:1 using computer-generated randomisation Baseline characteristics were similar across the groups, however p values were not reported. The study was open label due to practicalities of cap usage, which may introduce bias. No information was reported on a power calculation. The EAC carried out separate analysis, which demonstrated it to be adequately powered.

Weiss et al. 2021 **Design:** retrospective observational study **Location:** multi-centre sites) in the US	**Participants:** 5,934 participants **Intervention** n=4614 **Comparator** n=1320 **Patient demographics:** **5**3% male, mean age 61.3years.	**Intervention:** ClearGuard HD caps **Comparator**: standard CVC caps	**Primary: CLABSI**	**CLABSI:** 0.09/1000 days to 0.63/1000 days in the ClearGuard HD cap group compared to standard CVC caps for the two study periods combined. 0.03/1000 days to 0.70/1000 days in ClearGuard HD caps compared to standard caps for the first 5-month study period.	Company funded by ICU Medical	The study was reported to be of moderate quality, however there were methodological weaknesses in its non-randomised, unblinded retrospective trial design. There was limited patient characteristic data reported. Within the design, the majority of patients switched to the ClearGuard HD cap group during the second study period. However as the second study period was not reported on separately, it was not possible to compare.
Abbreviations: *CVC central venous catheter, SD standard deviation, PBC positive blood culture, CBRSI catheter related bloodstream infection, CLABSI central line associated bloodstream infection, ABSI access related bloodstream infection, IRR incidence rate ratio, BSI blood stream infection*						

No meta-analysis was conducted by the company or EAC due to the small number of full text studies and the heterogeneity in the comparators and outcomes reported in the literature.

Overall, the evidence base consistently reported lower bloodstream infection rates (CRBSI, CLABSI, ARBSI, PBC, bacteremia) in ClearGuard HD cap groups, compared with various comparator groups. Rates of hospital admission were also found to be lower from 3 studies (Brunelli et al. 2018, Hymes et al. 2017 and Sibbel et al. 2020), although not always significantly (Brunelli et al. 2018). There is limited reported information on length of hospital stay and rates of mortality in the literature, and no data on use of IV antibiotics or staff time. Furthermore, no evidence was found of ClearGuard HD caps being used in the home setting.

To assess device related adverse events, the EAC carried out a search of MHRA and FDA databases as referenced in section 6 of the Assessment Report. Nine records were located on the FDA (MAUDE) database. These consisted of 2 entries of caps coming off for one individual and further 6 entries of caps becoming detached whilst individuals were asleep. The final entry reported the rod breaking loose in the catheter. No patients were injured due to these events. No adverse events were reported in the full text papers (Brunelli et al, 2018, Hymes et al, 2017 and Weiss et al, 2021).

4.2 Summary of economic evidence

The company submission identified 1 relevant abstract (Glennon et al, 2020). On review the EAC found the search strategy to be appropriate and confirmed after completing their own search that there were no additional relevant papers (see section 9.1 of the assessment report). The EAC accepted the abstract (Glennon et al) to be considered as part of the economic evidence.

The abstract reports on the study comparing CA-BSI rates and costs associated with antimicrobial locks (AMLs) versus ClearGuard HD caps of 4 high risk patients in the paediatric dialysis setting. The results from the abstract shows reduced CA-BSI rate with ClearGuard HD caps, resulting in total annual cost per patient for ClearGuard HD caps versus AMLs to be £7,078 vs £18,050. The EAC notes there was no sensitivity analysis performed to ascertain the robustness of the cost and rate and importantly the applicability of the results from a paediatric to adult setting is uncertain.

De novo analysis

The company submitted a do novo cost model for the technology (see figure 1, section 9.2 of the assessment report) since published economic evidence included only one abstract. The model structure included a decision tree that looked at cost savings of ClearGuard HD caps against 4 relevant comparators. These included interventions of (1) ClearGuard HD Antimicrobial Barrier Caps, (2) Standard CVC caps, combined with the use of alcohol wipes for disinfection, (3) Standard CVC caps, combined with the use of an antimicrobial lock solution and alcohol wipes for disinfection, (4) Tego haemodialysis connectors used with Curos disinfecting caps (Tego + Curos), or (5) Tego haemodialysis connectors on their own, with manual decontamination of the catheter hub with alcohol wipes, in the hospital setting. The model was developed with cost and health outcomes over a 1-year time horizon.

The EAC agreed the structure of the model, time horizon, population, most comparators, outcomes and assumptions to be acceptable and appropriate for

the assessment. One comparator, Tego haemodialysis connectors alone (5) is a connector alone not an alternative cap and therefore out of scope. However, the EAC did not exclude it from the analysis. The EAC provided additional analysis in the ClearGuard arm to address the use of disinfection protocols when using ClearGuard HD caps. This was based on discussions with clinical experts, who suggested that it is likely these disinfection protocols would still be used.

Model assumptions

The model makes a number of assumptions which can be seen in section 9.2 of the Assessment report. Key assumptions are discussed below:

- CRBSI is the primary outcome however some of the data used may be based on CLABSI, CABSI and PBC data. The assumption was discussed with experts and acceptable to the EAC. The EAC performed sensitivity analysis to address this.

- No costs associated with training health care staff on the use of the device were included in the model. This assumption is based upon company and expert comment and is reasonable to the EAC.

- The company assumed an opportunity cost of staff time not disinfecting the cap of 15 seconds of Band 5 nurses' time. However, none of the papers included reported information on clinician time or resource use. Furthermore, experts advised that, even when using ClearGuard HD caps, their practice would be unlikely to change, and they would continue with manual disinfection protocols of scrubbing the hub with alcohol wipes. This was also noted on a previous guidance on a similar product (MTG44 Curos). The EAC provided additional analysis (seen in table 6, 7 and 8) to add disinfection costs to the ClearGuard arm to address this practice.

- No adverse events were included in the model. The EAC accepts this as any adverse events located (see section 4.1) did not adversely affect patients.

- The company included mortality branch in the model using evidence from the literature (Goto et al, 2013), which highlighted the increased mortality risk associated with infection. Whilst this is a reasonable assumption, the EAC noted that this evidence base was overall bloodstream infections in North America and Europe (rather than CRBSI). The EAC felt the model with cost of caps and cost of treating CRBSI was adequate without the need for the mortality branch to be included.

Clinical parameters

Assumptions in the base analysis are reported in section. Key assumptions and any amendments made by the EAC are reported in the table 4 below:

Table 4: Clinical parameters used in the company's model and any changes made by the EAC

Variable	Company value	Source	EAC value	EAC comment
Incidence rate of CRBSI per 1000 CVC days using standard CVC caps	0.70	NICE MTG44	0.70	This company value was not specific to CVCs and HD population, however in the absence of other evidence, the EAC finds this value acceptable and recommends that a wider range of values is incorporated in the sensitivity analysis (50% SA 0.53; 0.88) based on clinical studies (Kanaa et al, 2015, Aitken et al, 2016, Crowley et al, 2017, Youssouf et al, 2017, Hymes et al, 2017).
Incidence rate of CRBSI per 1,000 CVC-days using antimicrobial lock solution	0.61	Glennon et al, 2020	0.598	The company value is identified from a study (Glennon et al, 2020) using CABSI (not CRBSI). The population is also paediatric which, based on expert opinion, is likely to have lower incidence to average haemodialysis

with standard CVC caps				population who are likely to be on haemodialysis for longer. The EAC broadly accepts this value of 0.61, however using a different calculation approach recommends it be changed to 0.598 with a broader range of the value incorporated into sensitivity analysis.
Incidence rate of CRBSI per 1,000 CVC-days using Tego + Curos	0.75	Brunelli et al, 2018	0.75	The EAC accepts this estimate, but recommends (based on Merrill et al. 2014), that a CRBSI estimate for Curos of 0.577 (95% CI: 0.393-0.842) be used to account for this range in the sensitivity analysis. EAC recommends 50% SA range (0.56; 0.94)
Incidence rate of CRBSI per 1,000 CVC-days using Tego alone	0.63	Weiss et al, 2017	0.63	The EAC accepts the statistical validity of this value with a recommendation that a wider range of values is explored in the sensitivity analysis in the absence of further clinical evidence. EAC recommends 50% SA range (0.47; 0.79)
IRR of CRBSI using ClearGuard HD caps compared to standard CVC caps	0.44	Hymes et al, 2017	0.44	The EAC accepts this value with recommendation of 50% SA range (0.23; 0.83)
IRR of CRBSI using ClearGuard HD caps compared to using antimicrobial lock solution with standard CVC caps	0.14	Glennon et al, 2020	0.14	The EAC accepts this estimate with recommendation of 50% SA range (0.11; 0.18).
IRR of CRBSI using ClearGuard HD caps compared to Tego + Curos caps	0.37	Brunelli et al, 2018	0.37	The EAC accepts this value, however, informed by (Voor In't Holt et al. 2017) they recommend using 50% SA range (0.2; 0.68).
IRR of CRBSI using	0.14	Weiss et al, 2017	0.14	The EAC accepts this value, with a recommendation that a wider range

ClearGuard HD caps compared to Tego alone				(50%) is explored in the sensitivity analysis 0.11;0.18 (based on Brunelli et al. 2018).
Probability of death following CRBSI	0.15	Goto et al, 2013	0.15	Whilst the study is BSI in North America and Europe, the EAC accept the value given the lack of other relevant mortality rate to CRBSI in the UK (as confirmed in MTG44 and MTG25). Expansion of values in the sensitivity analysis is used, based on clinical expert opinion. EAC recommends 50% SA range (12%; 32%)
Average number of CVC days per patient per year	132	Kwak et al, 2012. Crowley et al, 2017, Hymes et al, 2017	132	The EAC accepts this value and recommends 50% SA range (123; 141)
Total number of HD patient-years (CVC) at risk	7,026	Crowley et al, 2017	7,026	The EAC accepts this value.
Abbreviations: *EAC external assessment centre, CVC central venous catheter, HD haemodialysis, SA sensitivity analysis, BSI bloodstream infections.*				

Costs and resource use

The main costs included in the model were the costs associated with bloodstream infections. The cost parameters and any changes made by the EAC are described in table 5.

Table 5: Cost parameters used in the company's model and by the EAC.

Parameter	Company value	Source	EAC model value	Comment
ClearGuard HD caps (price per pair of caps)	4.00	ICU Medical, Inc. (company list price)	4.00	EAC recommends 50% SA range 2 - 6
Standard CVC caps (price per cap)	0.35	NICE MIB234 (2020)	0.35	EAC recommends 50% SA range: 0.175-0.525
Curos caps (price per unit)	0.35	NICE MTG44 (2018)	0.33	EAC amended cost inflation and recommends 50% SA range: 0.165-0.495
Cost of Tego (price per unit)	2.29	Science Equip (company list price)	2.29	EAC recommends 50% SA range: 1.145-3.435
Cost of antimicrobial lock solution (TauroLock) per dialysis session	10	Valiant Medical (company list price)	10	EAC recommends 50% SA range: 5–15
Average cost of alcohol wipes	0.02	NICE MTG44 (2018)	0.02	EAC recommends 50% SA range: 0.01-0.03
Hourly cost of a Band 5 nurse	40.00	Curtis & Burns (2020)	40.00	Unchanged
Nurse time for manual disinfection (minutes)	0.25	NICE MTG44 (2018)	0.25	EAC recommends 50% SA range: 0.125-0.375
Cost of nurse time for disinfection	0.17	Company calculation	0.17	EAC recommends 50% SA range: 0.085-0.255
Average cost of treating CRBSI	11,071	NICE MTG44 (2018)	11,094	EAC amended cost inflation and recommends 50% SA range: 5,547-16,641
ICU length of stay due to CRBSI (days)	2.5	NICE MTG44 (2018)	2.5	EAC recommends 50% SA range: 1.25-3.75
General hospital ward length of stay due to CRBSI (days)	5.5	NICE MTG44 (2018)	5.5	EAC recommends 50% SA range: 2.75 – 8.25

The final results showed ClearGuard HD caps to be cost saving when compared to all the four comparators. The company submission reports cost savings of £408 per patient against standard caps and wipes and cost savings of £1,167 per patient against standard caps, AML solution and wipes. The EAC revised base case cost savings, with added disinfection costs in the ClearGuard arm, demonstrated cost savings of £387 per patient against standard caps and wipes and cost savings of £1,132 per patient against standard caps, AML solution and wipes.

Sensitivity Analysis

The company presented a one-way sensitivity analyses, varying all model parameters by 25% or by a relevant range informed by the evidence. A probabilistic sensitivity analysis assigning distributions to the parameters was also performed. The company predicts, based on the sensitivity analyses, that ClearGuard is a cost-saving intervention across the 4 comparators.

Given the US informed evidence base, and the uncertainty raised by the experts surrounding the transferability of these findings to UK practice, the EAC recommended that all parameters lacking clinical data validation to be varied up and down by 50% in the sensitivity analysis. In the additional sensitivity analysis performed, the EAC results are similar and have not changed the conclusions significantly. One noticeable difference was noted for comparator 2 (standard CVC caps and antimicrobial lock solution) with Taurlock cost per dialysis session being the main driver of costs in the EAC sensitivity analyses as opposed to it being a third main contributor to costs in the company model. The parameters that had the largest impact on cost results were; baseline incidence rate of infection associated with the comparator, the IRR associated with ClearGuard and average cost of treating CBRSI.

The company also conducted 5 scenario analyses, (please see sections 9.2 and 9.3 in the assessment report for full details) which demonstrated ClearGuard HD caps to be cost saving in all scenarios. The main amendment

by the EAC, was the addition of manual disinfection costs to the ClearGuard arm in an updated model, to address expert comments that this practice would likely continue regardless of which cap was in use.

A series of 'worst case' scenario analyses (B – E) were conducted in which the base-case baseline infection rate associated with each of the 4 comparators was based on the lower-end of the value range, and the IRR of CRBSI with ClearGuard was based on the upper-end of the value range. For these scenarios, based on clinical expert opinion and a variability of clinical estimates from published studies, the EAC recommended that the parameters be varied up and down by 50% or by a different range (as informed by the evidence base) rather than up and down by 25%. In Scenario A, despite the reduction in the cost of antimicrobial locks, the intervention remains cost saving (-£418). In scenarios B-E, where the base-case baseline infection rate with each of the comparators has been reduced, and the base-case IRR of CRBSI with the intervention has been increased, ClearGuard remains cost saving. These scenario analyses demonstrated that even when the incidence rate of CRBSI with ClearGuard HD caps is increased, cost savings reduce but remain positive.

Table 6. Cost savings of ClearGuard HD caps vs Standard caps and wipes

Cost category	Company's base-case			EAC's base-case		
	ClearGuard HD cap cost	**Comparator cost standard caps + wipes**	**Cost savings per patient**	**ClearGuard HD cap cost**	**Comparator cost standard caps + wipes**	**Cost savings per patient**
Cost of intervention	£ 226	£ 61	+ £165	£226	£61	+£165
Cost of treating CRBSI	£ 450	£ 1,023	−£ 573	£451	£1,025	-£574
Total	£ 676	£1,084	**-£ 408**	£677	£1,086	**-£408**
				ClearGuard HD cost and disinfection costs*	**Standard caps + wipes**	**Cost savings per patient**
Cost of intervention				£247	£61	+£187
Cost of treating CRBSI				£451	£1,025	-£574
Total				**£698**	**£1,086**	**-£387****

**Disinfection costs were added to the ClearGuard arm following expert opinion that this practice would continue for both interventions.*

Following on from discussion with experts and lead committee members, discrepancies were reported in the cost of standard caps from the cost model likely due to volume discounts in practice. As a result, the EAC input the reported value of £0.03 for cost of standard caps and found cost savings remained but were reduced* ***in this scenario to a saving of -£351.

Table 7. Cost savings of ClearGuard HD caps vs Standard caps, antimicrobial lockline solution and wipes

Cost category	**ClearGuard HD caps cost**	**Comparator cost standard caps, AML solutn + wipes**	**Cost savings per patient**	**ClearGuard HD caps cost**	**Comparator cost standard caps, AML solutn + wipes**	**Cost savings per patient**
Cost of intervention	£ 226	£ 626	- £400	£226	£626	-£400
Cost of treating CRBSI	£ 125	£ 891	−£ 766	£123	£876	-£753
Total	**£ 351**	**£ 1,518**	**-£ 1,167**	**£349**	**£1,502**	**-£1,153**
				ClearGuard HD cap cost + disinfection cost	**Standard caps, AML solutn + wipes**	**Cost savings per patient**
Cost of intervention				£247	£626	-£379
Cost of treating CRBSI				£123	£876	-£753
Total				**£370**	**£1,502**	**-£1,132****

**Disinfection costs were added to the ClearGuard arm following expert opinion that this practice would continue for both interventions.*

Following on from discussion with experts and lead committee members, discrepancies were reported in the cost of standard caps from the cost model likely due to volume discounts in practice. As a result, the EAC input the reported value of £0.03 for cost of standard caps and found cost savings remained but were reduced* ***in this scenario to a saving of -£1096.

Table 8. Cost savings of ClearGuard HD caps vs Tego connector and Curos caps.

Cost category	**ClearGuard HD caps cost**	**Comparator cost Tego and Curos**	**Cost savings per patient**	**ClearGuard HD caps cost**	**Comparator cost Tego and Curos**	**Cost savings per patient**
Cost of intervention	£ 226	£ 126	+ £100	£226	£124	£103
Cost of treating CRBSI	£ 406	£ 1,096	−£ 690	£406	£1,098	-£692
Total	**£ 632**	**£ 1,222**	**-£ 590**	**£633**	**£1,222**	**-£589**
Cost category				**ClearGuard HD caps cost + disinfection cost**	**Comparator cost Tego and Curos**	**Cost savings per patient**
Cost of intervention				£247	£124	£123
Cost of treating CRBSI				£406	£1,098	-£692
Total				**£654**	**£1,222**	**-£568**
**Disinfection costs were added to the ClearGuard arm following expert opinion that this practice would continue for both interventions.*						

5 Ongoing research

The company and the External Assessment Centre are not aware of any ongoing research on ClearGuard HD caps.

6 Issues for consideration by the Committee

Clinical evidence

- The evidence base is within the US and North America. Experts reported a key discrepancy in practice to be the use of high concentrate citrate in the UK, which is not used within the US (due to FDA authorisation). Are the committee satisfied the evidence can be generalised to the UK?

- The pivotal studies in the evidence base address comparators of; standard caps with wipes, standard caps, AML solution and wipes, alternative cap Curos and connector Tego, however it does not include use of high concentrate citrate as experts advised is in practice in the UK. Do the committee feel the evidence can be generalised to the NHS care pathway?

- There was no clinical evidence identified on the use of ClearGuard HD caps in the home setting. Experts reported this to be a growing population in the UK and the company have stated that ClearGuard is used by people at home in the US. Do the committee consider the evidence base generalisable to the home setting?

- There is limited clinical evidence on the use of ClearGuard HD caps in the paediatric population. How generalisable is the evidence for this population? Are committee satisfied to recommend across all ages?

- The EAC reported there were no significant safety concerns with the use of the ClearGuard HD caps. Are the committee satisfied that the use of the caps across the population to be safe?

Cost evidence

- Do the committee accept US based evidence to inform parameters in the model? Are the committee satisfied the sensitivity analysis effectively address the uncertainty in baseline infection rates given the lack of appropriate evidence in this outcome and population specifically?

- Do the committee accept the use of paediatric data to inform parameters in the model and feel the sensitivity analysis effectively addresses discrepancies in the populations?

- The EAC provided additional analyses including disinfection costs to the ClearGuard arm of the model to address expert reports that “scrub the hub practice” would likely continue, regardless of cap in use. Are the committee satisfied with this model?

- The evidence base reports on three comparators of varying applicability to UK practice. All show ClearGuard HD caps to be cost saving. Are the committee satisfied the baseline infection rates with these comparators are effectively addressed and that this data can be used to inform costs in the UK care pathway?

7 Authors

Samantha Baskerville, HTA analyst

Kimberley Carter, HTA adviser

Victoria Fitton, Project Manager

NICE Medical Technologies Evaluation Programme, July 2021

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

A Details of assessment report:

- Erskine, J, Isaaq, A., Kwong, E, Manounah, L, Shokraneh, F, Ha Bui, K, Buylova Gola, A, Kartha, M, ClearGuard HD Antimicrobial Barrier Cap for preventing haemodialysis catheter-related bloodstream infections. External Assessment Centre report (July 2021).

B Submissions from the following sponsors:

- ICU medical

C Related NICE guidance

- NICE clinical guideline [CG139] (2017) Healthcare associated infections: prevention and control in primary and community care. Available at: https://www.nice.org.uk/guidance/cg139.
- NICE clinical guideline [NG107] (2018) Renal replacement therapy and conservative management. Available at https://www.nice.org.uk/guidance/ng107
- NICE clinical guideline [MTG44] (2019) Curos for preventing infections when using needleless connectors. Available at: https://www.nice.org.uk/guidance/mtg44.
- NICE medical technology innovation briefing [MIB234] (2020) ClearGuard HD Antimicrobial Barrier Cap for preventing haemodialysis catheter-related bloodstream infections. Available at: https://www.nice.org.uk/advice/mib234.

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Kanaa M, Wright MJ, Akbani H, et al. (2015). Cathasept Line Lock and Microbial Colonization of Tunneled Hemodialysis Catheters: A Multicenter Randomized Controlled Trial. American journal of kidney diseases : the official journal of the National Kidney Foundation. 66(6):1015-23.

Kwak, I, Song, S, Seong, E, et al. (2012) Bacterial Colonization of Tunnelled Cuffed Catheter in Patients with Hemodialysis. Nephrology Dialysis Transplantation.

Li W, Otto C, Nakeshbandi M et al. (2019) Dialysis-related bloodstream infections: A pre-and post-ClearGuard HD cap conception study. Open Forum Infectious Diseases 6(Supplement 2): S417-8. (Abstract)

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

NICE (2017) Healthcare associated infections: prevention and control in primary and community care (CG139). Available at: : https://www.nice.org.uk/guidance/cg139.

NICE (2018) Renal replacement therapy and conservative management (NG107). Available at https://www.nice.org.uk/guidance/ng107

NICE (2019) Curos for preventing infections when using needleless connectors (MTG44). Available at: https://www.nice.org.uk/guidance/mtg44.

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Sibbel S, Hunt A, Jordan L et al. (2020) Association between antimicrobial barrier cap use and outcomes among hemodialysis patients using a central venous catheter. Journal of the American Society of Nephrology 31: 53. (Abstract)

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Youssouf S, Nache A, Wijesekara C, et al. (2017). 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. 136(2):75-84.

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 Albert Power

Lead for Haemodialysis and Renal Research, North Bristol NHS Trust

Dr Sandip Mitra

Consultant Nephrologist, Manchester Royal Infirmary

Dr Kay Tyerman

Paediatric Nephrologist, Leeds Teaching Hospitals NHS Trust

Dr Peter Dupont

Consultant Nephrologist, Royal Free Hospital

Dr Pritpal Virdee

Renal Consultant, Epsom and St Helier University Hospitals

Sue Rowlands

Specialist Nurse Team Manager, Royal Wolverhampton NHS Trust

Carole Hallam

Independent Infection Prevention Nurse Consultant

Marlies Ostermann

Consultant in Nephrology, Guys and St Thomas Hospital

Please see the clinical expert statements included In the pack for full details.

Appendix C: Comments from patient organisations

Advice and information was sought from patient and carer organisations. The following patient organisations were contacted and no response was received.

- Kidney Care UK
- National Kidney Foundation
- Kidney Research UK
- Kidney Kids
- Kidney federation

Appendix D: decision problem from scope

Population	People with central venous catheters undergoing haemodialysis
Intervention	ClearGuard HD antimicrobial cap in place of standard care

Comparator(s)	• Standard CVC caps, decontaminated using;
	  ○ Alcohol wipes
	  ○ Alcohol containing solution of chlorhexidine gluconate
	  ○ Clorox wipes
	  ○ Lock line solutions
	• Alternative disinfecting caps, with / without needless connectors.

Outcomes	The outcome measures to consider include: • incidence of infection, this might be in the form of; catheter related bloodstream infection (CRBSI), catheter related infection (CRI), central line associated bloodstream infection (CLABSI), positive blood cultures (PBC), access related bloodstream infections (ARBSI) • hospital admissions for bloodstream infection (BSI) • length of stay • mortality • reinsertion of CVC lines • intravenous antibiotic use • time taken to disinfect • overall staff time • environmental impact of number of wipes disposed and number of caps disposed of • reduced use of chlorhexidine • device-related adverse events
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect 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	○ Settings for haemodialysis using central venous catheters include community and hospital settings.
Special considerations,	ClearGuard HD may be used with central venous catheters for haemodialysis for end stage kidney disease (Stages 4

including those related to equality	and 5). People who have dialysis which impairs their day-to-day functioning are protected as a disability under the equality act. Kidney disease occurs more frequently in males, people over the age of 60 and those of South-Asian, African or African-Caribbean family origin.	
Special considerations, specifically related to equality	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 characteristic?	No
	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 the Medical Technologies Advisory Committee will have relevant information to consider equality issues when developing guidance?	No
	This device is indicated for use for haemodialysis. Some people with chronic kidney disease have haemodialysis. People with chronic kidney disease are covered by the Equality Act 2010, but this device does not pose an equality issue as access to the device is not restricted.	
Any other special considerations	• Antimicrobial stewardship considerations • People with known allergy to chlorohexidine • People with allergies to nylon or polypropylene	

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance scope

ClearGuard HD Antimicrobial Barrier Cap for preventing haemodialysis catheter-related bloodstream infections.

1 Technology

1.1 Description of the technology

ClearGuard HD Antimicrobial Barrier Cap (ICU Medical) is for use with central venous catheters (CVC) in haemodialysis. The cap includes a rod that extends into the CVC hub. Both the rod and cap threads are coated with chlorhexidine acetate, a broad-spectrum antimicrobial agent. Chlorhexidine acetate is intended to reduce the presence of pathogenic organisms in the CVC lock to reduce the risk of catheter-related bloodstream infections (CRBSI). When the ClearGuard HD cap is inserted into the liquid-filled catheter, chlorhexidine acetate is released from the rod into the catheter lock solution. The antimicrobial agent is held inside the catheter hub in between treatments using the existing catheter clamp. ClearGuard HD caps are used in place of a standard cap or connector and need to be replaced during every dialysis session, it cannot be reused once removed. The recommended maximum use time for the cap is 3 days. The ClearGuard HD cap is intended to replace the need to clean the connector port with 2% chlorhexidine in 70% alcohol and then have to wait for it to air dry.

1.2 Relevant diseases and conditions

The ClearGuard HD antimicrobial cap is intended for use on central venous catheters to reduce the risk of catheter related bloodstream infections

(CRBSI) in the management of haemodialysis for end stage kidney disease (ESKD).

End stage kidney disease is an irreversible and progressive deterioration in kidney function. Haemodialysis is a type of renal replacement therapy (RRT) used for ESKD. According to the 22nd annual report by the UK Renal Registry (on 31st December 2018), 36.8% (24,366 adults) of the adult UK RRT (dialysis and transplant) population received haemodialysis in hospital or specialist renal units for ESKD. And a further 11.4% (107) children and young people receiving haemodialysis as their treatment option for ESKD.

Haemodialysis requires intravenous (IV) access to allow blood to flow outside of the body to be filtered through a dialysis machine, it also enables the administration of drugs and fluids directly into the blood. This may be required to remain in place for days to months. Types of haemodialysis access most commonly involve central venous catheters and arteriovenous fistula. A non-cuffed central venous catheter is used for emergency, acute and shorter-term dialysis. More routinely tunnelled (cuffed) central venous catheters are utilised for dialysis. These catheters are placed under the skin and include a cuff to inhibit the migration of microorganisms and attempt to minimise CRBSI. Arteriovenous fistula (AVF) is used for a longer-term dialysis access point, which is a surgically created access point made between an artery and vein. Each time treatments are administered through an access point there is a risk of introducing microorganisms that can cause blood stream infections. It is considered that the rate of bloodstream infections (BSIs) is higher in more temporary access approaches.

CRBSI causes fever, red skin and soreness around the access site and is associated with the need for additional treatment that may include line changes, prolonged antibiotic treatment, prolonged hospital stays, increased risk of morbidity, mortality and resultant healthcare costs.

1.3 Current management

NICE Guideline for renal replacement therapy promotes the choice of dialysis mode and location be discussed with the individual and family encompassing clinical considerations and individual preference. The UK Renal register (31/12/2018) reported the majority of haemodialysis to take place in hospital or community clinic setting with only 4% of the haemodialysis being carried out in the home setting. The coronavirus pandemic has highlighted the benefits of home dialysis and although statistics are not yet available, it may well impact on the uptake of home dialysis seen in the future. Haemodialysis in clinic routinely takes place three times a week, for 3-5 hours, but duration and frequency can vary in the home setting.

When managing haemodialysis using central venous catheters (CVC) NICE clinical guideline for healthcare-associated infections: prevention and control in primary and community care recommends decontaminating the vascular access device catheter hub before and after accessing the system. This consists of scrubbing the connector hub of the CVC before and after each access to the catheter with 2% chlorhexidine gluconate in 70% alcohol wipes and allow the hub to air dry, for a minimum of 15 seconds (NICE, 2017). This method requires the CVC cap to dry before it can be used which takes at least 15 seconds.

1.4 Regulatory status

ClearGuard HD Antimicrobial Barrier Cap received a CE mark in April 2019 as a class IIb device for haemodialysis catheters.

1.5 Claimed benefits

The benefits to patients claimed by the company with the use of ClearGuard HD are:

- Reduced risk of catheter related bloodstream infections (CRBSI)
- Reduced hospital attendances and length of stay due to CRBSI
- Reduced mortality as a result of reduced risk of CRBSI

Improved patient experience through the prevention of avoidable infections and reduced length of inpatient stay.

The benefits to the healthcare system claimed by the company are:

- Reduced length of stay and reduced intensive care bed days for treatment of CRBSI
- Reduced readmissions due to CRBSI
- Cost savings due to reduced need for antibiotic use, replacement of CVC and critical care cost for treatment of CRBSI
- Reduced mortality as a result of reduced risk of CRBSI.

2 Decision problem

Population	People with central venous catheters undergoing haemodialysis
Intervention	ClearGuard HD antimicrobial cap in place of standard care

Comparator(s)	• Standard CVC caps, decontaminated using;
	  ○ Alcohol wipes
	  ○ Alcohol containing solution of chlorhexidine gluconate
	  ○ Clorox wipes
	  ○ Line lock solutions
	• Alternative disinfecting caps, with / without needleless connectors.

Outcomes	The outcome measures to consider include: • incidence of infection, this might be in the form of; catheter related bloodstream infection (CRBSI), catheter related infection (CRI), central line associated bloodstream infection (CLABSI), positive blood cultures (PBC), access related bloodstream infections (ARBSI) • hospital admissions for bloodstream infection (BSI) • length of stay • mortality • reinsertion of CVC lines • intravenous antibiotic use • time taken to disinfect • overall staff time • environmental impact of number of wipes disposed and number of caps disposed of • reduced use of chlorhexidine • device-related adverse events

Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect 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	○ Settings for haemodialysis using central venous catheters include community and hospital settings.	
Special considerations, including those related to equality	ClearGuard HD may be used with central venous catheters for haemodialysis for end stage kidney disease (Stages 4 and 5). People who have dialysis which impairs their day-to-day functioning are protected as a disability under the equality act. Kidney disease occurs more frequently in males, people over the age of 60 and those of South-Asian, African or African-Caribbean family origin.	
Special considerations, specifically related to equality	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 characteristic?	No
	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 the Medical Technologies Advisory Committee will have relevant information to consider equality issues when developing guidance?	No
	This device is indicated for use for haemodialysis. Some people with chronic kidney disease have haemodialysis. People with chronic kidney disease are covered by the Equality Act 2010, but this device does not pose an equality issue as access to the device is not restricted.	
Any other special considerations	• Antimicrobial stewardship considerations • People with known allergy to chlorohexidine • People with allergies to nylon or polypropylene	

3 Related NICE guidance

Published

- ClearGuard HD Antimicrobial Barrier Cap for preventing haemodialysis catheter related bloodstream infections (2020) Medical technology innovation briefing [MIB234]

- Renal replacement therapy options in critical care (2020) NICE COVID-19 NHSE/ I specialty guide
- Curos for preventing infections when using needleless connectors (2019) NICE guidance [MTG44].
- Renal replacement therapy and conservative management (2017) NICE guideline [NG107]
- Healthcare-associated infections: prevention and control in primary and community care (2017) NICE guideline CG139
- Healthcare-associated infections (2016) NICE Quality standard [QS113]
- Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) NICE Guideline [NG15]
- Infection prevention and control (2014) NICE Quality standard [QS61]
- Chronic kidney disease in adults: assessment and management (2014) Clinical Guideline [CG182]
- Guidance on the use of ultrasound locating devices for placing central venous catheters (2002) Technology appraisal guidance [TA49]

In development

NICE is developing the following guidance:

- Chronic kidney disease: assessment and management (update). In development [GID-NG10118]. Expected publication date 20 July 2021.

4 External organisations

4.1 Professional

The following organisations have been asked to comment on the draft scope:

- Association of Nephrology Nurses
- British Association of Critical Care Nurses
- British Association of Paediatric Nephrology
- British Association of Parenteral and Enteral Nutrition
- British Infection Association
- British Renal Society

- European Kidney Health Alliance
- Healthcare Infection Society
- Infection Prevention Society
- Intensive Care Society
- International Society of Nephrology
- National infusion and Vascular access society
- NHS Blood and Transplant
- Paediatric Intensive Care Society
- Renal Physicians Association
- Royal College of Nursing
- Royal College of Physicians
- Royal Society of Medicine
- Society for General Microbiology
- The UK Renal Register
- The Renal Association.

4.2 Patient

NICE's Public Involvement Programme contacted the following organisations for patient commentary and asked them to comment on the draft scope:

- Kidney Care UK
- Kids Kidney Research.
- Kidney Research UK
- National Kidney Federation

NICE National Institute for Health and Care Excellence

Adoption report: GID-MT561 ClearGuard HD Antimicrobial Barrier Cap for preventing haemodialysis catheter-related bloodstream infections

Summary

Adoption levers identified by contributors

- Concept was well received. Infections are a problem for people needing dialysis so prevention of these is important.
- Possible saving of the time needed to clean the connector port when removing the cap to prepare for dialysis.
- Simple implementation.

Adoption barriers identified by contributors

- Cost.
- Queries about need if using antimicrobial line lock solutions.

1 Introduction

The adoption team has collated information from 4 healthcare professionals working within NHS organisations. None of these have experience of using ClearGuard HD as the technology only become available in the UK in April 2021 and is not yet in use within the NHS. It has been developed for the medical technologies advisory committee (MTAC) to provide context from current practice and an insight into the potential levers and barriers to adoption and includes adoption considerations for the routine NHS use of the technology. It does not represent the opinion of NICE or MTAC.

2 Contributors

The adoption team spoke to 4 NHS clinicians - three consultant nephrologists (one paediatric) and one dialysis nurse.

3 Current practice in clinical area

Contributors report that between 25-30% of people on haemodialysis have central venous catheters (CVCs). This is in line with the Renal Associations' recommendation of having no more than 30% of this group with a CVC. Reasons given for using a CVC were time pressures (creating vascular access requires preparation, planning and shared decision making), patient choice, patients presenting late and contraindication to surgery to create fistulas. CVCs are more common in children and young people.

Clinicians preparing people for haemodialysis wear full PPE (gloves, gowns, face masks, visors) and use a sterile technique. Caps are removed and the connector port is cleaned with 2% chlorhexidine in 70% alcohol and then allowed to air dry.

Once the haemodialysis session is complete the same cleaning approach is repeated. Catheter lines are locked and capped with standard catheter caps. One contributor reported using Tego needle free connectors to cap CVCs. There are various antimicrobial line lock solutions available to the NHS. Two contributors use TauroLock and one previously used Citra-Lock. Contributors questioned if ClearGuard HD would be needed if antimicrobial line lock solutions are being used.

Once CVC caps are in place the catheter is covered with a transparent airtight dressing which removes any concern about the caps being a choke hazard. This also helps to prevent infection as the catheter is not exposed to the air in between dialysis sessions.

One contributor explained that infections rates in haemodialysis patients have reduced over the last 5 years due to a national campaign and the adoption of sterile techniques and procedures. Infections are however still a problem and contributors agreed that anything that could help reduce this further would be well received.

The paediatric nephrologist indicated that incidence of infections in children and young people is lower. The reason given for this is that a two-nurse technique is used, one sterile nurse who prepares the catheter and another looking after the dialysis machine. Adult services do not have the capacity to adopt this.

Haemodialysis sessions were reported to be repeated around three times per week.

If infection is detected, the CVC lines are cultured, and antibiotics are started immediately. All infections are reported. The paediatric contributor commented that they do not report infections nationally.

4 Use of ClearGuard HD in practice

ClearGuard HD is not yet in use within the UK. The company have recently trained their sales team in preparation for its roll-out. They report use in 4000 facilities in the US.

5 Reported benefits

The potential benefits of adopting ClearGuard HD, as reported to the adoption team by the healthcare professionals contributing to this report are:

- Possible reduction in CVC related infections.
- Possible saving of time needed to clean the connector port when removing the cap to prepare for dialysis.
- Simple implementation.

6 Insights from the NHS

Clinician confidence/acceptance

All contributors report that the technology looks interesting and that they would adopt them if they proved to be both clinically and cost effective.

All contributors reported that they did not have a negative opinion of using antimicrobials in this way. Some are currently using antimicrobial line lock solutions which do not contribute to antibiotic resistance.

Resource impact

All contributors thought the cost of ClearGuard HD would be a significant barrier to adoption. Caps are supplied in pairs for £4, and are replaced after each haemodialysis session (approximately £12 per week). Contributors stated that evidence is required to show clinical and cost effectiveness through reduced infections.

One contributor reported that this would be a particular issue for adult dialysis units provided by commercial companies.

Training

Contributors report that ClearGuard HD appears easy to use and similar to a standard CVC catheter cap. The company report that in the US, facilities implemented ClearGuard HD by having their clinicians watch a three-minute video.

7 Comparators

One contributor reported using Tego needle free connectors to cap CVC lines.

Two contributors reported using TauroLock and one previously used Citra-Lock. Contributors questioned if ClearGuard HD would be needed if antimicrobial line lock solutions are being used. The company state that ClearGuard HD replaces the need for TauroLock and high concentration citrate locks. They explain that ClearGuard HD is typically used in combination with a low concentration citrate lock or other options including heparin locks and saline locks.

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Medical technologies guidance

GID-MT561 ClearGuard HD Antimicrobial Barrier Cap for preventing haemodialysis catheter-related bloodstream infections

Company evidence submission

Part 1: Decision problem and clinical evidence

Company name	ICU Medical
Submission date	17 May 2021
Regulatory documents attached	CE certificate and instructions for use (IFU)
Contains confidential information	No

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1 Decision problem

	Scope issued by NICE	Variation from scope (if applicable)	Rationale for variation
Population	People with central venous catheters undergoing haemodialysis.	None	Enter text.
Intervention	ClearGuard HD antimicrobial cap in place of standard care.	None	Enter text.
Comparator(s)	• Standard CVC caps, decontaminated using; ○ Alcohol wipes, ○ Alcohol containing solution of chlorhexidine gluconate, ○ Clorox wipes, ○ Lock line solutions. • Alternative disinfecting caps, with / without needleless connectors.	None	Enter text.
Outcomes	The outcome measures to consider include: • incidence of infection, this might be in the form of; catheter related bloodstream infection (CRBSI), catheter related infection (CRI), central line associated bloodstream infection (CLABSI), positive blood cultures (PBCs), access related bloodstream infections (ARBSIs), • hospital admissions for bloodstream infection (BSI), • length of stay, • mortality, • reinsertion of CVC lines, • intravenous antibiotic use, • time taken to disinfect, • overall staff time, • environmental impact of number of wipes disposed and number of caps disposed of,	None	Enter text.

	• reduced use of chlorhexidine, • device-related adverse events.		
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect 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.	None	Enter text.
Subgroups to be considered	Settings for haemodialysis using central venous catheters include community and hospital settings.	None	Enter text.
Special considerations, including issues related to equality	ClearGuard HD may be used with central venous catheters for haemodialysis for end stage kidney disease (Stages 4 and 5). People who have dialysis which impairs their day-to-day functioning are protected as a disability under the equality act. Kidney disease occurs more frequently in males, people over the age of 60 and those of South-Asian, African or African-Caribbean family origin. This device is indicated for use for haemodialysis. Some people with chronic kidney disease have haemodialysis. People with chronic kidney disease are covered by the Equality Act 2010, but this device does not pose an equality issue	None	Enter text.

	as access to the device is not restricted. Other special considerations include: • Antimicrobial stewardship considerations. Excluded populations include: • People with known allergy to chlorohexidine, • People with allergies to nylon or polypropylene.		

2 The technology

Give the brand name, approved name and details of any different versions of the same device (including future versions in development and due to launch). Please also provide links to (or send copies of) the instructions for use for each version of the device.

Brand name	ClearGuard HD Antimicrobial Barrier Cap (available in pairs only)
Approved name	ClearGuard HD Antimicrobial Barrier Cap
CE mark class and date of authorisation	Class IIb March 25, 2019

Version(s)	**Launched**	**Features**
CGHD-100	2017	Case of 100 (pairs of caps)
Enter text.	Enter text.	Enter text.
Enter text.	Enter text.	Enter text.
Enter text.	Enter text.	Enter text.
Enter text.	Enter text.	Enter text.

What are the claimed benefits of using the technology for patients and the NHS?

Claimed benefit	Supporting evidence	Rationale
Patient benefits		
Reduced risk of catheter related bloodstream infections (CRBSI)	Brunelli et al, 2018 (1), Hymes et al, 2017 (2), Weiss et al, 2021 (3), Li et al, 2019 (4), Sibbel et al, 2020 (5), Nitz et al, 2021 (6), Glennon et al, 2020 (7)	All studies focussed on impact of the device on BSIs, CRBSIs, CLABSIs, PBCs, and/or ARBSIs. Identified studies showed the beneficial impact of the intervention on all above outcomes. Data from the three, large, clinical studies (1, 2, 3) demonstrate a 56-86% reduction in BSI rates associated with introduction of the intervention.
Reduced hospital attendances and length of stay due to CRBSI	Brunelli et al, 2018 (1), Hymes et al, 2017 (2), Sibbel et al, 2020 (5)	Hospital admission rates in the three referenced studies were shown to have been reduced with use of ClearGuard by 45%, 43% and by 0.22 per patient-year, respectively. Hymes et al, 2017 (2) also demonstrated a 51% reduction in hospitalisation days following introduction of ClearGuard.
Reduced mortality as a result of reduced risk of CRBSI	Brunelli et al, 2018 (1)	BSI is the second leading cause of death in HD patients (8). Although results were not statistically significant, Brunelli et al, 2018 (1) reported no deaths in the ClearGuard group compared to three deaths in the comparator group.
Improved patient experience through the prevention of avoidable infections and reduced length of inpatient stay	Enter text.	No studies focussing on patient satisfaction or quality-of-life were identified.
System benefits		
Reduced length of stay and reduced intensive care bed days for treatment of CRBSI	Brunelli et al, 2018 (1), Hymes et al,	All of the referenced studies indicated lower hospitalisation rates

	2017 (2), Sibbel et al, 2020 (5)	associated with ClearGuard (45%, 43% and a reduction of 0.22 per patient-year, respectively), while Hymes et al, 2017 (2) also demonstrated a 51% reduction in hospitalisation days following introduction of ClearGuard. These data, combined with the lower infection rates associated with the intervention (described earlier) indicate that the intervention reduces burden on the health care system, in terms of the need to treat infections and to provide hospital bed-days for patients.
Reduced readmissions due to CRBSI	Enter text.	None of the identified studies focussed on re-admission rates.
Cost savings due to reduced need for antibiotic use, replacement of CVC and critical care cost for treatment of CRBSI	Glennon et al, 2020 (7)	One study referenced the cost savings associated with introduction of the intervention. Glennon et al, 2020 (7) indicated that the total costs in the comparator group (prophylactic use of antimicrobial locks amongst 4 high risk patients) were approximately $15,000 higher than amongst patients in the ClearGuard group, for patients in a pediatric dialysis setting.
Reduced mortality as a result of reduced risk of CRBSI	Brunelli et al, 2018 (1)	As described earlier, Brunelli et al, 2018 (1) have shown a reduced mortality rate amongst patients receiving ClearGuard than amongst a comparator group (although study notes that the results were not statistically significant).

Easy to use with no change to procedure workflow	Hymes et al, 2017 (2), Weiss et al, 2021 (3)	The studies by Hymes et al, 2017 (2) and Weiss et al, 2021 (3), which were large studies involving comparisons between ClearGuard and standard CVC caps and Tego connectors, respectively, reported no disruption to workflow through use of the intervention, and reported that there was widespread acceptance of use of the intervention caps amongst clinical staff and patients.
Keep patients healthy and out of hospital, which frees up limited hospital resources and benefits the healthcare system as a whole	Brunelli et al, 2018 (1), Hymes et al, 2017 (2), Weiss et al, 2021 (3), Li et al, 2019 (4), Sibbel et al, 2020 (5), Nitz et al, 2021 (6), Glennon et al, 2020 (7)	All identified studies focussing on use of the intervention reported improved outcomes related to infection rates associated with ClearGuard. Brunelli et al, 2018 (1), Hymes et al, 2017 (2), and Sibbel et al, 2020 (5) also reported reduced hospital attendances and shorter length of stay in hospital, associated with ClearGuard.
Cost benefits		
Cost savings due to reduced need for antibiotic use, replacement of CVC and critical care cost for treatment of CRBSI	Glennon et al, 2020 (7)	One study referenced the cost savings associated with introduction of the intervention. Glennon et al, 2020 (7) indicated that the total costs in the comparator group (prophylactic use of antimicrobial locks amongst 4 high risk patients) were approximately $15,000 higher than amongst patients in the ClearGuard group, for patients in a pediatric dialysis setting.
Sustainability benefits		
Re-allocation of infection-related bed days	Brunelli et al, 2018 (1), Hymes et al,	As indicated in Brunelli et al, 2018 (1), Hymes et al, 2017 (2), and Sibbel et

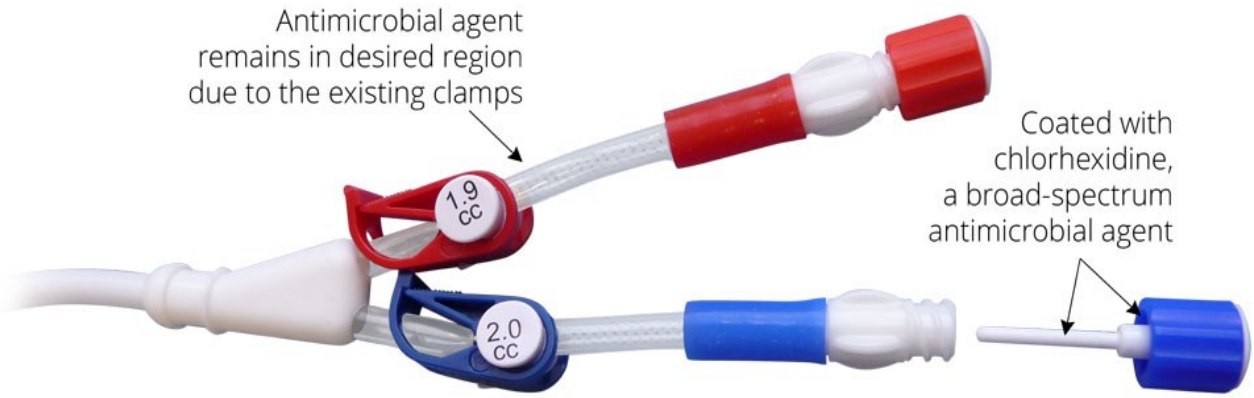
	2017 (2), Sibbel et al, 2020 (5)	al, 2020 (5), there are reduced hospital attendances and shorter length of stay in hospital, associated with ClearGuard. Hospital beds that would otherwise be occupied by infected patients may be used for other purposes, freeing up hospital resources and improving patient quality-of-life and satisfaction.
Re-allocation of infection-related staff time	Brunelli et al, 2018 (1), Hymes et al, 2017 (2), Weiss et al, 2021 (3), Li et al, 2019 (4), Sibbel et al, 2020 (5), Nitz et al, 2021 (6), Glennon et al, 2020 (7)	All referenced studies have shown improved infection-related outcomes associated with ClearGuard, while select studies have also demonstrated a reduction in hospital attendances and shorter length of stay in hospital following implementation of the intervention. These improved outcomes consequently allow the time of health care staff, which would otherwise be occupied in treating infected patients, to be re-allocated.
Facilitates earlier patient discharge	Hymes et al, 2017 (2)	Hymes et al, 2017 (2) demonstrated a 51% reduction in hospitalisation days following introduction of ClearGuard. Haemodialysis patients may therefore be discharged earlier through use of ClearGuard.

Briefly describe the technology (no more than 1,000 words). Include details on how the technology works, any innovative features, and if the technology must be used alongside another treatment or technology.

The ClearGuard HD Antimicrobial Barrier Cap (shown below) is for use with central venous catheters (CVC) in haemodialysis. The cap includes a rod that extends into the CVC hub. Both the rod and cap threads are coated with chlorhexidine acetate, a broad-spectrum antimicrobial agent. Chlorhexidine acetate is intended to reduce the presence of pathogenic organisms in the CVC lock to reduce the risk of catheter-related bloodstream infections (CRBSIs). When the ClearGuard HD cap is inserted into the liquid-filled catheter, chlorhexidine acetate is released from the rod into the catheter lock solution. The antimicrobial agent is held inside the catheter hub in between treatments using the existing catheter clamp. ClearGuard HD caps are used in place of a standard cap or connector and need to be replaced during every dialysis session; it cannot be reused once removed. The recommended maximum use time for the cap is 3 days. The ClearGuard HD cap is intended to replace the need to clean the connector port with 2% chlorhexidine in 70% alcohol and then have to wait for it to air dry.

We provide two short videos (from the ICU Medical website) to demonstrate how catheter-related bloodstream infections start and how ClearGuard HD works:

- How Catheter Infections Begin (49 sec) https://player.vimeo.com/video/427903103,
- How ClearGuard HD Works (38 sec) https://player.vimeo.com/video/427903947.



Briefly describe the environmental impact of the technology and any sustainability considerations (no more than 1,000 words).

As one of the world's leading infusion therapy companies, ICU Medical is committed to delivering quality, innovation, and value to our customers worldwide. We operate our business in an ethical, sustainable, and environmentally conscious manner. We are also dedicated to supporting the wellbeing of our shareholders, customers, and employees, and the communities in which they live. If you want to learn more about sustainability at ICU Medical, please visit our sustainability website or see the attached document.

ClearGuard HD is manufactured in the US state of Minnesota where our facility's environmental considerations include best practices in Waste Management (safely disposing of hazardous waste, recycling, etc.) and Workplace Safety and Health (daily cleaning and sanitation, illness and injury prevention, etc.).

Finally, by preventing BSI, ClearGuard also eliminates the extra devices and waste associated with CVC replacement and hospitalization needed to treat bloodstream infection.

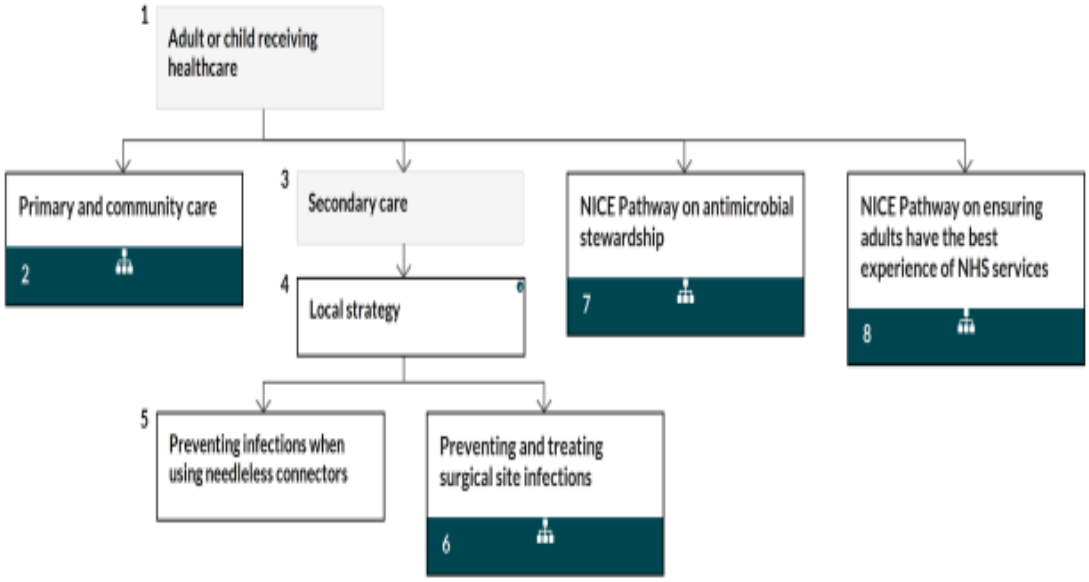
3 Clinical context

Describe the clinical care pathway(s) that includes the proposed use of the technology, ideally using a diagram or flowchart. Provide source(s) for any relevant pathways.

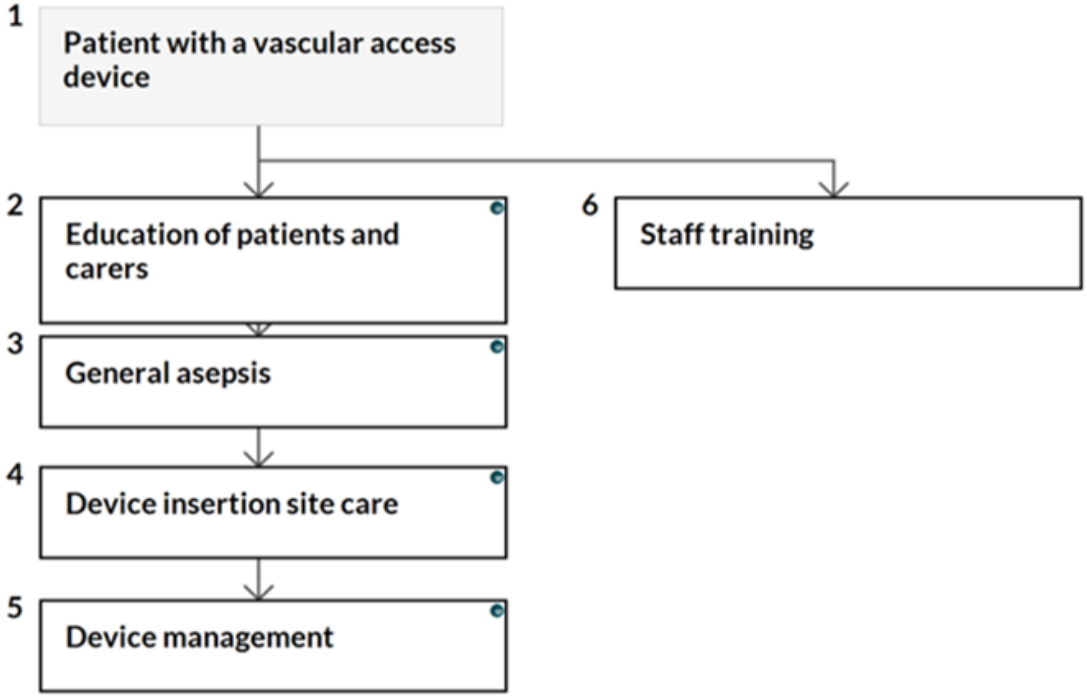
As part of NICE Clinical Guidelines (CG139), guidelines are provided on the prevention and control of healthcare-associated infections (9). In Flow diagram 1 below, guidelines on the prevention of infections using needleless connectors in a secondary care setting are provided. These guidelines reference NICE MTG44 (*Curos for preventing infections when using needleless connectors*) in Step 5 (Preventing infections when using needleless connectors) of the pathways, which advise that although Curos shows promise for preventing infections when using needleless connectors, there is insufficient evidence currently available on its clinical benefits (10). ClearGuard HD Antimicrobial Barrier Cap has the potential to act as a clinically beneficial alternative technology in this setting.

Flow diagram 2 presents the NICE CG139 guidelines on the prevention and control of healthcare-associated infections in a primary and community care setting, specifically related to vascular access devices (9). Point 5 in this diagram describes the process of device management as it relates to infection prevention. Use of the ClearGuard HD Antimicrobial Barrier Cap would sit at this point of the treatment pathway. After locking the catheter lumen, the ClearGuard device would be attached to prevent haemodialysis catheter-related bloodstream infections. Other than this, there would be no further impact on the treatment pathway currently described.

Flow diagram 1



Flow diagram 2



Describe any training (for healthcare professionals and patients) and system changes that would be needed if the NHS were to adopt the technology.

ClearGuard HD caps have no special training requirements. The simple, intuitive design is similar to using a standard CVC cap with no change to workflow.

Over 4,000 centres in the United States are currently using ClearGuard HD caps as their standard of care. The majority of these facilities implemented ClearGuard using (e.g., nurses and technicians) a three-minute in-service video on our website as part of the training:

- ClearGuard HD In-service Video (3 mins 26 sec) https://vimeo.com/423704523

This success of staff training is documented in the two, large randomized controlled trials:

- Brunelli et al, 2018, ClearGuard vs. Tego + Curos caps, *"Also, all facilities had indicated willingness to adhere to treatment allocation upon eventual randomization and all underwent a 30-minute training session describing procedures necessary to both study arms."* JASN, page 1340 (1).
- Hymes et al, 2017, ClearGuard vs. Standard CVC caps, *"Facility staff members were trained on device use via a group webinar."* AJKD, page 221 (2).

On-site training is available, but most facilities find this unnecessary.

We have not encountered any issues with implementation across the US, or in training our sales teams in the UK, France, and Spain.

Finally, the ClearGuard HD technology enables haemodialysis to more easily be carried out in the home setting. The coronavirus pandemic has highlighted the benefits of home dialysis and patient self-care and may well impact on the uptake of home dialysis seen in the future. Without ClearGuard, it can be very difficult for a home patient to properly disinfect their catheter because this consists of scrubbing the connector hub before and after each access to the catheter with 2% chlorhexidine gluconate in 70% alcohol wipes and allowing the hub to air dry for a minimum of 15 seconds. With ClearGuard, the process is safe, simple, automatic, and clinically proven to reduce bloodstream infections in haemodialysis catheter patients. Minimal, if any, training is required for at-home patients to understand the ClearGuard treatment process.

4 Published and unpublished clinical evidence

Identification and selection of studies

Complete the following information about the number of studies identified.

Please provide a detailed description of the search strategy used, and a detailed list of any excluded studies, in appendix A.

Number of studies identified in a systematic search.		9 (Following initial de-duplication of identified studies and title and abstract screening)
Number of studies identified as being relevant to the decision problem.		7 (Following removal of studies not relevant after full-text screening)
Of the relevant studies identified:	Number of published studies (included in table 1).	3
	Number of abstracts (included in table 2).	4
	Number of ongoing studies (included in table 3).	0

List of relevant studies

In the following tables, give brief details of all studies identified as being relevant to the decision problem.

- Summarise details of published studies in table 1.
- Summarise details of abstracts in table 2.
- Summarise details of ongoing and unpublished studies in table 3.
- List the results of all studies (from tables 1, 2 and 3) in table 4.

For any unpublished studies, please provide a structured abstract in appendix A. If a structured abstract is not available, you must provide a statement from the authors to verify the data.

Any data that is submitted in confidence must be correctly highlighted. Please see section 1 of the user guide for how to highlight confidential information. Include any confidential information in appendix C.

Table 1 Summary of all relevant published studies

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
Cluster-Randomized Trial of Devices to Prevent Catheter-Related Bloodstream Infection	Brunelli et al, 2018 (1) Location: USA	Prospective, multicentre cluster-randomized clinical study to perform a comparative-effectiveness analysis.	*Patient population:* All patients with central venous catheters (CVCs) dialyzing in participating facilities (forty dialysis facilities in total – 20 in the intervention group, and 20 in the comparator group). Patients with a known allergy to chlorhexidine were excluded (n=0). *Patient numbers in the two stages of the analysis:* Initial run-in period (Aug 2015-Oct 2015) = 304 (intervention group), 323 (comparator group). Intervention period (Nov 2015-Nov 2016) = 826 (intervention group), 845 (comparator group). *Key characteristics:* Initial run-in period = 48% male in intervention group, 50% male in comparator group. Average age of 63.7 (± 15.6) in intervention group, 62.2 (± 15.5) in comparator group. In intervention group, 44% of patients were white, 35% were black, 12% were	ClearGuard HD Antimicrobial Barrier Cap (Pursuit Vascular, Inc.).	Tego Needlefree Hemodialysis Connector (ICU Medical, Inc.) used in combination with Curos Disinfecting Cap for Tego (3M Healthcare).	Study looked at the occurrence of the following in each group: • Occurrence of positive blood cultures (PBCs). This was the primary analysis. • Occurrence of catheter-related bloodstream infections (CRBSIs). • Occurrence of central-line associated bloodstream infections (CLABSIs). Study authors also undertook further analyses, including access-related bloodstream infection (ARBSI) analysis, organism analysis, de novo CVCs analysis, intravenous antibiotic analysis, and subsequent exploratory and sensitivity analysis. **Results:** *PBCs (primary analysis):* During the 3-month run-in period, 18 positive blood cultures (PBCs) occurred during 18,739 CVC-days in the ClearGuard group, and 22 PBCs occurred during 20,454 CVC-days in the control group, corresponding to rates of 1.02 and 1.08 per 1,000 CVC-days, respectively. Between-group differences in rates were nonsignificant (P=0.8). During the 13-month intervention period, 23 PBCs occurred during 83,064 CVC-days in the ClearGuard group, and 75 PBCs occurred during 100,042 CVC-days in the Tego + Curos group, corresponding to rates of 0.28 and 0.75 PBCs per 1,000 CVC-days, respectively. Twenty-one and 63 unique patients experienced PBCs, respectively. The incidence rate ratio (IRR) was 0.37 (P=0.001) favouring ClearGuard. *CRBSIs:* IRR was 0.37 (P=0.003) favouring ClearGuard.

			Hispanic, 9% were of another race, while in the comparator group, 38% of patients were white, 46% were black, 11% were Hispanic, 5% were of another race. Intervention period = 51% male in intervention group, 51% male in comparator group. Average age of 63.7 (± 14.4) in intervention group, 62.0 (± 15.3) in comparator group. In intervention group, 50% of patients were white, 32% were black, 10% were Hispanic, 7% were of another race, while in the comparator group, 43% of patients were white, 42% were black, 10% were Hispanic, 5% were of another race. There were no withdrawals, or loss-to-follow-up reported.			*CLABSIs:* IRR was 0.35 (P=0.003) favouring ClearGuard. *ARBSIs:* IRR was 0.32 (P<0.001) favouring ClearGuard. *Organism analysis:* ARBSI events were analyzed according to organism type. When considering only ARBSIs comprising Gram-positive organisms, the IRR was 0.40 (P=0.01) favouring ClearGuard. For ARBSIs comprising only Gram-negative organisms, the IRR was 0.19 (P=0.001) favouring ClearGuard. The IRR for multidrug resistant organisms was 0.60 (P=0.5); there were 4 PBCs in the ClearGuard group and 8 PBCs in the Tego + Curos group. *De novo CVCs analysis:* To account for potential latent effects due to colonization of catheters before entering the study, a subgroup analysis was performed among patients entering the study with a new CVC (called de novo CVC); thus, all patients in this subgroup start with a CVC vintage of zero. The resulting IRR was 0.28 (P<0.001) favouring ClearGuard. *Sensitivity analysis:* The primary analysis did not consider infections that occurred within 21 days of patient start. A sensitivity analysis was conducted in which all patients with CVCs were considered from their study start. The resulting IRR was 0.35 (P=0.002) favouring ClearGuard. *Intravenous antibiotic analysis:* An analysis was performed to investigate whether an increase in antibiotic use could be responsible for the decreased infection rates. The rate of intravenous (IV) antibiotic starts decreased by 0.6 per 1,000 CVC-days from run-

						in period to intervention period, with the greatest decrease in the ClearGuard group. In addition, an analysis was performed to investigate whether there was a corresponding decrease in the rate of IV antibiotics associated with PBCs. The resulting IRR was 0.37 (P<0.001) favouring ClearGuard. *Other analyses:* CVC exchange rate was not statistically different in the ClearGuard group versus Tego + Curos (0.94 versus 1.03 per 1,000 CVC-days, respectively; P=0.8). CVC removal rate was similar between the two groups (7.57 versus 7.56 events per 1,000 CVC days, respectively; P=0.9). Thrombolytic use rate was not significantly different between the two groups (1.84 versus 1.89 per 1,000 CVC-days, respectively; P=0.9). Hospital admissions for BSI were analyzed using the dialysis facilities' records of admission (no other hospital records were available); the rate of hospitalizations for BSI was lower in the ClearGuard group versus Tego + Curos (0.06 versus 0.11 per 1,000 CVC-days, respectively), but the difference was not statistically significant (IRR=0.55; P=0.5). There were no deaths within 30 days of a PBC in the ClearGuard group, and three deaths in the Tego + Curos group; however, these results were statistically insignificant. Lock solutions were not required to be reported. However, they were recorded in 33% of all procedures. Within both groups, the vast majority (>95%) of procedures used saline as the lock solution. *Adverse events:* No device-related adverse events were reported in the study.
Dialysis Catheter–Related Bloodstream Infections: A Cluster-Randomized	Hymes et al, 2017 (2) Location: USA	Prospective, multicentre cluster-randomized comparative effectiveness trial.	*Patient population:* Hemodialysis patients with a tunnelled CVC in participating facilities (forty dialysis facilities in total – 20 in the intervention group, and 20 in the	ClearGuard HD Antimicrobial Barrier Cap.	Standard CVC caps.	The primary end point was comparison of the overall rate of BSIs (represented by positive blood culture episodes divided by CVC-days) between patients in the intervention group (ClearGuard HD cap facilities) and the control group (standard CVC cap facilities). Greater than 93% of blood cultures were analyzed by a single central laboratory. Secondary end points were

Trial of the ClearGuard HD Antimicrobial Barrier Cap			comparator group). Patients with a known allergy to chlorhexidine were excluded (n=0). *Patient numbers in the two stages of the analysis:* 1-month pre-intervention baseline period (Nov 2014) = 618 (intervention group), 611 (comparator group). 12-month intervention period (Dec 2014-Nov 2015) = 1,245 (intervention group), 1,225 (comparator group). In the 12-month intervention period, the number of patients that transitioned to fistula or graft in the intervention group was n = 509, and the number that left the facility due to death or loss-to-follow-up was n = 264. The number of patients that transitioned to fistula or graft in the comparator group was n = 483, and the number that left the facility due to death or loss-to-follow-up was n = 283. *Key characteristics:* Baseline period = 52% male in intervention group, 50% male in comparator group.			rates of hospital admissions and hospitalization-days for BSI and IV antibiotic starts. **Results:** *Positive blood cultures:* During the baseline period, there was no significant difference between the intervention and control groups (0.56 vs 0.60/1,000 CVC-days; P = 0.8). During the follow-up period, there were 153 positive blood cultures, with 46 in the intervention group and 107 in the control group. There were 346,946 CVC days during the follow-up period, with 169,609 CVC-days in the intervention group and 177,337 CVC-days in the control group. The resultant follow-up positive blood culture rate (adjusted for facility cluster effect) was 0.26/1,000 CVC-days in the intervention group versus 0.59/1,000 CVC-days in the control group (56% less in the intervention group; P = 0.01). The positive blood culture IRR of the intervention compared to the control was 0.44 (95% CI, 0.23-0.83). The rate of positive blood cultures between groups during the last 6 months of the study indicated a significant difference: 0.22/1,000 CVC-days in the intervention group versus 0.72/1,000 CVC-days in the control group (69% less in the intervention group; P = 0.01). The positive blood culture IRR of the intervention compared to the control was 0.31 (95% CI, 0.12-0.79). In addition, subgroup analysis of de novo CVCs, defined as patients who entered the study with a new CVC, demonstrated a significantly lower positive blood culture rate: 0.16/1,000 CVC-days in the intervention group versus 0.50/1,000 CVC days in the control group (68% less in the intervention group; P = 0.02; n = 678 patients). The positive blood culture IRR of the intervention compared to the control was 0.32. *Hospital admissions for BSI:* During the baseline period, there was no significant difference between the intervention and control groups (P = 0.6) for hospital admissions for BSI. During the follow-up period, the rate of hospital admissions for BSI

			Average age of 61.5 (± 15.6) in intervention group, 60.7 (± 15.3) in comparator group. In intervention group, 48% of patients were white, 50% were black, 1% were of another race and 1% were missing, while in the comparator group, 48% of patients were white, 46% were black, 3% were of another race and 3% were missing. Intervention period = 53% male in intervention group, 54% male in comparator group. Average age of 61.5 (± 15.1) in intervention group, 60.6 (± 15.1) in comparator group. In intervention group, 49% of patients were white, 46% were black, 1% were of another race and 5% were missing, while in the comparator group, 52% of patients were white, 40% were black, 3% were of another race and 5% were missing .			between groups demonstrated a significant improvement: 0.28/1,000 CVC-days in the intervention group versus 0.47/1,000 CVC-days in the control group (40% less in intervention group; P = 0.04). Comparing rates between groups during the last 6 months of the study indicated a significant difference: 0.28/1,000 CVC-days in the intervention group versus 0.48/1,000 CVC-days in the control group (43% less in intervention group; P = 0.04). *Hospitalization days for BSI:* During the baseline period, there was no significant difference between the intervention and control groups (P = 0.7) for hospitalization-days for BSI. During the follow-up period, there were nominally fewer hospitalization-days in the intervention group (3.24/1,000 CVC-days) compared to the control group (4.68/1,000 CVC-days), but the difference was not statistically significant (31% less in the intervention group; P = 0.2). Comparing the rates between groups during the last 6 months of the study indicated a significant difference: 2.42/1,000 CVC-days in the intervention group versus 4.94/1,000 CVC-days in the control group (51% less in intervention group; P = 0.04). *IV antibiotic starts:* During the baseline period, there was no significant difference between the intervention and control groups (P = 0.4) for new IV antibiotic starts. During the follow-up period, there were nominally fewer IV antibiotic starts in the intervention group (1.68/1,000 CVC-days) compared to the control group (1.78/1,000 CVC-days), but the difference was not statistically significant (6% less in intervention group; P = 0.6). *Adverse events:* No device-related adverse events were reported in the study.
Evaluating a novel hemodialysis central	Weiss et al, 2021 (3)	Retrospective observational analysis of a multicentre quality	*Patient population:* Patients utilizing CVCs for haemodialysis at 13	Use of a novel chlorhexidine-coated CVC end cap -	Haemodialysis with the components and procedures	CVC patients and days per study group were estimated from the total number of CVC patients per month. CLABSI counts were recorded by month, and rates were reported as CLABSI/1,000 CVC days. Chi-

venous catheter cap in reducing bloodstream infections: A quality improvement initiative	Location: USA	improvement assessment at a US-based outpatient dialysis network.	outpatient dialysis clinics across New York, United States. *Patient numbers in the two stages of the analysis:* Initial 5-month study period (May 2018 – September 2018), data were evaluated from a group of patients using chlorhexidine end caps ('chlorhexidine group', n = 967 patient-months) as well as a group using standard needlefree connectors ('standard group', n = 1,044 patient-months). Second study period (October 2018 – June 2019); most patients were subsequently switched to chlorhexidine by February 2019, and data were collected until June 2019. In the second study period, the totals were – chlorhexidine group, n = 3,647 patient-months, and standard group, n = 276 patient-months. *Key characteristics:* Mean age of population was 61.3 and 52.9% of patients were male.	ClearGuard HD Antimicrobial Barrier Caps (ICU Medical, San Clemente, CA, USA) during haemodialysis.	previously used at the dialysis network, i.e., standard practice. The catheters were capped by needlefree connectors (Tego, ICU Medical, San Clemente, CA, USA), which remained on the catheter during and after dialysis.	Squared tests assessed significance of CLABSI/1,000 CVC days between the chlorhexidine and standard groups. Organism analysis was also conducted. **Results:** CLABSI rates during the first study period were significantly lower in the chlorhexidine group relative to the standard group (0.03 vs 0.70 respectively; p<0.0001). Monthly CLABSI rates remained low during the second study period in the chlorhexidine group despite increasing CVC days due to conversion. Combined results (both study periods) showed significantly lower CLABSI rates in the chlorhexidine group relative to the standard group (0.09 vs 0.63 respectively; p<0.0001). Additionally, no increase in thrombosis was reported in clinics converting to the chlorhexidine-coated CVC caps while using saline as the standard locking solution. A total of 38 CLABSIs with 42 isolates were identified in this analysis: 34 CLABSIs were monomicrobial and 4 CLABSIs were polymicrobial. Out of the 42 isolates, 59.5% were gram-positive organisms, the most common of which were coagulase-negative staphylococci (26.2%, n=11), followed by methicillin-resistant Staphylococcus aureus (11.9%, n=5). Gram-negative organisms accounted for 40.5% of all identified isolates, with Acinetobacter baumannii being the most common organism in this group (9.5%, n=4). Based on the reduction in CLABSI rates shown in this analysis, findings from this quality improvement report indicate that using chlorhexidine-coated CVC caps may provide a therapeutic improvement to standard practice. Additional potential benefits of this conversion include improvement in a facility's Quality Incentive Program (QIP) score and reduced costs of treating infections with medications that are not

						billable outside of the Medicare bundled reimbursement rate. Reduced infection rates also have the potential to decrease hospitalization rates and increase patient satisfaction, both of which may increase unit revenue. Finally, given that every infection carries mortality risk, this analysis suggests that chlorhexidine-coated CVC caps also have the potential to decrease a dialysis unit's mortality rate.
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Table 2 Summary of all relevant abstracts

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
Dialysis-Related Bloodstream Infections: A Pre- and Post ClearGuard HD Cap Conception Study	Li et al, 2019 (4) Location: USA	Retrospective review of patient data from an outpatient centre. Patient data assessed before and after the introduction of the intervention.	*Patient population:* 150 patients receiving haemodialysis at a single, outpatient centre in Brooklyn, NY from January 1, 2015 to January 31, 2019. As of February 1, 2019, the ClearGuard cap was implemented for all patients. There were no withdrawals, or loss-to-follow-up reported.	ClearGuard HD chlorhexidine impregnated catheter (ClearGuard cap).	Practice prior to the introduction of ClearGuard, i.e., current practice, including use of tunnelled dialysis catheters and standard CVC caps.	Outcomes assessed included clinical event rates, including infection, pre- and post-intervention. **Results:** Median total tracking period (including post infection follow-up) was 1.75 years (range 0.02–4.26) for pre intervention cases; 0.19 years (range 0.08–0.21) for post-intervention cases. Event rate was estimated as 9.7 events per 100 person-years (95% CI 6.7, 14.1) for pre-intervention cases; zero (95% CI 0.0, infinity) for post intervention cases (P = 0.318 for pre- vs. post comparison) with a clear limitation being lack of power given recent implementation date. Study found a statistically significant risk for infection in patients with tunnelled dialysis catheter (P < 0.001). The results therefore indicate that the

						preliminary post ClearGuard cap conception data currently being followed is promising for a significant reduction in catheter-related bacteremia.
Association Between Antimicrobial Barrier Cap Use and Outcomes Among Hemodialysis Patients Using a Central Venous Catheter	Sibbel et al, 2020 (5) Location: USA	Real-world analysis of a haemodialysis population following the implementation of the intervention in a large dialysis organization.	*Patient population:* Adults receiving in-centre haemodialysis treatment 3x/week using a CVC in a large dialysis organization from May 2019, with analysis based on two 3-month periods, Jul-Oct 2018 and Jul-Oct 2019. A total of 37,642 patients in the pre-period and 40,498 patients in the post-period met eligibility criteria. There were no withdrawals, or loss-to-follow-up reported.	Antimicrobial barrier cap (AmBC; ClearGuard® HD, Pursuit Vascular Inc, Maple Grove, MN, USA).	Practice prior to the introduction of ClearGuard, i.e., current practice.	The analysis looked at crude outcome rates for individual months, and for the pre- and post-intervention periods overall. Outcomes included BSI rates, and hospitalization rates. **Results:** Overall BSI rate fell from 0.54/100 CVC days in the pre-period to 0.36/100 CVC days after AmBC implementation. Hospitalization rates were lower during the post-period versus the pre-period overall and within each calendar month; the contribution of underlying temporal changes (e.g., background year-over year change) could not be quantified. Results therefore indicate that the intervention results in reduced BSI and hospitalization rates.

						Adoption of AmBCs for use in haemodialysis patients using a CVC for vascular access was associated with an early 34% reduction in infections assessed on the basis of positive blood cultures and 0.22 fewer hospital admissions per patient-year.
Prevention of central line associated blood stream infections in a pediatric dialysis unit	Nitz et al, 2021 (6) Location: USA	Evaluation of a quality improvement initiative designed to lower the haemodialysis-associated CLABSI rate in a single, paediatric dialysis program.	*Patient population:* 28 (17 male = 61%) haemodialysis patients were observed over a combined 283.8 patient months from 26/10/2017 to 13/11/2020. *Key characteristics:* Mean (range) patient age was 11.7 (0.4-21) years. There were no withdrawals, or loss-to-follow-up reported.	Five infection prevention measures were implemented: 1) Video audits of clinical staff while performing self-hand hygiene and patient care to ensure consistency and promote accountability; 2) Implementation of a standardized protocol for catheter connection/disconnection and exit site care; 3) Reinforcement of patient restrictions regarding patient showers and other water exposures; 4) Standard use of ClearGuard Caps and StatLock stabilizers; and 5) Patient and staff participation in frequent education activities.	Current practice.	Outcomes assessed included compliance with the program and the occurrence of CLABSIs. **Results:** Compliance with established protocols fluctuated from 88 to 97%. Multiple Plan-Do-Study-Act (PDSA) improvement cycles occurred and resulted in practice changes being implemented, including wrapping the lines of all patients under the age of 5 and those with developmental delay, and scrubbing the outside of the disconnect cap in the same manner as the hub. In terms of infection outcomes, there were no outpatient CLABSIs

						experienced by the patient cohort over the observation period of 1,115 consecutive days. The results indicate that use of ClearGuard caps and StatLock stabilizers, in combination with other infection prevention measures, can successfully be implemented in a paediatric dialysis program and can result in effective catheter care and a substantial decrease in the risk for infectious complications.
Cost-effective and prophylactic use of Clear Guard Caps for a sustained reduced catheter associated blood stream infection rate.	Glennon et al, 2020 (7) Location: USA	Retrospective analysis of the costs and outcomes associated with use of the intervention and comparator in the paediatric dialysis setting.	*Patient population:* Haemodialysis patients with a CVC. Further details of patient population not reported, other than that the setting is a paediatric dialysis unit. There were no withdrawals, or loss-to-follow-up reported.	ClearGuard caps.	Prophylactic use of antimicrobial locks (AMLs).	Outcomes assessed included CA-BSI rates and costs associated with intervention and comparator. **Results:** The CA-BSI rate for FY18 was 1.82 per 100 patient months with the cost of prophylactic AML usage in 4 high risk patients totalling $25,896. In FY19, AML usage was discontinued and ClearGuard caps were used for all haemodialysis patients

						with CVCs (inclusive of high risk and non-high risk patients) with a total annual cost of $10,140 and the CA-BSI rate dropped to 0.26 per 100 patient months. The results indicate that use of ClearGuard caps is a proven cost-effective tool in helping achieve a low CA-BSI rate in the paediatric dialysis unit. The combination of ClearGuard caps and good catheter care practices may, therefore, substantially decrease the risk of haemodialysis CA-BSI.
Text	Text	Text	Text	Text	Text	Text
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Text	Text	Text	Text	Text	Text	Text

Table 3 Summary of all relevant ongoing or unpublished studies

Data source	Author, year (expected completion) and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Outcomes
Text	Text	Text	Text	Text	Text	Text
Text	Text	Text	Text	Text	Text	Text
Text	Text	Text	Text	Text	Text	Text
Text	Text	Text	Text	Text	Text	Text
Text	Text	Text	Text	Text	Text	Text
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Text	Text	Text	Text	Text	Text	Text

Table 4 Results of all relevant studies (from tables 1, 2 and 3)

Study	Results	Company comments
Brunelli et al, 2018 (1) Cluster-Randomized Trial of Devices to Prevent Catheter-Related Bloodstream Infection	Study results indicate that ClearGuard caps are superior to Tego + Curos for reducing bloodstream infection across all nine analyses. Summary of IRRs and 95% confidence intervals, ClearGuard facilities versus Tego+Curos facilities, for (A) primary analysis and (B–I) exploratory sensitivity analyses presented below. Estimates <1 favour ClearGuard. A) Primary analysis (All PBC): IRR = 0.37 (0.20, 0.68), B) CRBSI analysis: IRR = 0.37 (0.19, 0.72), C) CLABSI analysis: IRR = 0.35 (0.17, 0.70), D) ARBSI analysis: IRR = 0.31 (0.16, 0.61), E) ARBSI, gram-positive organisms: IRR = 0.39 (0.19, 0.79),	Supports claimed benefits of the technology: • Reduced risk of CRBSI, • Reduced hospital attendances and length of stay due to CRBSI, • Reduced mortality as a result of reduced risk of CRBSI.

	F) ARBSI, gram-negative organisms: IRR = 0.18 (0.06, 0.51), G) De novo PBCs: IRR = 0.28 (0.13, 0.59), H) No initial 21-day censor (all PBC): IRR = 0.35 (0.18, 0.67), I) IV antibiotic starts within 3d of PBC: IRR = 0.37 (0.21, 0.62). Additional exploratory analyses were performed in addition to the analyses presented above. Although there was no statistically significant difference in CVC exchange rate, CVC removal rate, thrombolytic use rate, hospital admissions and mortality between the groups, all findings (other than CVC removal rate) favoured ClearGuard. All results presented above show the superior results associated with ClearGuard.	
Hymes et al, 2017 (2) Dialysis Catheter–Related Bloodstream Infections: A Cluster-Randomized Trial of the ClearGuard HD Antimicrobial Barrier Cap	Results presented below are shown in terms of episodes/1,000 CVC-days (12-month comparison): <u>Primary end-point: positive blood culture episodes</u> Intervention group = 0.26, Control group = 0.59, IRR = 0.44 (0.23, 0.83) (P = 0.01). <u>Number of hospital admissions for BSI</u> Intervention group = 0.28, Control group = 0.47, IRR = 0.60 (0.37, 0.97) (P = 0.04). <u>Number of hospitalization-days for BSI</u> Intervention group = 3.24, Control group = 4.68, IRR = 0.69 (0.41, 1.16) (P = 0.2). <u>Number of IV antibiotic starts</u> Intervention group = 1.68,	Supports claimed benefits of the technology: • Reduced risk of CRBSI (Note: Study focussed on PBC event rates rather than CRBSIs specifically), • Reduced hospital attendances and length of stay due to CRBSI (Note: Study focussed on admissions and length of stay related to BSIs rather than CRBSIs specifically).

	Control group = 1.78, IRR = 0.94 (0.74, 1.19) (P = 0.6). Results presented below are shown in terms of episodes/1,000 CVC-days (last 6 months): <u>Primary end-point: positive blood culture episodes</u> Intervention group = 0.22, Control group = 0.72, IRR = 0.31 (0.12, 0.79) (P = 0.01). <u>Number of hospital admissions for BSI</u> Intervention group = 0.28, Control group = 0.48, IRR = 0.57 (0.33, 0.98) (P = 0.04). <u>Number of hospitalization-days for BSI</u> Intervention group = 2.42, Control group = 4.94, IRR = 0.49 (0.25, 0.96) (P = 0.04). All results presented above, for both time periods, show the superior results associated with ClearGuard.	
Weiss et al, 2021 (3) Evaluating a novel hemodialysis central venous catheter cap in reducing bloodstream infections: A quality improvement initiative (Unpublished study)	Comparison of CLABSI rates by study group: <u>First study period</u> Chlorhexidine group: Number of patient-months = 967, CVC-days = 29,010, CLABSI = 1, CLABSI/1,000 CVC days = 0.03. Standard therapy: Number of patient-months = 1,044,	Supports claimed benefits of the technology: • Reduced risk of CRBSI (Note: Study focussed on CLABSI event rates rather than CRBSIs specifically).

	CVC-days = 31,320, CLABSI = 22, CLABSI/1,000 CVC-days = 0.70. The CLABSI rate in the chlorhexidine group was 0.03/1,000 CVC-days versus 0.70/1,000 CVC-days in the standard therapy group (p<0.0001) <u>First and second study periods</u> Chlorhexidine group: Number of patient-months = 4,614, CVC-days = 138,420, CLABSI = 13, CLABSI/1,000 CVC-days = 0.09. Standard therapy: Number of patient-months = 1,320, CVC-days = 39,600, CLABSI = 25, CLABSI/1,000 CVC-days = 0.63. The combined CLABSI rate in the chlorhexidine group was 0.09/1,000 CVC-days versus 0.63/1,000 CVC-days in the standard therapy group (p<0.0001). Causative organisms isolated from central-line associated bloodstream infections among patients dialyzed via central venous catheters: Isolates (n=42) *Gram-positive organism = 25% (59.5%)* Coagulase-negative Staphylococcus Species (CoNS) = 11% (26.2), Methicillin-resistant Staphylococcus aureus (MRSA) = 5% (11.9),	

	Staphylococcus epidermidis = 3% (7.1), Staphylococcus aureus = 2% (4.8), Staphylococcus capitis = 1% (2.4), Enterococcus faecalis = 1% (2.4), Vancomycin-resistant Enterococcus faecalis = 1% (2.4), Streptococcus salivarius = 1% (2.4). *Gram-negative organism = 17% (40.5%)* Acinetobacter baumannii = 4% (9.5), Entereobacter clocae = 3% (7.1), Pantoea agglomerans = 2% (4.8), Escherichia coli = 2% (4.8), Klebsiella pneumoniae = 2% (4.8), Serratia marcescens = 1% (2.4), Stenotrophomonas maltophilia = 1% (2.4), Raoultella planticola = 1% (2.4), Citrobacter Freundii = 1% (2.4).	
Li et al, 2019 (4) Dialysis-Related Bloodstream Infections: A Pre- and Post-ClearGuard HD Cap Conception Study	No additional results, beyond those presented in Table 2, reported in this abstract. Results highlighted below: Median total tracking period (including post infection follow-up) was 1.75 years (range 0.02–4.26) for pre intervention cases; 0.19 years (range 0.08–0.21) for post-intervention cases. Event rate was estimated as 9.7 events per 100 person-years (95% CI 6.7, 14.1) for pre-intervention cases; zero (95% CI 0.0, infinity) for post intervention cases (P = 0.318 for pre- vs. post comparison) with a clear limitation being lack of power given recent implementation date. Study found a statistically significant risk for infection in patients with tunnelled dialysis catheter (P < 0.001). The results therefore indicate that the preliminary post ClearGuard cap conception data currently being followed is	Supports claimed benefits of the technology: • Reduced risk of CRBSI (Note: Study focussed on bacteremia/infection event rates rather than CRBSIs specifically).

	promising for a significant reduction in catheter-related bacteremia.	
Sibbel et al, 2020 (5) Association Between Antimicrobial Barrier Cap Use and Outcomes Among Hemodialysis Patients Using a Central Venous Catheter	No additional results, beyond those presented in Table 2, reported in this abstract. Results highlighted below: Overall BSI rate fell from 0.54/100 CVC days in the pre-period to 0.36/100 CVC days after AmBC implementation. Hospitalization rates were lower during the post-period versus the pre-period overall and within each calendar month; the contribution of underlying temporal changes (e.g., background year-over year change) could not be quantified. Results therefore indicate that the intervention results in reduced BSI and hospitalization rates. Adoption of AmBCs for use in haemodialysis patients using a CVC for vascular access was associated with an early 34% reduction in infections assessed on the basis of positive blood cultures and 0.22 fewer hospital admissions per patient-year.	Supports claimed benefits of the technology: • Reduced risk of CRBSI (Note: Study focussed on BSI event rates rather than CRBSIs specifically), • Reduced hospital attendances and length of stay due to CRBSI (Note: Study focussed on admissions related to BSIs rather than CRBSIs specifically).
Nitz et al, 2021 (6) Prevention of central line associated blood stream infections in a pediatric dialysis unit	No additional results, beyond those presented in Table 2, reported in this abstract. Results highlighted below: Compliance with established protocols fluctuated from 88 to 97%. Multiple Plan-Do-Study-Act (PDSA) improvement cycles occurred and resulted in practice changes being implemented, including wrapping the lines of all patients under the age of 5 and those with developmental delay, and scrubbing the outside of the disconnect cap in the same manner as the hub. In terms of infection outcomes, there were no outpatient CLABSIs experienced by the patient cohort over the observation period of 1,115 consecutive days. The results indicate that use of ClearGuard caps and StatLock stabilizers, in combination with other infection prevention measures, can successfully be implemented in a paediatric dialysis program and can result in effective catheter care and a substantial decrease in the risk for infectious complications.	Supports claimed benefits of the technology: • Reduced risk of CRBSI (Note: Study focussed on CLABSI event rates rather than CRBSIs specifically).

Glennon et al, 2020 (7) Cost-effective and prophylactic use of Clear Guard Caps for a sustained reduced catheter associated blood stream infection rate	No additional results, beyond those presented in Table 2, reported in this abstract. Results highlighted below: The CA-BSI rate for FY18 was 1.82 per 100 patient-months with the cost of prophylactic AML usage in 4 high risk patients totalling $25,896. In FY19, AML usage was discontinued and ClearGuard caps were used for all haemodialysis patients with CVCs (inclusive of high risk and non-high risk patients) with a total annual cost of $10,140 and the CA-BSI rate dropped to 0.26 per 100 patient-months. The results indicate that use of ClearGuard caps is a proven cost-effective tool in helping achieve a low CA-BSI rate in the paediatric dialysis unit. The combination of ClearGuard caps and good catheter care practices may, therefore, substantially decrease the risk of haemodialysis CA-BSI.	Supports claimed benefits of the technology: • Reduced risk of CRBSI (Note: Study focussed on CA-BSI event rates rather than CRBSIs specifically), • Cost savings.

5 Details of relevant studies

Please give details of all relevant studies (all studies in table 4). Copy and paste a new table into the document for each study. Please use 1 table per study.

Brunelli et al, 2018 (1) Cluster-Randomized Trial of Devices to Prevent Catheter-Related Bloodstream Infection	
How are the findings relevant to the decision problem?	Study evaluated use of ClearGuard HD antimicrobial barrier caps amongst patients with CVCs dilayzing in participating facilities. Findings highlight the beneficial impact that the intervention has on PBC, CRBSI, CLABSI, and ARBSI rates.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes: • Reduced risk of CRBSI, • Reduced hospital attendances and length of stay due to CRBSI, • Reduced mortality as a result of reduced risk of CRBSI.
Will any information from this study be used in the economic model?	Yes: Data to inform the incidence rate ratio of CRBSI amongst patients receiving ClearGuard HD compared to Tego + Curos caps.
What are the limitations of this evidence?	No limitations of the analysis are reported.
How was the study funded?	Pursuit Vascular sponsored the study and thus paid DaVita Clinical Research, the clinical research organization of DaVita, for conducting the study. No additional financial relationships exist between DaVita and Pursuit Vascular.

Hymes et al, 2017 (2) Dialysis Catheter–Related Bloodstream Infections: A Cluster-Randomized Trial of the ClearGuard HD Antimicrobial Barrier Cap	
How are the findings relevant to the decision problem?	Study evaluated use of ClearGuard HD antimicrobial barrier caps amongst haemodialysis patients with a tunnelled CVC in participating facilities. Findings highlight the beneficial impact that the intervention has on PBC rates, hospital admissions for BSI, hospitalization days for BSI, and IV antibiotic starts.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes: • Reduced risk of CRBSI (Note: Study focussed on PBC event rates rather than CRBSIs specifically), • Reduced hospital attendances and length of stay due to CRBSI (Note: Study focussed

	on admissions and length of stay related to BSIs rather than CRBSIs specifically).
Will any information from this study be used in the economic model?	Yes: Data to inform the incidence rate ratio of CRBSI amongst patients receiving ClearGuard HD compared to standard CVC caps.
What are the limitations of this evidence?	Limitations of the analysis were: • Study was open label, and intervention patients occasionally received dialysis at non-participating facilities, which likely diminished the effectiveness of the intervention. • Not all positive blood culture measurements were captured, such as during hospitalization; therefore, BSI rates are under-reported. • Diagnosis-specific hospitalizations are not always accurately coded and were likely underestimated due to barriers preventing complete access to hospital discharge records.
How was the study funded?	Pursuit Vascular sponsored the study and thus paid Frenova Renal Research, the clinical research organization of Fresenius, for conducting the study. No additional financial relationships exist between Fresenius and Pursuit Vascular.

Weiss et al, 2021 (3) Evaluating a novel hemodialysis central venous catheter cap in reducing bloodstream infections: A quality improvement initiative	
How are the findings relevant to the decision problem?	Study involved a retrospective observational analysis to compare use of ClearGuard HD with standard needlefree connectors, amongst patients utilising CVC for haemodialysis. Findings indicate that use of the intervention results in a lower infection rate than with the comparator.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes: • Reduced risk of CRBSI (Note: Study focussed on CLABSI event rates rather than CRBSIs specifically).
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Since this was a retrospective analysis of a quality improvement initiative, it was not possible to match data from the chlorhexidine and standard groups because detailed patient demographics and medical history were limited. Therefore, direct comparison was not possible, hindering the

	generalizability of this study's results to a larger outpatient hemodialysis patient population.
How was the study funded?	Financial support for this study was provided by ICU Medical, Inc, 951 Calle Amanecer, San Clemente, CA 92673 in the form of editorial support and statistical analysis.

Li et al, 2019 (4) Dialysis-Related Bloodstream Infections: A Pre- and Post-ClearGuard HD Cap Conception Study	
How are the findings relevant to the decision problem?	This retrospective review study looked at event rates in the pre- and post-intervention period. Findings indicate that clinical event rates, including infection, are higher when the ClearGuard HD Cap is not used.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes: • Reduced risk of CRBSI (Note: Study focussed on bacteremia/infection event rates rather than CRBSIs specifically).
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Limitation is the lack of power in the study, as the abstract was prepared relatively soon after introduction of the intervention in the post-intervention period.
How was the study funded?	Source of funding not reported in this abstract.

Sibbel et al, 2020 (5) Association Between Antimicrobial Barrier Cap Use and Outcomes Among Hemodialysis Patients Using a Central Venous Catheter	
How are the findings relevant to the decision problem?	Study assessed use of AmBC amongst CVC patients in a large dialysis organization and their impact on clinical outcomes. Findings indicate that BSI and hospitalization rates fall after implementation.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes: • Reduced risk of CRBSI (Note: Study focussed on BSI event rates rather than CRBSIs specifically), • Reduced hospital attendances and length of stay due to CRBSI (Note: Study focussed on admissions related to BSIs rather than CRBSIs specifically).

Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	No limitations reported in this abstract.
How was the study funded?	Source of funding not reported in this abstract.

Nitz et al, 2021 (6) Prevention of central line associated blood stream infections in a pediatric dialysis unit	
How are the findings relevant to the decision problem?	Study involves an evaluation of a quality improvement initiative (including use of ClearGuard HD) in a single pediatric dialysis program. Findings indicate that the initiative results in a lower risk of infectious complications.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes: • Reduced risk of CRBSI (Note: Study focussed on CLABSI event rates rather than CRBSIs specifically).
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	No limitations reported in this abstract.
How was the study funded?	Source of funding not reported in this abstract.

Glennon et al, 2020 (7) Cost-effective and prophylactic use of Clear Guard Caps for a sustained reduced catheter associated blood stream infection rate	
How are the findings relevant to the decision problem?	Study looked at the CA-BSI rates associated with use of ClearGuard HD caps compared to prophylactic use of AMLs in the pediatric dialysis setting. Findings indicate that use of the intervention results in lower infection rates and is a cost-effective use of health service resources.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes: • Reduced risk of CRBSI (Note: Study focussed on CA-BSI event rates rather than CRBSIs specifically),

	• Cost savings.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	No limitations reported in this abstract.
How was the study funded?	Source of funding not reported in this abstract.

6 Adverse events

Describe any adverse events and outcomes associated with the technology in national regulatory databases such as those maintained by the MHRA and FDA (Maude). Please provide links and references.

A search of the Medicine and Healthcare Products Regulatory Agency (MHRA) website (30th April 2021) showed no manufacturer field safety notices or medical device alerts have been issued for ClearGuard® HD Antimicrobial Barrier Cap (https://www.gov.uk/drug-device-alerts).

ICU Medical, Inc. has received US FDA 510(k) clearance for the ClearGuard® HD Antimicrobial Barrier Cap with a classification product code "PEH" (Hemodialysis Catheter Luer End Cap) (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm). ClearGuard® HD Antimicrobial Barrier Cap pre-market notification submission (510(k)) awarded.

Search of the FDA recall database (30th April 2021) with the terms "ClearGuard" and "Clear Guard" returned no result. (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm).

A search of the FDA adverse databases (MAUDE, MDR and MedSun) with search dates from 1976 to 30th April 2021 using the product code "PEH" and, and brand name "ClearGuard" identified 6 records related to mis-assembly by user, installation-related problem or detachment of device or device component. In no cases were there adverse consequences for the patient. Therefore, we can conclude that the device is safe when used as intended.

Since the search period, there have been no vigilance reports or recalls.

Describe any adverse events and outcomes associated with the technology in the clinical evidence.

Adverse events reported in clinical studies identified:

- Brunelli et al, 2018 (1): No protocol deviation or device-related adverse events reported during the study.
- Hymes et al, 2017 (2): No protocol changes or device-related adverse events reported during the study.
- Weiss et al, 2021 (3): No device-related adverse events reported during this study.
- Li et al, 2019 (4): No device-related adverse events reported in this abstract.
- Sibbel et al, 2020 (5): No device-related adverse events reported in this abstract.
- Nitz et al, 2021 (6): No device-related adverse events reported in this abstract.
- Glennon et al, 2020 (7): No device-related adverse events reported in this abstract.

7 Evidence synthesis and meta-analysis

Although evidence synthesis and meta-analyses are not necessary for a submission, they are encouraged if data are available to support such an approach.

If an evidence synthesis is not considered appropriate, please instead complete the section on qualitative review.

If a quantitative evidence synthesis is appropriate, describe the methods used. Include a rationale for the studies selected.

A quantitative synthesis was not possible due to the differing comparators included in identified, full-text studies (1, 2, 3).

Report all relevant results, including diagrams if appropriate.

Not applicable.

Explain the main findings and conclusions drawn from the evidence synthesis.

Not applicable.

Qualitative review

Please only complete this section if a quantitative evidence synthesis is not appropriate.

Explain why a quantitative review is not appropriate and instead provide a qualitative review. This review should summarise the overall results of the individual studies with reference to their critical appraisal.

As outlined previously, a quantitative evidence synthesis was not appropriate due to the fact that comparators differed across the three full-text studies (1, 2, 3). All identified, full-text published studies were critically appraised using appropriate and validated quality assessment instruments. The Critical Appraisal Skills Programme Checklists (for randomised controlled trials (11), and for cohort studies (12)) were used to critically appraise the three full-text studies identified (1, 2, 3). Identified abstracts were not included due to the limited data presented.

Study author: Brunelli et al, 2018 (1)		
Study question	**Response (Yes/Can't tell/No/N/A)**	**Comments**
Did the trial address a clearly focussed issue?	Yes	Study involved a rigorous analysis of the impact of

		introducing ClearGuard HD amongst patients undergoing HD with CVCs. Population, intervention, comparator, and outcomes of interest were all clearly outlined.	
Was the assignment of patients to treatments randomised?	Yes	Patients across forty dialysis facilities were randomised to intervention or control groups. Study was a cluster-randomised study, with a cluster defined as a pair of facilities that were matched for pre-study BSI rate, geographic location and number of patients with CVCs.	
Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes	The study was carried out over its intended duration, with the flow of patients at each stage of the study clearly presented. All patients were properly accounted for at its conclusion.	
Were patients, health workers and study personnel 'blind' to treatment?	No	Randomisation was performed with the facility as the cluster, with all patients receiving the corresponding treatment.	
Were the groups similar at the start of the trial?	Yes	At the run-in phase of the study, characteristics of participants in the two study groups were reasonably balanced, with the exception of race (35% versus 46% black, respectively; omnibus P=0.02) and diabetes (55% versus 64%, respectively; P=0.02). PBC rates across groups were also similar during this baseline period (1.02 PBCs per 1,000 CVC-days in the ClearGuard group and 1.08 per 1,000 CVC-days in the comparator group: p=0.8). At the intervention phase of the study, characteristics of participants across groups were reasonably balanced, with the exception of age (63.7 versus 62.0 years, respectively; P=0.02) and race (32% versus 42%	

		black, respectively; omnibus P<0.001).
Aside from the experimental intervention, were the groups treated equally?	Yes	Patients were treated equally, other than administration of intervention/comparator.
How large was the treatment effect?	N/A	Study results indicate that ClearGuard caps are superior to Tego + Curos for reducing bloodstream infection across all of the nine analyses presented: A) Primary analysis (All PBC): IRR = 0.37 (0.20, 0.68), B) CRBSI analysis: IRR = 0.37 (0.19, 0.72), C) CLABSI analysis: IRR = 0.35 (0.17, 0.70), D) ARBSI analysis: IRR = 0.31 (0.16, 0.61), E) ARBSI, gram-positive organisms: IRR = 0.39 (0.19, 0.79), F) ARBSI, gram-negative organisms: IRR = 0.18 (0.06, 0.51), G) De novo PBCs: IRR = 0.28 (0.13, 0.59), H) No initial 21-day censor (all PBC): IRR = 0.35 (0.18, 0.67), I) IV antibiotic starts within 3d of PBC: IRR = 0.37 (0.21, 0.62).
How precise was the estimate of the treatment effect?	N/A	In the intervention phase of the study, p-values related to the incidence rate ratio associated with the occurrence of PBC, CLABSI, and ARBSI were all <0.004. Confidence intervals around results were also reported.
Can the results be applied to the local population, or in your context?	Yes	Results are generalizable across countries/settings given the similarities in treatment processes. Additionally, the patient population included in this study is similar to that which would receive the intervention in other countries/settings.
Were all clinically important outcomes considered?	Yes	Study looked at multiple different infection outcomes, while also considering

		impact of the intervention on hospital admissions and mortality.
Are the benefits worth the harms and costs?	Can't tell	Given the statistically significant benefit that the intervention has been shown to have on infection outcomes, while also reducing hospital admission rates and mortality, it is likely that the benefits of the intervention outweigh the costs. However, a formal economic evaluation would need to be conducted to definitively answer the question.
Adapted from the CASP Checklist: 11 questions to help you make sense of a randomised controlled trial (11)		

Study author: Hymes et al, 2017 (2)		
Study question	**Response (Yes/Can't tell/No/N/A)**	**Comments**
Did the trial address a clearly focussed issue?	Yes	Study explored the impact of introducing ClearGuard HD on infection and hospitalisation outcomes amongst patients undergoing HD with CVCs, compared to standard CVC caps.
Was the assignment of patients to treatments randomised?	Yes	Patients across forty dialysis facilities were randomised to intervention or control groups. Study was a cluster-randomised study, with a cluster defined as a pair of facilities that were matched for pre-study BSI rate and number of patients with CVCs.
Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes	The study was carried out over its intended duration (1-month pre-intervention period and 12-month follow-up), with the flow of patients at each stage of the study clearly presented. All patients were properly accounted for at its conclusion.
Were patients, health workers and study personnel 'blind' to treatment?	No	Randomisation was performed with the facility as the cluster, with all patients receiving the corresponding treatment.

Were the groups similar at the start of the trial?	Yes	Patients in intervention and control groups were broadly similar at both the pre-intervention and follow-up stages of the study. The study reports information on average age, sex and race of patients and the number of diabetic patients amongst each cohort. Presented data highlight the similarities between the groups. Additionally, during the pre-intervention period, there was no significant difference between the intervention and control groups in terms of PBC rates (0.56 vs 0.60/1,000 CVC-days; P = 0.8).	
Aside from the experimental intervention, were the groups treated equally?	Yes	Patients were treated equally, other than administration of intervention/comparator.	
How large was the treatment effect?	N/A	A 69% reduction in PBC rate following introduction of ClearGuard HD was demonstrated during the last 6 months of the study. Hospital admissions for BSI in the last 6 months of the study were reduced by 43%. Similarly, hospitalisation days in this same period were reduced by 51%.	
How precise was the estimate of the treatment effect?	N/A	In the last 6 months of the study, p-values related to the outcomes presented in the previous response were all <0.005. Confidence intervals around results were also reported.	
Can the results be applied to the local population, or in your context?	Yes	Results are generalizable across countries/settings given the similarities in treatment processes. Additionally, the patient population included in this study is similar to that which would receive the intervention in other countries/settings.	
Were all clinically important outcomes considered?	Yes	Study looked at the most important infection outcome relevant for this patient population (PBC rate), while also considering impact of	

		the intervention on hospital admissions and hospital bed-days.
Are the benefits worth the harms and costs?	Can't tell	Given the statistically significant benefit that the intervention has been shown to have on infection outcomes, while also reducing hospital admission rates and hospital bed-days, it is likely that the benefits of the intervention outweigh the costs. However, a formal economic evaluation would need to be conducted to definitively answer the question.
Adapted from the CASP Checklist: 11 questions to help you make sense of a randomised controlled trial (11)		

Study author: Weiss et al, 2021 (3)		
Study question	**Response (Yes/Can't tell/No/N/A)**	**Comments**
Did the study address a clearly focussed issue?	Yes	Study involved a retrospective analysis comparing CLABSI rates amongst patients receiving ClearGuard HD, with patients receiving Tego needlefree connectors (standard therapy group), whilst undergoing HD with CVCs.
Was the cohort recruited in an acceptable way?	Yes	This was a retrospective analysis of data collected from a quality improvement assessment conducted at 13 outpatient dialysis clinics. Patient consent was not required since this was a retrospective assessment of a quality improvement project. Additionally, all patient data were de-identified, and confidentiality of data was maintained throughout the course of the study.
Was the exposure accurately measured to minimise bias?	Yes	The procedures regarding use of the intervention, and steps taken in treating patients, are well described and it doesn't appear that there is likely to be bias present in relation to

		measurement of the exposure.
Was the outcome accurately measured to minimise bias?	Yes	Standard procedures were applied to measure occurrence of CLABSIs.
Have the authors identified all important confounding factors?	Yes	The authors acknowledge that since this was a retrospective analysis of a quality improvement initiative, it was not possible to match data from the chlorhexidine and standard groups because detailed patient demographics and medical history were limited. Therefore, direct comparison was not possible, hindering the generalizability of this study's results to a larger outpatient haemodialysis patient population.
Have they taken account of the confounding factors in the design and/or analysis?	Yes	The authors acknowledge that since this was a retrospective analysis of a quality improvement initiative, it was not possible to match data from the chlorhexidine and standard groups because detailed patient demographics and medical history were limited. Therefore, direct comparison was not possible, hindering the generalizability of this study's results to a larger outpatient haemodialysis patient population.
Was the follow up of subjects complete enough?	N/A	The outcome measure was the number of CLABSI cases, i.e., patients were not followed-up over the longer-term.
Was the follow up of subjects long enough?	N/A	The outcome measure was the number of CLABSI cases, i.e., patients were not followed-up over the longer-term.
What are the results of this study?	N/A	Findings indicate that use of the intervention results in a lower infection rate than with the comparator. First and second study periods Chlorhexidine group:

		Number of patient-months = 4,614, CVC-days = 138,420, CLABSI = 13, CLABSI/1,000 CVC-days = 0.09. Standard therapy (Tego): Number of patient-months = 1,320, CVC-days = 39,600, CLABSI = 25, CLABSI/1,000 CVC-days = 0.63. The combined CLABSI rate in the chlorhexidine group was 0.09/1,000 CVC-days versus 0.63/1,000 CVC-days in the standard therapy group (p<0.0001).	
How precise are the results?	N/A	Results were statistically significant, with a p-value <0.0001 related to the reduction in CLABSI rates following introduction of the intervention.	
Do you believe the results?	Yes	Methods of the study are robust and well-described. Additionally, the results are statistically significant, adding to the credibility of the findings.	
Can the results be applied to the local population?	Not clear	The authors acknowledge that detailed patient demographics and medical history were limited, which hinders the generalizability of this study's results to a larger outpatient haemodialysis patient population.	
Do the results of this study fit with other available evidence?	Yes	Study has shown the beneficial impact of the intervention on infection outcomes, which is consistent with the results presented in the two, large, trial publications (1, 2).	
What are the implications of this study for practice?	Yes	Combined with the results presented in the other two full-text publications identified (1, 2), the results of this analysis suggest that ClearGuard HD may be an appropriate alternative to existing methods used	

		amongst patients undergoing HD with CVCs.
Adapted from the CASP Checklist: 12 questions to help you make sense of a cohort study (12)		

Based on the evidence presented above, overall, the studies were found to be of good quality which allows one to consider the presented results as robust and to be an accurate reflection of the outcomes and potential benefits associated with ClearGuard HD.

8 Summary and interpretation of clinical evidence

Summarise the main clinical evidence, highlighting the clinical benefit and any risks relating to adverse events from the technology.

The clinical evidence indicates that use of the ClearGuard HD Antimicrobial Barrier Cap amongst patients utilizing CVCs during HD results in decreased rates of BSIs, CLABSIs, CRBSIs, CRIs, PBCs and ARBSIs. Additionally, those studies which conducted antibiotic analysis, and/or looked at differences in hospital admission rates, length of stay in hospital, mortality rates, CVC exchange rates and thrombolytic use rates between groups, showed results which either favoured ClearGuard HD or which showed no statistically significant difference between the groups. Finally, the identified study which involved an economic analysis showed that costs associated with patients in the ClearGuard HD group were lower than amongst patients in the comparator group. Therefore, the evidence is consistent with the conclusion that using the ClearGuard HD Antimicrobial Barrier Cap is an effective way of reducing infection rates, and associated hospitalisations, mortality, and costs, amongst patients utilizing central venous catheters during haemodialysis.

The three full-text publications identified (Brunelli et al, 2018 (1), Hymes et al, 2017 (2) and Weiss et al, 2021 (3)) all showed statistically significant results in favour of the intervention. In Brunelli et al, 2018 (1), the relative risk of the following events occurring amongst patients receiving ClearGuard were all less than 1 (and all were statistically significant): - PBC rates, - CRBSI rates, - CLABSI rates, - ARBSI rates, - ARBSI, gram-positive organisms, - ARBSI gram-negative organisms, - de novo PBCs, - PBC when no initial 21-day censor, - IV antibiotic starts within 3 days of PBC. Additional findings, although not statistically significant, showed lower hospital admission and mortality rates amongst patients receiving ClearGuard. In Hymes et al, 2017 (2), results from the last 6 months of the study showed statistically significant results in favour of the intervention. The relative risks associated with the occurrence of PBC episodes, hospital admissions for BSI and hospitalization days for BSI were all less than 1, with statistically significant results in all cases. The final full-text publication identified (Weiss et al, 2021 (3)) showed that over the entire study period, there was an 86% reduction in the occurrence of CLABSIs, with statistically significant results (p-value = <0.0001).

Results from the four identified abstracts all showed results which favoured ClearGuard. Li et al, 2019 (4) highlighted the statistically significant risk for infection in patients receiving tunnelled dialysis catheter (p-value = <0.001) and identified zero events amongst patients in the post-intervention period. Sibbel et al, 2020 (5) showed a 33% reduction in BSI rates in the post-intervention period, and also highlighted that hospitalization rates were lower in the post-period than prior to introduction of the intervention. Nitz et al, 2021 (6) reported that use of ClearGuard as part of a multi-component quality improvement initiative resulted in no outpatient CLABSIs amongst a patient cohort of 1,115 over the observation period. Finally, Glennon et al, 2020 (7) reported an 86% decrease in CA-BSI rates amongst patients receiving ClearGuard, with annual costs substantially higher amongst patients receiving prophylactic AML ($25,896) compared to those receiving the intervention ($10,140).

A critical appraisal of the full-text studies identified was conducted, where it was found that overall, the studies were of good quality, and the results can be considered to be robust, and an accurate reflection of the outcomes and potential benefits associated with ClearGuard HD.

A targeted search was also performed in order to identify any information around adverse events associated with the technology (Section 6). No ClearGuard HD-related adverse events (that would result in adverse consequences for the patient) were found in searches of the MHRA and FDA databases or reported in any of the clinical studies identified.

Although the majority of the clinical studies identified have involved comparisons between ClearGuard and standard CVC caps or Tego connectors, without providing much commentary on locking solutions, the clinical issues associated with antimicrobial locking solutions should also be considered when evaluating the benefits of ClearGuard over alternative technologies. ClearGuard may be used in combination with a safe, low-concentration 4% citrate lock, or options including heparin locks (as seen in Hymes et al, 2017 (2)) and saline locks (as seen in Brunelli et al, 2018 (1)). However, in the UK, high-concentration citrate and taurolidine are used as locking solutions, both of which have associated clinical issues. High-concentrate sodium citrate anticoagulant (30% and 46.7%) has previously been linked with patient death in the USA and to this day, is not permitted for use (13). However, despite these safety issues, high-concentrate citrate locks are still frequently used in the UK. Similarly, taurolidine has been associated with catheter occlusion (14). The ability for ClearGuard to be used with low-concentrate citrate locking solutions, as well as heparin and saline solutions, is therefore a clear benefit of the intervention over certain, existing methods.

Briefly discuss the relevance of the evidence base to the scope. This should focus on the claimed benefits described in the scope and the quality and quantity of the included studies.

The evidence base includes studies involving evaluations of ClearGuard HD use amongst patients undergoing HD. The relevance of this evidence to the scope is provided below.

ClearGuard HD Evidence: 3 published manuscripts and 4 published abstracts/posters.

- These studies were conducted in the USA.
- Patients included in the studies were those utilizing CVCs for haemodialysis.
- All of the evidence was collected in real-world use settings, which demonstrates the ability of the intervention to act as an alternative option to routine standard of care.
- Comparative studies involved control groups that involved standard CVC groups or Tego combined with Curos, as an example of a specified comparator.
- Outcomes included in the scope are represented in the evidence collected, including: incidence of infection, in the form of; CRBSI, CRI, CLABSI, PBC, ARBSIs, hospital admissions for BSI, length of stay, mortality, intravenous antibiotic use and device-related adverse events.
- Results were generally in favour of the intervention, as described in the previous section as well as in Sections 4, 5 and 7.
- All identified, full-text studies were critically appraised using appropriate and validated quality assessment instruments (11, 12). Overall, the studies were found to be of good quality which allows one to consider the presented results as robust and to be an accurate reflection of the outcomes and potential benefits associated with ClearGuard HD.

The evidence relates directly to the claimed benefits of the technology, in that it highlights the beneficial impact that the intervention has on patient outcomes, as well as for the NHS.

Identify any factors which might be different between the patients in the submitted studies and patients having routine care in the UK NHS.

None identified. Although studies were US-based, the treatment process (and benefits) associated with the use of ClearGuard HD should be the same.

Describe any criteria that would be used in clinical practice to select patients for whom the technology would be most appropriate.

The ClearGuard HD Antimicrobial Cap is intended for use amongst patients with central venous catheters undergoing haemodialysis, in place of standard care. The studies included in this clinical evidence submission are pragmatic "real-world" studies and do not represent a small sub-group of patients.

Briefly summarise the strengths and limitations of the clinical evidence for the technology.

Strengths:

- A comprehensive systematic review has been conducted focussing on clinical evidence related to use of the device, across all relevant databases.
- A number of studies focusing on the clinical effectiveness of ClearGuard HD have been identified (3 full-text, published studies and 4 abstracts).
- The evidence is based on evaluations conducted in real-world use settings.
- All studies which looked at the impact of the intervention on BSI, CRBSI, CRI, CLABSI, PBC and ARBSI rates showed results in favour of ClearGuard HD.
- All studies which assessed hospital admission rates, length of stay and mortality rates showed results in favour of ClearGuard HD.
- Studies which undertook intravenous antibiotic analysis either reported no statistically significant difference between the comparators or showed results in favour of ClearGuard HD.
- Studies which also involved an economic analysis (Glennon et al, 2020 (7)) showed the economic benefits associated with introduction of the intervention.

Limitations:

- The countries in which studies have been conducted are not varied, with all being carried out in the USA.
- One study (Hymes et al, 2017 (2)) commented on the fact that the effectiveness of the intervention may have been diminished due to the open label nature of the study and because intervention patients occasionally received dialysis at non-participating facilities.
- One study (Hymes et al, 2017 (2)) reported the under-reporting of BSI rates due to the fact that not all positive blood culture measurements were captured, such as during hospitalization.
- One study (Hymes et al, 2017 (2)) reported that diagnosis-specific hospitalizations were not always accurately coded and were likely underestimated due to barriers preventing complete access to hospital discharge records.

- One study (Weiss et al, 2021 (3)) reported that it was not possible to match data from the chlorhexidine and standard groups because detailed patient demographics and medical history were limited. Therefore, direct comparison was not possible, hindering the generalizability of this study's results to a larger outpatient hemodialysis patient population.
- One study (Li et al, 2019 (4)) reported a lack of power due to the fact that the abstract was prepared relatively soon after introduction of the intervention in the post-intervention period.

9 References

Please include all references below using NICE's standard referencing style.

1. Brunelli, SM, van Wyck, DB, Njord, L., et al. Cluster-Randomized Trial of Devices to Prevent Catheter-Related Bloodstream Infection (2018). J Am Soc Nephrol 29: 1336–1343, 2018.
2. Hymes, JL, Mooney, A, van Zandt, C, et al. Dialysis Catheter–Related Bloodstream Infections: A Cluster-Randomized Trial of the ClearGuard HD Antimicrobial Barrier Cap (2017). Am J Kidney Dis. 69(2):220-227.
3. Weiss, S, & Qureshi, MN. Evaluating a novel hemodialysis central venous catheter cap in reducing bloodstream infections: A quality improvement initiative (2021). International Journal of Nephrology and Renovascular Disease. 14 125–131.
4. Li, W, Otto, C, Nakeshbandi, M, et al. Dialysis-Related Bloodstream Infections: A Pre- and Post-ClearGuard HD Cap Conception Study (2019). Conference Abstract – Poster Abstract at OFID 2019.
5. Sibbel, S, Hunt, A, van Wyck, DB, et al. Association Between Antimicrobial Barrier Cap Use and Outcomes Among Hemodialysis Patients Using a Central Venous Catheter (2020). Conference Abstract at Peritoneal Dialysis and Vascular Access: Research Abstracts.
6. Nitz, K, Grimes, J, Nau, A, et al. Prevention of central line associated blood stream infections in a pediatric dialysis unit (2021). Conference Abstract – Annual Dialysis Conference 2021.
7. Glennon, L, Enochs, K, Butaud, M, et al. Cost-effective and prophylactic use of Clear Guard Caps for a sustained reduced catheter associated blood stream infection rate (2020). Conference Abstract – Hemodialysis International 2020.
8. United States Renal Data System: 2018 USRDS Annual Data Report: End-stage Renal Disease in the United States, Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2018.
9. NICE. Healthcare-associated infections: prevention and control in primary and community care (2012). NICE Clinical Guidelines [CG139].
10. NICE. Curos for preventing infections when using needleless connectors (2019). NICE Medical Technologies Guidance [MTG44].
11. Critical Appraisal Skills Programme (2020). CASP (Randomised Controlled Trial) Checklist. [online] Available at: https://casp-uk.b-cdn.net/wp-content/uploads/2020/10/CASP_RCT_Checklist_PDF_Fillable_Form.pdf. Accessed: 15/05/2021.
12. Critical Appraisal Skills Programme (2018). CASP (Cohort Study) Checklist. [online] Available at: https://casp-uk.b-cdn.net/wp-content/uploads/2018/01/CASP-Cohort-Study-Checklist_2018.pdf. Accessed: 15/05/2021.
13. FDA Alerts. FDA issues warning on TRICITRASOL (2000). Available online at <fda_warning_letter 46.7 sodium citrate APR2000.pdf> [Accessed on 06/05/2021].
14. Allon, M. Prophylaxis against Dialysis Catheter–Related Bacteremia with a Novel Antimicrobial Lock Solution (2003). CID 2003:36.
15. Butaud, M, Enochs, K, Glennon, L, et al. Cost-effective use of ClearGuard® Caps in Pediatric Hemodialysis (2020). Conference Abstract – Poster Abstract at Annual Dialysis Conference 2020.
16. ClinicalTrials.gov. Product Evaluation for the Effectiveness of the ClearGuard® HD End Cap (2019). ClinicalTrials.gov, Accessed at: [file:///C:/Users/eoinm/OneDrive/1.%20OAX/3.%20DAX%20projects/16.%20ICU%20Medical/7.%20SLR/Clinical/Identified%20studies/Full-texts/Product%20Evaluation%20for%20the%20Effectiveness%20of%20the%20ClearGuard%C2%AE%20HD%20End%20Cap%20-%20Full%20Text%20View%20-%20ClinicalTrials.gov.html] on 12/04/2021.

10 Appendices

Appendix A: Search strategy for clinical evidence

Describe the process and methods used to identify and select the studies relevant to the technology. Include searches for published studies, abstracts and ongoing studies in separate tables as appropriate. See section 2 of the user guide for full details of how to complete this section.

Date search conducted:	09/04/2021
Date span of search:	Until 09/04/2021 (please see search strategies below for precise date ranges)
List 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). List the databases that were searched.	

Database: Ovid MEDLINE(R) ALL <1946 to April 9, 2021>

		Result
1	Catheters, indwelling/ or central venous catheters/	20826
2	Catheter*.ti,ab.	208259
3	exp Catheterization, Peripheral/	12071
4	Cardiac Catheterization/	49509
5	Catheter-Related Infections/	5318
6	(catheter$ or microcatheter$ or cannula$ or microcannula$ or canula$ or microcanula$).ti,ab,kf.	256993
7	((hemodialysis and (catheter or "central venous catheter" or CVC) and infection) or bacteremia).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	41022
8	Vascular access*.ti,ab.	10106
9	(CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs).ti,ab,kf.	17112
10	((PIC or CVP) adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kf.	135
11	((central or subclavian or jugular or femoral) adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kf.	19912
12	(peripheral adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kf.	7698
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.	33486
14	((arterial or intraarterial or artery or arteries) adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kf.	9719
15	Catheters, Indwelling/ or Bacteremia/ or Catheter-Related Infections/ or catheter-related bloodstream infections.mp. or Catheterization, Central Venous/ or Central Venous Catheters/	57415

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).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1944
17	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	384842
18	Clearguard.mp.	3
19	Clear Guard/	0
20	CGHD/	0
21	Pursuit Vascular/	0
22	Antiseptic cap/	0
23	Antiseptic cap.mp.	1
24	Antimicrobial barrier cap.mp.	1
25	Antimicrobial lock.mp.	87
26	18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	90
27	17 and 26	87

Database: Embase <1974 to April 9, 2021>

		Result
1	Vascular access/	28094
2	Hemodialysis/	114156
3	Catheters, indwelling/ or central venous catheters/	28768
4	exp catheter/	196356
5	Catheter infection/	18826
6	(catheter$ or microcatheter$ or cannula$ or microcannula$ or canula$ or microcanula$).ti,ab,kw.	388620
7	(CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs).ti,ab,kw.	27819
8	((PIC or CVP) adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kw.	260
9	((central or subclavian or jugular or femoral) adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kw.	32187
10	(peripheral adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kw.	10663
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.	53652
12	((arterial or intraarterial or artery or arteries) adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kw.	15596
13	catheter-related bloodstream infections.mp. or catheter infection/	19033
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).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	3929
15	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	637843
16	clearguard$2.ti,ab,kw,dv.	10
17	Clear Guard/	40
18	CGHD/	0

19	Antimicrobial barrier cap/	0
20	Antimicrobial lock/	2
21	Antiseptic lock/	0
22	Antiseptic cap/	0
23	Pursuit Vascular/	0
24	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23	51
25	15 and 24	16

Database: Cochrane <to April 9, 2021>

		Result
1	clearguard OR Clear Guard OR Pursuit Vascular OR Antimicrobial barrier cap OR Antimicrobial lock in All Text - (Word variations have been searched)	32

Database: ClinicalTrials.gov <to April 9, 2021>

		Result
1	Clearguard OR Pursuit "Vascular" OR "Clear Guard" OR "Antimicrobial barrier cap" OR "Antiseptic lock"	13

Database: ICTRP <to April 9, 2021>

		Result
1	Clearguard OR Pursuit "Vascular" OR "Clear Guard" OR "Antimicrobial barrier cap" OR "Antiseptic lock"	2

Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):

References of the identified studies were checked for relevant studies. We also consulted with key personnel in the Company to ensure that we had not missed any relevant studies that they were aware of.

Inclusion and exclusion criteria:

Inclusion criteria

Population: The target population for this review is patients undergoing HD using CVCs.

Intervention: The intervention being considered in this review is the ClearGuard™ HD Antimicrobial Barrier Cap to minimize the risk of CRBSIs amongst patients undergoing HD using CVCs.

Comparator(s): The comparators are current standard care, which includes the use of alcohol wipes and alcohol containing solution of chlorhexidine gluconate (2% chlorhexidine gluconate in 70% alcohol), as well as alternative barrier caps.

As we aim to include all possible comparators in the review, we will exclude the search terms related to comparators in the search strategy.

Outcomes: Relevant health outcomes included:

- Adverse and beneficial effects of intervention and comparator(s),
- Efficacy,
- Effectiveness,
- Usability,
- Safety outcomes.

Country: There will be no limitation of included studies based on study country. All studies meeting the inclusion criteria which were conducted in any country to be included in the review.

Language: Only studies with full text in English will be included in this review. Studies with abstracts in English but full text published in any language other than English will be excluded.

Publication timeframe: All studies published from database start to present will be included in this review in order to obtain all available evidence.

Study design: We will include all types of study designs (Observational studies (Cross-sectional; Case-control; Cohort) and clinical trials)) in this systematic review. Additional hand-searching will be conducted to identify any unpublished studies.

Exclusion criteria

The following study types will be excluded:

- Animal studies,
- Case-reports,
- Editorials; commentary,
- Device name not reported as intervention or comparator,
- Incorrect population,
- Incorrect outcomes,
- Economic analysis.

Additionally, any studies not meeting any other of the inclusion criteria outlined above will be excluded.

Data abstraction strategy:

Data from all included studies will be extracted using a pre-designed form. Data on the following information will be extracted: study setting, study population, inclusion/exclusion criteria, baseline characteristics, study methodology, recruitment, study completion rate, details of intervention including how the intervention was delivered, outcomes and type of measurement, potential confounding factors, funding, and conflicts of interest. Data extraction will be undertaken by one reviewer and checked by a second independent reviewer. Disagreements between the review authors will be resolved by discussion and consensus with involvement of a third review author where necessary.

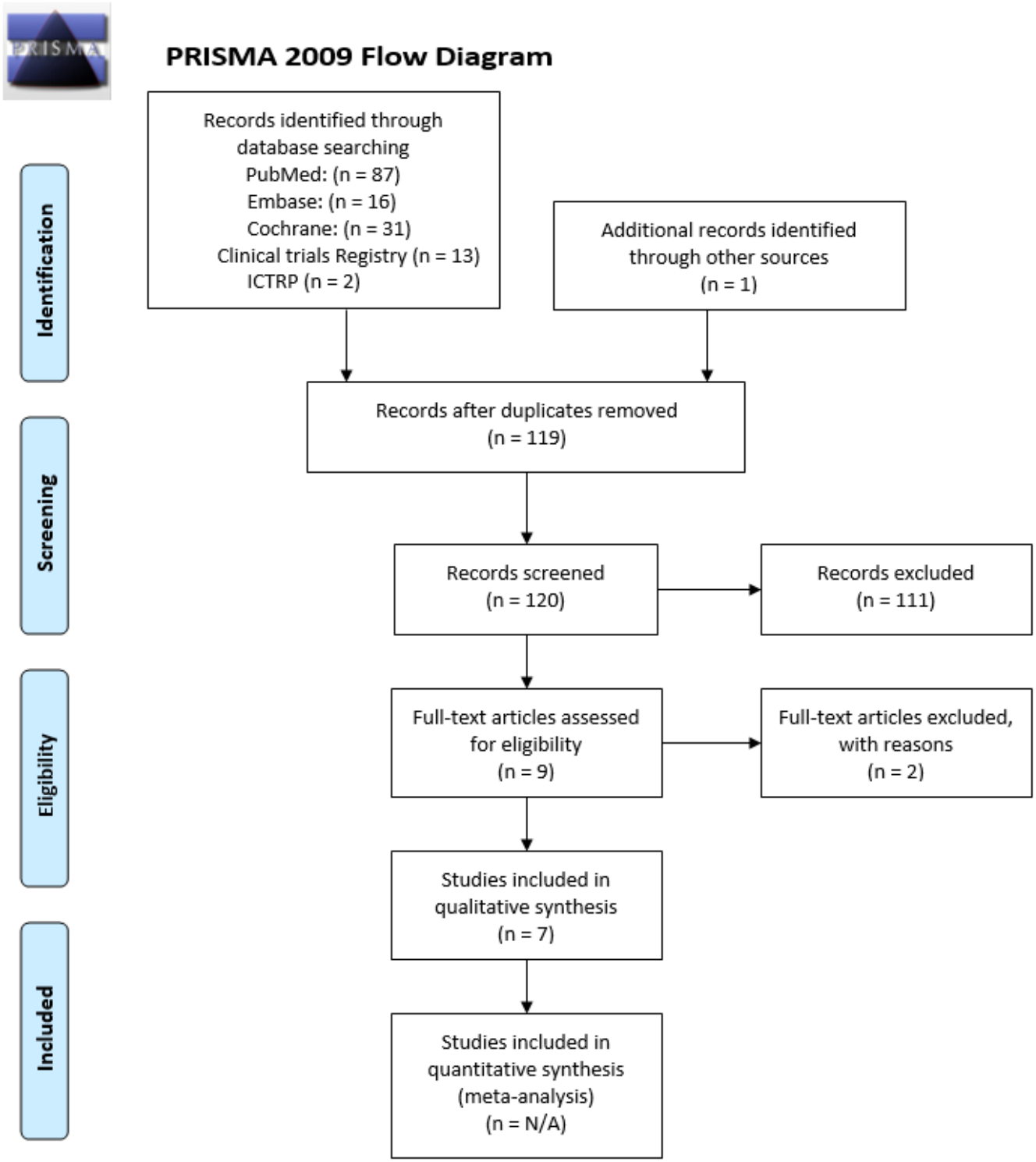
The authors of each study will be consulted when there is incomplete or missing relevant data.

Excluded studies

List any excluded studies below. These are studies that were initially considered for inclusion at the level of full text review, but were later excluded for specific reasons.

Excluded study	Design and intervention(s)	Rationale for exclusion	Company comments
Cost-effective use of ClearGuard® Caps in Pediatric Hemodialysis (15)	Retrospective analysis of the costs and outcomes associated with use of ClearGuard compared with prophylactic use of antimicrobial locks in the paediatric dialysis setting.	This was a duplicate of the analysis presented in Glennon et al, 2020 (7) and was thus omitted. It was identified as a duplicate at the full-text screening stage.	None
Product Evaluation for the Effectiveness of the ClearGuard® HD End Cap (16)	Comparison of ClearGuard with Tego/Curos as part of a cluster-randomized, open-label trial.	This was a record, and overview, of the clinical study published in Brunelli et al, 2018 (1). Therefore, it is not a unique publication in its own right, rather it is a duplication of an already identified study. It was identified as a duplicate at the full-text screening stage.	None
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).



Structured abstracts for unpublished studies

Study title and authors
Introduction
Objectives
Methods
Results
Conclusion
Article status and expected publication: Provide details of journal and anticipated publication date

Appendix B: Search strategy for adverse events

Date search conducted:	30/04/2021
Date span of search:	Please see Section 6.
List 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). List the databases that were searched.	
Please see Section 6.	
Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):	
Please see Section 6.	
Inclusion and exclusion criteria:	
Enter text.	
Data abstraction strategy:	
Enter text.	

Adverse events evidence

List any relevant studies below. If appropriate, further details on relevant evidence can be added to the adverse events section.

Study	Design and intervention(s)	Details of adverse events	Company comments
Text	Text	Text	Text
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Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).

Enter text.

Appendix C: Checklist of confidential information

Please see section 1 of the user guide for instructions on how to complete this section.

Does your submission of evidence contain any confidential information? (please check appropriate box):

No ☒ If no, please proceed to declaration (below)

Yes ☐ If yes, please complete the table below (insert or delete rows as necessary). Ensure that all relevant sections of your submission of evidence are clearly highlighted and underlined in your submission document, and match the information in the table. Please add the referenced confidential content (text, graphs, figures, illustrations, etc.) to which this applies.

Page	Nature of confidential information	Rationale for confidential status	Timeframe of confidentiality restriction
#	☐ Commercial in confidence ☐ Academic in confidence	Enter text.	Enter text.
Details	Enter text.		
#	☐ Commercial in confidence ☐ Academic in confidence	Enter text.	Enter text.
Details	Enter text.		

Confidential information declaration

I confirm that:

- all relevant data pertinent to the development of medical technology guidance (MTG) has been disclosed to NICE
- all confidential sections in the submission have been marked correctly
- if I have attached any publication or other information in support of this notification, I have obtained the appropriate permission or paid the appropriate copyright fee to enable my organisation to share this publication or information with NICE.

Please note that NICE does not accept any responsibility for the disclosure of confidential information through publication of documentation on our website that has not been correctly marked. If a completed checklist is not included then NICE will consider all information contained in your submission of evidence as not confidential.

Signed*: ** Must be Medical Director or equivalent*		**Date:**	16 May 2021
Print:	John Beard, MD	**Role / organisation:**	Head of Medical Affairs ICU Medical Inc.
Contact email:	[redacted]		

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

GID-MT561 ClearGuard HD Antimicrobial Barrier Cap for preventing haemodialysis catheter-related bloodstream infections

Company evidence submission

Part 2: Economic evidence

Company name	ICU Medical, Inc.
Submission date	15 June 2021
Contains confidential information	No

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1 Published and unpublished economic evidence

Identification and selection of studies

Complete the following information about the number of studies identified.

Please provide a detailed description of the search strategy used, and a detailed list of any excluded studies, in appendix A.

Number of studies identified in a systematic search.		1 (Following initial de-duplication of identified studies and title and abstract screening)
Number of studies identified as being relevant to the decision problem.		1 (Following removal of studies not relevant after full-text screening)
Of the relevant studies identified:	Number of published studies.	0
	Number of abstracts.	1 (Note: This abstract was also included in the Part 1 clinical submission for GID-MT561, as it presents both clinical and economic outcomes. Details of the study are presented below, as in the clinical submission).
	Number of ongoing studies.	0

List of relevant studies

In table 1, provide brief details of any published or unpublished economic studies or abstracts identified as being relevant to the decision problem.

For any unpublished studies, please provide a structured abstract in appendix A. If a structured abstract is not available, you must provide a statement from the authors to verify the data provided.

Any data that is submitted in confidence must be correctly highlighted. Please see section 1 of the user guide for how to highlight confidential information. Include any confidential information in appendix C.

Table 1 Summary of all relevant studies (published and unpublished)

Data source	Author, year and location	Patient population and setting	Intervention and comparator	Unit costs	Outcomes and results	Sensitivity analysis and conclusion
Cost-effective and prophylactic use of Clear Guard Caps for a sustained reduced catheter associated blood stream infection rate.	Glennon et al, 2020 (1) Location: USA	*Patient population:* Haemodialysis patients with a CVC. Further details of patient population not reported. There were no withdrawals, or loss-to-follow-up reported. *Setting:* The paediatric dialysis setting.	Intervention: ClearGuard caps. Comparator: Prophylactic use of antimicrobial locks (AMLs).	Information pertaining to the cost of AMLs and the ClearGuard® caps was obtained from the pharmacy and supply chain purchasing departments. No further information on unit costs included in the analysis are reported.	Outcomes assessed included CA-BSI rates and costs associated with intervention and comparator. **Results:** The CA-BSI rate for FY18 (comparator) was 1.82 per 100 patient months with the cost of prophylactic AML usage in 4 high risk patients totalling $25,896. In FY19 (intervention), AML usage was discontinued and ClearGuard caps were used for all haemodialysis patients with CVCs (inclusive of high risk and non-high risk patients) with a total annual cost of $10,140 and the CA-BSI rate dropped to 0.26 per 100 patient months.	The results indicate that use of ClearGuard caps is a proven cost-effective tool in helping achieve a low CA-BSI rate in the paediatric dialysis unit. The combination of ClearGuard caps and good catheter care practices may, therefore, substantially decrease the risk of haemodialysis CA-BSI. No sensitivity analyses were reported.
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2 Details of relevant studies

Please give details of all relevant studies (all studies in table 1). Copy and paste a new table into the document for each study. Please use 1 table per study.

Glennon et al, 2020 (1) Cost-effective and prophylactic use of Clear Guard Caps for a sustained reduced catheter associated blood stream infection rate	
What are main differences in resource use and clinical outcomes between the technologies?	The CA-BSI rate for FY18 (comparator arm) was 1.82 per 100 patient months with the cost of prophylactic AML usage in 4 high risk patients totalling $25,896. In FY19 (intervention arm), AML usage was discontinued and ClearGuard caps were used for all haemodialysis patients with CVCs (inclusive of high risk and non-high risk patients) with a total annual cost of $10,140 and the CA-BSI rate dropped to 0.26 per 100 patient months.
How are the findings relevant to the decision problem?	Study looked at the CA-BSI rates associated with use of ClearGuard HD caps compared to prophylactic use of AMLs in the pediatric dialysis setting. Findings indicate that use of the intervention results in lower infection rates and is a cost-effective use of health service resources.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes: • Reduced risk of CRBSI (Note: Study focussed on CA-BSI event rates rather than CRBSIs specifically), • Cost savings.
Will any information from this study be used in the economic model?	Yes – data to inform the baseline rate of infection associated with antimicrobial lock solutions, and the incidence rate ratio (IRR) associated with the use of ClearGuard caps.
What cost analysis was done in the study? Please explain the results.	Study looked at total costs amongst a group of patients utilising ClearGuard HD in the paediatric dialysis setting, compared to a group of patients undergoing current practice. Total costs for the entire group of patients utilising each method are reported. No further details of the cost analysis are reported in the abstract.
What are the limitations of this evidence?	No limitations reported in this abstract.
How was the study funded?	Source of funding not reported in this abstract.

3 Economic model

This section refers to the de novo economic model that you have submitted.

Description

Patients

Describe which patient groups are included in the model.

All patients with tunnelled central venous catheters (CVCs) undergoing haemodialysis (HD).

Technology and comparator(s)

State the technology and comparators used in the model. Provide a justification if the comparator used in the model is different to that in the scope.

The technology being evaluated is ClearGuard HD Antimicrobial barrier caps, which are coated with an antimicrobial agent (chlorhexidine acetate). The device will be compared with: (1) standard CVC caps, which require separate manual decontamination of the catheter hub with alcohol wipes containing solution of chlorhexidine gluconate, (2) standard CVC caps used in combination with an antimicrobial lock solution, and separate manual decontamination of the catheter hub with alcohol wipes, (3) Tego haemodialysis connectors used with Curos disinfecting caps (Tego + Curos), and (4) Tego haemodialysis connectors, and manual decontamination of the catheter hub. The technology and comparators are as defined in the scope. Further details on the use of resources involved in intervention and comparator arms of the model are provided in later sections. The use of standard CVC caps is common practice in England, and existing practice on disinfection of the catheter hub typically involves use of alcohol wipes with 2% chlorhexidine and 70% alcohol (see NICE Clinical Guidelines [CG139] for healthcare-associated infections (2), and Hymes et al, 2017 (3)). Additionally, the Tego needleless connector, and the combination of Tego + Curos are commonly used for the prevention of bloodstream infections amongst patients undergoing HD. Based on 2020 data, 72% of CVC-based HD treatments in the UK utilised standard CVC caps, with the remaining 28% utilising Tego connectors (with, or without, an alcohol disinfecting cap) (ICU Medical, Inc.). Therefore, both are included as comparators in the analysis. A comparison with Curos alone (i.e., without the Tego needleless connector) was not considered due to lack of comparative effectiveness data. A lock solution would be instilled inside the CVC at the end of each dialysis treatment; however, it is assumed in this analysis that the use of standard lock solution would not vary depending on the intervention used and therefore, their associated costs are not formally considered. Commonly used lock solutions include citrate 4%, heparinized saline and saline. However, a comparator has been included in the model to consider the cost implications of using *antimicrobial* lock solutions with current practice, which may also be used during this process. Examples of such antimicrobial solutions include gentamicin and taurolidine, which may be used in combination with for instance, citrate.

While the use of standard CVC caps in combination with alcohol wipes (without chlorhexidine gluconate) and Clorox wipes are also outlined in the scope as potential comparators, there are no clinical data available on the relative effectiveness of the intervention compared with practice involving use of these wipes. However, it should be noted that as part of NICE CG139 the recommendation around device management is that the injection port or vascular access device catheter hub is decontaminated using chlorhexidine gluconate in 70% alcohol [2], and this is also highlighted in related literature (4). Therefore, the recommended method for current practice has been captured in the analysis as a comparator, while the use of alcohol wipes (without chlorhexidine gluconate) and Clorox wipes have not been formally considered. However, the costs associated with regular alcohol wipes are likely to be very similar to the cost of alcohol wipes including chlorhexidine gluconate (see NICE MTG44 (5) cost analysis where reported costs are identical for both), while the unit cost of Clorox wipes (£0.04) is also very similar to the cost of alcohol wipes included in the economic analysis presented here (£0.02), and therefore is not likely to impact the overall results (assuming similar impact on subsequent infection rates).

Model structure

Provide a diagram of the model structure you have chosen in Appendix B.

Justify the chosen structure of the model by referring to the clinical care pathway outlined in part 1, section 3 (Clinical context) of your submission.

A de novo economic model was developed, consisting of a decision tree model structure, as no published studies were identified which looked at the cost-effectiveness of the intervention compared to all relevant comparators. The model was developed to simulate a hypothetical cohort of HD patients, with a tunnelled CVC, undergoing dialysis and receiving one of five interventions: (1) ClearGuard HD Antimicrobial Barrier Caps, (2) Standard CVC caps, combined with the use of alcohol wipes for disinfection, (3) Standard CVC caps, combined with the use of an antimicrobial lock solution and alcohol wipes for disinfection, (4) Tego haemodialysis connectors used with Curos disinfecting caps (Tego + Curos), or (5) Tego haemodialysis connectors on their own, with manual decontamination of the catheter hub with alcohol wipes, in the hospital setting.

The model was developed from the perspective of the NHS and Personal Social Services (PSS) in England. The aim of the analysis was to assess the costs and health outcomes associated with introduction of ClearGuard HD, with benefits assessed in terms of reduction in infection rates (and associated costs) and subsequent mortality. Infection rates are the key drivers of costs (in that infection needs to be diagnosed and treated and may result in prolonged length-of-stay in hospital) amongst this patient group, and therefore ClearGuard HD may be considered a disease prevention device. The clinical evidence (part 1) submission for GID-MT561 has highlighted the beneficial impact that the device may have on infection rates amongst this population, and these benefits will be formally explored in this economic analysis.

The model structure begins at the point where all HD patients receive one of the alternative methods being compared, i.e., intervention or comparator(s). Following this, patients may either experience a catheter-related bloodstream infection (CRBSI) or they may be infection-free. Note: *Although CRBSIs, central-line-associated bloodstream infections (CLABSIs) and catheter-associated bloodstream infections (CABSI) have slightly different formal definitions, the terms are often used interchangeably*

*in the literature. Similarly, the reporting of positive blood culture episodes (PBCs) to highlight baseline infection rates is commonly used, in the absence of baseline data associated with CRBSI/CLABSI/CABSI. Therefore, although the model structure shows CRBSI as the relevant infection outcome, some of the data used in the analysis may be based on CLABSI, CABSI or PBC data rather than CRBSI data***.** Where patients experience a CRBSI they may ultimately recover from the infection, or they may die. The model structure can be seen in Appendix B.

A decision tree structure was considered sufficient due to the short-term occurrence, and progression, of CRBSI amongst HD patients utilising a tunnelled CVC. Occurrence of bloodstream infections (BSIs) is the primary outcome of interest associated with introduction of the intervention, while additional outcomes including length of stay in hospital (including the general ward and the intensive care unit (ICU)) and mortality are subsequently captured in the model through the estimation of differing CRBSI rates associated with the alternative interventions. The baseline risk of CRBSI for HD patients with CVCs was estimated for each comparator in the model, with the incidence rate ratios (IRRs) for ClearGuard HD used to estimate the differing occurrence rates of CRBSIs associated with introduction of the intervention. Data on baseline risk of infection with each comparator, and IRRs for ClearGuard HD compared to each comparator, were derived from the literature, and are presented in more detail in a later section.

The model structure is simple as introduction of ClearGuard HD is a straightforward replacement of one barrier cap method for another, with minimal impact on the existing patient pathway. Additionally, it is not believed that the intervention has any further impact on other adverse effects associated with catheterisation, including catheter colonisation leading to local infection or hypersensitivity reactions. Therefore, these adverse events were not modelled.

Due to the structure of the model and the short-term implications of CRBSI, costs and health outcomes were only assessed over the short-term (1-year time horizon). Therefore, discounting was not required. The model uses data on the total number of patients at risk each year in England to estimate the total costs and outcomes amongst the entire population, as well as on an individual patient basis. Costs were estimated for a 2020 price year (£).

Table 2 Assumptions in the model

In this table, list the main assumptions in the model and justify why each has been used.

Assumption	Justification	Source
The model assumes that all patients are receiving haemodialysis, and the intervention, in the hospital setting.	Although the community setting is also specified in the scope, there are no relevant data to support an analysis of the intervention in the community setting. It has therefore, not been included in the analysis. However, based on input from the company, the relative effectiveness of the intervention is likely to translate to the community setting due to the similarities in practices. Note: The same omission of the community setting was made in NICE MTG44 (5), for the submission of the Curos device, which was accepted by the NICE External Assessment Centre (EAC). Additionally, the model assumes that haemodialysis is being conducted in the general hospital ward setting, although impact of infection on length of stay in other settings (i.e., ICU) is also considered through the modelling. Clinical data related to the effectiveness of the intervention have primarily been collected based on analyses conducted in dialysis clinics, or outpatient centres (see clinical evidence (part 1) submission for GID-MT561), which are assumed to be reflective of the population that would undergo haemodialysis in the UK hospital setting.	Clinical evidence.

No costs associated with training health care staff on use of the device are included in the model.	Based on input from the company, it has been assumed that minimal, if any, training would be required on use of the device. The use of barrier caps is standard practice in many centres, and the introduction of ClearGuard HD would have no further impact on the patient pathway. For information on the specific use of the device, the company provide a three-minute in-service video on their website: https://vimeo.com/423704523. This video may be used for training purposes, when required. The company can also provide on-site training, but most facilities that currently use the device have found this unnecessary. Therefore, it is thought that the training requirements associated with use of the device are minor and that the cost per patient would be negligible.	ICU Medical Inc.
No device-related adverse events are considered in the model.	No adverse events that would have an effect on patients were identified in the review of clinical evidence, or in the specific search for information on device-related adverse events, conducted as part of this clinical submission (Part 1 submission for GID-MT561). Therefore, device-related adverse events were not considered in the analysis.	Clinical evidence submission.
The model considers the occurrence of CRBSI/CLABSI/CABSI/PBC only, and impact of the intervention on CRBSI/CLABSI/CABSI/PBC rates and the subsequent impact on hospital stay and mortality. Therefore, additional catheter-associated outcomes are not considered.	It is not believed that the intervention has any additional impact on other adverse effects associated with catheterisation, including catheter colonisation leading to local infection or hypersensitivity reactions.	Expert clinical input.

	Therefore, these events were not modelled.	
The model assumes, based on evidence from the literature, that there will be an increase in mortality risk associated with a catheter-related infection. Therefore, mortality has been modelled by counting the number of deaths associated with each comparator. However, as the model is not interested in longer-term outcomes, and quality-adjusted life-years (QALYs) are not required for this submission, quality-of-life impact is not modelled.	Evidence from the literature highlights the increased mortality risk associated with infection.	Goto et al, 2013 (6).
For the purpose of the costing exercise, compliance with the intervention and comparator(s) is not explicitly considered.	This assumption was made on the basis of a lack of available evidence associated with compliance to appropriate practices related to use of the device(s). As a result, we were unable to link compliance with effectiveness data. Therefore, 100% compliance was assumed in the analysis. This assumption is consistent with that made in NICE MTG44 (5).	Clinical evidence, NICE MTG44 (5).
It is assumed that the use of standard CVC caps and the use of Tego haemodialysis connectors on their own would require manual disinfection with alcohol wipes, while it is assumed that no manual disinfection is required with Tego + Curos or ClearGuard HD.	This assumption was made to account for the fact that the introduction of ClearGuard HD would eliminate the need to manually clean the connector port(s).	NICE MIB234 (7), NICE MTG44 (5), Expert clinical input.
Additional length of stay in the hospital general ward, and intensive care unit (ICU), following an infection, is captured in the model. However, the cost of an infection is based on data derived from NICE MTG44 (5), and is inclusive of diagnosis, treatment, and length of stay costs. This cost assumes that the cost of treating patients in the general ward and ICU is the same.	Cost of an infection is inclusive of treatment, diagnosis and additional length of stay costs.	NICE MTG44 (5).
The model assumes that three sessions of haemodialysis are carried out per week with a day typically between treatments, i.e., ‘Monday, Wednesday, Friday’ or ‘Tuesday, Thursday, Saturday’. It is assumed that there are two catheter ports that would be accessed as part of	Assumption made on the basis of recommended practices with the respective devices.	Expert clinical input.

haemodialysis. Therefore, two ClearGuard HD caps would be required for each session of haemodialysis (replaced after treatment); two standard CVC caps would be required for each session of haemodialysis (replaced after treatment); two Curos caps would be required for each session of haemodialysis (replaced after treatment); while two Tego haemodialysis connectors would be required for the entire week, i.e., for the three sessions of haemodialysis. In addition, antimicrobial lock solution would be used for each session of haemodialysis, while manual disinfection with alcohol wipes (when relevant) would also be conducted at each session of haemodialysis (for both ports). These assumptions were made on the basis of recommended guidelines for the respective devices and procedures.		
The cost of the time associated with connecting a cap (either standard CVC cap, Curos or ClearGuard HD) was not included in the model as this would be consistent across the different approaches.	No difference in associated time for each comparator.	Expert clinical input.
The cost savings associated with ClearGuard HD were estimated based on its potential for certain common practices (such as the manual disinfection of the catheter hub) to be replaced by using this innovative cap. However, clinical evidence on the effectiveness of the cap used in the model may be derived from studies which did not remove existing practices following introduction of the intervention, i.e., practices outside of use of the intervention remained the same in both arms of the clinical study.	To account for the full cost saving potential of the intervention.	Clinical evidence.

Table 3 Clinical parameters, patient and carer outcomes and system outcomes used in the model

In this table, describe the clinical parameters, patient and carer outcomes and system outcomes used in the model.

Parameter/outcomes	Source	Relevant results	Range or distribution	How are these values used in the model?
Incidence rate of CRBSI per 1,000 CVC-days using standard CVC caps	NICE MTG44 (5), Kanaa et al, 2015 (8), Aitken et al, 2016 (9), Crowley et al, 2017 (10), Youssouf et al, 2017 (11), Hymes et al, 2017 (3).	0.70	Gamma distribution (Lower limit = 0.53, Upper limit = 0.88)	This value is used to define the incidence rate of CRBSI amongst those patients receiving standard CVC caps, along with manual disinfection of the catheter hub. In effect, this is the baseline incidence rate against which we can compare the incidence rate associated with ClearGuard. Values for standard CVC caps were identified from multiple sources, with the final selected value derived from NICE MTG44 (5).
Incidence rate of CRBSI per 1,000 CVC-days using antimicrobial lock solution with standard CVC caps	Glennon et al, 2020 (1).	0.61	Gamma distribution (Lower limit = 0.46, Upper limit = 0.76)	This value is used to define the incidence rate of CRBSI amongst those patients receiving antimicrobial lock solution with standard CVC caps. In effect, this is the baseline incidence rate against which we can compare the incidence rate associated with ClearGuard. This value was identified from a published abstract related to use of the intervention (1).
Incidence rate of CRBSI per 1,000 CVC-days using Tego + Curos	Brunelli et al, 2018 (12).	0.75	Gamma distribution (Lower limit = 0.56, Upper limit = 0.94)	This value is used to define the incidence rate of CRBSI amongst those patients receiving Tego + Curos. In effect, this is the baseline incidence rate against which we can compare the incidence rate associated with ClearGuard. This value was identified from a published US clinical trial related to use of the intervention (12).
Incidence rate of CRBSI per 1,000 CVC-days using Tego alone	Weiss et al, 2017 (13).	0.63	Gamma distribution (Lower limit = 0.47, Upper limit = 0.79)	This value is used to define the incidence rate of CRBSI amongst those patients receiving Tego alone. In effect, this is the baseline incidence rate against which we can compare the incidence rate associated with ClearGuard. This value was identified from a published US clinical trial related to use of the intervention (13).
IRR of CRBSI using ClearGuard Caps compared to standard CVC caps	Hymes et al, 2017 (3).	0.44	Log Normal distribution (Lower limit =	This value is used to define the risk of occurrence of CRBSI in the ClearGuard arm, relative to the risk in the standard CVC caps arm of the model.

			0.23, Upper limit = 0.83)	
IRR of CRBSI using ClearGuard Caps compared to using antimicrobial lock solution with standard CVC caps	Glennon et al, 2020 (1).	0.14	Log Normal distribution (Lower limit = 0.11, Upper limit = 0.18)	This value is used to define the risk of occurrence of CRBSI in the ClearGuard arm, relative to the risk in the standard CVC caps with antimicrobial lock solution arm of the model.
IRR of CRBSI using ClearGuard Caps compared to Tego + Curos caps	Brunelli et al, 2018 (12).	0.37	Log Normal distribution (Lower limit = 0.20, Upper limit = 0.68)	This value is used to define the risk of occurrence of CRBSI in the ClearGuard arm, relative to the risk in the Tego + Curos arm of the model.
IRR of CRBSI using ClearGuard Caps compared to Tego alone	Weiss et al, 2017 (13).	0.14	Log Normal distribution (Lower limit = 0.11, Upper limit = 0.18)	This value is used to define the risk of occurrence of CRBSI in the ClearGuard arm, relative to the risk in the Tego alone arm of the model.
Probability of death following CRBSI	Goto et al, 2013 (6).	0.15	Beta distribution (Lower limit = 0.12, Upper limit = 0.32)	This value is used to define the probability of death having experienced a CRBSI.
Average number of CVC days per patient per year	Kwak et al, 2012 (14), Crowley et al, 2017 (10), Hymes et al, 2017 (3).	132	Gamma distribution (Lower limit = 123, Upper limit = 141)	This value is used to define the average number of CVC days that patients have per year.
Total number of HD patient-years (CVC) at risk	Crowley et al, 2017 (10).	7,026	Not applicable	This value was derived from Crowley et al, 2017 (10), which reports the estimated number of patient years at risk amongst patients receiving CVCs, in their report on patients receiving dialysis in England in 2015. This value was used to calculate the total number of patients at risk each year in England, i.e., 7,026/132, and the total number of CVC days at the starting point of the decision tree model.

Total number of CVC days	Calculation	2,564,490	Not applicable	Calculated by: 7,026 * 365.

If any outcomes listed in table 4 are extrapolated beyond the study follow-up periods, explain the assumptions that underpin this extrapolation.

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

Table 4 Other parameters in the model

Describe any other parameters in the model. Examples are provided in the table. You can adapt the parameters as needed.

Parameter	Description	Justification	Source
Time horizon	1 year.	CRBSI/CLABSI occurs, and progresses, over the short-term and a 1-year time horizon was considered sufficient to be able to capture all relevant costs and health outcomes associated with introduction of the intervention.	Clinical expert input.
Discount rate	Not applicable.	Time horizon does not extend beyond 1 year, so discounting was not necessary.	Not applicable.
Perspective (NHS/PSS)	NHS and PSS.	Costs and health outcomes considered from the NHS and PSS perspective, as defined in the scope.	As defined in the scope.
Cycle length	Not applicable	Decision tree model structure used, therefore cycle length was not applicable.	Not applicable
Transition probabilities	The parameters which determine the transition of patients through the decision tree model are as follows:	These are the key parameters which inform the transition of patients through the decision tree model.	Kwak et al, 2012 (14), Crowley et al, 2017 (10), Hymes et al, 2017 (3),

	Average number of CVC days per patient per year = 132, Incidence rate of CRBSI per 1,000 CVC-days using standard CVC caps = 0.70, Incidence rate of CRBSI per 1,000 CVC-days using standard CVC caps with antimicrobial lock solution = 0.61, Incidence rate of CRBSI per 1,000 CVC-days using Tego + Curos = 0.75, Incidence rate of CRBSI per 1,000 CVC-days using Tego alone = 0.63, IRR of CRBSI using ClearGuard Caps compared to standard CVC caps = 0.44, IRR of CRBSI using ClearGuard Caps compared to standard CVC caps with antimicrobial lock solution = 0.14, IRR of CRBSI using ClearGuard Caps compared to Tego + Curos caps = 0.37, IRR of CRBSI using ClearGuard Caps compared to Tego alone = 0.14, Probability of death following CRBSI = 0.15.	All data were derived from published information and previous literature (see sources listed and details provided below). A scoping search of the literature was conducted to identify appropriate values. Details on each of these parameter values are described below. **Average number of CVC days per patient per year:** Data to inform the average number of CVC days that a HD patient would have per year were derived from a combination of sources, including Kwak et al, 2012 (14), Crowley et al, 2017 (10), and Hymes et al, 2017 (3). All studies involved analyses amongst an appropriate population. **Incidence rate of CRBSI per 1,000 CVC-days using standard CVC caps:** A number of viable studies were identified in the search for relevant data to inform the incidence rate of CRBSI amongst patients using standard CVC caps (standard practice). Kanaa et al, 2015 (8) conducted a multicentre randomised controlled study (including patients in Yorkshire, UK) exploring the effectiveness of Cathasept line lock solution compared with standard practice (heparin 5,000 U/ml locks), amongst a group of patients with tunnelled HD catheters. They reported that the incidence rate of CRBSI in the	NICE MTG44 (5), Kanaa et al, 2015 (8), Aitken et al, 2016 (9), Youssouf et al, 2017 (11), Goto et al, 2013 (6), Brunelli et al, 2018 (12), Weiss et al, 2017 (13), Glennon et al, 2020 (1). Solomon et al, 2012 (15) Winnicki et al, 2018 (16).

		standard practice group was 0.68/1,000 catheter days. Aitken et al, 2016 (9) conducted an observational study and budget-impact analysis in order to compare the use of early cannulation arteriovenous grafts with tunnelled CVCs, based on data from a large, tertiary referral vascular access centre in the West of Scotland. They found that the observed bacteraemia rate amongst those with tunnelled CVCs was 1.4/1,000 catheter days. Data from the UK Renal Registry 19th Annual Report (Crowley et al, 2017 (10)) reported an incidence rate of 0.24. Youssouf et al, 2017 (11) looked at the outcomes associated with a multifaceted dialysis programme and reported that the baseline incidence rate of CRBSIs (i.e., prior to introduction of the quality improvement programme) was 2.65/1,000 catheter days. In the US population, Hymes et al, 2017 (3) reported a baseline rate of PBC episodes of 0.6/1,000 catheter days (baseline rates for CRBSI and CLABSI not reported individually). The final source of evidence identified to inform the baseline incidence rate associated with the use of standard	

		CVC caps was the NICE MTG44 submission (5), focussing on use of the Curos caps for the prevention of bloodstream infection. This analysis included a targeted literature search and meta-analysis to identify specific UK sources to inform the baseline CLABSI/CRBSI rate per 1,000 days amongst patients resulting from CVCs or peripherally inserted central catheter lines (PICCs) (with a view to applying this as a baseline rate of infection associated with the comparator in the model, which was 'use of alcohol wipes as current practice'). While the population included in the search was not haemodialysis patients specifically (although they were included in studies identified), the values identified are still likely to be representative of the baseline infection rate amongst patients receiving standard CVC caps (in combination with alcohol wipes) in our own population. Included in their final list of identified studies were the studies by Aitken et al, 2016 (9), Kanaa et al, 2015 (8), and Youssouf et al, 2017 (11), all of which were conducted amongst dialysis patients (not specific to critically ill patients). A final selected infection rate of 0.7/1,000 catheter days was used in the economic model, although authors acknowledged the wide variation in infection definitions and incidence rates across studies.	

		A value of 0.7 was selected for this analysis also, with extensive sensitivity analysis conducted to explore uncertainty in this parameter. This value appears a reasonable selection, given the range of alternative values reported across studies. While many of the studies presented above don't necessarily refer to the use of 'standard CVC caps', but rather 'traditional catheter hub care (including the use of alcohol wipes)' or 'current practice' or 'historic controls', the description of 'current practice' in each of the respective studies was considered to be reflective of the standard CVC group (with alcohol wipes) in our own analysis. While it is also acknowledged that the value of 0.7 derived from NICE MTG44 (5) is not specific to haemodialysis patients, or CVCs, a targeted search was conducted in the PubMed database to identify a more reasonable UK source for this parameter (using a combination of the search terms: 'Haemodialysis', 'Central venous catheter', 'CVC', 'CRBSI' and 'CLABSI'). However, aside from a selection of the studies already highlighted above, no further studies were identified to inform this parameter. **Incidence rate of CRBSI per 1,000 CVC-days using standard CVC caps with antimicrobial lock solution:**	

		A rapid search in the PubMed database was conducted to identify appropriate data to inform this parameter. The search was focussed on the use of taurolidine as an antimicrobial lock solution amongst patients undergoing haemodialysis. Two relevant publications were identified. The first; a randomized clinical trial conducted in the UK, reported bacteremia episodes of 1.4/1,000 CVC days amongst patients receiving the intervention (15), and the second; a European randomized controlled trial focussing specifically on TauroLock, reported infection rates of 0.67 per 1,000 CVC days (16). However, one of the studies identified during the clinical submission (the US-based abstract from Glennon et al, 2020 (1)), also describes a comparison between antimicrobial locks and ClearGuard caps. Given that the data to inform the IRR of ClearGuard would also ultimately be derived from this source, it was thought to be the most appropriate source for this data (even though the 'antimicrobial locks' described in the abstract do not necessarily refer specifically to taurolidine, for which the costs were estimated). Data from this abstract were converted to reflect the incidence rate per 1,000 CVC days. The final included value (0.61) was broadly similar to the value reported in the European study	

		(0.67) (16) identified during the literature search. **Incidence rate of CRBSI per 1,000 CVC-days using Tego + Curos:** A rapid search in the PubMed database was conducted to identify appropriate data to inform this parameter. However, no appropriate UK-based data were identified. Therefore, the base-case value was derived from the publication by Brunelli et al, 2018 (12). **Incidence rate of CRBSI per 1,000 CVC-days using Tego alone:** A rapid search in the PubMed database was conducted to identify appropriate data to inform this parameter. However, no appropriate UK-based data were identified. Therefore, the base-case value was derived from the publication by Weiss et al, 2018 (13). **IRR of CRBSI using ClearGuard Caps compared to standard CVC caps:** No appropriate UK-based data were identified to inform this parameter. Therefore, the value was derived from the study by Hymes et al, 2017 (3). The comparator in the analysis was existing practice at the clinic, which included the use of standard CVC caps and alcohol wipes with chlorhexidine.	

		IRR of CRBSI using ClearGuard Caps compared to standard CVC caps with antimicrobial lock solution: This parameter was informed through the same source from which the baseline infection rate associated with antimicrobial locks, was derived (1). This analysis compared the use of ClearGuard caps with antimicrobial locks. **IRR of CRBSI using ClearGuard Caps compared to Tego + Curos caps:** This value was derived from the US study by Brunelli et al (12), which compared use of ClearGuard caps with Tego + Curos. **IRR of CRBSI using ClearGuard Caps compared to Tego alone:** This value was derived from the US study by Weiss et al (13), which compared use of ClearGuard caps with Tego alone. **Probability of death following CRBSI:** The probability of death following CRBSI was informed by a study by Goto et al, 2013 (6) which looked at the overall burden of bloodstream infection and nosocomial bloodstream infection in North America and Europe.	

Health states	Not applicable.	Decision tree model structure used, therefore health states were not applicable. Modelled outcomes are the rate of CRBSI with each comparator and the resource use and costs associated with the initial device/process and treating infections (described in following section).	Not applicable.
Sources of unit costs	Average cost of treating CRBSI (£) = 11,071, Average cost of alcohol wipes (£) = 0.02, Unit cost of standard caps (price per cap) (£) = 0.35, Unit cost of Curos caps (price per cap) (£) = 0.35, Cost of Tego (price per unit) (£) = 2.29, Unit cost of ClearGuard caps (price per pair of caps) (£) = 4.00, Antimicrobial lock solution (TauroLock) per dialysis session (£) = 10.00, Hourly cost of a band 5 nurse (£) = 40.00, Nurse time for manual disinfection (minutes) = 0.25,	Presented are the resource use parameters included in the model. These parameter values were derived from a combination of previous literature, company information and routine cost sources. Further details on all resource use parameters included in the model are presented in the 'Resource identification, measurement and valuation' section.	NICE MTG44 (5), NICE MIB234 (7), Science Equip (17), ICU Medical, Inc., PSSRU (18), Valiant Medical (19).

	Cost of nurse time for disinfection (£) = 0.17, ICU length of stay due to CRBSI (days) = 2.5, General ward length of stay due to CRBSI (days) = 5.		

Explain the transition matrix used in the model and the transformation of clinical outcomes, health states or other details.

Not applicable. Parameters described previously in Tables 3 and 4 used to inform the transition of patients through the model.

Resource identification, measurement and valuation

Technology costs

Provide the list price for the technology (excluding VAT).

Cost of ClearGuard HD Antimicrobial Barrier Caps used in the model = £4.00 (price for a pair of caps, as provided by ICU Medical, Inc.). Assuming that haemodialysis would normally be needed 3 times a week, and the caps would need to be replaced at each dialysis session, the weekly cost is £12.00. Based on data from Kwak et al, 2012 (14), haemodialysis patients would need a CVC for an average of 132 days, which leads to a cost of £226 per patient over this period.

In the model, no additional cost associated with the use of ClearGuard HD caps is considered given that introduction of the intervention does not lead to any additional resource use.

If the list price is not used in the model, provide the price used and a justification for the difference.

Not applicable.

NHS and unit costs

Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs, the national tariff and unit costs (from PSSRU and HSCIC). Please provide relevant codes and values (e.g. OPCS codes and ICD codes) for the operations, procedures and interventions included in the model.

Included in the table below are the costs associated with the included technologies, and clinical complications that are modelled. Their use in the model is described in the text that follows. Relevant values and sources for all costs included in the model are presented below:

Cost	Value (£)	Source
Technologies		

ClearGuard HD caps (price per pair of caps)	4.00	ICU Medical, Inc.
Standard CVC caps (price per cap)	0.35	NICE MIB234 (7).
Curos caps (price per unit)	0.35	NICE MTG44 (5).
Cost of Tego (price per unit)	2.29	Science Equip (17).
Cost of antimicrobial lock solution (TauroLock) per dialysis session	10	Valiant Medical (19).
Additional materials		
Average cost of alcohol wipes	0.02	NICE MTG44 (5).
Hourly cost of a Band 5 nurse	40.00	PSSRU (18).
Nurse time for manual disinfection (minutes)	0.25	NICE MTG44 (5).
Cost of nurse time for disinfection	0.17	Calculation.
Complications		
Average cost of treating CRBSI	11,071	NICE MTG44 (5).
Hospital stay		
ICU length of stay due to CRBSI (days)	2.5	NICE MTG44 (5).
General hospital ward length of stay due to CRBSI (days)	5.5	NICE MTG44 (5).

Patients in the model initially undergo HD utilising one of the alternative comparators being assessed, i.e., intervention or comparator(s). Costs associated with the different types of caps, solutions and alcohol wipes included in the analysis are presented above. These values were either sourced from the device company (ICU Medical, Inc.), in the case of ClearGuard HD, or from available sources reporting the costs of the comparators.

The cost of ClearGuard HD caps is presented on the basis of a pair of caps (£4 total). Haemodialysis is assumed to be carried out three times per week, with the two caps needing to be replaced at each dialysis session for the two ports being used, i.e., £4 x 3. No additional costs associated with the use of ClearGuard HD are considered in the model, given that it is a straightforward replacement for existing methods. Manual disinfection of the catheter hub is not required when ClearGuard HD caps are used.

In NICE MIB234, the cost of a standard CVC cap is presented in the range £0.30-£0.40 (7). The mid-point of this range has been selected for use in the model (£0.35). Two standard CVC caps would be used at each session of dialysis in combination with two alcohol wipes (one used on each port), which are required to disinfect the hub. The cost of an alcohol wipe included in the model is £0.02, based on information derived from NICE MIB234 (7) and NICE MTG44 (5). This cost is also applicable to those wipes containing 2% chlorhexidine gluconate. It is advised that 'scrub the hub' procedures should last for 15 seconds, with 30 seconds drying time to follow. However, in NICE MTG44 (5), the NICE EAC, as part of their review of the company submission, disputed that 30 seconds drying time should be considered when evaluating the use of alcohol wipes, given that this time could be used to undertake alternative tasks. Therefore, the cost of 15 seconds disinfection time from a Band 5 nurse (x 2, for

each one of the ports) has been included in our model to estimate the total cost of standard CVC caps. A Band 5 nurse was considered an appropriate level of staff to carry out manual disinfection, based on clinical expert input presented in NICE MTG44 (5).

The cost of standard CVC caps in combination with antimicrobial lock solution includes all of the elements described in the previous paragraph, as well as the additional cost associated with the lock solution. This solution is considered an addition to the standard solutions (such as citrate 4%, heparinized saline or heparin) that would be used regardless of the intervention being used, and which are not formally considered as part of the economic analysis due to the consistency across methods. In this analysis, the antimicrobial lock solution is assumed to be TauroLock, with the cost of this solution per dialysis session (£10) presented in the table above (19). This cost was based on the TauroLock 2+1 protocol, which would include the cost of Hep 500 used twice a week at £2.50 per vial and use of TauroLock urokinase once a week at £25.00 per vial (i.e., £30 for three dialysis sessions, averaged to £10 per session). However, to account for the fact that when TauroLock is used not all clinicians would use the protocol version including urokinase, an alternative value was explored in scenario analysis where it is assumed that Hep 500 is used three times per week (£7.50 for three dialysis sessions, averaged to £2.50 per session) (19).

The costs of Tego needleless connector and Curos caps, have been derived from Science Equipment providers (17) and from NICE MTG44 (5), respectively. The unit cost of Tego (£2.29) was based on a 100-pack cost of £228.65 (17), and two Tego needleless connectors would be required for haemodialysis for the two ports being used. The cost of a Curos cap is presented on the basis of one cap (£0.35), however, as is the case with standard CVC caps and ClearGuard HD caps, two caps would be required per dialysis session. Therefore, the weekly cost of using Curos caps is calculated as: (£0.35 x 2) x 3. Tego, on the other hand, only needs to be replaced once per week. Therefore, for this same duration of time the cost of Tego would be £2.29 x 2. The overall weekly cost of using Tego + Curos caps can, therefore, be calculated as: ((£2.29 x 2) + ((£0.35 x 2) x 3)). Tego + Curos is assumed to not require manual disinfection of the catheter hub with an alcohol wipe.

Finally, the cost of Tego alone would include the cost of the Tego needleless connector (one used for the three dialysis sessions per week for each catheter hub, i.e., £2.29 x 2 per week), as well as the cost of manual disinfection of the catheter hub with an alcohol wipe (given that an antimicrobial barrier cap is no longer being used) at each dialysis session.

As use of the intervention would require minimal (if any) training given the similarity of the new caps to existing methods, training costs and costs associated with attaching the caps were not included in the analysis.

Where a patient experiences a CRBSI, a cost of £11,071 is incurred. This cost was derived from NICE MTG44 (5), which in turn sourced this cost from the NICE MTG25 costing template (20). This cost is inclusive of diagnosis, treatment and additional length-of-stay associated with the infection. While a number of additional costs for infection were sourced in the NICE MTG44 submission (5), the cost presented above was believed to be most appropriate as it has been published previously by NICE and has been validated by clinical experts as part of the NICE MTG25 submission (5). Therefore, we have followed the same approach, with sensitivity analysis performed on this value (and all other values presented above) to explore its impact on the overall results (presented in a subsequent section).

Also presented in the table above are data on the average length of stay in hospital following the occurrence of an infection, in both general ward and ICU settings. These are estimated in the model to show the differing lengths of stay related to infection rates associated with each one of the comparators in the model. However, as noted above, the cost of infection included in the model already captures costs associated with increased length of stay, and therefore these costs are not

estimated separately based on the length of stay data generated in the model (as this would result in double-counting).

Note: Where costs have been derived from previous literature and outdated sources, values have been inflated accordingly to 2020 values using the hospital and community health services index and the PSS pay and price index, available from the PSSRU report on unit costs of health and social care (18).

Resource use

Describe any relevant resource data for the NHS in England reported in published and unpublished studies. Provide sources and rationale if relevant. If a literature search was done to identify evidence for resource use then please provide details in appendix A.

See previous section for full details of resources included in the model. A scoping search of the literature was conducted to identify any material which may have been useful in informing the resource use information, and costs, included in this analysis.

Describe the resources needed to implement the technology in the NHS. Please provide sources and rationale.

No additional costs related to use of the technology (other than the cost of the technology itself) are included in the model. ClearGuard would be implemented as a straightforward replacement for existing barrier cap methods. It would have no additional impact on the patient pathway, other than removing existing steps in the pathway (such as eliminating the need to manually disinfect the hub with alcohol wipes).

Describe the resources needed to manage the change in patient outcomes after implementing the technology. Please provide sources and rationale.

No additional resources will be required to manage the change in patient outcomes. The model captures the change in clinical outcomes (occurrence of CRBSIs, associated hospital stays and mortality) following introduction of the intervention. However, increased resource use will only be required if the intervention results in increased complication rates. This is not the case, as infection rates are reduced through introduction of the intervention (see results section).

Describe the resources needed to manage the change in system outcomes after implementing the technology. Please provide sources and rationale.

Not applicable. Please see previous paragraph; the same applies to impact on system outcomes.

Table 5 Resource use costs

In this table, summarise how the model calculates the results of these changes in resource use. Please adapt the table as necessary.

	Technology costs (ClearGuard HD) (£)	Comparator 1 costs (standard CVC caps) (£)	Comparator 2 costs (standard CVC caps with AML) (£)	Comparator 3 costs (Tego + Curos) (£)	Comparator 4 costs (Tego alone) (£)	Difference in resource use costs (technology vs comparator 1) (£)	Difference in resource use costs (technology vs comparator 2) (£)	Difference in resource use costs (technology vs comparator 3) (£)	Difference in resource use costs (technology vs comparator 4) (£)
Cost of resource use to implement technology	**4.00 (per haemodialysis session)**	0.35 * 2 (standard CVC caps) + 0.02 * 2 (alcohol wipes) + 0.17 * 2 (manual disinfection cost) = **1.08 (per haemodialysis session)**	0.35 * 2 (standard CVC caps) + 0.02 * 2 (alcohol wipes) + 0.17 * 2 (manual disinfection cost) + 10.00 (TauroLock) = **11.08 (per haemodialysis session)**	(2.29 x 2) / 3 (Tego for one haemodialysis session) + 0.35 x 2 (Curos caps) = **2.23 (per haemodialysis session)**	(2.29 x 2) / 3 (Tego for one haemodialysis session) + 0.02 * 2 (alcohol wipes) + 0.17 * 2 (manual disinfection cost) = **1.91 (per haemodialysis session)**	**+ 2.92 (per haemodialysis session)**	**- 7.08 (per haemodialysis session)**	**+ 1.77 (per haemodialysis session)**	**+ 2.09 (per haemodialysis session)**
Cost of resource use associated with patient outcomes	See modelling results, as implementation of ClearGuard HD reduces infection rates	See modelling results	See modelling results	See modelling results	See modelling results	See modelling results, as implementation of ClearGuard HD reduces infection rates	See modelling results, as implementation of ClearGuard HD reduces infection rates	See modelling results, as implementation of ClearGuard HD reduces infection rates	See modelling results, as implementation of ClearGuard HD reduces infection rates
Cost of resource use associated with system outcomes	See modelling results	See modelling results	See modelling results	See modelling results	See modelling results	See modelling results	See modelling results	See modelling results	See modelling results
Total costs	**4.00** (cost for one haemodialysis session, omitting resource use and costs associated with patient outcomes)	**1.08** (cost for one haemodialysis session, omitting resource use and costs associated with patient outcomes)	**11.08** (cost for one haemodialysis session, omitting resource use and costs associated with patient outcomes)	**2.23** (cost for one haemodialysis session, omitting resource use and costs associated with patient outcomes)	**1.91** (cost for one haemodialysis session, omitting resource use and costs associated with patient outcomes)	**+ 2.92** (cost difference for one haemodialysis session, omitting resource use and costs associated with patient outcomes)	**- 7.08** (cost difference for one haemodialysis session, omitting resource use and costs associated with patient outcomes)	**+ 1.77** (cost difference for one haemodialysis session, omitting resource use and costs associated with patient outcomes)	**+ 2.09** (cost difference for one haemodialysis session, omitting resource use and costs associated with patient outcomes)

Adverse event costs

If costs of adverse events were included in the analysis, explain how and why the risk of each adverse event was calculated.

The following complications (and associated costs) were included in the model, based on the fact that these are the most relevant outcomes amongst this patient population:

(1) CRBSI.

The occurrence of CRBSIs has implications for resource use and therefore, it was modelled. Please see Table 4 for details on the risk of CRBSIs occurring for the different strategies compared in the model, and the 'NHS and unit costs' section and Table 6 (following section), for details on costs associated with CRBSIs.

No additional adverse events were included in the model, as detailed in the description of the model structure and in the model assumptions, presented in Table 2.

Table 6 Adverse events and costs in the model

In this table, summarise the costs associated with each adverse event included in the model. Include all adverse events and complication costs, both during and after long-term use of the technology. Please explain whether costs are provided per patient or per event.

Note: In the table below the cost of CRBSI included in the model has been presented. Due to the fact that the source from which these costs were derived presented costs in an aggregated way (NICE MTG44 (5)), costs have been assigned to 'hospital costs' and 'total costs' in the table below, although it should be noted that these costs include costs associated with diagnosis, treatment, additional length of stay and catheter replacement; therefore, the cost will be inclusive of technology, staff and hospital-related resources. The cost is presented per occurrence of CRBSI.

Adverse event	Items	Cost	Source
Cost of CRBSI	Technology	Text	Text
	Staff	Text	Text
	Hospital costs	£11,071	NICE MTG44 (5).
	[Other items]	Text	Text
	Total	£11,071	NICE MTG44 (5).

Miscellaneous costs

Describe any additional costs or resource considerations that have not been included elsewhere (for example, PSS costs, and patient and carer costs). If none, please state.

Not applicable, all costs included in the model have been presented in previous sections.

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

The device has the potential to reduce infection rates amongst patients undergoing HD using CVCs. Therefore, ClearGuard HD may reduce hospital and health care provider pressures and work overload associated with treating infection, as well as the resulting morbidity, mortality, and increased occupancy of hospital beds. The cost-savings and improvement in patient outcomes associated with

re-assigning health care staff to other matters and using hospital beds for other patient groups has not been captured in this analysis, as it was beyond the scope.

Total costs

In the following tables, summarise the total costs:

- Summarise total costs for the technology in table 7.
- Summarise total costs for the comparator in table 8. This can only be completed if the comparator is another technology.

Table 7 Total costs for the technology in the model

Description	Cost (£)	Source
Cost per treatment/patient over lifetime of device	Note: Costs presented are based on one session of haemodialysis. 4.00 (cost of the intervention per haemodialysis session; ClearGuard HD caps are replaced following each round of dialysis).	ICU Medical, Inc.
Consumables per year (if applicable) and over lifetime of device	0	Not applicable
Maintenance cost per year and over lifetime of device	0	Not applicable
Training cost over lifetime of device	0	Not applicable
Other costs per year and over lifetime of device	0	Not applicable
Total cost per treatment/patient over lifetime of device	4.00 (cost of the intervention per haemodialysis session; ClearGuard HD caps are replaced following each round of dialysis).	ICU Medical, Inc.

Table 8 Total costs for the comparator in the model

Description	Cost (£)	Source
Cost per treatment/patient over lifetime of device	Note: Costs presented are based on one session of haemodialysis. 0.35 * 2 (standard CVC caps) + 0.02 * 2 (alcohol wipes) + 0.17 * 2 (manual disinfection cost) = 1.08 **(Comparator 1 - Standard CVC caps)**, 0.35 * 2 (standard CVC caps) + 0.02 * 2 (alcohol wipes) + 0.17 * 2 (manual disinfection cost) + 10.00 (TauroLock) = 11.08 **(Comparator 2 - Standard CVC caps with antimicrobial lock solution)**, (2.29 x 2) / 3 (Tego for one haemodialysis session) + 0.35 x 2 (Curos caps) = 2.23 **(Comparator 3 – Tego + Curos)**, (2.29 x 2) / 3 (Tego for one haemodialysis session) + 0.02 * 2 (alcohol wipes) + 0.17 * 2 (manual disinfection cost) = 1.91 **(Comparator 4 – Tego alone)**.	NICE MTG44 (5), NICE MIB234 (7), Science Equip (17), PSSRU (18), Valiant Medical (19).
Consumables per year (if applicable) and over lifetime of device	0	Not applicable.
Maintenance cost per year and over lifetime of device	0	Not applicable.
Training cost over lifetime of device	0	Not applicable.
Other costs per year and over lifetime of device	0	Not applicable.
Total cost per treatment/patient over lifetime of device (£)	**1.08** (Comparator 1 - Standard CVC caps), **11.08** (Comparator 2 - Standard CVC caps with antimicrobial lock solution), **2.23** (Comparator 3 – Tego + Curos),	NICE MTG44 (5), NICE MIB234 (7), Science Equip (17), PSSRU (18).

	1.91 (Comparator 3 – Tego alone).	

Results

Table 9 Base-case results

In this table, report the results of the base-case analysis. Specify whether costs are provided per treatment or per year. Adapt the table as necessary to suit the cost model. If appropriate, describe costs by health state.

	Mean discounted cost per patient using the technology (£)	**Mean discounted cost per patient using the comparator 1 (£)**	**Mean discounted cost per patient using the comparator 2 (£)**	**Mean discounted cost per patient using the comparator 3 (£)**	**Mean discounted cost per patient using the comparator 4 (£)**	**Difference in mean discounted cost per patient (£): technology vs comparator 1***	**Difference in mean discounted cost per patient (£): technology vs comparator 2***	**Difference in mean discounted cost per patient (£): technology vs comparator 3***	**Difference in mean discounted cost per patient (£): technology vs comparator 4***
Device cost per year (costs associated with procedure/caps/process only (excluding CRBSI costs))	226	61	626	126	107	+ 165	- 400	+ 100	+ 119
Adverse events per year (CRBSI)	450	1,023	891	1,096	921	- 573	- 441	- 646	- 471
Total	**676**	**1,084**	**1,518**	**1,222**	**1,028**	**- 408**	**- 841**	**- 546**	**- 352**
			* Negative values indicate a cost saving. Adapt this table as necessary.						

The economic modelling focussed on impact of introduction of ClearGuard HD on health system costs, as well as patient outcomes (incidence of infection and mortality). Base-case cost results from the model (Table 9) indicate that the technology is cost saving per patient when compared with all included comparators. Table 9 shows the costs for each technology on a per-patient basis, with costs presented for resource use associated with the device and resource use associated with managing infections. Total costs per patient are less with ClearGuard HD than with all of the comparators modelled (range from -£352 to -£841). Base-case model results also indicate that introduction of the intervention results in improved patient outcomes when compared with all alternative technologies (see results presented in table below, which shows the incremental number of CRBSIs, and incremental deaths, associated with introduction of ClearGuard HD amongst the entire population receiving treatment). The results show that ClearGuard HD results in a reduction in infection rates, and mortality, in all comparisons presented.

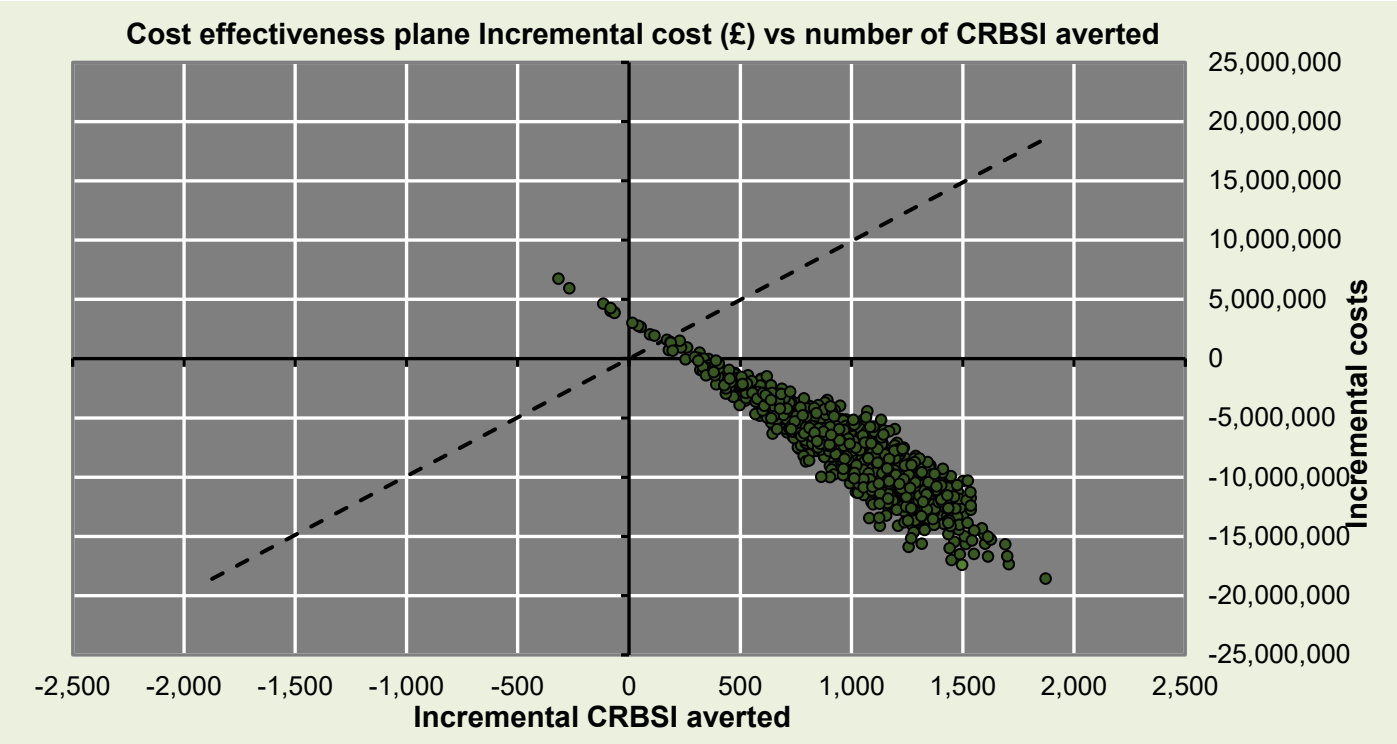
As the intervention is both cost saving, and results in improved patient outcomes (albeit without capturing impact on quality-of-life), the intervention can be considered a ‘dominant’ strategy, in that it is less costly and more effective than all comparators.

Base-case analysis incremental infections and incremental deaths (entire population)

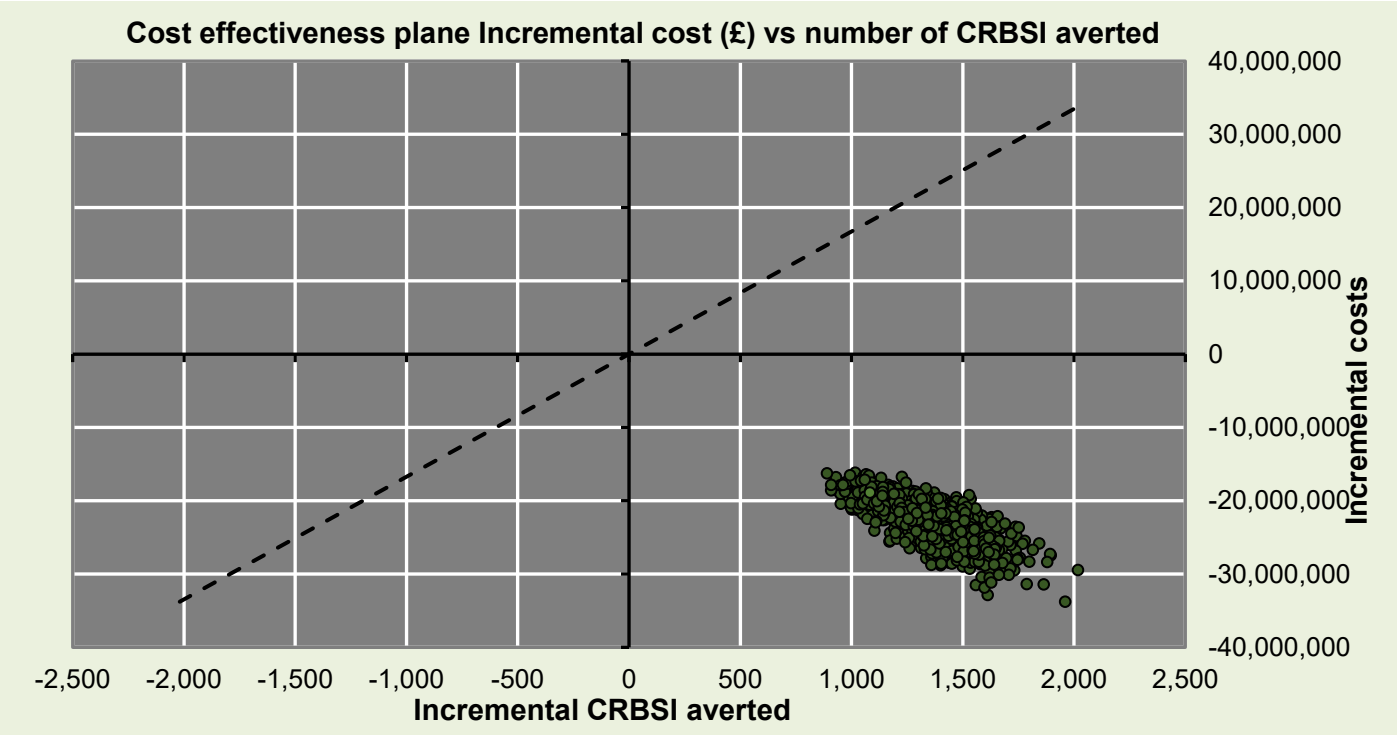
	ClearGuard HD	Comparator 1 - Standard CVC caps	Comparator 2 - Standard CVC caps in combination with antimicrobial lock solution	Comparator 3 - Tego + Curos	Comparator 4 - Tego alone
Total number of CRBSI	790	1,795	1,564	1,923	1,616
Total number of deaths	118	269	235	289	242
Number of CRBSI averted with ClearGuard HD when compared with each comparator	----------	1,005	774	1,133	826
Number of deaths averted with ClearGuard HD when compared with each comparator	----------	151	117	171	124

Probabilistic results (which account for uncertainty in the model/parameter estimates based on a number of model simulations) following 1,000 model simulations are presented below. Each graph (cost-effectiveness plane) represents a comparison between ClearGuard HD and one of the included comparators. The results show that the majority of points (representing individual iterations of the model) are in the south-east quadrant indicating that the intervention is likely to be less costly and more effective (i.e., result in CRBSI's averted) than the comparator in all comparisons.

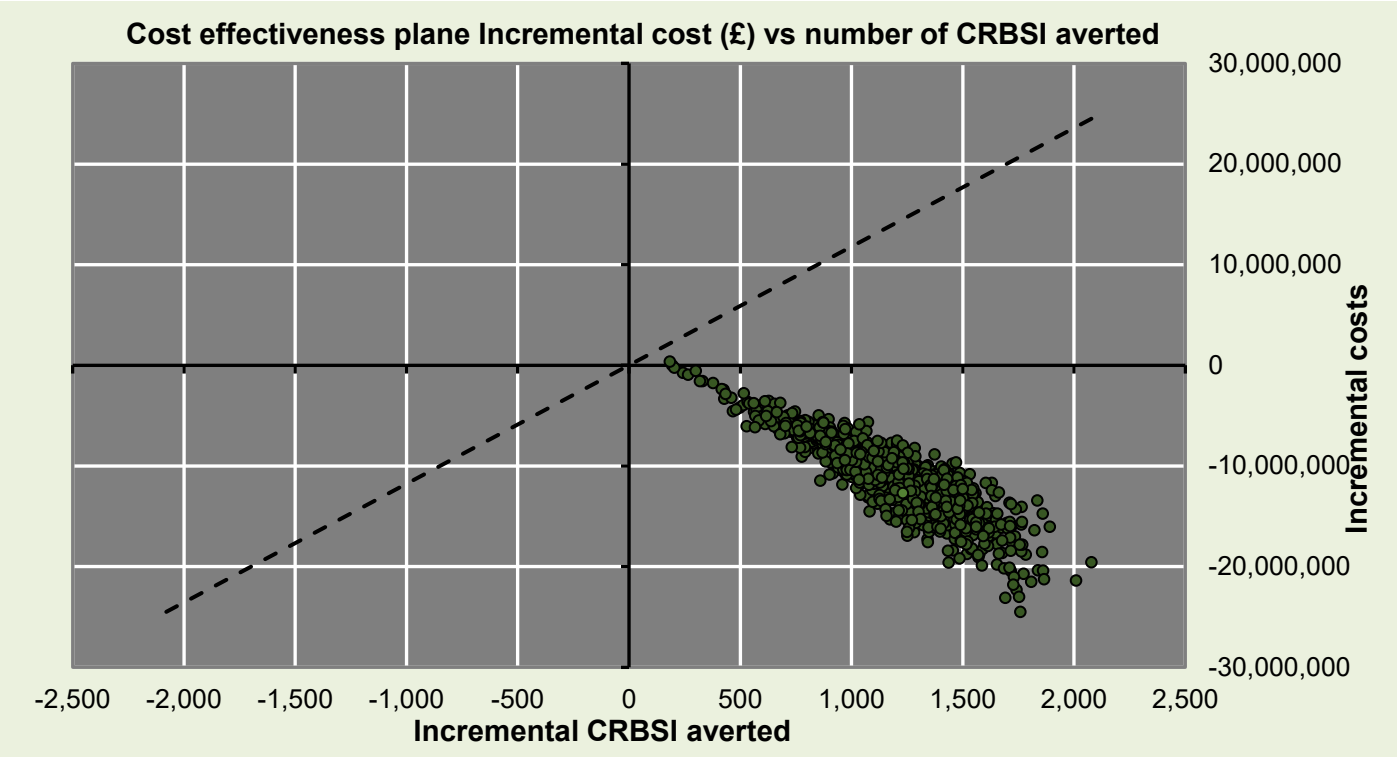
Comparison 1 with standard CVC caps



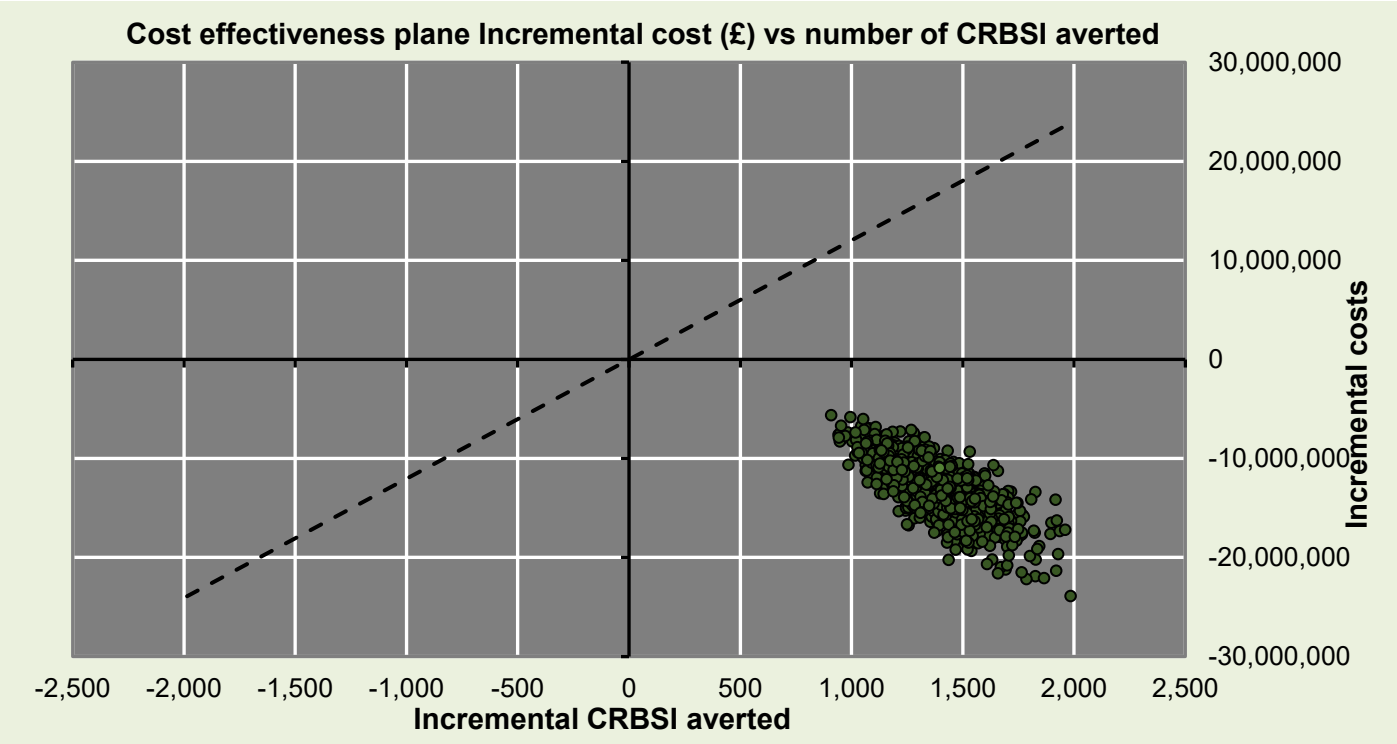
Comparison 2 with standard CVC caps combined with antimicrobial lock solution



Comparison 3 with Tego + Curos



Comparison 4 with Tego alone



Scenario analysis

If relevant, explain how scenario analyses were identified and done. Cross-reference your response to the decision problem in part 1, section 1 of the submission.

Various sensitivity analyses exploring uncertainty in model parameters, and impact on the model outputs, are presented in the next section.

Specific scenario analyses were carried out to explore the impact of varying key parameters, including costs associated with comparators, the baseline rate of infection with each of the comparators, and the IRR of ClearGuard compared to each of the comparators, in combination. As highlighted in the model parameters section, there was wide variation in associated values identified in the literature. Therefore, these base-case values were varied to explore the impact on the model outputs.

Describe the differences between the base case and each scenario analysis.

Scenario A: In the first scenario analysis, an alternative value was assigned to TauroLock (antimicrobial lock solution) to account for varying practices in the UK. A value of £7.50 per week was applied, as opposed to the base-case value of £30, to account for the fact that many practices would use TauroLock with three £2.50 vials of Hep 500 per week rather than utilising the '2+ 1' protocol, including the use of urokinase as well as two vials of Hep 500 per week.

Scenario B-E: A series of 'worst case' scenario analyses were conducted in which the base-case baseline infection rate associated with each of the four comparators was based on the lower-end of the value range, and the IRR of CRBSI with ClearGuard was based on the upper-end of the value range. Ranges of data are presented in the model and in the table in the sensitivity analysis section. The table below shows the variations made:

Scenario	Base-case values	Variation
Scenario B	Incidence rate of CRBSI with standard CVC caps = 0.70; IRR with ClearGuard = 0.44	Incidence rate of CRBSI with standard CVC caps = 0.53; IRR with ClearGuard = 0.83
Scenario C	Incidence rate of CRBSI with standard CVC caps and antimicrobial lock solution = 0.61; IRR with ClearGuard = 0.14	Incidence rate of CRBSI with standard CVC caps and antimicrobial lock solution = 0.46; IRR with ClearGuard = 0.18
Scenario D	Incidence rate of CRBSI with Tego + Curos = 0.75; IRR with ClearGuard = 0.37	Incidence rate of CRBSI with Tego + Curos = 0.56; IRR with ClearGuard = 0.68
Scenario E	Incidence rate of CRBSI with Tego alone = 0.63; IRR with ClearGuard = 0.14	Incidence rate of CRBSI with Tego alone = 0.47; IRR with ClearGuard = 0.18

Describe how the scenario analyses were included in the cost analysis.

The cost analysis was re-run, as in the base-case analysis, with the scenarios outlined above.

Describe the evidence that justifies including any scenario analyses.

For scenario analysis A, information provided by the company supplying the cost of TauroLock (19) indicated that the use of TauroLock in the UK may not necessarily involve the use of urokinase; therefore, an alternative scenario was explored where this vial (urokinase) was omitted.

The other analyses (B-E) were informed by the upper and lower-bound ranges of those included parameters.

Table 10 Scenario analyses results

In this table, describe the results of any scenario analyse that were done. Adapt the table as necessary.

	Mean discounted cost per patient using the technology (£)	**Mean discounted cost per patient using the comparator (£)**	**Difference in cost per patient (£)***
Scenario A (total costs)	676 (as in the base-case analysis)	1,094 (reduction from £1,518 in the base-case analysis)	-418
Scenario B (total costs)	676 (as in the base-case analysis)	835 (reduction from £1,084 in the base-case analysis)	-159
Scenario C (total costs)	676 (as in the base-case analysis)	1,299 (reduction from £1,518 in the base-case analysis)	-623
Scenario D (total costs)	676 (as in the base-case analysis)	944 (reduction from £1,222 in the base-case analysis)	-268
Scenario E (total costs)	676 (as in the base-case analysis)	794 (reduction from £1,028 in the base-case analysis)	-118

* Negative values indicate a cost saving.
Adapt this table as necessary.

Scenario A: Despite the reduction in the cost of antimicrobial locks, the intervention remains cost saving (-£418).

Scenarios B-E: In these scenarios where the base-case baseline infection rate with each of the comparators has been reduced, and the base-case IRR of CRBSI with the intervention has been increased, ClearGuard HD remains cost saving in all cases.

Sensitivity analysis

Describe what kinds of sensitivity analyses were done. If no sensitivity analyses have been done, please explain why.

Multiple sensitivity analyses were conducted to explore the impact of parameter variations on the model outputs. In these analyses (multiple one-way sensitivity analyses), all model parameters were either varied by 25% (increased and decreased) or by a range available from the evidence, to explore the impact that this had on the incremental cost of the intervention (with results presented in the form of a tornado diagram). The range of sensitivity analyses are presented in the next section, with results presented afterwards.

Summarise the variables used in the sensitivity analyses and provide a justification for them. This may be easier to present in a table (adapt as necessary).

Sensitivity analysis:

Multiple one-way sensitivity analyses were conducted, in which all model parameters were varied by 25% (increased and decreased) or by a range available from the evidence, to look at the impact that this had on the incremental cost of the intervention. A list of parameters included in the analysis, and the range by which each parameter was varied, is presented in the table below.

Variable	Base-case value	Range of values
Average number of CVC days per HD patient per year	132	123-141 (25% increase/decrease)
Incidence rate of CRBSI per 1,000 CVC-days (Standard CVC caps)	0.70	0.53-0.88 (25% increase/decrease)
IRR of CRBSI compared to standard caps	0.44	0.23-0.83 (based on data from Hymes et al, 2017 (3))
Incidence rate of CRBSI per 1,000 CVC-Days (Antimicrobial lock solution)	0.61	0.46-0.76 (25% increase/decrease)
IRR of CRBSI compared to antimicrobial lock solution	0.14	0.11-0.18 (25% increase/decrease)
Incidence rate of CRBSI per 1,000 CVC-Days (Tego + Curos caps)	0.75	0.56-0.94 (25% increase/decrease)
IRR of CRBSI compared to Tego + Curos caps	0.37	0.20-0.68 (based on data from Brunelli et al, 2018 (12))
Incidence rate of CRBSI per 1,000 CVC-Days (Tego only)	0.63	0.47-0.79 (25% increase/decrease)
IRR of CRBSI compared to Tego only	0.14	0.11-0.18 (25% increase/decrease)
Probability of death post CRBSI	0.15	0.12-0.32 (based on data from Goto et al, 2013 (6))
Average cost of treating CRBSI (£)	11,071.00	8,303.00-13,839 (25% increase/decrease)
Unit cost of ClearGuard Caps (price per a pair of caps) (£)	4.00	3.00-5.00 (25% increase/decrease)

Average cost of alcohol wipes (£)	0.02	0.02-0.03 (25% increase/decrease)
Unit cost of standard caps (price per cap) (£)	0.35	0.26-0.44 (25% increase/decrease)
Cost of Curos caps (price per unit) (£)	0.35	0.26-0.44 (25% increase/decrease)
Cost of Tego (price per unit) (£)	2.29	1.72-2.86 (25% increase/decrease)
TauroLock cost per dialysis session (£)	10.00	7.50-12.50 (25% increase/decrease)

If any parameters or variables listed in table 3 were omitted from the sensitivity analysis, please explain why.

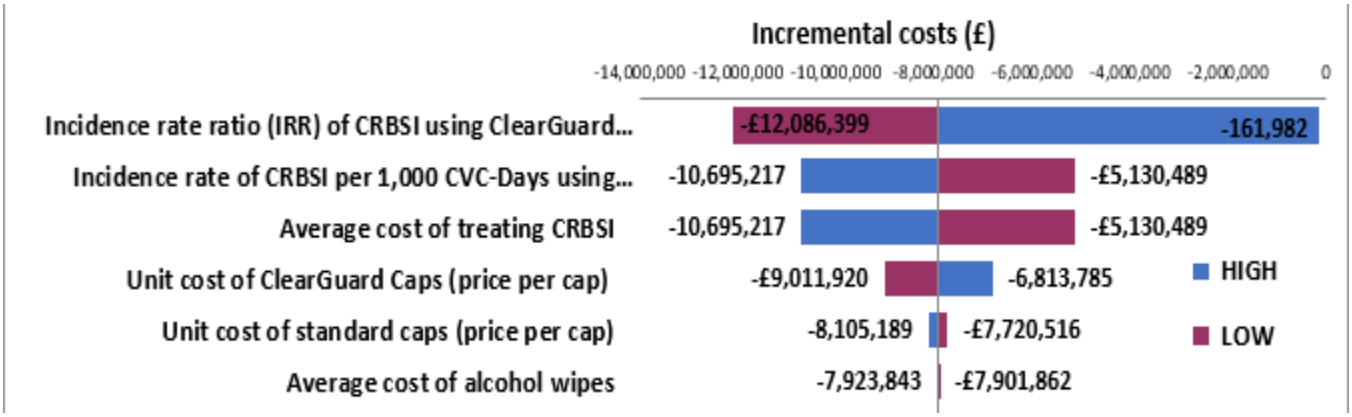
All relevant parameters were included in the multiple one-way sensitivity analyses.

Sensitivity analyses results

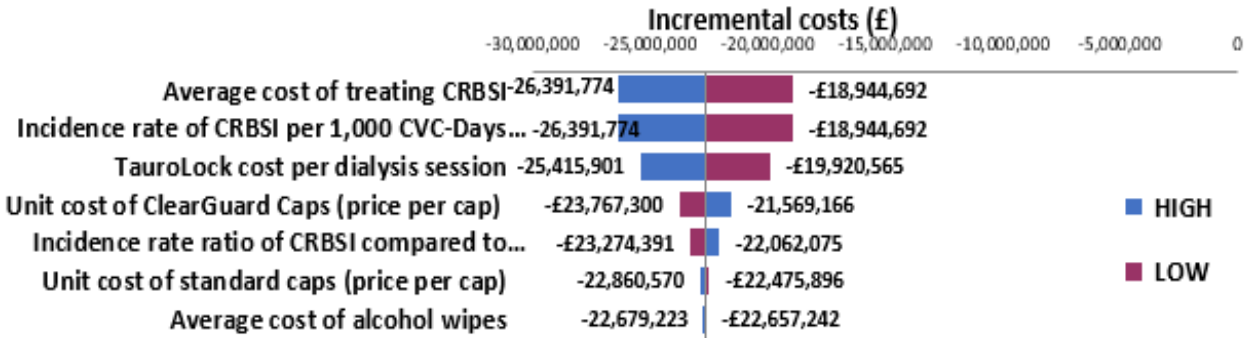
Present the results of any sensitivity analyses using tornado plots when appropriate.

Sensitivity analysis: Impacts of changing values of the input parameters on the estimated incremental cost of the intervention. Tornado diagrams are presented for each comparison below.

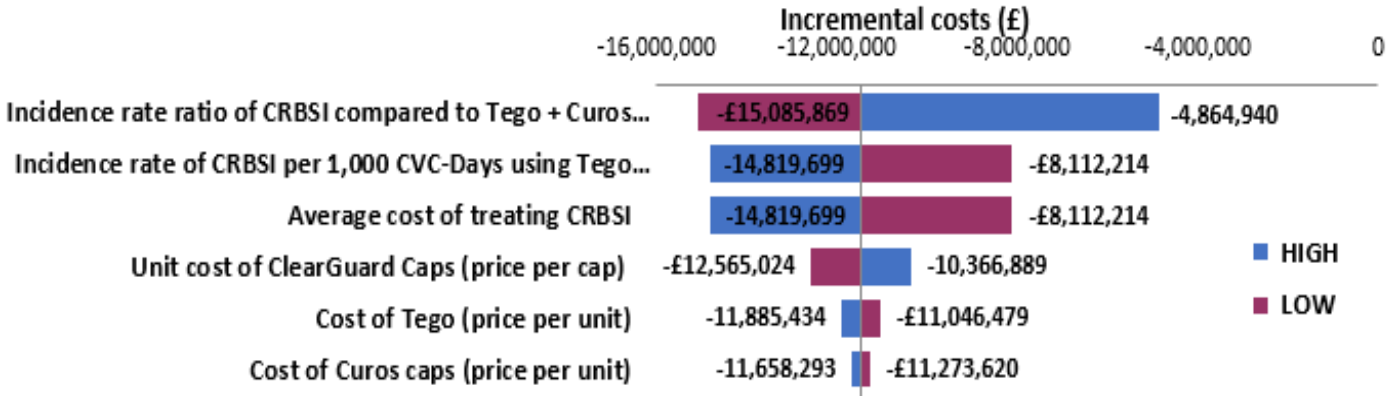
Comparison 1 with standard CVC caps



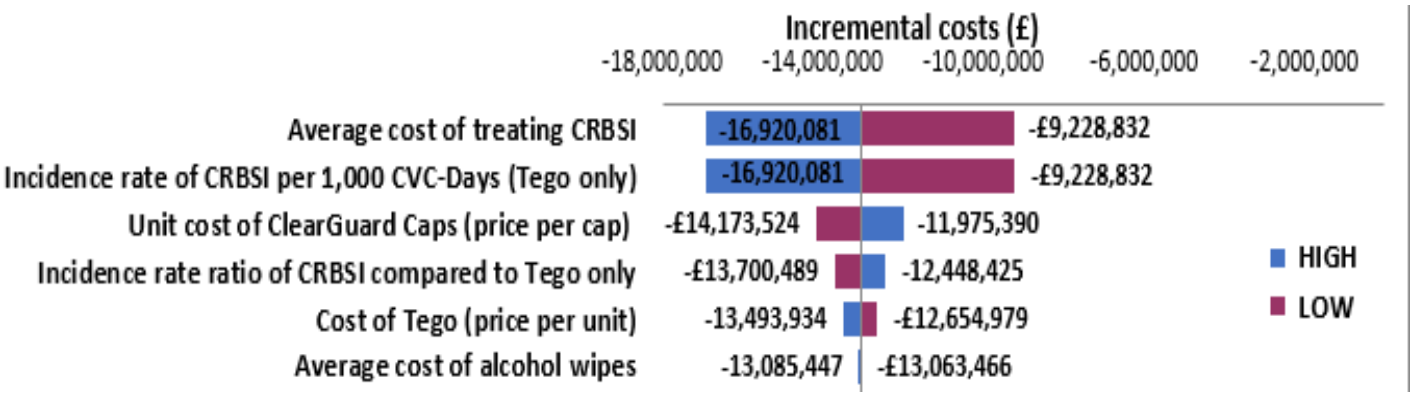
Comparison 2 with standard CVC caps combined with antimicrobial lock solution



Comparison 3 with Tego + Curos



Comparison 4 with Tego alone



What were the main findings of each of the sensitivity analyses?

Sensitivity analysis: In the tornado diagram(s), which shows the results of the multiple one-way sensitivity analyses (parameter variations), parameters are displayed in order, with those which have the greatest impact on incremental cost displayed at the top and those with have the least impact displayed at the bottom of the graph. Four tornado diagrams are presented in the results above, each one representing a comparison between ClearGuard HD and one of the four comparators included in the analysis. Each tornado diagram shows the impact on the incremental cost of the intervention following variation of the base-case value for that parameter. As outlined previously, parameters were either varied by 25% (higher and lower) or by a ranged defined by the identified data.

In the majority of cases from the analyses presented above, the results show that the parameters which have the largest impact on cost results are the baseline incidence rate of infection associated with the comparator, and the IRR associated with ClearGuard. When the baseline incidence rate associated with the comparator is increased, cost savings associated with the introduction of the intervention increase also. Conversely, when the IRR of ClearGuard is increased, i.e., it has less of an impact on the occurrence of CRBSIs, cost savings are reduced. These two parameters have a large impact in all comparisons. Notably, it is in the comparisons with antimicrobial lock solutions and Tego alone, where variation of the base-case IRR for ClearGuard appears to have less of an impact on the results than for the other two comparisons presented. This is likely due to the fact that the base-case value for this IRR is 0.14 in both comparisons, and a 25% variation of this value does not result in as extreme values as with the other two comparisons (where the base-case IRRs are 0.44 and 0.37, respectively).

The tornado diagrams presented above show the change in the incremental cost of the intervention amongst the entire population who may benefit from treatment. However, the model also calculates the percentage change in incremental cost following the variation of each of the parameters in each comparison. It should be highlighted that for each comparison, there is no parameter variation which results in the intervention becoming more costly than the comparator, i.e., the value in the diagram(s) is always negative, indicating that the intervention is cost saving.

Results from the sensitivity analyses highlighted above show the parameters which have the greatest impact on the incremental cost of the intervention. Notably, in all four analyses, regardless of the variation made to all included model parameters, the overall conclusion (i.e., ClearGuard HD is a cost saving intervention) remains the same.

What are the main sources of uncertainty about the model's conclusions?

As much of the important data regarding baseline incidence rates of infection, and IRRs associated with the use of ClearGuard were derived from data from the US, the largest source of uncertainty is surrounding the transferability of findings to the UK.

However, to account for this, extensive sensitivity analyses were conducted on all model parameters (and in particular, on the parameters which are likely to be drivers of the model results, including baseline rate of infection and IRR associated with ClearGuard). The sensitivity analyses results highlight the importance of the parameters outlined, but also indicate that regardless of the variation made to these parameters, the intervention remains cost saving.

Miscellaneous results

Include any other relevant results here.

Not applicable.

Validation

Describe the methods used to validate, cross-validate (for example with external evidence sources) and quality assure the model. Provide sources and cross-reference to evidence when appropriate.

In order to evaluate the face validity of the model, the model structure, input parameters and results were presented to clinical experts with significant experience working in this clinical area, and who are well-respected in this field of research. They evaluated the model structure and assumptions in comparison to real-world circumstances. A large number of sensitivity analyses were also conducted to assess the internal validity of the model. Alternative values were assigned to input parameters and the model was run to test the robustness of the results. The model was developed by one health economist and was checked for errors and validated by a second health economist.

Give details of any clinical experts who were involved in validating the model, including names and contact details. Highlight any personal information as confidential.

Dr Mohsen Rezaie Hemami, Glasgow. Contact address: mohsen_rez@yahoo.com.

4 Summary and interpretation of economic evidence

Describe the main findings from the economic evidence and cost model. Explain any potential cost savings and the reasons for them.

Findings from the economic modelling indicate that introduction of ClearGuard HD Antimicrobial Barrier Caps for use amongst patients undergoing haemodialysis with tunnelled central venous catheters, results in cost savings for the health care service in England and improved patient outcomes (both a reduction in the infection rate, and a reduction in mortality). A probabilistic model was developed, which allows one to quantify the uncertainty present in the model results. Based on 1,000 iterations of the model, results indicate that the intervention is likely to be cost saving and more effective than all comparators included in the analysis. Base-case model results indicate that total cost savings (inclusive of costs associated with devices and costs associated with infection) of between £352 to £841 would be made per patient per year (depending on comparator selected), as well as a reduction in CRBSIs and mortality per patient in all comparisons. Therefore, the intervention can be considered to be a 'dominant' strategy in that it is less costly and more effective than the comparator(s).

Following introduction of ClearGuard HD, cost savings are driven by the reduction in infection rates, which is a resource intensive and costly event for the health care service (£11,071 per CRBSI). These events are associated with high treatment and management costs. Although not formally explored in this analysis, these improved patient outcomes are also likely to translate to improvements in patient quality-of-life. Additionally, this reduction in infection rates results in reduced mortality rates amongst the patient population.

In summary, the reduction in CRBSI event rates associated with introduction of the intervention, combined with the relatively low technology acquisition cost for ClearGuard HD (£4 per pair of caps per round of haemodialysis) results in meaningful improvements in clinical outcomes as well as a significant reduction in healthcare costs. Introduction of the technology is therefore likely to represent a cost-effective use of health service resources.

Briefly discuss the relevance of the evidence base to the scope.

The following claimed benefits of ClearGuard HD caps are included in the scope:

- Reduced risk of catheter related bloodstream infections (CRBSI),
- Reduced hospital attendances and length of stay due to CRBSI,
- Reduced mortality as a result of reduced risk of CRBSI,

All of the above claimed benefits have been demonstrated in the economic model, as well as the cost savings related to these claimed benefits.

A robust decision-analytic model estimates that the introduction of ClearGuard HD is less costly and more effective in reducing infection rates, hospital length of stay and mortality rates, compared to existing methods used to prevent CRBSIs amongst haemodialysis patients. Therefore, the evidence provided directly aligns with the scope.

Briefly discuss if the results are consistent with the published literature. If they are not, explain why and justify why the results in the submission be favoured over those in the published literature.

One abstract involving an analysis of the use of ClearGuard HD caps was identified in the search for relevant economic evidence. Glennon et al, 2020 (1) carried out a retrospective analysis of the costs and outcomes associated with use of the intervention and comparator (antimicrobial locks) in the paediatric dialysis setting. The study found that the CA-BSI rate for the control arm was 1.82 per 100 patient months, with the cost of prophylactic AML usage in 4 high risk patients totalling $25,896. In the intervention arm, AML usage was discontinued and ClearGuard caps were used for all haemodialysis patients with CVCs (inclusive of high risk and non-high risk patients) with a total annual cost of $10,140 and the CA-BSI rate dropped to 0.26 per 100 patient months.

The study by Glennon et al, 2020 (1) was an identified abstract, and therefore the reporting of methods and results are limited. However, their findings are consistent with the results presented in this de novo cost analysis, in that they highlight the potential cost-effectiveness of the intervention, while indicating that the combination of ClearGuard caps and good catheter care practices may substantially decrease the risk of haemodialysis CA-BSI.

No additional studies focussing on the costs/cost-effectiveness of the intervention have been identified in the literature.

Describe if the cost analysis is relevant to all patient groups and NHS settings in England that could potentially use the technology as identified in the scope.

The analysis is relevant to all patients with tunnelled CVCs undergoing HD. It is relevant to the NHS hospital setting. Although analyses for other settings (i.e., community) were not possible due to insufficient data, the results of the hospital setting analysis are likely transferrable to other settings which deliver the procedure(s) and intervention(s) outlined.

Briefly summarise the strengths and limitations of the cost analysis, and how these might affect the results.

Strengths:

A robust decision-analytic model was developed, which accounts for the uncertainty present through the probabilistic output produced. Additionally, as described, extensive sensitivity analyses have been conducted to explore the impact of individual, and multiple, parameter variation on the results of the economic analysis. The model was informed by clinical guidelines, published literature and expert clinical input, and any assumptions that were made in the analysis can be rectified by using more robust data in later studies, as a model now exists for re-analysis once additional information becomes available. Data on the effectiveness of the intervention, while primarily derived from US-based studies, were all sourced from robust clinical trials which are likely to accurately reflect the effectiveness of the intervention.

Limitations:

Limitations of this analysis were as follows:

- No UK-based data were available on the effectiveness of the intervention in reducing CRBSI rates.

However, despite this limitation, the base-case analysis results, and the results of scenario and sensitivity analyses, indicated that the cost savings are significant and that only substantial variation in model parameters is likely to impact the overall conclusions of the analysis.

Detail any further analyses that could be done to improve the reliability of the results.

Further analyses should focus on identifying UK-specific data to inform the parameters outlined in the limitations above, to ensure that the conclusions are reliable for the UK setting.

5 References

Please include all references below using NICE's standard referencing style.

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13. Weiss, S, & Qureshi, MN. Evaluating a novel hemodialysis central venous catheter cap in reducing bloodstream infections: A quality improvement initiative (2021). International Journal of Nephrology and Renovascular Disease. 14 125–131.

14. Kwak, I, Song, S, Seong, E, et al. Bacterial Colonization of Tunnelled Cuffed Catheter in Patients with Hemodialysis. Nephrology Dialysis Transplantation, Volume 27, Issue suppl_2, May 2012, Pages ii252–ii267, https://doi.org/10.1093/ndt/gfs226.
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6 Appendices

Appendix A: Search strategy for economic evidence

Describe the process and methods used to identify and select the studies relevant to the technology being evaluated. See section 2 of the user guide for full details of how to complete this section.

Date search conducted:	18/05/2021
Date span of search:	Until 18/05/2021 (please see search strategies below for precise date ranges)

List 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). List the databases that were searched.

Database: Ovid MEDLINE(R) ALL <1946 to May 18, 2021>

		Result
1	Catheters, indwelling/ or central venous catheters/	20919
2	Catheter*.ti,ab.	209193
3	exp Catheterization, Peripheral/	12144
4	Cardiac Catheterization/	49684
5	Catheter-Related Infections/	5371
6	(catheter$ or microcatheter$ or cannula$ or microcannula$ or canula$ or microcanula$).ti,ab,kf.	258266
7	((hemodialysis and (catheter or "central venous catheter" or CVC) and infection) or bacteremia).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	41253
8	Vascular access*.ti,ab.	10191
9	(CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs).ti,ab,kf.	17265
10	((PIC or CVP) adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kf.	135
11	((central or subclavian or jugular or femoral) adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kf.	20057
12	(peripheral adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kf.	7748
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.	33720
14	((arterial or intraarterial or artery or arteries) adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kf.	9787
15	Catheters, Indwelling/ or Bacteremia/ or Catheter-Related Infections/ or catheter-related bloodstream infections.mp. or Catheterization, Central Venous/ or Central Venous Catheters/	57713
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).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1964

17	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	386823
18	Clearguard.mp.	3
19	Clear Guard/	0
20	CGHD/	0
21	Pursuit Vascular/	0
22	Antiseptic cap/	0
23	Antiseptic cap.mp.	1
24	Antimicrobial barrier cap.mp.	1
25	Antimicrobial lock.mp.	87
26	18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	90
27	Economics/	27325
28	exp "Costs and Cost Analysis"/	245202
29	exp Economics, Hospital/	25100
30	exp Economics, Medical/	14260
31	Budgets/	11428
32	expenditure$.tw.	60194
33	(cost or costs or costing$ or costly or costed).tw.	615846
34	(price$ or pricing$).tw.	43567
35	(pharmacoeconomic$ or (pharmaco adj economic$)).tw.	4168
36	(value adj3 (money or monetary)).tw.	2715
37	27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36	832876
38	17 and 26 and 37	17

Database: Embase <1974 to May 18, 2021>

		Result
1	Vascular access/	28276
2	Hemodialysis/	114136
3	Catheters, indwelling/ or central venous catheters/	28884
4	exp catheter/	197908
5	Catheter infection/	18858
6	(catheter$ or microcatheter$ or cannula$ or microcannula$ or canula$ or microcanula$).ti,ab,kw.	387995
7	(CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs or PVC or PVCs).ti,ab,kw.	27910
8	((PIC or CVP) adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kw.	261
9	((central or subclavian or jugular or femoral) adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kw.	32304
10	(peripheral adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kw.	10667
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.	53721
12	((arterial or intraarterial or artery or arteries) adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kw.	15597
13	catheter-related bloodstream infections.mp. or catheter infection/	19067

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).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	3969
15	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	638489
16	clearguard$2.ti,ab,kw,dv.	10
17	Clear Guard/	44
18	CGHD/	0
19	Antimicrobial barrier cap/	0
20	Antimicrobial lock/	2
21	Antiseptic lock/	0
22	Antiseptic cap/	0
23	Pursuit Vascular/	0
24	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23	55
25	15 and 24	16
26	health economics/	33398
27	exp economic evaluation/	318340
28	exp health care cost/	302943
29	exp fee/	40902
30	budget/	30450
31	funding/	52322
32	resource allocation/	22018
33	budget*.ti,ab.	40918
34	cost*.ti,ab.	877877
35	(economic* or pharmaco?economic*).ti,ab.	372969
36	(price* or pricing*).ti,ab.	61462
37	(financ* or fee or fees or expenditure* or saving*).ti,ab.	342943
38	(value adj2 (money or monetary)).ti,ab.	3492
39	resourc* allocat*.ti,ab.	12796
40	(fund or funds or funding* or funded).ti,ab.	152269
41	(ration or rations or rationing* or rationed).ti,ab.	17161
42	26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41	1789120
43	25 and 42	6

Database(s): NHS EED, DARE, HTA via CRD <to May 18, 2021>

		Result
1	clearguard OR Clear Guard OR Pursuit Vascular OR ICU Medical OR icumedical OR Antimicrobial barrier cap OR Antimicrobial lock OR Antiseptic lock	10

Database: CEA Registry via Centre for the Evaluation of Value and Risk in Health <to May 18, 2021>

		Result
1	clearguard OR Clear Guard OR Pursuit Vascular OR ICU Medical OR icumedical OR Antimicrobial barrier cap OR Antimicrobial lock OR Antiseptic lock	1

Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):

References of the identified studies were checked for relevant studies. We also consulted with key personnel in the Company to ensure that we had not missed any relevant studies that they were aware of.

Inclusion and exclusion criteria:

Inclusion criteria

Population: The target population for this review is patients undergoing HD using CVCs.

Intervention: The intervention being considered in this review is the ClearGuard™ HD Antimicrobial Barrier Cap to minimize the risk of CRBSIs amongst patients undergoing HD using CVCs.

Comparator(s): The comparators are current standard care, which includes the use of alcohol wipes and alcohol containing solution of chlorhexidine gluconate (2% chlorhexidine gluconate in 70% alcohol), as well as alternative barrier caps. As we aim to include all possible comparators in the review, we will exclude the search terms related to comparators in the search strategy.

Outcomes: Relevant health outcomes reported in the economic studies will be extracted and may include:

- Life-years gained,
- Quality-adjusted life-years (QALYs) gained,
- Incremental cost-effectiveness ratios (ICERs),
- Clinical effectiveness (e.g., survival rates, healing rates, etc.),
- Details of the results of sensitivity analyses.

Country: There will be no limitation of included studies based on study country. All studies meeting the inclusion criteria which were conducted in any country to be included in the review.

Language: Only studies with full text in English will be included in this review. Studies with abstracts in English but full text published in any language other than English will be excluded.

Publication timeframe: All studies published from database start to present will be included in this review in order to obtain all available evidence.

Study design: The study designs to be included in this systematic review are economic evaluations, including budget impact models, and cost analysis studies. The details of study designs relevant to the economic review are presented in the table below. Surveys and database analyses will be excluded as they are not relevant to the research question.

Study designs	Inclusion	Rationale/Comments
Cost-effectiveness analyses (CEA)	Yes	Full economic evaluations will address the study question. Budget impact models and cost studies will provide information for parameterization of the economic model.
Cost-utility analyses (CUA)	Yes	
Cost-benefit analyses (CBA)	Yes	
Cost-minimization analyses (CMA)	Yes	
Cost-consequence analyses (CCA)	Yes	
Budget impact models	Yes	
Cost analysis studies	Yes	

Surveys/database analyses	No	Surveys and database analyses are not relevant to the study question.

Exclusion criteria

The following study types will be excluded:

- Animal studies,
- Surveys,
- Database analyses,
- Editorials; commentary,
- Device name not reported as intervention or comparator,
- Incorrect population,
- Incorrect outcomes.

Additionally, any studies not meeting any other of the inclusion criteria outlined above will be excluded.

Data abstraction strategy:

Data from all included studies will be extracted using a pre-designed form. Data extraction will be undertaken by one reviewer and checked by a second reviewer. Disagreements between the review authors will be resolved by discussion and consensus, with involvement of a third review author where necessary.

The authors of each original study will be consulted when there is incomplete or missing relevant data. The main findings of the data extraction will be presented in 'summary of included studies' tables.

The table below outlines the relevant categories and specific data that will be extracted from all studies that meet the inclusion criteria.

Outcome categories	Relevant outcomes
Study details	• Study name • Year of publication • Cost year and currency(ies) • Study design • Country(ies) • Intervention and comparator details • Type of evaluation
Population characteristics	• Mean/median age • Comorbidities
Modeling methodologies	• Perspective (e.g., healthcare payer, societal) • Time horizon • Discounting • Markov or decision tree or other types • Cycle length • Health state names (if applicable) • Simulation method (e.g., cohort, patient-level) • Sensitivity analyses type • Model assumptions • Mortality modelling
Model structure, key data sources and risk equations	• Incorporation of treatment effects • Incorporation of complications/adverse events • Incorporation of health-related quality-of-life

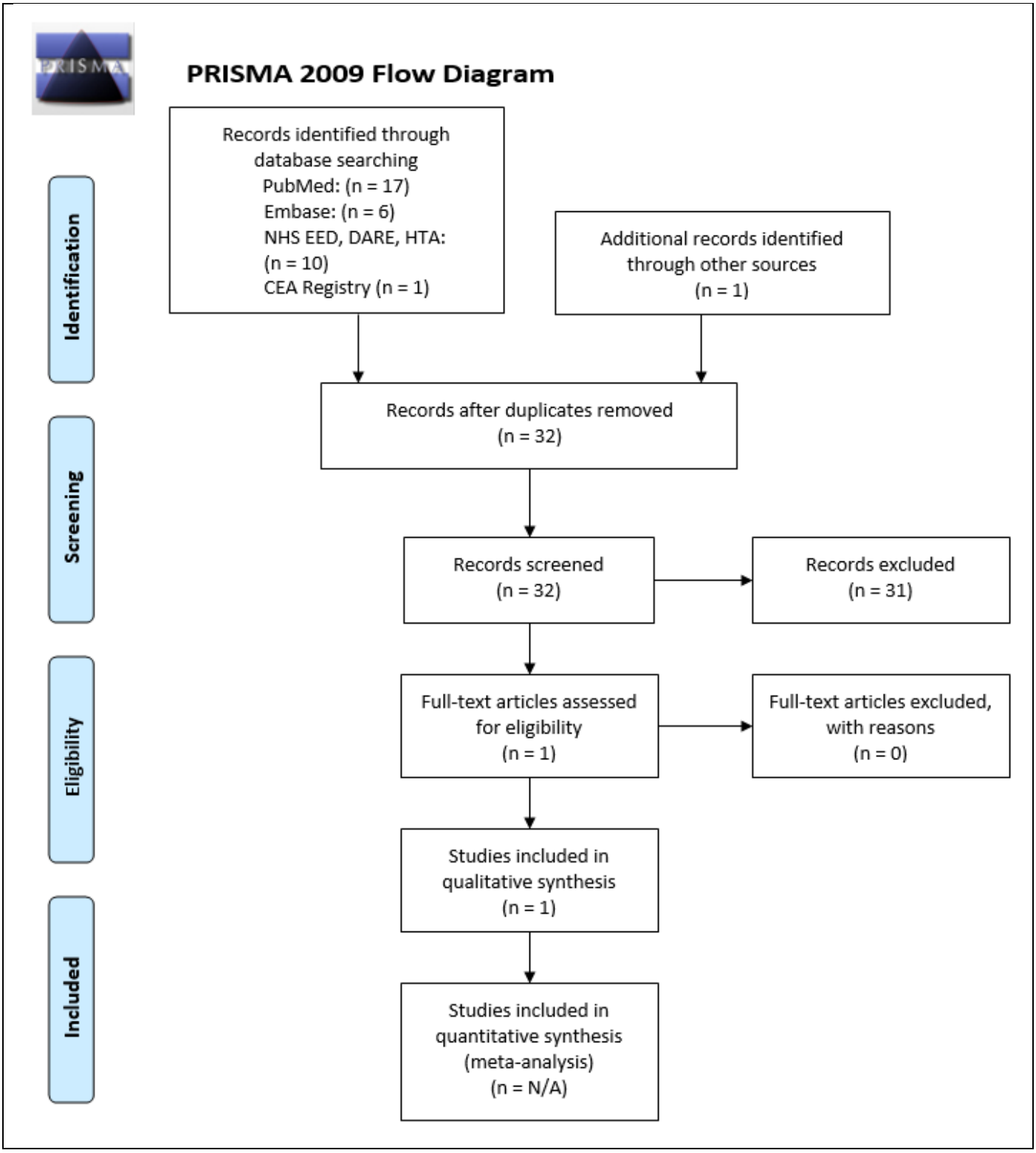
	• Incorporation of resource use and costs
Input source	• Input source for resource use • Input source for unit costs • Input source for clinical effectiveness • Input source for health utility/quality-of-life
Outcomes	• Life-years gained • Quality-adjusted life-years gained (QALYs) • Incremental cost-effectiveness ratios (ICERs) • Clinical effectiveness (survival rates, healing rates etc.) • Details of sensitivity analyses results

Excluded studies

List any excluded studies below. These are studies that were initially considered for inclusion at the level of full text review, but were later excluded for specific reasons.

Excluded study	Design and intervention(s)	Rationale for exclusion	Company comments
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).



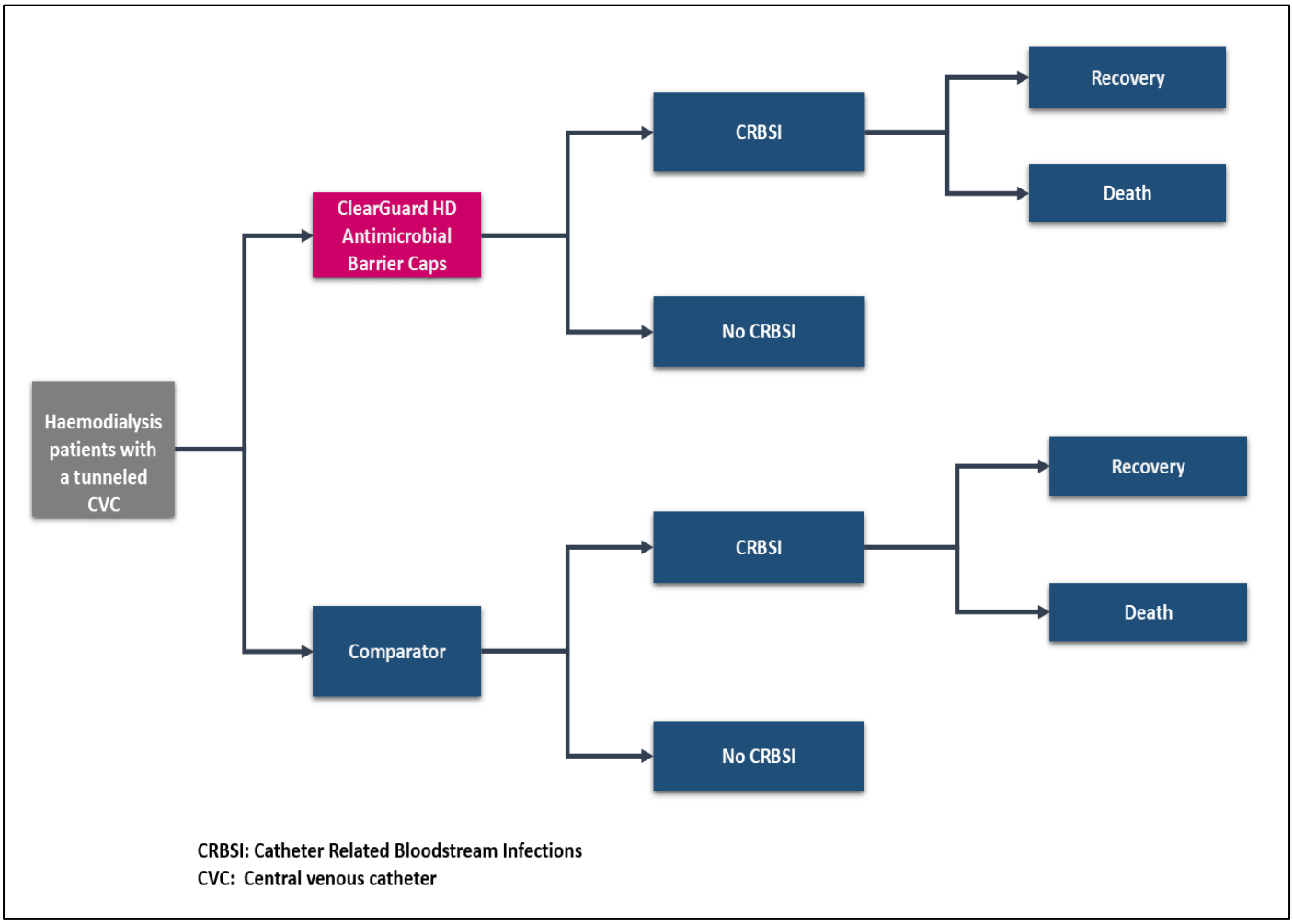
Structured abstracts for unpublished studies

Study title and authors
Introduction
Objectives
Methods
Results
Conclusion

Article status and expected publication: Provide details of journal and anticipated publication date

Appendix B: Model structure

Please provide a diagram of the structure of your economic model.



Appendix C: Checklist of confidential information

Please see section 1 of the user guide for instructions on how to complete this section.

Does your submission of evidence contain any confidential information? (please check appropriate box):

No ☒ If no, please proceed to declaration (below)

Yes ☐ If yes, please complete the table below (insert or delete rows as necessary). Ensure that all relevant sections of your submission of evidence are clearly highlighted and underlined in your submission document, and match the information provided in the table. Please add the referenced confidential content (text, graphs, figures, illustrations, etc.) to which this applies.

Page	Nature of confidential information	Rationale for confidential status	Timeframe of confidentiality restriction
#	☐ Commercial in confidence ☐ Academic in confidence	Enter text.	Enter text.
Details	Enter text.		
#	☐ Commercial in confidence ☐ Academic in confidence	Enter text.	Enter text.
Details	Enter text.		

Confidential information declaration

I confirm that:

- all relevant data pertinent to the development of medical technology guidance (MTG) has been disclosed to NICE
- all confidential sections in the submission have been marked correctly
- if I have attached any publication or other information in support of this notification, I have obtained the appropriate permission or paid the appropriate copyright fee to enable my organisation to share this publication or information with NICE.

Please note that NICE does not accept any responsibility for the disclosure of confidential information through publication of documentation on our website that has not been correctly marked. If a completed checklist is not included then NICE will consider all information contained in your submission of evidence as not confidential.

Signed*: ** Must be Medical Director or equivalent*		**Date:**	15 June 2021
Print:	John Beard, MD	**Role / organisation:**	Chief Medical Officer ICU Medical, Inc.

Contact email: [redacted]

National Institute for Health and Care Excellence

Collated comments table

MTG Medtech Guidance: GID-MT561 ClearGuard HD Antimicrobial Barrier Cap for preventing haemodialysis catheter-related bloodstream infections

Expert contact details and declarations of interest:

Expert #1	Carole Hallam, Independent Infection Prevention Nurse Consultant, Self Employed, Click here to enter text.
	Nominated by: IPSPA
	DOI: NONE
Expert #2	Kay Tyerman, Consultant Paediatric Nephrologist, Leeds Teaching Hospitals NHS Trust, Click here to enter text.
	Nominated by: NICE
	DOI: NONE
Expert #3	Dr Peter Dupont, Consultant Nephrologist, Royal Free Hospital,
	Nominated by : NICE
	DOI: NONE
Expert #4	Susan Rowlands, Specialist Nurse Team Manager, Royal Wolverhampton NHS Trust, Click here to enter text.
	Nominated by: IPSPA
	DOI: NONE
Expert #5	Dr Pritpal Virdee, Renal Consultant, Epsom and St Helier University Hospitals NHS Trust,
	Nominated by: Expert
	DOI- NONE
Expert #6	Dr Partha Das, Chief Medical Officer | Honorary Consultant Nephrologist, Davita International | King's College Hospital NHS Foundation Trust,
	Nominated by: Company
	DOI: YES - *Chief Medical Officer of Davita International – subsidiary group of Davita Inc in USA. Davita dialysis clinics in the USA were the site of one of the studies on ClearGuard quoted in the evidence summary. I have not been involved in the research nor were any of the clinics outside of the USA for which I have governance oversight part of the research. We do not use ClearGuard in my jurisdiction*

Expert #7	Dr Nicola Kumar, Consultant Nephrologist, Guy's and St Thomas' NHS Trust,
	Nominated by: Expert
	DOI: NONE
Expert #8	Marlies Ostermann, Consultant in Nephrology, Guys and St Thomas' NHS Foundation Trust,
	Nominated by: Company
	DOI: Non-financial- attended an advisory expert meeting arranged by the company
Expert #9	Dr Sandip Mitra
	Nominated by: NICE
	DOI: None. Our Trust (MFT) may evaluate the technology in the future in patients in the next 12 month period
Expert #10	Dr Albert Power
	Nominated by: NICE
	DOI:

1	Please describe your level of experience with the procedure/technology, for example: Are you familiar with the procedure/technology? Have you used it or are you currently using it? Do you know how widely this procedure/technology is used in the NHS or what is the likely speed of uptake? Is this procedure/technology performed/used by clinicians in specialities other than your own? – If your specialty is involved in patient selection or referral to another	I am familiar with the practice of disinfecting catheter hubs and needless connectors as an infection prevention practitioner rather than a frontline nurse. I have also aware of the curos caps but practice in the UK is to disinfect the catheter hub with alcohol and chlorhexidine 2% (Epic3 guidelines) so even when the curos caps are used there is still advice to use manually disinfect with alcohol and chlorhexidine I have not used the ClearGuard product. I am not aware of the wide use of this product but suspect there would be some interest. My speciality is infection prevention and control and not in renal medicine but I have a special interest in vascular access	

	specialty for this procedure/technology, please indicate your experience with it.	Expert #2 I was appointed to my consultant post as a paediatric Nephrologist in April 2004 and have led our paediatric haemodialysis service from 2004 -2020, dialysing between 7-12 chronic patients at any one time as well as providing acute dialysis for acute kidney injury. We have not used Clear guard in our paediatric unit. Line related sepsis and protection of vascular access is a priority as children with chronic kidney disease are likely to require further periods on dialysis over their lifetime. A small number of patients have fistula access but the majority of children have a tunnelled central venous line and this technology would be used if evidence of decreased infection risk. I'm not aware that this technology is used in any of the 13 paediatric nephrology centres carrying out paediatric haemodialysis in the UK. There could also be potential uptake in paediatric intensive care units with patients undertaking CVVHD and or plasma exchange.	
		Expert 3 I'm familiar with the standard process for locking tunnelled dialysis catheters but not this specific device.	
	–	Expert #4 I am a Vascular Access Clinical Nurse Specialist with an especial interest in Infection Prevention issues. I have been invited to participate in my role as the IV Co-ordinator of the Infection Prevention Society's IV Forum.	

		I am not directly involved in renal line care, but heavily involved in general iv line care and maintenance. I have not used these caps. I am aware that renal dialysis lines are routinely capped when not in use, and that other alternatives of antimicrobial caps are already implemented in some NHS dialysis units. Similarly alternative antimicrobial caps are in use in general patients for vascular access device hub protection of which I have greater experience.	
	-	Expert #5 I have not used this technology. In our centres we replace the cap each session and do not use the Tego system as used in one of the studies. I am not aware of anyone using this technology in the London area.	
	-	Expert #6 I am familiar with the technology and it has been demonstrated to me. I do not use it in regular current practice. I have not been involved in the development of the product and it is not widely used in the NHS as far as I am aware.	
	-	Expert #7 I am familiar with Tego and Curos caps Within our institution we are not using ClearGuard as far as I am aware I have not previously been involved in any research or development on this technology I do not know how widely this technology is used in the NHS	

	−	Expert #8 I have a special interest in preventing infections in patients with renal disease, in particular in those who need dialysis treatment. I have reviewed studies evaluating the ClearGuard device. I am familiar with the technology from reading the literature but have never used it in clinical practice. As far as I know, the device has not been used in the NHS. The device is only relevant to clinicians caring for patients who need dialysis treatment, ie Nephrology and potentially Critical Care. Not applicable	
	−	Expert #9: Aware of the procedure and technology and similar products, aware of published high impact data, Not widely, recently introduced Mainly US experience data, some pilot evaluation sites being setup Routine use of vascular catheters for dialysis and other procedures	
2	− Please indicate your research experience relating to this procedure (please choose one or more if relevant):	Expert #1: I have had no involvement in research on this procedure.	
		Expert #2 I have had no involvement in research on this procedure.	
		Expert #3 I have had no involvement in research on this procedure.	

	–	Expert #4 I have had no involvement in research on this procedure	
	–	Expert #5	
	–	Expert #6	
	–	Expert #7	
	–	Expert #8 I have done bibliographic research on this procedure	
	–	Expert #9 I have done bibliographic research on this procedure. I have had no involvement in research on this procedure.	

Current management

3	How innovative is this procedure/technology, compared to the current standard of care? Is it a minor variation or a novel approach/concept/design? Which of the following best describes the procedure (please choose one):	Expert #1: Definitely novel and of uncertain safety and efficacy.	
		Expert #2 This is a minor change in current care but with potential important benefit in preserving vascular access for dialysis and avoiding morbidity and mortality from line sepsis. Definitely novel and of uncertain safety and efficacy.	
		Expert #3 Novel approach Definitely novel and of uncertain safety and efficacy.	
		Expert #4 Although I am aware of hub antimicrobial caps, I have not encountered any with an integral rod. A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy. Definitely novel and of uncertain safety and efficacy.	
		Expert #5 N/A	

		This is a minor variation	
		Expert #6 NO The chlodhexidine impregnated rod incorporated into the cap is a novel design.	
		Expert #7 N/A On the evidence provided ClearGuard is a variation on existing technology but it is novel in that it the mode of action is different.	
		Expert #8 The device is innovative. At present we put special caps onto dialysis catheters to prevent infections. The ClearGuard offers extended protection. Definitely novel and of uncertain safety and efficacy.	
		Expert #9 Highly innovative and improves care, and patient outcomes in a highly priority area of catheter related sepsis in dialysis which is associated with very high mortality and potentially avoidable Definitely novel with supportive safety and efficacy from US experience The first in a new class of procedure.	

4	Does this procedure/technology have the potential to replace current standard care or would it be used as an addition to existing standard care?	Expert #1: In my opinion, there is still a need to disinfect the catheter hub/connector with alcohol and chlorhexidine otherwise any microbial contaminants on the surface of the hub/connector will then be plunged into the catheter when applying the ClearGuard	
		Expert #2 Yes it would replace standard caps for dialysis access.	
		Expert #3 May replace standard of care if shown to be safe and effective (and cost-effective)	
		Expert #4 An addition to existing standard care.	
		Expert #5 addition	
		Expert #6 Would replace current standard of care in terms of CVC hub scrubbing	
		Expert #7 N/A	
		Expert #8 Yes	

		Expert #9 Augment standard of care and redcue catheter related sepsis	

Potential patient benefits

5	Please describe the current standard of care that is used in the NHS.	Expert #1: Current practice in the NHS is guided by Epic3 guidelines (Loveday et al 2014) which states that catheter hubs and connectors should be decontaminated using alcohol 70% and chlorhexidine 2%.	
		Expert #2 Combi-lock cap (standard cap)	
		Expert #3 Cleaning connector port with chlorhexidine/alcohol solution	
		Expert #4 Renal lines are flushed with saline at the end of haemodialysis. Depending on the organisation they can be locked with antimicrobial solution. Alcohol containing caps can be used to protect the hub of the line when it is not in use.	
		Expert #5	
		Expert #6	

		Expert #7	
		Expert #8 At present, we use locking solutions +/- special caps to prevent infections in dialysis patients	
		Expert #9 Nursing practice of cleaning hubs before connecting with blood and extracorporeal procedure (technique variably performed), poor practic eleads to bipfilm formation within cathters colonised with microorganisms	
6	Are you aware of any other competing or alternative procedure/technology available to the NHS which have a similar function/mode of action to this? If so, how do these differ from the procedure/technology described in the briefing?	Expert #1: RCN infusion guidelines acknowledges passive disinfection with alcohol impregnated caps and these should be used in line with local policies. These caps have an alcohol impregnated sponge that when applied to a catheter hubs/connector will sit flush to the device allowing the alcohol to have direct contact with the hub/connector allowing the disinfection process. The ClearGuard contains aqueous chlorhexidine and has contact with the internal part of the hub rather than the surface.	
		Expert #2 Not aware	
		Expert #3 No	
		Expert #4	

		Yes – alcohol based hub caps as mentioned above, made by a variety of manufacturers. However, these do not include a rod component, and as far as I am aware, do not contain chlorhexidine.	
		Expert #5 There are line locks administered into the dialysis catheter (e.g. Taurolock) which have antibacterial property that extends throughout the length of the catheter rather than just the luminal proximal to the clamp. Also cheaper to use and does not generate additional plastic waste.	
		Expert #6 Approaches currently include the Tego dialysis CVC line connector which can be combined with an alcohol containing cap (Curos). The issue with these is that there are two separate components whereas the ClearGuard is one component.	
		Expert #7 I am not aware of any other competing technologies other than Curos and Tego	
		Expert #8 I am not aware of alternative technologies	
		Expert #9 None is routine use in NHS	
7		Expert #1:	

	What do you consider to be the potential benefits to patients from using this procedure/technology?	Expert #2 Reduced central venous line infection thereby reducing hospital admission, need for antibiotics and maintaining vascular access for dialysis.	
		Expert #3 Reduction in frequency of line infections and decreased need for line changes	
		Expert #4 Potential reduction in infection risk.	
		Expert #5 Reduction in catheter related infections, use of antibiotics, hospitalisations and removal of infected lines.	
		Expert #6 Reduction in blood stream infections in dialysis patients	
		Expert #7 Reduction in CRBSI.	
		Expert #8 Prevention of catheter related bloodstream infections and secondary complications.	
		Expert #9 Reduce catheter related sepsis, reduce hospital admissions, reduce morbidity and patient mortality	

Potential system impact

8	Are there any groups of patients who would particularly benefit from using this procedure/technology?	Expert #1:	
		Expert #2 Any young child with central venous line for chronic haemodialysis	
		Expert #3 Long term haemodialysis patients dialysing via tunnelled catheters. Potentially also any patient with a long term central venous catheter e.g. for TPN or chemotherapy	
		Expert #4 Patient with long term vascular access devices who require IV therapy minimum of 3 daily.	
		Expert #5 Patients with difficult access and no plan for definitive access such as a fistula. In these patients preservation of the line and prevention of infections would be even more pressing.	
		Expert #6 Haemodialysis patients who need to dialyse by a central venous catheter	
		Expert #7	

		Patients with recurrent bacteraemia episodes. Patients with poor skin hygiene. Patients with a history of IVDU.	
		Expert #8 Dialysis patients who are immunosuppressed, dialysis patients with poor vascular access and dialysis patients with skin conditions	
		Expert #9 Dialysis patients (Haemodialysis)	
9	Does this procedure/technology have the potential to change the current pathway or clinical outcomes to benefit the healthcare system? Could it lead, for example, to improved outcomes, fewer hospital visits or less invasive treatment?	Expert #1:	
		Expert #2 Yes, reduced line infections would reduce hospital admissions, avoid need for line change/ switch dialysis modality and ultimately preserve vascular access for future haemodialysis via fistulas or lines over lifetime.	
		Expert #3 Yes - fewer line infections /line changes as above	
		Expert #4 Yes, potentially, if infections were reduced.	
		Expert #5 Potentially would reduce need for antibiotics, hospitalisation and line removal but already an existing technology that offers the same and no evidence this is superior.	

		Less use of antibiotics, less in hospital admissions and use of bed space, less operator time in removing and replacing dialysis lines.	
		Expert #6 The real benefit is on reducing blood stream infections. This would reduce hospitalisations and discomfort for patients. Often CVC lines need to be removed if the infection is severe enough and then replaced invasively. This causes further discomfort for patients and can theoretically put the patient at risk from complications of the CVC replacement procedure. Positive impact on resource utilisation related to management of blood stream infection ie. hospital bed days for infection treatment, cost of replacement of CVC line in context of admission, cost/resource use from complications of disseminated blood stream infection/septicaemia	
		Expert #7 More evidence needed . Reduction in CRBSI and Antibiotic use.	
		Expert #8 The technology has potential to reduce the risk of bloodstream infections in dialysis patients. The potential results are: reduced risk of infectious complications (incl endocarditis and discitis), reduced antibiotic use, prevention of hospital admission, reduced risk of development of resistant organisms, longer lifetime of dialysis catheters. Yes.	

		Expert #9 Yes, to improve outcomes , less hospitalisations, reduce length of stay, morbidity and mortality	
10	Considering the care pathway as a whole, including initial capital and possible future costs avoided, is the procedure/technology likely to cost more or less than current standard care, or about the same? (in terms of staff, equipment, care setting etc)	Expert #1:	
		Expert #2 Probably more	
		Expert #3 More but might be cost-effective if it prevents infections, hospital admissions or the need for line changes	
		Expert #4 More expensive than routine alcohol based hub protecting caps.	
		Expert #5 Would likely cost a considerable amount more and generate more clinical waste. Saving made by avoiding some infections and line exchanges would be far outweighed by the total costs of using this product widespread for all dialysis patients.	
		Expert #6 Once factoring in bed days saved this should be less than current care	
		Expert #7	

		It is likely to cost more than the current standard of care	
		Expert #8 It is likely to prevent hospitalisations and antibiotic use which will contribute to cost effectiveness.	
		Expert #9 Will cost more than standard of care but by reducing complications there is likely to be significant cost savings for NHS	
11	What do you consider to be the resource impact from adopting this procedure/technology (is it likely to cost more or less than standard care, or about same-in terms of staff, equipment, and care setting)?	Expert #1:	
		Expert #2 May reduce line infection rate by small proportion - < 10% Overall will either be cost neutral or an increase in cost.	
		Expert #3 More. We dialyse 800 patients thrice weekly on a year round basis and the device would need to be changed each session.	
		Expert #4 If infections were reduced it may save money. The nursing time however would remain the same as for alcohol based protection caps.	
		Expert #5 Would not change staffing or need for additional equipment. Care setting would not be altered.	

		Expert #6 Would need retraining of nurses using CVC but skill uplift likely to be minimal. Potentially this could be used in other areas where long term CVCs are required eg. oncology – also potential benefit in acute setting eg. ICU	
		Expert #7 Unlikely to impact on staff resources.	
		Expert #8 The device will cost more than current standard therapy but it is possible that it will be cost-effective longer-term.	
		Expert #9: Cost savings, reduce hospitalisation burden, reduce morbiditya nd mortality	
12	What clinical facilities (or changes to existing facilities) are needed to do this procedure/technology safely?	Expert #1:	
		Expert #2 No change needed	
		Expert #3 None	
		Expert #4 Training	
		Expert #5 No	

		Expert #6 Training of staff in use of the produce	
		Expert #7 Not from the information provided.	
		Expert #8 If adopted, no major changes are necessary. Instead of attaching a standard cap, dialysis staff will be asked to connect the new device to the dialysis catheters	
		Expert #9 None	

General advice

13	Is any specific training needed in order to use the procedure/technology with respect to efficacy or safety?	Expert #1:	
		Expert #2 Unlikely to require specific training of existing haemodialysis team.	
		Expert #3 Minimal	
		Expert #4 Training of all staff is necessary – unsafe practice re cap use is common without thorough mass staff training.	

		Expert #5	
		Expert #6	
		Expert #7	
		Expert #8 unlikely	
		Expert #9 Minimal training – negligible, as part of routine procedure	

Other considerations

14	What are the potential harms of the procedure/technology? Please list any adverse events and potential risks (even if uncommon) and, if possible, estimate their incidence: Adverse events reported in the literature (if possible, please cite literature) Anecdotal adverse events (known from experience) Theoretical adverse events	Expert #1:	
		Expert #2 Only concern would be that product unexpectedly increases risk of line infection or line occlusion. Need to ensure compatible with heparin/ alteplase line lock.	
		Expert #3 Potential patient exposure to a very small volume of chlorhexidine in the lock solution. Low risk of harm.	

		Expert #4 Risk of chlorhexidine reacting with lock solution. Risk of chlorhexidine allergy. Potential risk of rod detachment and entry into the lumen of the line/ potentially blood stream. Risk of unsafe application (eg device reuse) without adequate training.	
		Expert #5	
		Expert #6	
		Expert #7	
		Expert #8 It is unlikely that potential harm occurs. Allergic reactions (very unlikely)	
		Expert #9 Negligible , chlorhexidine allergy patients will need to be avoided, incidence is rare	
15	Please list the key efficacy outcomes for this procedure/technology?	Expert #1:	
		Expert #2 - Rate of central venous line infection - Rate of central venous line occlusion - Loss of vascular access requiring switch in dialysis modality	

		Other thrombotic event	
		Expert #3 Reduction in catheter-associated bacteraemia, increased catheter longevity, reduction in hospitalisation, decreased empiric antibiotic use	
		Expert #4 Potential dialysis procedure and nurse time savings. Potential reduction in line replacement. Potential reduction in bacteraemias.	
		Expert #5	
		Expert #6	
		Expert #7	
		Expert #8 Incidence of blood stream infections. Allergic reactions	
		Expert #9 Reduce catheter related infections, sepsis, avoid or reduce hospitalisation due to sepsis, redcue antibiotic usage, improve morbidity and mortality	
16	Please list any uncertainties or concerns about the efficacy and safety of this procedure/?	Expert #1:	
		Expert #2	

		Compatibility with line locks Compatibility with paediatric lines	
		Expert #3 Efficacy vs current standard of care unknown. Unknown but likely negligible risk of harm.	
		Expert #4 As in 14	
		Expert #5 No	
		Expert #6 No	
		Expert #7 The product stated no adverse incidents related to the product.	
		Expert #8 Cost-effectiveness	
		Expert #9 None	
17	Is there controversy, or important uncertainty, about any aspect of the procedure/technology?	Expert #1:	
		Expert #2 No	
		Expert #3	

		No	
		Expert #4 Uncertain.	
		Expert #5	
		Expert #6	
		Expert #7	
		Expert #8 It is not clear whether this device is effective only in chronic dialysis patients or has a role in acute dialysis patients, too, including patients in the ICU.	
		Expert #9 None	
18	If it is safe and efficacious, in your opinion, will this procedure be carried out in (please choose one):	Expert #1: Most or all district general hospitals. A minority of hospitals, but at least 10 in the UK. Fewer than 10 specialist centres in the UK. Cannot predict at present.	
		Expert #2 A minority of hospitals, but at least 10 in the UK (for paediatrics).	
		Expert #3 Most or all district general hospitals. – Any with a dialysis unit A minority of hospitals, but at least 10 in the UK.	

		Fewer than 10 specialist centres in the UK. Cannot predict at present.	
		Expert #4 Cannot predict at present.	
		Expert #5	
		Expert #6	
		Expert #7	
		Expert #8 Most or all district general hospital	
		Expert #9 Likely across All Renal specialist centres in the UK and dialysis units	
19	Please list any abstracts or conference proceedings that you are aware of that have been recently presented / published on this procedure/technology (this can include your own work). Please note that NICE will do a comprehensive literature search; we are only asking you for any very recent abstracts or conference proceedings which might not be found using standard literature searches. You do not need to supply a comprehensive reference list but it will help us if you list any that you think are particularly important.	Expert #1:	
		Expert #2 Nil	
		Expert #3 None beyond published literature	

		Expert #4	
		Expert #5 NO NO	
		Expert #6 No No	
		Expert #7 No, I am not aware of any issues. No, I am not aware of any further research or audit relating to this product.	
		Expert #8 Cluster-Randomized Trial of Devices to Prevent Catheter-Related Bloodstream Infection. Brunelli SM, Van Wyck DB, Njord L, Ziebol RJ, Lynch LE, Killion DP.Brunelli SM, et al. J Am Soc Nephrol. 2018 Apr;29(4):1336-1343. Dialysis Catheter-Related Bloodstream Infections: A Cluster-Randomized Trial of the ClearGuard HD Antimicrobial Barrier Cap. Hymes JL, Mooney A, Van Zandt C, Lynch L, Ziebol R, Killion D.Hymes JL, et al. Am J Kidney Dis. 2017 Feb;69(2):220-227	
		Expert #9 Catheter related sepsis Papers published	

		High Impact Publication J AmSoc Nephrol 29: 1336–1343, 2018 International Journal of Nephrology and Renovascular Disease 2021:14 125–131 Am J Kidney Dis. 2017;69(2):220-227	
20	Are there any major trials or registries of this procedure/technology currently in progress? If so, please list.	Expert #1:	
		Expert #2 Not known	
		Expert #3 Not that I am aware of	
		Expert #4 Uncertain – other caps have done trials	
		Expert #5	
		Expert #6	
		Expert #7	
		Expert #8 I don't know	

		Expert #9 Not aware	
21	Approximately how many people each year would be eligible for an intervention with this procedure/technology, (give either as an estimated number, or a proportion of the target population)?	Expert #1:	
		Expert #2 Approximately 100 - 120 children on chronic haemodialysis across the UK	
		Expert #3 Approximately 20% of Royal Free haemodialysis patients dialyse via a line. Other units may have higher rates of line use. The UK haemodialysis population is around 27,000 patients so that would be >5000 dialysing long term via a line.	
		Expert #4 Uncertain – haemodialysis patients with haemodialysis lines.	
		Expert #5 Unselected cases and generic use for my organisation would be almost 1000 patients a year. More selective use in high risk patients on long term lines, complex venous anatomy and no option for fistula/AVG formation would be approximately 30 patients.	
		Expert #6 Approx 25k people are on in centre haemodialysis in the UK (source UK Renal Registry Report 2018) and 30% of these have a CVC and would benefit from the product (7500 people)	

		Expert #7 On the basis of the data provided I would expect this product's use to be limited to named patients only i.e. those patients identified as high risk for CRBSI and not used widely.	
		Expert #8 All patients receiving chronic haemodialysis	
		Expert #9 All patients on dialysis with vascular catheters	

22	Are there any issues with the usability or practical aspects of the procedure/technology?	Expert#1	
		Expert#2 No	
		Expert#3 No	
		Expert #4 Need for training	
		Expert #5 No	
		Expert #6 It is well designed from an ergonomic perspective and easy to use	
		Expert #7 None identified.	
		Expert #8 The device is slightly bigger than routine caps and needs more storage space	
		Expert #9 None	
23	Are you aware of any issues which would prevent (or have prevented) this procedure/technology being adopted in your organisation or across the wider NHS?	Expert#1	
		Expert#2 No	
		Expert#3 Cost and a limited evidence base supporting efficacy	
		Expert #4	

		Financial and concerns regarding chlorhexidine allergy and antimicrobial resistance	
		Expert #5 No specific issues but cost would be prohibitive and difficult to justify when existing use of antibacterial line lock has not been proven to be inferior and is cheaper.	
		Expert #6 If a centre has a low baseline prevalence of CVC associated blood stream infections or if the number of people with CVCs is low in a centre then there may not be a need to switch to this device as potential ROI would be less	
		Expert #7 No, I am not aware of any issues	
		Expert #8 I am not aware	
		Expert #9 None, possibly cost	
24	Is there any research that you feel would be needed to address uncertainties in the evidence base	Expert#1	
		Expert#2 Impact on line longevity and reduction in line sepsis	
		Expert#3 A UK based trial – North American commercial dialysis units have a patchy reputation for quality of care	
		Expert #4 Yes, regarding the risk of chlorhexidine reacting with the lock solution and proven improved infection rates.	

		Expert #5 The evidence presented does not compare use of antibacterial line lock against the Clearguard caps	
		Expert #6 NO	
		Expert #7 More information of cost comparison versus antibiotic use, hospitalisation, and line changes. Bigger data to see if there is any impact on thrombosis risk, mortality & hospitalisation.	
		Expert #8 It is important to establish whether there is a role for this device in patients receiving acute dialysis in the ICU.	
		Expert #9 Clinical Evaluation in UK dialysis units , health economic modelling	
25	Please suggest potential audit criteria for this procedure/technology. If known, please describe: − Beneficial outcome measures. These should include short- and long-term clinical outcomes, quality-of-life measures and patient-related outcomes. Please suggest the most appropriate method of measurement for each and the timescales over which these should be measured.	Expert#1 Beneficial outcome measures: - Reduction line sepsis - Reduction in number of line changes for vascular access Adverse outcome measures: - Increase line sepsis - Increase line change - Increase line occlusion - Thrombotic events related to haemodialysis line	

	− Adverse outcome measures. These should include early and late complications. Please state the post procedure timescales over which these should be measured		
		Expert#2	
		Expert#3 Beneficial outcome measures: Reduction in catheter-associated bacteraemia, increased catheter longevity, reduction in hospitalisation, decreased empiric antibiotic use Adverse outcome measures: Adverse reactions to product	
		Expert #4 Beneficial outcome measures: as for point 15. Adverse outcome measures:	
		Expert #5	

		Expert #6	
		Expert #7	
		Expert #8 Beneficial outcome measures: Prevention of blood stream infections, hospitalisations, secondary infections and antibiotic use. Quality of life. Adverse outcome measures: Development of resistant organisms allergies	
		Expert #9 Beneficial outcome measures: Line related sepsis rates (Bacteremia) Less catheter change procedures in dialysis Hospitalisation due to Catheter related bacteremiaMortality from Catheter related Bacteremia in dialysis. Adverse outcome measures: Staff experience	

26	Please add any further comments on your particular experiences or knowledge of the procedure/technology,	Expert#1 No further comments	
		Expert# 2	
		Expert#3 Nil to add	
		Expert #4	
		Expert #5	
		Expert #6 N/A	
		Expert #7 It is important to consider how education on line care impacts on the reduction of CRBSI, and interesting that both groups had a reduction in CRBSI after the 3m run in.	
		Expert #8 No other comments	
		Expert #9	

NICE National Institute for Health and Care Excellence

External Assessment Centre correspondence log

GID-MT561 ClearGuard

The purpose of this log is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the company's original submission. This is normally where the External Assessment Centre:

a) become aware of additional relevant evidence not submitted by the company;
b) needs to check "real world" assumptions with NICE's expert advisers, or;
c) needs to ask the company for additional information or data not included in the original submission, or;
d) needs 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 captured. The table is shared with the NICE medical technologies advisory committee (MTAC) as part of the committee documentation, and is published on the NICE website at public consultation.

#	Date	Who / Purpose	Question/request	
X.	*XX/XX/XXX X*	*Who was contacted? (if an expert, include clinical area of expertise) Why were they contacted? (keep this brief)*	*Insert question here. If multiple questions, please break these down and enter them as new rows*	*Only include significant correspondence and attach additional documents/graphics/tables in Appendix 1, citing question number*

1.	28/05/2021	**Company** Response to minutes from initial company meeting.		Thank you for the draft minutes. We look forward to reviewing and will let you know if we have any amendments / additions. In the meantime, I heard back from our head of regulatory yesterday regarding question 13. She said NICE is correct and CGHD will likely become class III under MDR. We are and continue to operate under MDD as a Class IIb device and will have the product registered in the UK before the end of August. We intend to submit our MDR Technical File in Sept/Oct which likely will enable us to obtain MDR certification as a Class III device by mid-2022. This work is planned for completion well in advance of the UK regulations (which are in process of being developed) slated to take effect 1 July 2023.
2.	04/06/2001	**Expert adviser** **Dr Peter Dupont (Consultant Nephrologist)**	*"haemodiafiltration is a type of haemodialysis"*	Being pedantic, this isn't correct. They are two different forms of "blood purification treatment" to use the broadest term. In practice they look near-identical and achieve the same end-result. Crudely the difference lies in how "porous" the semi-permeable membrane in the dialyzer is. In haemodiafiltration (HDF), the filter is very porous and allows a high ultrafiltration rate achieving normalisation of blood chemistry by both dialysis and convection/solute drag. High volumes of ultrafiltrate removed during treatment must be replaced by infusing highly purified dialysate directly into the patients circulation. There is debate as to whether haemodiafiltration is a better treatment than haemodialysis (HD) as it can remove larger "middle molecules" and clears phosphate more efficiently. There is also a suggestion that it may be associated with better correction of anaemia and less haemodynamic instability though this remains unproven. HDF is popular in the UK and Europe but my understanding is that is not permitted by the FDA in the USA.
3.			*Most of the evidence base on the device is from the US. Do you have any understanding on differences in practice that may impact on haemodialysis CVC population, BSI rates compared to the UK?*	Anecdotally, dialysis in the USA has been operated as a commercial enterprise and standards have been poor. Fistula rates historically were at very low levels compared to the UK and standards of line care reputed to be poor. Dialysis survival rates remain inferior to those which apply in the UK. The fact that citrate locks aren't used in the USA might contribute to a higher risk bloodstream infections vs UK. Comparative data may be hard to come by due to differences in definitions and what is being measured.

4.			*Weiss et al. 2021 reported that "... no increase in thrombosis was reported in clinics converting to the chlorhexidine-coated CVC caps while using saline as the standard locking solution." Does chlorhexidine increase the risk of thrombosis? Would you expect a further product such as heparin be used alongside the cap?*	*Not aware that chlorhexidine increases the risk of thrombosis but nor is it an anticoagulant so would be used alongside a citrate lock if applied at our centre. The additive antimicrobial effect might thus be less than if used combined with a saline line lock.*
5.			*The same paper reports various organisms that were found in the blood: gram-positive such as coagulase-negative staphylococci and Staphylococcus aureus; as well as gram-negative such as Acinetobacter baumannii. What differences do these organisms have to clinical outcomes, and how they may be combatted?*	*The bulk of infections are with gram positive organisms which can often be treated as an outpatient and without removing the line. Gram negative organisms or fungal infections will usually necessitate line removal. As a rule gram negative or fungal infections are more serious and more likely to be associated with serious illness, hospitalisation and death.*
6.			*Is it correct to interpret that the hospital / tertiary centre is always the provider of dialysis, through either; in house hospital clinics, dedicated community hubs or supporting home dialysis.*	In London, the bulk of the dialysis units are owned and run by the NHS. Outside London, many units are run by commercial companies in partnership with the NHS with Fresenius being the largest provider. Arrangements are likely to vary; this might be just providing the equipment, dialysates and servicing or could include nurse staffing and lease of the building.

			And that all provisions and expenses are procured through the tertiary care centre? Are you aware of any commercial / sponsored dialysis units where the procurement pathway may differ from this?	
7.	04/06/2021	**Expert adviser** **Dr Kay Tyerman (Consultant Paediatric Nephrologist)**	Most of the evidence base on the device is from the US. Do you have any understanding on differences in practice that may impact on haemodialysis CVC population, BSI rates compared to the UK?	My perception is that paediatric practices in US are similar to the UK and centre-centre variation
8.			Weiss et al. 2021 reported that "... no increase in thrombosis was reported in clinics converting to the chlorhexidine-coated CVC caps while using saline as the standard locking solution." Does chlorhexidine increase the risk of thrombosis? Would you expect a further product	I would expect need for heparin/alteplase line lock alongside cap in paediatric practice although have no evidence base for this statement.

			such as heparin be used alongside the cap?	
9.			The same paper reports various organisms that were found in the blood: gram-positive such as coagulase-negative staphylococci and Staphylococcus aureus; as well as gram-negative such as Acinetobacter baumannii. What differences do these organisms have to clinical outcomes, and how they may be combatted?	Staphylococcuus aureus and gram negative organisms usually make patients more systemically unwell and result in the need eventually for line removal. Coagulase - negative staphylococcus can sometimes be successfully cleared with treatment and avoid need for change in access.
10			Is it correct to interpret that the hospital / tertiary centre is always the provider of dialysis, through either; in house hospital clinics, dedicated community hubs or supporting home dialysis. And that all provisions and expenses are procured through the tertiary care centre? Are you aware of any commercial / sponsored dialysis units where the	Yes in paediatrics that would be the case across 13 UK centres.

			procurement pathway may differ from this?	
11		**Expert adviser** **Carole Hallam (Independent Infection Prevention Nurse Consultant)**	Most of the evidence base on the device is from the US. Do you have any understanding on differences in practice that may impact on haemodialysis CVC population, BSI rates compared to the UK?	I am unable to comment on as I have no experience in this area.
12			Weiss et al. 2021 reported that "... no increase in thrombosis was reported in clinics converting to the chlorhexidine-coated CVC caps while using saline as the standard locking solution." Does chlorhexidine increase the risk of thrombosis? Would you expect a further product such as heparin be used alongside the cap?	I am unaware chlorhexidine increasing the risk of thrombosis. Apologies, I can't advise on the use of heparin for renal line as not my area of expertise.

13			The same paper reports various organisms that were found in the blood: gram-positive such as coagulase-negative staphylococci and Staphylococcus aureus; as well as gram-negative such as Acinetobacter baumannii. What differences do these organisms have to clinical outcomes, and how they may be combatted?	All these organisms found in the blood could serious affect the clinical outcome, including inpatient care for treatment. S. aureus line blood stream infection may need prolonged course of antibiotics. A. baumannii are increasing in antibiotic resistance so more difficult to treat. S. aureus may also be an antibiotic resistant strain (MRSA). Provision of care: staff should be trained and competency assessed to manage the lines. Line infections are preventable with good care (hand hygiene, aseptic non-touch technique for all access and maintenance of the line, securement and dressing and daily /each clinic attendance assessment for complications).
14			Is it correct to interpret that the hospital / tertiary centre is always the provider of dialysis, through either; in house hospital clinics, dedicated community hubs or supporting home dialysis. And that all provisions and expenses are procured through the tertiary care centre? Are you aware of any commercial / sponsored dialysis units where the procurement pathway may differ from this?	Apologies again, unable to answer this question as not my specialist area.

15	16/06/2021	**Company** Follow-up action from initial company meeting.		As indicated above, the systematic literature review conducted as part of the NICE MTG44 submission led to a baseline infection rate (current practice/alcohol wipes) of 0.7/1,000 CVC days applied to the economic model. As discussed during the meeting, this value did not relate specifically to a haemodialysis population, but their review did include a number of UK-based studies conducted amongst a dialysis population. Baseline infection rates across these studies ranged from 0.24/1,000 CVC days – 2.65/1,000 CVC days. No superior data to inform this parameter were identified since the previous meeting. Generally, infection rates across the UK and US appear similar. Taking the data from Hymes et al, 2017 (included in the clinical submission) as an example, which involved a comparison between the device and current practice including the use of standard CVC caps and alcohol wipes for disinfection of the catheter hub, the infection rate associated with current practice was 0.59/1,000 CVC days. I would say that there tends to be variation across studies but from the data we have, infection rates associated with current practice appear similar in the US/UK.
16	21/06/2021	**Company** Additional questions	Sibbel et al. 2020 reports a very large population (over 77,000) – is there likely to be any overlap with any other study of ClearGuard?	Response from Doug:There is no overlap with any other studies. As described by Sibbel, DaVita implemented ClearGuard as standard of care for all CVC patients in the US in Q2:2019 based on the findings of their prior study (Brunelli 2018). DaVita has more than 2,500 clinics in the US and over 200,000 total patients in their care, ~20% of which are dialyzed using a CVC (over 40,000 patients). This CVC percentage is consistent with the UK. As a result, Sibbel reported on 40,498 patients in the post period (July-Oct 2019).
17			Both Brunelli 2018 and Hymes 2017 report cluster RCTs in 40 dialysis centres – is there likely to be overlap between these studies?	Response from Doug:These studies were conducted independently by two different CROs (DaVita Clinical Research and Frenova Renal Research, respectively) and there was no overlap between them. However, a similar design was used for both (large, multicentre, cluster RCT at 40 dialysis centres) as this pragmatic design with broad inclusionary requirements (all patients) provides practical results which apply to the real-world haemodialysis setting.

18			Hymes 2017 reports that the included centres were in North America – are you aware if any of the centres included are in Canada, or are they all in the US?	Response from Doug:The study was conducted by Fresenius Medical Care North America (FMCNA), but all 40 centres were in the US.
19			The company used CRBSI (catheter-related bloodstream infections) as the relevant infection outcome. However, some of the parameters were derived from sources that used CLABSI (central-line-associated bloodstream infections), CABSI (catheter-associated bloodstream infections) or PBC (positive blood culture) data rather than CRBSI data. Although they acknowledged that CRBSI, CLABSI, CABSI, PBC have different formal definitions, the terms were used interchangeably.	Response from Eoin:Yes, this assumption was made in the economic model given the differing infection outcome descriptions across the studies involving ClearGuard (from which the IRR's related to ClearGuard were derived). Glennon et al report outcomes in terms of CA-BSIs; in Brunelli et al, IRRs are reported for PBCs, CLABSIs and CRBSIs (as well as for other outcomes) (given that baseline infection rates were reported for PBCs and not for CRBSIs or CLABSIs, data related to PBCs were used in the economic model from this study); Hymes et al report data on PBCs; Weiss et al report data on CLABSIs. Data from all of these studies were used in the analysis, depending on the comparator we were comparing ClearGuard with. In our description of the model, we clarify that although the model is interested in the impact of the intervention on infection (shown in the model image as CRBSI), the data to inform impact on infection rates is based on differing definitions of infection (as described above, i.e., not specific to CRBSI). We don't account for any differences in these types of infection in the economic analysis (in terms of cost), and this is an assumption of the model. We do describe clearly that this is an assumption that has been made, i.e., that each term can be used interchangeably. Response from Doug:I agree with Eoin and these terms are often used interchangeably. The definitions for each are slightly different but the results are similar. As Eoin mentions, this can be seen in Brunelli et al where several different exploratory analyses were completed on the same data set as part of the JASN manuscript review (e.g., CRBSI, CLABSI, PBC, ARBSI). As seen in Figure 3, the results for each were similar and ClearGuard provided a 61-82% reduction in BSI vs. Tego+Curos across all nine analyses.

				See appendix.
20			Incidence rate of CRBSI per 1,000 CVC days using standard CVC caps at 0.7 (taken from NICE MTG44) was not specific to HD patients or CVCs. Furthermore, the 15% mortality rate in the model, which was taken from Goto et al (2013), was associated with overall bloodstream infection in the North American and Europe population. Could this be different than the actual catheter-associated bloodstream infections?	Response from Eoin: Data to inform the baseline risk of infection amongst patients undergoing current practice (standard CVC caps and alcohol wipes) was derived from NICE MTG44 (the Curos submission), which involved a systematic review of UK-based data to identify a baseline risk of infection amongst patients with CVCs or PICCs undergoing current practice. As we have clarified in our submission, these studies were not specific to CVCs (as PICCs were included also) and they were also not specific to a HD population. However, from all of the studies identified in this systematic review we have also isolated the studies involving a HD population and we have reported the baseline rate of infection from these studies in our submission, for full transparency. From those UK studies which focussed on a HD population, baseline rates of infection (i.e., amongst those undergoing what was defined as 'current practice' in each study) ranged from 0.24-2.65/1,000 CVC days. Ultimately, the decision was made to use the same baseline rate of infection as was used in the Curos submission (0.7) even though this was not specific to CVCs or HD patients. Response from Doug: I am unaware of data to suggest that the baseline infection rate would differ. Response from Eoin: Regarding the second part of this query, in our economic model we capture mortality following infection, i.e., a certain percentage of patients who have infection die from this event. In our model, this figure (15%) was based on information on the in-hospital fatality rate from nosocomial bloodstream infection derived from Goto et al (which included North American and European populations). I have linked this study for your information: (https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(14)61507-X/fulltext) Response from Doug: Weiss et al, 2021 (included as part of clinical submission) states "In fact, central line-associated bloodstream infections (CLABSIs) are the second

				leading cause of death in haemodialysis patients, with an attributable mortality rate ranging between 12% and 25% and estimated costs of 45,000 USD per event.[3,4]". This is based on US data. The mortality rate used in the economic model is therefore, in line with the mortality rate range reported in the US-based study by Weiss et al, 2021. DaVita Clinical Research have also investigated mortality associated with BSI in haemodialysis patients with CVCs for us in 2014 as part of a retrospective, observational cohort study using the data from their Clinical Data Warehouse (pre-ClearGuard). Mortality rates were compared between in-centre haemodialysis patients who developed a CVC-associated BSI and patients who dialyzed via a CVC but did not have BSI. As seen in the table below, CVC patients with BSI have a 19% higher mortality rate than CVC patients without BSI. Again, this is based on US data. The data used in the model which includes a European population, therefore, is similar to the US-based figures I have identified (related to catheter-associated infections) and appears appropriate. See appendix.
21			While the average age of the population undergoing HD is 60-65, the IRR for Clearguard is derived from the paediatric population in the US with 4 high-risk patients (Glennon et al 2020). Are these 2 populations comparable?	Response from Eoin: The data we had to inform a comparison between ClearGuard and antimicrobial locks was available from Glennon et al, 2020 which was conducted amongst a paediatric population. Response from Doug: The IRR is significant (0.14) but not too dissimilar from the IRR reported in Weiss et al, 2021 (0.14) and some of the exploratory analyses presented in Brunelli et al, 2018 (Figure 3 in the manuscript). Glennon is small but I believe it is fair to use since it is the only AML vs. ClearGuard data that is available, and the results are consistent with other much larger ClearGuard studies conducted amongst adult populations.

22			In the cost model, total number of HD patient-years (CVC) at risk(7026) is used. Could you please explain further what this patient years at risk mean? and how they were calculated.	Response from Eoin: The model looks at costs associated with comparators on a yearly basis. One of the model parameters is derived from the UK Renal Registry annual report, which reports the number of patients receiving dialysis in England in one year. This report includes key data associated with dialysis patients, including the number of infectious episodes reported to Public Health England in that year, and the number of infections per individual dialysis centre. This study also reports the total number of patient years at risk (7,026) associated with central venous catheters amongst HD patients in that year. They estimate this value based on the distribution of access type using data from all centres in England which provided access data in that year. They then use this distribution, in combination with the total number of patients on HD in that year, to assign an estimated number of patient years at risk associated with CVCs amongst this population in that year. In the model, we simply use this figure on number of patient years at risk in one year (7,026) to calculate the number of patients at risk in one year in England (7,026/132 (132 being the average number of CVC days that HD patients undergo in a year)). This total number of patients at risk each year in England is used to estimate total costs associated with the different comparators in the model.
23	21/06/21	**Expert adviser** **Dr Kay Tyerman (Consultant Paediatric Nephrologist)** Additional questions	What brand/model of caps are used as standard? Are these impregnated with alcohol?	In Paediatrics we generally use a combi- cap leur lock, they are not impregnated with alcohol.

24			Are you aware of any issues relating to equality that may need special consideration for this technology? In an RCT that we have reviewed, the study groups are imbalanced for race (in this case the ClearGuard group had significantly more white people, while the comparator group had significantly more black people) – could this have an impact on the clinical results of the study?	I don't think this should impact the study, however their is a preponderance of children of South East Asian descent on dialysis relative to the population in the UK. This ethnic group often has to wait longer on dialysis before a kidney transplant.
25			What length of follow up should we be looking for in studies measuring PBC and BSI rates? Most of the studies only include patients with more than 21 CVC days because they are following the 21 day rule for dialysis events – is this a reasonable threshold when measuring PBC/BSI rates? And is this	I would say that you should include all patients with dialysis catheter related sepsis as sepsis often occurs within a few weeks of line insertion particularly if infection related exit site problems.

			21-day rule applied in practice in the UK?	
26			Is bacteremia infection a type of BSI, or something different?	An interchangeable term for BSI.
			Could the use of high-concentrate citrate in the UK (but not the US) effect the comparative efficacy of ClearGuard? I.e. would you expect to see a higher baseline rate of PBC or BSI in a population using standard caps with high-concentrate citrate or a population using standard caps with low-concentrate citrate? Is there any other variation in practice between the UK and US that could impact the generalisability of study results from the US?	We don't use citrate in Paediatrics but my prediction would be that the infection rate would be lower with higher citrate as citrate may prevent formation of biofilm. I'm not aware of practice in Paediatrics.

			The company used CRBSI as the relevant infection outcome. However, some of the parameters were derived from sources that used CLABSI (central-line-associated bloodstream infections), CABSI (catheter-associated bloodstream infections) or PBC (positive blood culture) data rather than CRBSI data. The terms were used interchangeably-would you consider them to be equivalent?	PBC could be related to any form of sepsis eg urisepsis and could occur in patients with fistula as well. However if a study is discussing PBC I HD patients with CVL the terms would be interchangeable.
			Could the mortality rate associated with overall bloodstream infection in the North American and Europe population be equivalent to the actual catheter-associated bloodstream infections?	Yes but dependent on percentage of patients with CVL for dialysis access.

			While the average age of the population undergoing HD is 60-65, would you consider an IRR for this group to be comparable to the paediatric population (in the US)?	I'm not sure - does IRR mean return rate? My perception is may be greater in 60 -65 group ad likely to be on HD for a longer time before transplant.
			The company assume that 'compliance' in using ClearGuard and in using standard or alternative (Tego + Curos etc) caps is 100%. Do you think that this is a reasonable assumption? I.e. do you think that there is likely to be a difference in the rate of improper use of ClearGuard vs other caps (there is no evidence in the literature on this).	
			Are antimicrobial locking solutions always used alongside standard CVC caps and are they likely to always be used alongside alternative caps, like ClearGuard?	In Paediatrics we don't use antimicrobial locks but use heparin 1000 units per ml or alternate. Some centres use Taurolock for named patients but our experience with taurolock is that you get more problems with line occlusion and loss of dialysis access. There is a lock called taurolock hep 500 (with heparin) and taurolock u25,000 (with urokinase) but I'm not sure if they are licenced for use in paediatric population.

				My perception with ClearGuard is that it would remove need for taurolock but you would still need a heparin or alternate lock.
	28/06/2021	**Expert adviser** **Dr Peter Dupont (Consultant Nephrologist)**	What brand/model of caps are used as standard? Are these impregnated with alcohol?	We use Vygon. They are not impregnated with alcohol.
			Are you aware of any issues relating to equality that may need special consideration for this technology? In an RCT that we have reviewed, the study groups are imbalanced for race (in this case the ClearGuard group had significantly more white people, while the comparator group had significantly more black people) – could this have an impact on the clinical results of the study?	Unlikely though race might correlate with socio-economic status/education level which might have a bearing on infection rates.

			What length of follow up should we be looking for in studies measuring PBC and BSI rates? Most of the studies only include patients with more than 21 CVC days because they are following the 21 day rule for dialysis events – is this a reasonable threshold when measuring PBC/BSI rates? And is this 21-day rule applied in practice in the UK?	I'm guessing this helps to distinguish between non-tunnelled temporary catheters and tunnelled lines. Temporary non-tunnelled catheters have much higher infection rates.
			Is bacteremia infection a type of BSI, or something different?	Yes
			Could the use of high-concentrate citrate in the UK (but not the US) effect the comparative efficacy of ClearGuard? I.e. would you expect to see a higher baseline rate of PBC or BSI in a population using standard caps with high-	Yes it could, in theory at least. Historically, dialysis in USA was run commercially and employed staff with lower qualifications vs UK/Europe

			concentrate citrate or a population using standard caps with low-concentrate citrate? Is there any other variation in practice between the UK and US that could impact the generalisability of study results from the US?	
			The company used CRBSI as the relevant infection outcome. However, some of the parameters were derived from sources that used CLABSI (central-line-associated bloodstream infections), CABSI (catheter-associated bloodstream infections) or PBC (positive blood culture) data rather than CRBSI data. The terms were used interchangeably-would you consider them to be equivalent?	They are not synonymous but are overlapping terms. CLABSI might refer to central venous catheters other than dialysis catheters (dialysis catheters are a form of central line). Positive blood culture could be from any cause eg urinary infection, pneumonia.

			Could the mortality rate associated with overall bloodstream infection in the North American and Europe population be equivalent to the actual catheter-associated bloodstream infections?	Most infections resolve with antibiotics +/- line removal. So CABSI and mortality will be correlated but mortality rate should be much lower than CABSI rate.
			While the average age of the population undergoing HD is 60-65, would you consider an IRR for this group to be comparable to the paediatric population (in the US)?	Clearly not but all age groups are at risk of this complication.
			The company assume that 'compliance' in using ClearGuard and in using standard or alternative (Tego + Curos etc) caps is 100%. Do you think that this is a reasonable assumption? I.e. do you think that there is likely to be a difference in the rate of improper use of ClearGuard vs other caps (there is no	Seems reasonable. Highly unlikely you would leave a line uncapped and not have it noticed by the staff or patient.

			evidence in the literature on this).	
			Are antimicrobial locking solutions always used alongside standard CVC caps and are they likely to always be used alongside alternative caps, like ClearGuard?	I suspect there is variable practice across the UK. We use a citrate lock solution which is antimicrobial but I suspect some units will still be locking with heparin. Clearguard is intended to avoid the need to wipe down the cap with chlorhexidine in alcohol so I would imagine one would still combine it with an antimicrobial lock solution if that is your unit practice.
		Expert adviser **Dr Marlies Ostermann (Consultant in Nephrology and Critical Care)**	What brand/model of caps are used as standard? Are these impregnated with alcohol?	At GSTT, we use 3M-Curos caps. No.
			Are you aware of any issues relating to equality that may need special consideration for this technology? In an RCT that we have reviewed, the study groups are imbalanced for race (in	No. Unlikely.

			this case the ClearGuard group had significantly more white people, while the comparator group had significantly more black people) – could this have an impact on the clinical results of the study?	
			What length of follow up should we be looking for in studies measuring PBC and BSI rates? Most of the studies only include patients with more than 21 CVC days because they are following the 21 day rule for dialysis events – is this a reasonable threshold when measuring PBC/BSI rates? And is this 21-day rule applied in practice in the UK?	12 months. 21 days is very short. In the UK, we do not apply this rule.
			Is bacteremia infection a type of BSI, or something different?	Bacteraemia is a type of blood stream infection. Blood stream infection incorporates bacteraemia but also fungaemia.

			Could the use of high-concentrate citrate in the UK (but not the US) effect the comparative efficacy of ClearGuard? I.e. would you expect to see a higher baseline rate of PBC or BSI in a population using standard caps with high-concentrate citrate or a population using standard caps with low-concentrate citrate? Is there any other variation in practice between the UK and US that could impact the generalisability of study results from the US?	I would expect to see a lower baseline rate of infections in patients who receive standard caps with high concentrate citrate. In the UK, high dose citrate locking solutions are used more widely. They reduce the risk of infections.
			The company used CRBSI as the relevant infection outcome. However, some of the parameters were derived from sources that used CLABSI (central-line-	CLABSI and CABSI describe the same type of infection. The term PBC is more generic and broader. For instance, if you have a CLABSI or CABSI, you will always have a PBC. However, you can have a PBC which may be related to a serious kidney infection or pneumonia but not to CABSI.

			associated bloodstream infections), CABSI (catheter-associated bloodstream infections) or PBC (positive blood culture) data rather than CRBSI data. The terms were used interchangeably-would you consider them to be equivalent?	
			Could the mortality rate associated with overall bloodstream infection in the North American and Europe population be equivalent to the actual catheter-associated bloodstream infections?	Catheter-associated blood stream infections contribute a proportion to the outcome from overall bloodstream infections.
			While the average age of the population undergoing HD is 60-65, would you consider an IRR for this group to be comparable to the paediatric population (in the US)?	I would expect them to differ.

			The company assume that 'compliance' in using ClearGuard and in using standard or alternative (Tego + Curos etc) caps is 100%. Do you think that this is a reasonable assumption? I.e. do you think that there is likely to be a difference in the rate of improper use of ClearGuard vs other caps (there is no evidence in the literature on this).	In our practice, the compliance rate with Curos caps is 100%. The only reason for not using them is unavailability / low stock. If ClearGuard was available, I would expect near 100% compliance.
			Are antimicrobial locking solutions always used alongside standard CVC caps and are they likely to always be used alongside alternative caps, like ClearGuard?	I assume that all dialysis units use antimicrobial citrate locks following the NICE evaluation: https://www.evidence.nhs.uk/document?id=1732839&returnUrl=search%3Fpa%3D5%26ps%3D50%26q%3Dheparin&q=heparin

Insert more rows as necessary

Appendix 1.

During correspondence with the company and experts, additional information is sometimes included as file attachments, graphics and tables. Any questions that included additional information of this kind is added below in relation to the relevant question/answer:

File attachments/additional information from question 19:

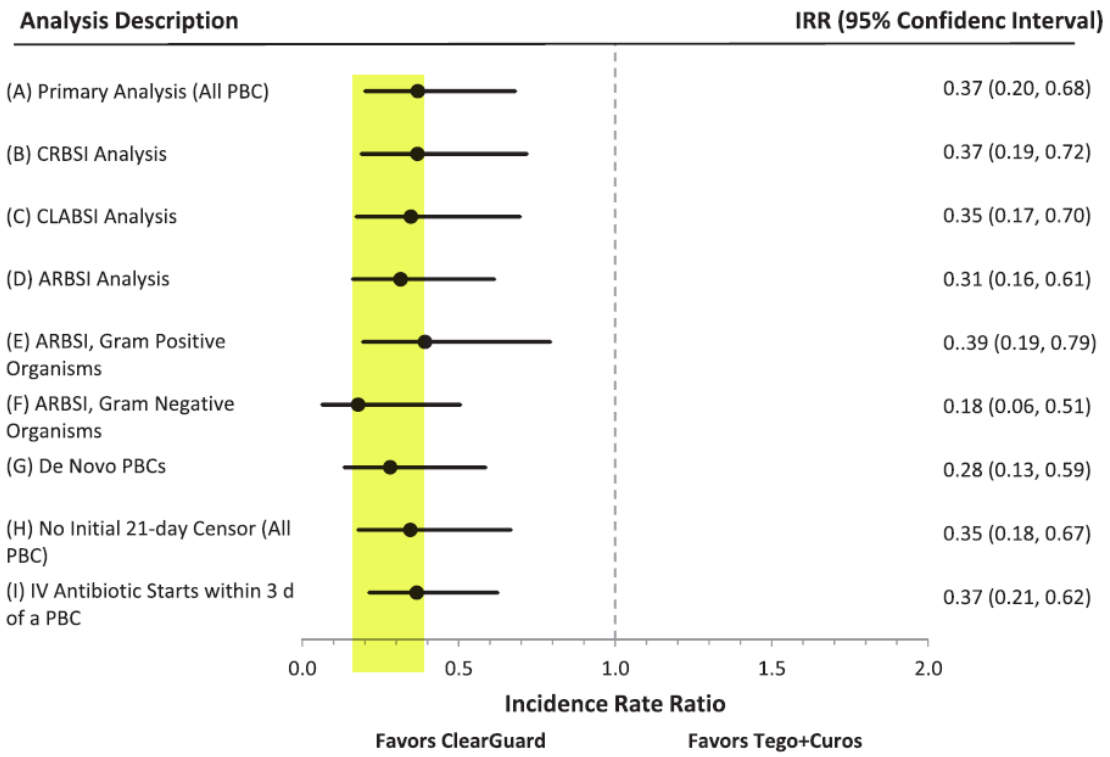


Figure 3. Study results demonstrate that ClearGuard caps are superior to Tego +Curos for reducing bloodstream infection across all nine analyses. Summary of IRRs (dots) and 95% confidence intervals (whiskers), ClearGuard facilities versus Tego +Curos facilities, for (A) primary analysis and (B–I) exploratory sensitivity analyses. Estimates<1 favor ClearGuard.

File attachments/additional information from question 20:

Table 12: Overall Mortality Rates and Incidence Rate Ratios (Without Censoring for Post Baseline BSI)

	Cases (with BSI)	Controls (no BSI)
Events	143	498
Follow-up Time (patient years)	658.8	2,722.2
Event Rates (deaths/patient-year)	0.217	0.183
IRR (95% CI)	1.19 (0.99, 1.43)	(ref)

Abbreviations: BSI, bloodstream infection; CI, confidence interval; IRR, incidence rate ratio; ref, reference.

MT561 ClearGuard Company Meeting – minutes – 26.05.2021

Introductions and roles:

KiTEC:

- Jamie Erskine – Health Technology Assessor - project lead
- Lina Manounah – Health Technology Assessor
- Farhad Shokraneh (Systematic Reviewer)
- Emily Kwong (Clinical Engineer)
- Murali Kartha – Senior Health Economist
- Khanh Ha Bui – Health Economist
- Anna Buylova Gola – Health Economist
- Jo Boudour – Project Manager

NICE:

- Kimberley Carter – Technical Adviser
- Samantha Baskerville – Technical Analyst
- Farhaan Jamadar – Technical Analyst

Company:

- Douglas Killion – Vice President of Commercial Operations, ICU Medical
- Eoin Moloney – Senior Health Economist
- Michael Branagan-Harris – CEO, Device Access UK

Summary of the clinical evidence review and questions on the submission:

1) The clinical evidence submission document suggest that an advantage of ClearGuard HD cap is its potential to make home dialysis easier as it can be used by patients in a home setting, however, the instructions for use cautions that only qualified centre personnel or healthcare practitioners can place, manipulate or remove the ClearGuard HD caps. Please could you explain this discrepancy?
   a) Is it correct to assume that patients need to be trained by a healthcare practitioner/centre personnel?
   b) How long does training take?
   c) Is there a cost for training?
   d) Do you have any data for the uptake of ClearGuard HD cap for dialysis in a home setting?

DK - clinical use providers are free to do what they want. What the labelling says and what providers do in reality is sometimes different.
MB-H – this appears a lot in IFUs that come out of US companies, possibly an FDA requirement.
DK – Comprehensive haemodialysis training for the home patient in general is very extensive. ClearGuard would be an aspect of this for new home haemodialysis patients. There would be no special training for patients who are already on home haemodialysis and then move from standard CVC caps to ClearGuard.
DK – There is no cost for training, just substitute ClearGuard with the current cap.
DK - I am aware of at least 600 home centres (in the US) that have used ClearGuard exclusively for the past two years (since June 2019).

2) Two of the included abstracts, Glennon 2020 and Butaud 2020 use catheter-associated blood stream infections (CA-BSI) which is outside of the scope, what is the difference between CA-BSI and catheter-related blood stream infections (CR-BSI)?

DK – this is the same reference, one is a poster version of the abstract. People call it different things but CA-BSI is the same thing as a CR-BSI.

3) Is it usual practice to scrub the hub prior to using the ClearGuard HD cap or can it be used without doing that first?

DK – this is at the provider's discretion depending on their current policies or procedures. Time spent scrubbing the hub seems less important, people have naturally moved away from doing that.
EK – does this also hold true for trials?

DK – Probably not. They followed their current procedures.

4) You mention that High-concentrate sodium citrate anticoagulant is not permitted for use in the USA but is regularly used in the UK. Is this because standard caps cannot be used with "low-concentrate citrate locking solutions, as well as heparin and saline solutions", where ClearGuard HD can?
   a) Presumably there is no evidence for ClearGuard's safe use with high-concentration citrate locks used in the UK?

DK – because of safety concerns, if high-concentrate citrate gets into the bloodstream, patients can die. Our distributor in UK, Valiant Medical, sells high-concentrate (30% and 46.7%) citate locks and they launched ClearGuard last month. Their plan is to move the UK market to ClearGuard combined with a safe, low-concentrate (4%) citrate lock. A lot of users in the UK use high-concentrate citrate to prevent infection, it's not common practice outside of the UK.
JE – why is it used in the UK?
DK – this is to address the problem of catheter infections. I've never actually seen compelling evidence to show if this is a reality.
KC –we can follow up with our clinical experts on this point too.

5) ClearGuard HD cannot be replaced once it has been removed and is recommended to be used for a maximum of 3 days, how does this compare to standard CVC caps and alternative disinfecting caps such as Tego + Curos?
   a) What limits the amount of time that a ClearGuard cap can be used?

DK – ClearGuard is single use. Three days comes from the FDA looking at antimicrobial effectiveness bench testing during the typical two to three-day timeframe between dialysis sessions. The timeframe between dialysis session is generally two days (i.e. Mon, Wed, Fri) so it works well with this frequency.
DK – When you attach a ClearGuard it will work almost immediately and the CVC will remain sterile until you remove the cap, regardless of the number of days.

6) The comparator in the scope is standard CVC caps or alternative disinfecting caps, with/without needleless connectors.
   a) What do you consider the most common comparator cap (in the UK market)?

DK – Standard CVC caps are currently used in ~72% of CVC-based hemodialysis procedures in the UK, and the remaining ~28% use the Tego connector.

7) Tego needleless caps are often used in the literature – are we correct that this is also an ICU Medical product?

a) If so, do you expect ClearGuard caps to replace these?
b) Are you aware of any comparative literature between Tego (or other needleless caps) and those with needles?

Questions 7 and 8 answered together.

8) What do you consider the benefits/weaknesses of needless caps vs those with needles?

DK - The ICU market wanted to get rid of sharps and have syringe-activated plunger - you leave this needlefree connector on the hub and whenever you want you can inject medication in the patient. Other procedures can be done in hospital through a needle-free connector.
DK – ICU Medical offers a line of needlefree connectors in hospital called CLAVE. This is a market leader although there are lots of needlefree connectors in the market. Tego is unique for haemodialysis because you need high flow for several hours, unlike other procedures.
DK – Tego is the only needlefree connector indicated for hemodialysis as most can't deal with a high rate of flow necessary for this procedure. Tego is changed once a week instead of three times a week to reduce infection rates and you can put disinfecting cap on the end of it (Curos). ClearGuard has 70% less infection rate.
KC – can Tego be used with ClearGuard or are they separate devices?
DK – separate. ClearGuard would be used instead of Tego. We would say that ClearGuard is superior and will replace Tego.
DK – SwabCap is similar to Curos. You can attach a SwabCap onto the Tego.
DK –not aware of needle connectors, only needlefree connectors.
DK – Tego plus Curos was seen as industry leading for preventing CRBSI and so therefore it was used as the control group of the randomised clinical trial published in JASN.

9) Could you give us some more information on antimicrobial locking solutions, as mentioned in section 8 of the submission (regarding that ClearGuard can be used in combination with these)?

DK – there are two options: high-concentrate (30% and 46.7%) citrate or taurolidine TauroLock. Taurolidine alone is associated with catheter occlusion, so they added heparin and urokinase to help prevent the catheter from occluding.
DK - There is no strong literature on this. The TauroLock "2+1 Protocol" is very expensive - £30 a week versus ClearGuard - £12 a week for three sets of caps.
DK – you would use ClearGuard instead of these, not in combination with them.

10) Do you have any information on the bloodstream infection rate (BSI) for any NHS trusts, are they comparable to the studies conducted in the US?

EM – NICE guidance MTG44 for Curos - baseline infection rate in the UK, population rate was slightly different, there was a range of dialysis types. We have data to inform the infection rate – need to look to see if we can get anything more specific. Looks comparable to the US.
ACTION: EM – will look for further information on BSI and send response by email to KiTEC.

11) What impact does the company see ClearGuard would have on Device related adverse events? What are the advantages compare to conventional systems (what are those)? What are the failure modes of the cap itself, or the system (such as line occlusion?)?

DK – there were no device related Adverse Events in any of the published randomized clinical trials. Since launch, ClearGuard has been used in over 20 million dialysis procedures and has only received a small handful of product complaints. Heparin/saline or 4% citrate are the typical catheter lock solutions used with ClearGuard. Although not an endpoint of the published clinical studies, thrombolytic use rate and CVC exchange rate both favoured ClearGuard.

12) Operational questions: Will there be an increase in packaging and waste? How does it need to be stored compared to the previous systems?

DK - no increase in packaging and waste compared to standard CVC caps.
DK - storage is very standard, can store at room temperature, no special warehousing, no refrigeration. It's robust and lasts for three years. It is treated like a biohazard and incinerated when finished with.

13) The device may become Class III under MDR Special rules, does the company have a strategy for future proofing against regulatory changes in the UK?

DK - This is correct and CGHD will likely become class III under MDR. We are and continue to operate under MDD as a Class IIb device and will have the product registered in the UK before the end of August. We intend to submit our MDR Technical File in Sept/Oct which likely will enable us to obtain MDR certification as a Class III device by mid-2022. This work is planned for completion well in advance of the UK regulations (which are in process of being developed) slated to take effect 1 July 2023.

14) Any indication if the seal of the packaging is broken? How would clinician know to trust the packaging, and hence can be assured not needing to do additional disinfection?

DK – they should inspect the seal on the pouch, it's obvious and fairly wide. We do a lot of testing and we've never had a single packaging complaint. We sterilise it with gamma radiation.

15) How does the device ensures that it always has enough antimicrobial agent to kill infections within the tube? i.e. What if the clamps get repositioned, dose the concentration then change? Is this then still high enough to kill the harmful bacteria?

DK – a precise amount of chlorhexidine is applied to the ClearGuard rod and threads when we manufacture the device and are testing it frequently during production. Should be more than enough chlorhexidine than ever needed.

AOB:
KC – the minutes of this meeting will be added to the correspondence log and then published.

MT561 ClearGuard Expert Engagement Meeting – minutes – 28.05.2021

Introductions and roles:

KiTEC:

- Jamie Erskine – Health Technology Assessor - project lead (apologies)
- Lina Manounah – Health Technology Assessor
- Farhad Shokraneh - Systematic Reviewer
- Emily Kwong - Clinical Engineer
- Murali Kartha – Senior Health Economist
- Khanh Ha Bui – Health Economist
- Anna Buylova Gola – Health Economist
- Jo Boudour – Project Manager

NICE:

- Kimberley Carter – Technical Adviser
- Samantha Baskerville – Technical Analyst

- Farhaan Jamadar – Technical Analyst
- Alexa Forrester – NICE Senior Implementation and Adoption Manager

Expert advisers:

- Dr Albert Power, Lead for Haemodialysis and Renal Research, North Bristol NHS Trust
- Dr Peter Dupont, Consultant Nephrologist, Royal Free Hospital
- Dr Kay Tyerman, Paediatric Nephrologist, Leeds Teaching Hospitals NHS Trust
- Carole Hallam, Independent Infection Prevention Nurse Consultant
- Sue Rowlands, Specialist Nurse Team Manager, Royal Wolverhampton NHS Trust
- Dr Sandip Mitra, Consultant Nephrologist, Manchester Royal Infirmary
- Dr Pritpal Virdee, Renal Consultant, Epsom and St Helier University Hospitals

Current practice for haemodialysis:

1. Understanding the population that require haemodialysis using a central venous catheter. Why might individuals not be able to have arteriovenous fistula? Are adults and children different? Are these populations growing with increased chronic kidney disease, or decreasing with increased permanent access or transplants?

AP – different groups of patients will use a CVC for access – it's quick and easy. Fistulas need time to mature, can take 6 weeks or longer. Patients who have had previous surgeries may have no more vessels to use. Older patients tend to have higher catheter use than others. There is variation from renal unit to renal unit across the country. Growth rate of dialysis in the UK is slowing down due to better disease management and organ transplant.

PD – highly variable rates between units – agree with summary.

KT – much smaller numbers in children than in adults. Just over 100 children at any given time in the UK. Most children would get a transplant within 12 months, but due to Covid number is just under 150 currently. Some long-term patients access by fistulas. This technology doesn't have huge advantages over our current practice – but anything we can do to preserve vascular access is a good thing.

2. Setting: Understand that majority of haemodialysis take place in hospital or community clinic settings is this accurate? Is it ever appropriate for a CVC haemodialysis patient to have home haemodialysis and if so, would caps be changed by user/carer or by a trained professional?

PD- can use a line for home haemodialysis, most are in a hub or satellite clinic.

AP – Home haemodialysis patients are a small population. No reason why patients can't dialyse at home. Usually patients can change caps or carers can. For the future, aiming for a higher number of patients to do home dialysis.

SM – not just change in the UK but across the globe, more patients are being offered home haemodialysis. More prevalence of catheters as fistulas have decreased due to Covid break on fistula creation. Risk of infections is heightened. The cap can be put on by person doing the dialysis if patient is trained to do it.

KT – increasing numbers going forward with children – home will be an option to all across the UK going forward. Covid is slowing things down – often it's the more complex patients with underlying conditions or circumstances that are more likely to be on dialysis longer. Don't see a problem incorporating those caps in the home setting.

3. How often do patients receive a dialysis session? Does this vary significantly? Are dialysis sessions more frequent / shorter duration for home dialysis patients?

AP – vast majority receiving in centre, 3 treatments a week – 4 hour treatment. Some variation in treatment times. Registry reports will show the trends. In home dialysis there is a transfer over of default 3 times a week, however, some people might dialyse long hours overnight or 4 sessions of 2 hour sessions.

SM – alternate day dialysis is usually the most popular mode that patients like (50%). Others do three times a week (25%) and 25% prefer nocturnal or shorter more frequent sessions. Shared care haemodialysis may increase in the future e.g. patients come in to centre and are involved with haemodialysis. Choice – beauty of home treatment. Encouraging patients to be part of the treatment and empowering them.

SB – To confirm, if it's appropriate to use haemodialysis as broad terminology including haemodiafiltration?

PD – for the purpose of evaluating this technology there is no difference as the catheter connection is the same, haemodiafiltration is a type of haemodialysis. But yes we should be clear it is being used as an overarching term that includes the other blood cleaning methods.

4. Are the CVC caps usually only removed at each dialysis session? Or are there other reasons for them to be removed? In your experience how often do the CVC caps need to be removed?

PD – considered to be bad practice opening the line for anything other than dialysis.

KT – same applies to paediatrics.

SM – instances in A&E where they have used it for access to blood. Otherwise should be used at the start and end of dialysis. Sometimes trained nurses can do this outside dialysis.

SR – IV access team at Wolverhampton's policy is to never touch a renal line. Don't allow other people to use the line unless it's life or death. Cap changes only when getting on and off dialysis.

Reducing bloodstream infections (BSI)

5. When reporting BSI rates, various outcomes are used would you have agree to all of the below terminologies being used interchangeably to report on this? Are there others that should be captured?
    - CABSI Catheter associated bloodstream infections
    - CRBSI Catheter related bloodstream infections
    - VARBSI Vascular access related bloodstream infection
    - ARBSI Access related bloodstream infection
    - CLABSI Central line associated bloodstream infection
    - PBC Positive blood cultures

PD – there is a lot of overlap, the first option is the most appropriate.

CH – CRBSI – laboratory associated, CABSI – surveillance definition, not necessarily used for treatment – investigation type work.

https://www.ficm.ac.uk/sites/default/files/protocol_v3.4_07082018.pdf

AP –VARBSI could equally apply to fistulas and grafts not just catheter. Same for Access related. Central line could refer to other things such as PICC lines etc.- too broad. PBC confirms infection and can occur without a line even. Would tend to go for CRBSI.

AP and PD – might use antibiotics before knowing if there's an infection or not so will miss some episodes if have already given antibiotics.

SR – general vascular access research – standardising is amazingly complex, every organisation has got their own specific way. It's often instinctive.

6. What is the current clinical practice to reduce BSIs for haemodialysis patients:
    a. Scrub the hub of standard caps
    b. Use of needleless connectors (such as Tego) with or without Curos caps
    c. Lockline solutions (citrate, other)
    d. Do practices vary across groups; adults, paediatrics, high risk, low risk, settings; ICU, outpatient dialysis, community settings?
    e. How are current caps stored or disinfected before use? If wiped and air dried, how long does this process tend to take?
    f. Are these procedures packaged within a bundle of care and if so is this standardised?

AP – clean hub at connection and disconnection. Not seen needleless connectors. Lockline solutions – variable practices across UK, solutions other than plain saline. Taurolodine, heparin, etc. Main reason for the solution is to stop clotting. Some are antibacterial preparations.

CH – having simple steps, hand hygiene etc. Chlorhexidine has been beneficial too. If you ask a group of staff, they may do it for around 5 seconds even if asked to do for 30 seconds as people are busy.

EK – what is meant by passive disinfection?

CH -this is disinfection without need for human activity, such as caps impregnated with disinfectant.

SR – be careful with cap - people should be trained properly and training refreshed regularly.

KT –limited with citrates because of what is licensed for children. Lot of variation in 13 units in the UK.

LM – if using active disinfectant wipe with passive cap that has chlorhexidine, would you do both?

CH – yes if caps that were available were just alcohol impregnated. Passive cap on and would scrub the hub. Cap with alcohol and chlorhexidine wouldn't need to do both.

SR – use caps for high risk patients.

KT – my perception would be to still use a chlorhexidine wipe even with a chlorhexidine cap.

AP - dialysis patients don't have as good an immune response so need to take extra steps to be on the safe side.

KT - there is a paediatric improvement bundle.

AP - no standardisation for adults (bundle of care).

SR - high-impact care bundle is available for all sorts of device care – 2007 Department of Health.

https://www.clinell-srbija.com/files/Centralno%20venski%20kateteri%20za%20dijalizu.pdf

7. Are KDOQI guidelines widely used? (e.g. KDOQI recommends use of antimicrobial barrier caps in high risk patient https://www.kidney.org/professionals/guidelines).

PD – don't know across the UK. Same practice across our units. Generally they are well regarded.

Considerations around the use of ClearGuard in practice

8. Antimicrobial stewardship: Is there any evidence that ClearGuard (which is coated in Chlorhexidine acetate) will not contribute to antimicrobial resistance?

AP – not aware of any such mechanism.

SM – don't think so – there's a lack of evidence.

PD – can't think of a mechanism by which that would occur.

9. This technologies instructions for use indicate that those with allergies to chlorhexidine, nylon and polypropylene should not use the device. In your experience have you ever seen these allergies? Are there any other individuals you would be hesitant to use this device with?

SR – we are seeing patients who are allergic to chlorhexidine but it has a massive impact on reducing line infections. Alcohol only wipes kept for those patients. Always have iodine to use just in case. Caps with sponge, sponge can be dislodged – risks attached to these devices. Not sure how frequent. We just ask patients if they've ever had an allergy.

AP – on occasion have had patients with a bad topical reaction to chlorhexidine. Haven't seen full blown anaphylaxis. Not seen nylon or polypropylene.

PD- confirmed also only seen topical reactions but not anaphylaxis reactions to chlorhexidine.

SM – tends to be topical and skin, not seen anaphylaxis. It is in a lot of products. Just go by history and symptoms.

10. The company state that lock solution; high-concentrate sodium citrate anticoagulant is not permitted for use in the USA but is regularly used in the UK. Is this the case?
    a. If so, why? What concentration tends to be used? How is this decided?
    b. Are there any concerns around adverse events for patients?

AP – a case in the US where they put in a large amount of hypertonic citrate – the patient had a cardiac arrest and died. Calcium binding effects of citrate. They used a higher volume. There was a resulting FDA advisory against it. Decision around concentration is largely unit based, with commercial influence, UK provider is 46.7%. Bristol position is to use 30%.

SM – totally agree – risk is the large volume. Manchester use 30%. There is variability in practice.

KT – don't use in paediatrics as standard, occasionally in ICU but otherwise not.

EK – is line lock solution practice a UK practice, not US or Europe in general?

SM – UK more line lock friendly, but use of line locks does happen in Europe – citrate is one of the most common.

11. NICE guidelines do not recommend antibiotic lock solutions and systemic antimicrobial prophylaxis for preventing BSI, however, we understand that they are in used in practice. The company claim that ClearGuard can be used in combination with these solutions and list this as a benefit. What are the benefits of lock solutions and would you feel a technology such as ClearGuard could change this?

SM – goal is get to 0 bacterial rates, any measure that could improve that would be welcome. Measures in place then look at redefining practice. Can't comment until we can see efficacy data in clinical practice.

PD - don't routinely use antibiotic locks.

AP – not seen data of use in combination.

KT – don't use antibiotic as standard practice.

SR – don't use heparin for general vascular access, just use saline, renal lines are different.

PV – we use TauroLock in Epsom.

MT561 ClearGuard Company Engagement Meeting – minutes – 30.06.2021

KiTEC:

- Jamie Erskine – Health Technology Assessor - project lead
- Lina Manounah – Health Technology Assessor
- Farhad Shokraneh (Systematic Reviewer)
- Emily Kwong (Clinical Engineer)
- Murali Kartha – Senior Health Economist
- Khanh Ha Bui – Health Economist
- Anna Buylova Gola – Health Economist
- Jo Boudour – Project Manager

NICE:

- Kimberley Carter – Technical Adviser
- Samantha Baskerville – Technical Analyst
- Farhaan Jamadar – Technical Analyst
- Chris Chesters – Special Adviser

Company:

- Douglas Killion – Vice President of Commercial Operations, ICU Medical
- Eoin Moloney – Senior Health Economist
- Mehdi Javanbakht – Device Access UK

1. **Summary of assessment report:**

- JE – The company submitted seven studies: three full texts and four abstracts. We excluded one abstract – Nitz 2021, as this didn't match our scope. We included all the rest and didn't identify anything further in our systematic review.
- JE – overall the evidence is of moderate quality. Hymes and Brunelli are considered the strongest evidence. Hymes is more relevant to the NHS. We used the Cochrane risk of bias tool and we are checking with our statistician whether the studies are large enough to capture the outcomes we're looking at.
  JE – some patient characteristics in Brunelli could impart some bias into the results in favour of ClearGuard and we have discussed this with the expert advisers.
- JE – the third full study is Weiss 2021 – this is fairly weak methodologically as the study periods are unbalanced.
- JE – another consideration is that the studies were all conducted in the US.
- JE – BSI rates are consistently lower in ClearGuard versus various comparators and hospital admissions are shown to be lower but not always consistently.

- JE – some of the resource use and clinical utility outcomes are not present in the literature but we can address this in our sensitivity analysis in the economics section.
- DK – I understand why Hymes is more relevant to the NHS as standard CVC caps are used in ~70% of all CVC-based haemodialysis procedures in the UK (2020). This definitive study vs. standard CVC caps received the first-ever AJKD Editors' Choice Award due to the size of the study and the significance of the findings to the field of nephrology. However, the Tego connector is used in the remaining ~30% of procedures in the UK, so it may make sense to apply both large cluster RCTs and weight the findings 70/30 (Hymes/Brunelli). The two large RCTs are important overall for the dialysis community and the results are so demonstrably better for ClearGuard. In the real-world setting, this allows people to make purchasing decisions.

2. Further comments on questions to company:

1) Sibbel et al. 2020 reports a very large population (over 77,000) – is there likely to be any overlap with any other study of ClearGuard?

- JE – we wanted to check as this is a very large population.

2) Both Brunelli 2018 and Hymes 2017 report cluster RCTs in 40 dialysis centres – is there likely to be overlap between these studies?

- KC – no overlap has been confirmed.

3) Hymes 2017 reports that the included centres were in North America – are you aware if any of the centres included are in Canada, or are they all in the US?

- JE – confirmed all in the US – keeps things simple. We are still trying to understand the differences in practice from the experts.

4) The company used CRBSI (catheter-related bloodstream infections) as the relevant infection outcome. However, some of the parameters were derived from sources that used CLABSI (central-line-associated bloodstream infections), CABSI (catheter-associated bloodstream infections) or PBC (positive blood culture) data rather than CRBSI data. Although they acknowledged that CRBSI, CLABSI, CABSI, PBC have different formal definitions, the terms were used interchangeably.

- KC – definitions used somewhat interchangeably.
- JE – for us the difficulty is that they do have different formal definitions but are used interchangeably. The CDC state that the CLA-BSI definition may overestimate the true incidence of CR-BSI, so we will need to take that into account in sensitivity analysis.
- DK – regardless of which definition is used, there are always two comparators and the same definition is applied to both arms so the relative difference is correct.
- EM – the question is around costs associated with individual types of infection. Infection terms can be used interchangeably and there is no difference in cost. However, we explore uncertainty in the cost parameter for infection extensively in sensitivity analysis.
- MK – we have to use one definition for an economic model.

5) Incidence rate of CRBSI per 1,000 CVC days using standard CVC caps at 0.7 (taken from NICE MTG44) was not specific to HD patients or CVCs. Furthermore, the 15% mortality rate in the model, which was taken from Goto et al (2013), was associated with overall bloodstream infection in the North American and Europe population. Could this be different than the actual catheter-associated bloodstream infections?

- KC – no further comments.

6) While the average age of the population undergoing HD is 60-65, the IRR for Clearguard is derived from the paediatric population in the US with 4 high-risk patients (Glennon et al 2020). Are these 2 populations comparable?

- JE – we've inquired with our experts.
- AB – we felt rates would be different between the two populations – we will consider this in our sensitivity analysis.

7) In the cost model, total number of HD patient-years (CVC) at risk (7026) is used. Could you please explain further what this patient years at risk mean? and how they were calculated.

- MK – generally the model and the clinical parameters are fine. The cost parameters for inflation were different to those from the company.
- MK – using the Glennon paper in an adult setting was a problem. We will check this out in our sensitivity analysis.
- EM – the source we used to inflate costs was the CCEMG-EPPI-centre cost converter, while the PSSRU reference had been cited in the submission. So, our inflated cost parameters are correct; we are just seeing a slight difference given that the team at KCL have used the PSSRU inflator and we have used EPPI. The referenced source in the submission was incorrect, but our inflated cost parameters are correct.

3. Timelines:

- KC – confirmed the assessment report will be sent to the company on 13th July for a fact check and then should be returned by 16th July.
- KC – MTAC is scheduled for 20th August.
- SB – the patient involvement team at NICE is keen to have more patients involved. If the company knows any clinicians/teams who have any patients who would be keen to be involved, please let us know.

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

ClearGuard HD Antimicrobial Barrier Cap for preventing haemodialysis catheter-related bloodstream infections

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 Kitec to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 12pm, **16th July 2021** 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.

16th July 2021

NICE National Institute for Health and Care Excellence

Issue 1

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
On page 11, the commentary regarding CLABSI definition is somewhat dated (CDC 2011). A more recent and relevant CLABSI definition can be found on page 1338 of Brunelli et al. 2018.	"The central line–associated bloodstream infections (CLABSI) analysis was on the basis of the NHSN CLABSI definition.[12] In this analysis, the PBC (numerator) must either be (1) a recognized pathogen and not related to an infection at another site, or (2) a common commensal from two blood draws, not related to an infection at another site, and patient has at least one of: fever, chills, or hypotension."	Reference 12 of Brunelli et al is more recent and relevant.	Thank you for your comment. We have updated the reference.

Issue 2

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
On pages 15 and 16, for the description of Weiss et al., it is highlighted that the intervention is compared with standard caps and standard needlefree connectors. No mention that the connectors used were Tego connectors, and think this should be highlighted.	To avoid confusion with standard caps, specify that Tego connectors were used in this comparison. No standard caps (aka regular end caps) were used in this study. When Weiss et al. use the term "standard" in reference to a connector, cap or group, they are referring to the Tego connector.	Tego connectors used in the study.	Thank you for the clarification, we have updated this throughout.

	Suggested amendment: CLABSI 0.03/1,000 days in the chlorhexidine group vs 0.70/1,000 days in the Tego group (p< 0.0001) for the first 5-month study period 0.09/1,000 days in the chlorhexidine group vs 0.63/1,000 days in the Tego group (p<0.0001) for the two study periods combined.		

Issue 3

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
On page 16, the description of Glennon et al states “ClearGuard HD caps with and without antimicrobial locking”, and “ClearGuard + antimicrobial locks were used in the first year while ClearGuard only was used in the second year.” However, ClearGuard was never used in combination with AML solution in this study.	The design and participants columns should be updated to reflect that standard caps + AML solution were used during FY18, and ClearGuard-only was used during FY19.	Consistency with publication.	Thank you for your comment, this has been amended.

Issue 4

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
On page 17, EAC comments regarding Sibbel et al. 2020 include “Lack of information about the other antimicrobial carrier caps used.”	This comment can be deleted since ClearGuard is the only antimicrobial barrier cap available, and no other antimicrobial barrier caps were used in this study.	Consistency with publication.	Thank you for your comment, this has been removed.

Issue 5

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
On page 21, the study by Weiss et al. states “… while Weiss et al. 2021 uses standard needlefree connectors as a comparator.” When Weiss et al. use the term “standard needlefree connectors”, they are referring to Tego connectors.	To avoid confusion with standard caps, I suggest restating as “… while Weiss et al. 2021 uses Tego connectors as a comparator.”	Consistency with publication.	Thank you for your comment, this has been amended throughout.

Issue 6

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
On page 21, section 5.2 states "Some patient characteristics were also imbalanced (race, age and diabetes), which mean study results may be biased in favour of ClearGuard."	Patient characteristics go both ways (e.g., patients were older in the ClearGuard arm of both RCTs), so I'm not sure it is fair to only comment that results may be biased in favour of ClearGuard.	Consistency with publication.	Thank you for your comment, we have expanded this statement, it now reads, "Some patient characteristics were also imbalanced in Brunelli et al. 2018 (race, age and diabetes). The ClearGuard group were less likely to have diabetes and had a higher proportion of white participants which may bias results in favour of ClearGuard. However, the ClearGuard group was also significantly older, which may bias results in favour of Tego + Curos".

Issue 7

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
On page 22, the study by Weiss et al. states “It compared ClearGuard with standard needlefree connectors used alongside standard CVC caps in 13 US dialysis centres.” However, no standard caps (aka regular end caps) were used in this study. When Weiss et al. use the term “standard” in reference to a connector, cap or group, they are referring to the Tego connector.	To avoid confusion with standard caps, I suggest restating as “It compared ClearGuard with Tego connectors in 13 US dialysis centres.”	Consistency with publication.	Thank you for your comment, this has been amended.

Issue 8

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 22 states “Glennon et al. 2020, however, was the only study which compared ClearGuard with the use of antimicrobial locking to ClearGuard alone.” However, ClearGuard was never used in combination with AML solution in this study.	Suggest restating as “Glennon et al. 2020, however, was the only study which compared standard caps + AML solution to ClearGuard alone.”	Consistency with publication.	Thank you for your comment, this has been amended.

Issue 9

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
On page 27, the BSI rate for Sibbel et al. 2020 is shown as "0.54/100 CVC days in pre-period to 0.36/100 CVC days in the post-period of AmBC." However, "100 CVC days" noted in body of abstract is a typographical error and should be "1000 CVC days" as shown in graph of abstract.	Rather than repeating the same error from the abstract, I suggest "Sibbel et al. 2020 reported a BSI rate of 0.54 per 1000 CVC days in a study period prior to the adoption of ClearGuard and 0.36 per 1000 CVC days after adoption of ClearGuard."	Consistency with publication.	Thank you for your comment, we have amended this.

Issue 10

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
On page 28, the study by Weiss et al. states it compared ClearGuard with standard CVC caps. However, no standard caps (aka regular end caps) were used in this study. When Weiss et al. use the term “standard” in reference to a connector, cap or group, they are referring to the Tego connector.	To avoid confusion with standard caps, I suggest specifying that Tego connectors were used in this comparison. Suggested amendment: CLABSI 0.03/1,000 days in the chlorhexidine group vs 0.70/1,000 days in the Tego connector group (p < 0.0001) for the first 5-month study period 0.09/1,000 days in the chlorhexidine group vs 0.63/1,000 days in the Tego connector group (p<0.0001) for the two study periods combined.	Tego connectors used in the study.	Thank you for your comment this has been amended.

Issue 11

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
On page 30, the IRR for gram+ ARBSI is reported as 0.04 which is different than the 0.40 reported in Brunelli et al. 2018.	Update to 0.40.	Consistency with publication.	Thank you for your comment, we have updated this to “0.40”.

Issue 12

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
On page 30, the study by Weiss et al. states “Weiss et al. 2021 reported a significantly reduced rate of CLABSI in the ClearGuard group compared with standard needle-free connectors.” When Weiss et al. use the term “standard needle-free connectors”, they are referring to Tego connectors.	To avoid confusion with standard caps, I suggest restating as “Weiss et al. 2021 reported a significantly reduced rate of CLABSI in the ClearGuard group compared with Tego connectors.”	Consistency with publication.	Thank-you for your comment, this has been amended

Issue 13

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 31 states “Glennon et al. 2020 was another retrospective analysis and reported a CA-BSI rate of 1.82 per 100 patients months in paediatric participants using ClearGuard with antimicrobial locking and 0.26 per 100 patient months using ClearGuard alone” However, ClearGuard was never used in combination with AML solution in this study.	Suggest restating as “Glennon et al. 2020 was another retrospective analysis and reported a CA-BSI rate of 1.82 per 100 patient months in paediatric participants using standard caps + AML solution and 0.26 per 100 patient months using ClearGuard alone.	Consistency with publication.	Thank you for your comment, this has been amended

Issue 14

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 31 (first paragraph) states "Sibbel et al. 2020 reported a BSI rate of 0.54 per 100 (0.054 per 1000) CVC days in a study period prior to the adoption of ClearGuard and 0.36 per 100 (0.036 per 1000) CVC days after adoption of ClearGuard." However, "100 CVC days" noted in body of abstract is a typographical error and should be "1000 CVC days" as shown in graph of abstract.	Rather than repeating the same error from the abstract, I suggest "Sibbel et al. 2020 reported a BSI rate of 0.54 per 1000 CVC days in a study period prior to the adoption of ClearGuard and 0.36 per 1000 CVC days after adoption of ClearGuard."	Consistency with publication.	Thank you for your comment, we have amended this.

Issue 15

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
On page 31 (second paragraph), the study by Hymes et al, 2017 is referred to as Hayes et al, 2017.	Change to Hymes et al, 2017.	Incorrect study author used.	Thank you for your comment, this has been amended.

Issue 16

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
On page 39, an assumption is made as to how the company arrived at a baseline incidence rate value of 0.61 from the study by Glennon et al. Rather, this value was calculated by: 100 x 30 (days in a month) = 3,000/1,000 = 3; 1.82/3 = 0.61.	Adjust assumed description of how company calculated this value.	Slightly different method of calculation used than was described.	The EAC has assumed 365 days/ year for its calculation, and is more precise than assuming 360 days/year, as done by the company. The description has been amended in the report.

Issue 17

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
On page 40, the second bullet point states “The company reports an incidence rate of CRBSI per 1,000 CVC-days using Tego alone of 0.63 based on Brunelli et al. 2018.” However, the correct reference for Tego alone is Weiss et al. 2021.	Suggest restating as “The company reports an incidence rate of CRBSI per 1,000 CVC-days using Tego alone of 0.63 based on Weiss et al. 2021.”	Consistency with publication.	Thank you for your comment this amendment has been made in the report.

Issue 18

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
On page 45, it is stated that 'but on query the company admitted that they have used the online EPPI converter'. The use of the word 'admitted' is considered inappropriate and we would request that this is adjusted to 'clarified'.	Adjust 'admitted' to 'clarified'.	Don't think the word 'admitted' is appropriate in this context.	Thank you for your comment this amendment has been made in the report.

Issue 19

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
The calculation for Tego connectors alone (final bullet point on page 45) appears incorrect: you have multiplied (2.29 x2) x 3, when in fact the Tego connectors would only need to be replaced once per week. So, the correct value would be as presented in the company submission.	Revise calculation for Tego connectors alone.	Incorrect calculation currently used.	The EAC acknowledges that there is a mistake in the result of weekly cost of Tego connector alone. While the formula was correct in presenting the cost of Tego connectors per week as (£2.29 x 2) and taking into consideration the cost of manual disinfection per week, (((£0.02 + £0.17) x 2) x 3), the correct sum of these two elements should then be (£2.29 x 2) + (((£0.02 + £0.17) x 2) x3) = £5.72. This has been amended in the report. The electronic model has not been affected, because the EAC did not change the Tego cost as presented by the company.

Issue 20

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
On page 46 it is stated that 'The EAC reviewed the various sources on cost of CRBSI and was unable to reconcile the inflation of the data in MTG25 (2015) with the figures used in the company model.' The EAC is now aware that an alternative inflation calculator was used by the company, and we would request that this being the reason for the discrepancy in values between the EAC and the company is stated.	Remove 'was unable to reconcile the inflation of the data in MTG25 (2015) with the figures used in the company model' with something along the lines of 'due to the alternative inflation calculator used by the company….'.	To clarify reason for discrepancy in inflated values.	Necessary amendments have been made in the report to reflect the reason for discrepancy.

Issue 21

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
On page 70, a comment regarding Brunelli et al. in section 3.1 states "1671/1911 (87%) Patients were excluded if they had <21 CVC days." However, only 231 patients were excluded if they had <21 CVC days.	Suggest restating as "231/1911 (12%) Patients were excluded if they had <21 CVC days."	Consistency with publication.	Thank you for your comment, this has been amended.

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